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Review Article

Red Palm Oil and Palm-Derived Bioactives in Biomedicine: A Review of Mechanisms, Applications, and Translational Gaps

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Abstract

Red Palm Oil (RPO) is a phytonutrient-rich lipid matrix containing carotenoids, tocopherols, tocotrienols, phytosterols, squalene, and other minor bioactive compounds. Biomedical interest now extends from whole RPO and red palm olein to palm-derived Tocotrienol-Rich Fractions (TRF), individual tocotrienol isoforms, carotenoid-rich fractions, and emerging nano- and micro-delivery systems. This qualitative literature review critically interprets recent research on the biomedical benefits, mechanisms, safety, formulation, and translational potential of RPO and verified palm-derived bioactives. Literature was identified purposively and iteratively from major scholarly databases and through citation chaining, with emphasis on peer-reviewed studies published since 2020. Rather than pursuing exhaustive retrieval or quantitative pooling, the review uses purposive literature discovery, thematic reading, and cross-study comparison to connect compositional characteristics with nutritional and ocular health, cardiometabolic disorders, diabetes-associated complications, hepatic and renal disease, inflammation and immunity, neuroprotection, retinal disease, skeletal and joint health, tissue repair, pulmonary fibrosis, oncology, and delivery technologies. The literature suggests the most direct human support for vitamin-A-related applications and growing clinical interest in diabetic neuropathy, kidney disease, metabolic and hepatic disorders, rheumatoid arthritis, and selected cardiometabolic outcomes. Other applications remain predominantly preclinical. Across themes, recurrent mechanisms involve Nrf2/HO-1, NF-κB, apoptosis, PI3K/Akt/mTOR, TGF-β/Smad, endoplasmic-reticulum stress, and immunomodulatory signalling. Overall, RPO and its derivatives represent a promising biomedical platform, but their clinical value remains indication-specific and dependent on stronger translational validation.

Keywords: Red palm oil, Red palm olein, Tocotrienol-rich fraction, Tocotrienols, Carotenoids, Biomedical applications, Antioxidant activity, Inflammation, Translational medicine, Nano-delivery

Introduction

Red Palm Oil (RPO) is obtained from the mesocarp of Elaeis guineensis fruit through processing conditions designed to retain a substantial proportion of naturally occurring lipid-soluble phytonutrients that may be lost during conventional high-temperature refining. Consequently, RPO differs biologically and chemically from highly refined palm oil because it retains substantial carotenoid and vitamin E activity together with phytosterols, squalene, and other minor constituents. Red Palm Olein (RPOO), the more liquid fraction of RPO, likewise contains carotenoids and tocotrienols while possessing physicochemical properties that facilitate dietary incorporation. These compositional characteristics have renewed interest in RPO not only as a nutrient-dense edible oil but also as a potential platform for nutraceutical, pharmaceutical, dermatological, and biomedical applications

[30,33,57]. The biomedical rationale for RPO is strongly connected to its unusual combination of provitamin A carotenoids and vitamin E homologues. Tocotrienols are structurally related to tocopherols but contain an unsaturated isoprenoid side chain that can influence membrane distribution, cellular uptake, redox behaviour, and interactions with intracellular signalling networks. Palm-Derived Tocotrienol-Rich Fraction (TRF) preparations commonly contain α-, γ-, and δ-tocotrienols together with α-tocopherol in varying proportions. Recent reviews associate palm-derived tocotrienols with antioxidant, anti-inflammatory, neuroprotective, metabolic, skeletal, and anticancer activities, although the degree of clinical verification differs markedly among these indications [28,66].

The distinction between biological plausibility and clinically established benefit is central to evaluating the biomedical literature. Natural compounds may demonstrate strong molecular effects at concentrations used in cell culture or experimental animals, whereas clinically feasible exposures can be lower and pharmacokinetically more complex. Tocotrienols are particularly lipophilic, exhibit formulation-dependent absorption, and differ in bioavailability across isoforms and source materials. Contemporary reviews therefore emphasize that oral translation depends not only on dose but also on solubility, intestinal transport, formulation, food intake, release kinetics, and tissue distribution [32,37,53]. A second problem is source attribution. Tocotrienols occur not only in palm products but also in annatto, rice bran, and other botanical sources. A biomedical review specifically addressing RPO should therefore avoid treating every tocotrienol trial as direct evidence for red palm oil. This review applies a source-verification principle: whole RPO, red palm olein, palm-derived TRF, and clearly verified palm-derived tocotrienol preparations are considered direct evidence, whereas studies of tocotrienol isoforms whose palm origin cannot be demonstrated are used primarily as mechanistic or comparative evidence. This distinction is necessary because different tocotrienol preparations vary substantially in isomeric composition and pharmacokinetic behaviour [28,53].

Interest in RPO has also moved beyond conventional nutritional supplementation. Encapsulation, nanoliposomes, nanoemulsions, submicroemulsions, and other delivery approaches are now being explored to protect carotenoids and tocotrienols from oxidation, increase dispersion in aqueous environments, improve intestinal bioaccessibility, and potentially direct bioactive compounds toward specific biomedical applications. This technological transition is significant because inadequate stability and bioavailability are among the principal barriers separating bioactivity from therapeutic effectiveness [7,26,46,58]. Human evidence has also expanded in breadth. Recent randomized studies have assessed red palm olein in vitamin-A-deficient children and people with central obesity, palm-derived tocotrienol preparations in diabetic neuropathy and diabetic kidney disease, δ-tocotrienol in metabolic and hepatic disorders, TRF in rheumatoid arthritis, and tocotrienol-containing preparations in ageing-related outcomes. More recently, a randomized clinical trial reported dose-responsive immunomodulatory effects of palm-derived TRF following influenza vaccination, extending the clinical literature beyond chronic-disease biomarkers toward functional immune outcomes [12,14,24,34,59,62,67]. The objectives of this qualitative literature review are threefold. First, it interprets recent research concerning biomedical benefits attributed to RPO, red palm olein, and verified palm-derived bioactive derivatives. Second, it connects findings across molecular, preclinical, formulation, and human studies to identify recurring mechanisms and points of convergence or contradiction. Third, it critically examines how far different biomedical applications have progressed from biological plausibility toward clinically meaningful use. The review therefore asks: (1) what biomedical benefits and limitations are described in the recent literature, (2) through which molecular and physiological pathways are these effects plausibly mediated, and (3) which applications appear most translationally mature, and which remain primarily exploratory? The purpose is interpretive integration rather than exhaustive study enumeration or statistical effect estimation.

Literature Review: Conceptual and Theoretical Foundations

Red Palm Oil as a Multicomponent Bioactive Matrix

The biological properties of RPO cannot be understood by considering only its fatty-acid composition. The oil contains saturated and unsaturated fatty acids, particularly palmitic and oleic acids, while retaining carotenoids, tocopherols, tocotrienols, phytosterols, and squalene. Studies of red palm olein and palm-pressed mesocarp olein confirm that processing conditions strongly influence the concentration and preservation of these minor constituents. Red palm-pressed mesocarp olein has demonstrated substantial radical-scavenging and metal-chelating activity in laboratory assays, supporting the broader concept that palm-oil fractions may differ materially in antioxidant potential depending on processing and phytonutrient preservation [33,61]. Carotenoids are particularly relevant because α-carotene and β-carotene can provide provitamin-A activity while contributing to antioxidant protection. This biochemical property differentiates red palm olein from conventional refined palm olein and provides a direct nutritional mechanism through which RPO can influence vitamin-A status. The 2024 randomized trial of RPO-enriched biscuits in vitamin-A-deficient schoolchildren demonstrated increases in circulating provitamin-A carotenes and favourable changes in several haematological outcomes, while a subsequent cluster randomized trial reported improved prevention of xerophthalmia and conjunctival xerosis among at-risk children [59,60]. Tocotrienols provide a second major conceptual foundation. Palm TRF generally supplies a mixture of vitamin-E homologues rather than a single compound, which raises the possibility of additive or interacting effects. Tocotrienols are capable of chain-breaking antioxidant activity, but contemporary research increasingly focuses on non-antioxidant mechanisms, including modulation of transcription

factors, inflammatory enzymes, cell-survival pathways, apoptosis, lipid metabolism, and neurotrophic processes. Reviews of palm-derived vitamin E consequently emphasize that tocotrienol effects cannot be reduced to simple radical scavenging [2,66].

Redox and Inflammatory Signalling as Unifying Mechanisms

Oxidative stress and chronic low-grade inflammation are implicated in metabolic disease, vascular dysfunction, diabetic complications, neurodegeneration, retinal disease, liver injury, fibrosis, and cancer. One of the strongest mechanistic whole-RPO studies since 2020 used a lipopolysaccharide-induced hepatic injury model. RPO pretreatment reduced indices of lipid oxidation and pro-inflammatory cytokines while increasing endogenous antioxidant defence and upregulating Nrf2, glutamate-cysteine ligase, and haem oxygenase-1. At the same time, it suppressed NF-κB-associated inflammatory signalling. This provides a biologically coherent example in which a complex RPO matrix influenced both antioxidant defence and inflammation rather than merely acting as a chemical free-radical scavenger [3]. Palm-derived δ-tocotrienol has similarly demonstrated cellular anti-inflammatory activity. In microglial models, palm-derived δ-tocotrienol was rapidly taken up by cells and reduced nitric oxide production, inducible nitric oxide synthase, prostaglandin E2, COX-2, 5-lipoxygenase, and selected inflammatory cytokines. Such findings are relevant to neuroinflammatory mechanisms, although they remain cell-based and cannot independently establish clinical neuroprotection [1]. A systematic review of NF-κB signalling concluded that tocotrienol-mediated modulation occurs across several experimental disease settings, including inflammatory, skeletal, cardiovascular, and malignant processes. The recurring participation of NF-κB is important because it provides a possible mechanistic bridge between apparently unrelated biomedical outcomes. Nonetheless, evidence of pathway modulation should be interpreted as mechanistic support rather than as a substitute for disease-specific clinical trials [1].

Bioavailability as a Translational Constraint

The biomedical efficacy of tocotrienols and carotenoids depends on absorption, distribution, stability, metabolism, and the ability to reach biologically relevant tissue concentrations. The hydrophobic nature of RPO and its constituents limits dispersion in aqueous biological systems, while tocotrienol absorption is further constrained by low aqueous solubility, relatively rapid elimination, and transporter- and concentration-dependent intestinal uptake. Pharmacokinetic evidence also suggests meaningful differences among isoforms and formulations, indicating that oral dose alone is an inadequate description of biological exposure [32,37,53]. These constraints have stimulated formulation research. RPO microencapsulation can slow the degradation of carotenoids and vitamin E during storage, while nanoliposomes can provide high beta-carotene encapsulation and improved oxidative stability. Nanoemulsion and self-emulsifying systems are increasingly used to increase dispersion, protect labile compounds, and improve oral exposure, whereas vesicular topical systems can support sustained release across the skin barrier. Recent work on a palm-TRF proniosomal gel achieved high entrapment efficiency and controlled release, illustrating how delivery engineering may expand biomedical applications beyond conventional oral supplementation [7,8,18,26,32,46,58].

Methods

Review Design and Rationale

This article adopts a qualitative literature review design oriented toward critical interpretation and thematic integration rather than systematic evidence aggregation. A qualitative review is appropriate when the research objective is to connect concepts, mechanisms, findings, tensions, and emerging directions across a heterogeneous body of literature rather than to produce an exhaustive census of studies or a pooled estimate of effect. In this approach, literature is treated as an interpretive corpus from which patterns, contrasts, conceptual relationships, and translational questions are developed. Consistent with contemporary guidance on literature reviews as independent scholarly studies, the review prioritizes conceptual relevance, critical comparison, and contribution to understanding rather than procedural replication of a systematic-review protocol [25,43].

Literature Discovery and Purposive Source Selection

Relevant literature was discovered iteratively through PubMed/MEDLINE, Scopus, Web of Science Core Collection, Embase, Google Scholar, publisher databases, and backward and forward citation tracing. Search combinations included terms such as “red palm oil”, “red palm olein”, “palm tocotrienol”, “palm-derived tocotrienol”, “tocotrienol-rich fraction”, “palm vitamin E”, “palm carotenoid”, “red palm oil nanoemulsion”, and biomedical terms including “clinical”, “antioxidant”, “inflammation”, “diabetes”, “kidney”, “liver”, “neuropathy”, “retina”, “cancer”, “neuroprotective”, “bone”, “joint”, “wound”, “fibrosis”, “bioavailability”, and “drug delivery”. Searches were not treated as a closed or exhaustive retrieval protocol, instead, they were repeated and refined as new concepts and citation pathways emerged during reading. Sources were selected purposively for their ability to illuminate the review questions. Priority was given to peer-reviewed research published from 2020 to 21 August 2026, direct studies of whole RPO or red palm olein, clearly verified palm-derived tocotrienol or carotenoid preparations, clinically informative human trials, mechanistically informative preclinical studies, and recent high-quality review articles that helped contextualize a broader evidence pattern. Selection therefore reflected relevance, recency, conceptual richness, methodological informativeness, and diversity of biomedical applications rather than a predetermined target number of studies. This is a defining difference from an SLR: the present review does not claim exhaustive retrieval, fixed screening counts, or complete coverage of every eligible publication.

Analytical Scope and Source Attribution

The interpretive scope includes whole RPO, red palm olein, palm-derived TRF, explicitly identified palm-derived tocotrienol fractions or isoforms, palm-derived carotenoid preparations, and delivery systems containing RPO or verified palm bioactives. Human interventional and observational research, animal and cellular studies, formulation and pharmacokinetic studies, and secondary reviews were read together when they contributed complementary insight into biomedical activity, safety, mechanisms, bioavailability, or translation. Primary studies were prioritized when making application-specific claims, whereas reviews and meta-analyses were used mainly to contextualize consistency, heterogeneity, or knowledge gaps. Source attribution was treated as a substantive analytical issue. Tocotrienols can originate from palm, annatto, rice bran, and other botanical sources, accordingly, tocotrienol evidence was not automatically interpreted as evidence for RPO. Whole RPO, red palm olein, palm TRF, and preparations whose palm origin could be established were treated as direct evidence. Studies using non-palm tocotrienols, or products for which botanical origin was uncertain, were considered only when they contributed useful mechanistic comparison and were not used to support direct claims about red palm oil.

Qualitative Thematic Analysis

Analysis proceeded through repeated close reading, annotation, comparative coding, and thematic clustering. An initial set of deductive domains was derived from the review questions and the biomedical literature: composition and bioavailability, antioxidant and inflammatory signalling, nutritional and ocular applications, cardiometabolic effects, diabetes-related complications, hepatic and renal outcomes, immune and inflammatory applications, neuroprotection, retinal, skeletal, and regenerative applications, fibrosis, oncology, and delivery technologies. During reading, inductive themes were added when recurrent tensions or explanatory patterns emerged, including source attribution, endpoint-specific benefit, negative or null findings, formulation dependence, and the gap between mechanistic promise and clinical confirmation. Thematic analysis was used flexibly as an interpretive tool for identifying patterned meaning across a heterogeneous literature rather than as a coding-reliability exercise [9]. The synthesis compared findings across study settings instead of numerically aggregating outcomes. Particular attention was paid to whether conclusions converged across molecular mechanisms, animal models, human biomarkers, and clinical endpoints, whether apparently positive findings were counterbalanced by null or negative results, and whether differences in preparation, dose, duration, population, or delivery system could plausibly explain inconsistency. This interpretive comparison allowed the review to distinguish well-supported themes from promising but preliminary applications without imposing a formal evidence-grading algorithm.

Interpretive Credibility and Limitations

Credibility was strengthened through triangulation across study types, explicit separation of human from preclinical evidence, cautious treatment of surrogate biomarkers, attention to null and negative findings, and repeated checking of whether a derivative was genuinely palm-derived. The review did not use a fixed study-flow count, standardized appraisal checklist, or meta-analysis because its purpose was interpretive rather than exhaustive or aggregative. The trade-off is that a qualitative literature review cannot claim exhaustive coverage or calculate an unbiased pooled treatment effect. Its value instead lies in interpretive breadth, critical comparison, conceptual integration, and identification of research directions that become visible when heterogeneous biomedical literatures are read together [25] (Figure 1).

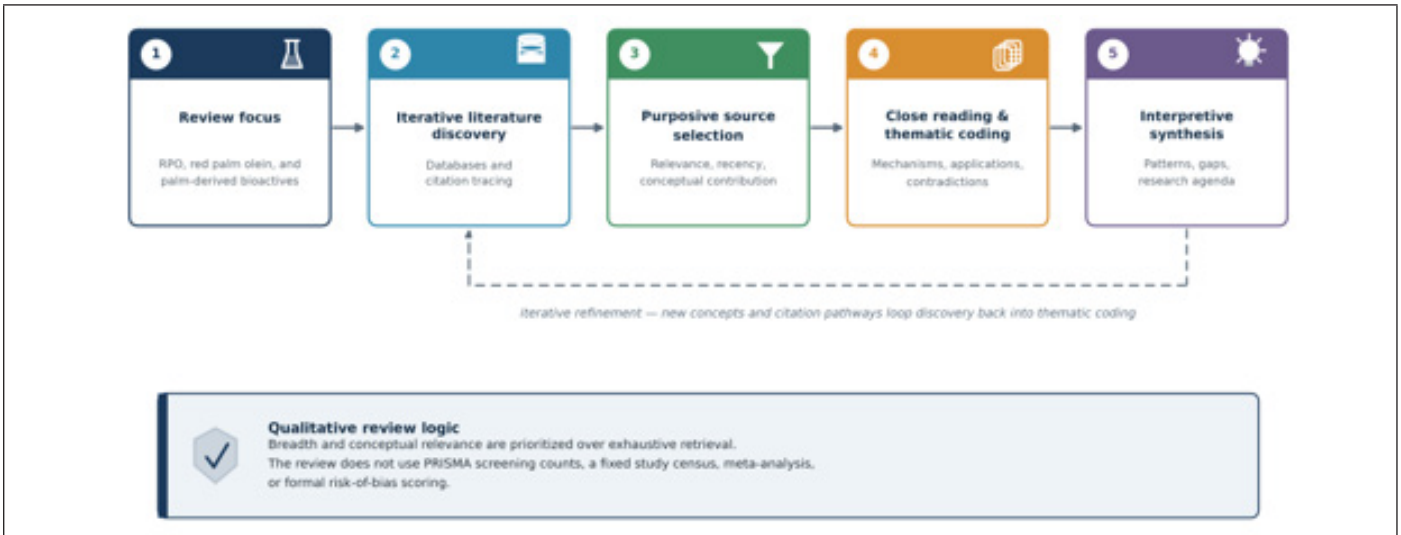

Figure 1: Interpretive pathway of the qualitative literature review. Source: author's synthesis. The figure emphasizes purposive discovery, close reading, thematic coding, and critical integration. It also makes explicit that the pathway represents an interpretive review process rather than a claim of exhaustive coverage or formal quantitative evidence grading.

Thematic Findings

Overview of the Literature Landscape

The contemporary evidence base is highly heterogeneous in both intervention and maturity. Direct whole-RPO and red-palm-olein human studies remain fewer than studies of concentrated palm-derived tocotrienols. Nevertheless, whole RPO has recently generated mechanistic evidence for antioxidant and inflammatory regulation, while RPOO trials have produced clinically relevant nutritional and ocular findings. Palm TRF has the broadest human biomedical literature, particularly in diabetes-related complications, metabolic disease, and emerging inflammatory applications [3,28,59]. A notable feature is that effects are endpoint-specific rather than uniformly beneficial. Tocotrienol meta-analyses do not demonstrate consistent reductions in all lipid, inflammatory, anthropometric, or glycaemic variables. For example, the 2020 lipid meta-analysis did not identify reliable reductions in LDL cholesterol, total cholesterol, or triglycerides overall, while a broader 2022 analysis reported substantial heterogeneity and limited effects for many metabolic biomarkers. This cautions against describing tocotrienol as a generalized cardiometabolic therapy [27,69].

Nutritional, Vitamin-A, and Ocular Applications

The most direct biomedical case for whole RPO or red palm olein is its ability to deliver provitamin-A carotenoids. In a double-blind randomized controlled trial, RPO-enriched biscuits consumed by vitamin-A-deficient primary-school children increased circulating α- and β-carotene and were associated with improvements in iron-related and erythropoietic measures. This finding is biologically plausible because the carotenoid-rich lipid matrix delivers provitamin A in a form supported by dietary fat, which facilitates intestinal absorption [59]. The subsequent 2025 cluster randomized study extended this evidence to clinically recognizable ocular outcomes. Six months of supplementation with RPO-enriched biscuits did not significantly improve the rate of resolution of established xerophthalmia relative to control, but prevention of xerophthalmia and conjunctival xerosis was significantly greater in the RPO group. Children receiving the RPO intervention were substantially less likely to develop xerophthalmia. This distinction between treatment and prevention is important: the study supports preventive utility among at-risk children more strongly than reversal of established disease [60]. RPO may also alter food functionality. Rice prepared with RPO demonstrated increased carotenoid content and antioxidant activity, while adding RPO before cooking reduced glycaemic response relative to regular rice under the studied conditions. The proposed mechanism involves formation of amylose–lipid complexes and physical protection of starch against enzymatic digestion. These findings are nutritionally interesting but should not yet be interpreted as evidence that RPO-treated foods constitute established therapy for diabetes [36]. Collectively, the vitamin-A literature provides one of the clearest examples of a mechanistically coherent pathway linking RPO composition to a clinically relevant human benefit. The combination of biochemical plausibility, measurable carotenoid exposure, and ocular outcomes makes this theme more translationally mature than many disease-modification claims associated with isolated palm bioactives. The evidence is particularly relevant to populations in which vitamin A deficiency persists and carotenoid-rich interventions can be incorporated into culturally acceptable foods [30,59,60].

Cardiometabolic Outcomes

A contemporary randomized comparison of RPOO, extra-virgin coconut oil, and extra-virgin olive oil among individuals with central obesity found broadly comparable effects on the primary inflammatory marker hs-CRP. However, extra-virgin olive oil produced lower mean LDL cholesterol than RPOO and coconut oil, whereas RPOO produced clearly higher circulating α- and β-carotene. Thus, RPOO increased antioxidant carotenoid exposure without demonstrating overall cardiometabolic superiority to olive oil [62]. This result illustrates why RPO evaluation should avoid simplistic "healthy versus unhealthy oil" classifications. A food oil simultaneously delivers fatty acids and non-lipid micronutrients, so individual biomarkers can move in different directions. The saturated-fat contribution of RPO must therefore be considered alongside carotenoid and tocotrienol delivery, and claims should remain endpoint-specific rather than implying universal cardioprotection [28,62]. Meta-analytic evidence for tocotrienols is similarly nuanced. Zuo et al., (2020) found an increase in HDL cholesterol in some analyses but no consistent overall reduction of LDL cholesterol, total cholesterol, or triglycerides. Li et al., (2022) likewise found limited effects across numerous obesity, inflammatory, glucose, and liver biomarkers. Such findings do not invalidate tocotrienol bioactivity, but they demonstrate that mechanistic antioxidant potential does not guarantee a large effect on conventional cardiovascular risk markers. More recent disease-specific studies remain exploratory. In chronic kidney disease, TRF supplementation was associated with reductions in LDL and total cholesterol in haemodialysis participants, although sample sizes were small and inflammatory responses were not uniformly improved. These findings require confirmation in adequately powered studies before clinical recommendations can be justified [63].

Type 2 Diabetes and Diabetic Neuropathy

Diabetic peripheral neuropathy is one of the strongest translational areas for palm-derived tocotrienol-rich vitamin E. A Phase II randomized trial demonstrated that 400 mg/day Tocovid improved nerve-conduction velocities and increased circulating nerve-growth factor over eight weeks relative to placebo. Importantly, this represented a physiological neurological endpoint rather than merely an antioxidant biomarker [34]. A longer Phase II trial subsequently found significant improvements in median and sural sensory nerve-conduction velocity after twelve months of supplementation, although benefits were not retained after washout. The trial did not produce corresponding changes in several serum biomarkers, suggesting that the neurological effect may not

be explained by conventional circulating inflammatory measures alone [14]. Recent meta-analytic evidence reinforces an effect on selected electrophysiological parameters. A 2026 systematic review and meta-analysis reported improvements in sural, median sensory, and tibial motor nerve-conduction velocities without corresponding changes in nerve-action-potential amplitude or HbA1c. This pattern supports a possible adjunct neuroprotective effect independent of improved glycaemic control and argues against positioning tocotrienol as a substitute for standard diabetes management [5]. The wider diabetes evidence is less uniform. A systematic review and meta-analysis focusing on TRF in type 2 diabetes found a small reduction in HbA1c under some dosing and duration conditions but no significant overall reduction in blood pressure or hs-CRP. Thus, diabetic neuropathy currently appears more convincingly supported than generalized glycaemic or anti-inflammatory efficacy in diabetes [42].

Diabetic Kidney Disease and Renal Applications

Palm tocotrienol-rich vitamin E has also been evaluated in diabetic kidney disease. A Phase IIb randomized trial involving patients with diabetic kidney disease reported improvements in serum creatinine and estimated glomerular filtration rate at selected time points, particularly among participants with stage-3 chronic kidney disease. However, urinary albumin-to-creatinine ratio and several mechanistic serum biomarkers were not consistently improved, and benefits diminished after washout [24]. This creates a clinically interesting but incomplete signal. Improvements in creatinine-derived indices may suggest renal protection, but replication using longer follow-up, adequately powered populations, hard renal outcomes, and careful accounting for background renoprotective therapy remains necessary. The literature therefore supports continued investigation rather than routine therapeutic use, especially because renal and cardiometabolic responses to tocotrienol supplementation are not uniformly consistent across studies [24, 28,63].

Metabolic Dysfunction and Liver Disease

δ-Tocotrienol has generated a substantial contemporary literature in non-alcoholic fatty liver disease, now increasingly conceptualized within metabolic dysfunction-associated steatotic liver disease. A randomized placebo-controlled study reported reductions in fatty-liver index, insulin resistance, hs-CRP, malondialdehyde, transaminases, and ultrasound-assessed steatosis following δ-tocotrienol supplementation [41]. A subsequent active-controlled study comparing δ-tocotrienol with α-tocopherol found improvement in hepatic steatosis, oxidative stress, and insulin resistance in both groups. δ-Tocotrienol produced greater reductions in several inflammatory and apoptosis-related indicators, including IL-6, TNF-α, leptin, and cytokeratin-18. These data provide a mechanistic bridge between metabolic, inflammatory, and hepatocellular effects [39]. Molecular follow-up works further suggested modulation of circulating microRNAs involved in hepatic pathophysiology, supporting the possibility that tocotrienol effects extend beyond conventional antioxidant biomarkers. Nevertheless, the clinical significance of microRNA modulation remains uncertain until it can be associated reproducibly with clinically meaningful liver outcomes [40]. Paediatric evidence is more preliminary. A trial in children with obesity and NAFLD reported reductions in selected inflammatory markers and DNA-damage indices following TRF supplementation, while hepatic-steatosis changes were not consistently superior to control. These mixed findings emphasize that promising biomarker responses cannot be assumed to represent disease reversal [4]. Combination interventions further complicate causal interpretation. A randomized study of δ-tocotrienol combined with resveratrol reported improvements in cardiometabolic risk factors in people with metabolic syndrome, but the effect cannot be attributed to tocotrienol independently because both bioactives were administered together. A similar attribution problem arises in experimental formulations that combine RPO with other plant-derived ingredients: a 2024 rat study reported favourable antioxidant, lipid-related, and BDNF-associated outcomes for a formulation containing RPO, Koja bay leaves, and passion-fruit seeds, yet the contribution of RPO itself cannot be isolated. Tocotrienol-enriched food matrices raise the same interpretive issue, making careful distinction between whole-formulation effects and compound-specific effects essential [17,35,51].

Inflammation, Immunity, and Rheumatoid Arthritis

The anti-inflammatory hypothesis surrounding palm TRF has now progressed into disease-specific clinical investigation. In 2025, a randomized double-blind placebo-controlled trial in patients with moderate-to-severe rheumatoid arthritis receiving stable conventional disease-modifying therapy reported reductions in disease-activity score, stiffness, swelling, pain, and functional impairment after six months of TRF supplementation. No major treatment-related safety signals were reported. This is noteworthy because the intervention was tested as an adjunct to standard therapy rather than as a replacement [67]. Immunomodulatory research has now progressed from protocol development to completed clinical testing. In a 2026 double-blind randomized trial involving 150 healthy adults, daily palm-derived TRF at 50, 100, 200, or 400 mg increased influenza-specific antibody responses compared with placebo, while higher-dose supplementation produced broader Th1-associated and antioxidant effects. The finding is important because it evaluates a functional immune challenge rather than relying solely on resting inflammatory biomarkers, while also suggesting that lower doses may be sufficient for enhancing humoral responses [12]. Ageing populations provide another emerging field. A tocotrienol-enriched beverage trial reported improvements in selected psychological well-being, antioxidant-defence, and genomic-stability measures among older adults. Although these endpoints are relevant to healthy ageing, replication and clearer attribution to the tocotrienol component are needed before broader geroprotective conclusions are justified [54]. Toxicological evidence also requires continued attention. A 2025 integrated assessment using computational methods and a zebrafish embryotoxicity model specifically evaluated palm-derived TRF and adds contemporary information regarding dose-related safety. Such work should be considered complementary to-

not a replacement for-long-duration human safety data [15].

Neuroprotective Applications

Neuroprotection is one of the most mechanistically developed yet clinically uncertain areas. Palm-derived TRF improved learning and biochemical abnormalities in a rat model of vascular dementia associated with type-2 diabetes, with changes involving acetylcholinesterase, glutathione, superoxide dismutase, homocysteine, hippocampal histology, and PDGF-C expression [52]. Cell-based Parkinson-related research demonstrates that TRF can regulate proteins associated with oxidative stress, mitochondrial function, and neurodegenerative pathways, including when investigated alongside levodopa. These findings contribute to mechanistic plausibility but remain distant from evidence that TRF alters clinical Parkinson's disease progression [31]. Research in aluminium-induced neurotoxicity has likewise suggested protective effects involving antioxidant and histological outcomes, adding further preclinical support [21]. Recent review literature emphasizes NF-κB-dependent neuroinflammation together with oxidative signalling, mitochondrial dysfunction, synaptic integrity, and brain ageing as recurring mechanistic themes. A 2025 scoping review of TRF similarly identified broad preclinical neuroprotective signals across oxidative stress, apoptosis, inflammation, and cognition, but highlighted continuing gaps in human translation. Across the literature considered here, human neurocognitive research therefore remains substantially less developed than experimental neurobiology [6,22,45,65]. The importance of negative evidence should also be emphasized. A randomized trial of a palm-derived tocotrienol-rich vitamin E complex in CADASIL reported no meaningful reduction in clinical progression over 24 months and met predefined criteria for futility. The formulation was well tolerated, but the result shows that antioxidant and neuroprotective plausibility does not necessarily translate into efficacy in established cerebral small-vessel disease [11]. Accordingly, the neuroprotection theme illustrates the review's central translational principle: the number of molecular pathways influenced by an intervention cannot substitute for successful clinical validation. Neuroprotective claims should remain indication-specific and calibrated to the level of available human evidence, especially where mechanistic or animal findings coexist with neutral clinical outcomes [11,22].

Retinal and Ophthalmic Neuroprotection

Experimental diabetic retinopathy represents a more focused ocular application of palm-derived TRF. A 2020 study showed that oral palm-derived TRF reduced diabetes-associated retinal neurodegenerative changes and VEGF expression, with oral administration appearing more effective than topical administration in the studied model [47]. A subsequent study reported reduced oxidative stress, lower retinal apoptosis, preservation of retinal morphology, and better visual-behaviour responses following oral TRF in diabetic rats. These outcomes were accompanied by higher glutathione, superoxide dismutase, and catalase and lower malondialdehyde and caspase-related apoptosis [48]. The potential relevance of tocotrienols to age-related macular degeneration has also been reviewed recently, particularly in relation to oxidative stress, inflammation, mitochondrial dysfunction, and retinal-cell survival. Yet clinical ophthalmic evidence remains inadequate, and currently available data should be viewed as hypothesis-generating rather than sufficient for recommending tocotrienol therapy for macular degeneration [49].

Skeletal and Joint Applications

Palm tocotrienol has shown bone- and cartilage-protective effects in experimental models of oestrogen deficiency and osteoarthritis. A 2024 study comparing emulsified and non-emulsified palm tocotrienol in ovariectomized rats with induced osteoarthritis found preservation of trabecular and subchondral bone parameters, improvements in selected mechanical outcomes, lower RANKL, and protection of cartilage histology. An important formulation-related finding was that emulsified palm tocotrienol produced comparable or superior effects despite containing less vitamin E, suggesting that delivery efficiency can materially influence biological outcome [16]. Mechanistic evidence also suggests that tocotrienols can influence osteoblast migration and signalling relevant to bone formation, while recent reviews identify antioxidant, anti-inflammatory, mevalonate-related, Wnt-associated, and osteoclast-regulatory mechanisms. Human clinical evidence, however, remains scarce, making skeletal applications predominantly preclinical at present [10,13].

Wound Healing and Tissue Regeneration

Topical TRF has been studied in experimental burn healing, particularly in combination with epidermal growth factor. In deep partial-thickness burn models, TRF-containing formulations were associated with accelerated healing and histological improvement. Follow-up gene-expression research indicated modulation of pathways associated with tissue repair and inflammation [19,20]. These data suggest potential use of palm-derived vitamin E fractions in topical regenerative formulations. However, the combination with epidermal growth factor creates attribution challenges because the observed effect may reflect interaction between ingredients rather than TRF alone. Recent formulation research has strengthened the delivery rationale by demonstrating sustained release and high entrapment efficiency of palm TRF in a proniosomal gel, but this remains a pharmaceutical-formulation advance rather than proof of clinical wound efficacy. Human wound and dermatological trials are therefore still needed before experimental findings can support routine clinical practice [18,19,20].

Pulmonary Fibrosis and Anti-Fibrotic Potential

A preclinical study evaluating TRF together with carotene in bleomycin-induced pulmonary fibrosis reported improvement in fibrotic and inflammatory abnormalities involving TGF-β/Smad, PI3K/Akt/mTOR, and NF-κB pathways. This is particularly interesting because the formulation combined two major palm-derived bioactive classes-tocotrienols and carotenoids-and therefore more closely approximates the multi-component logic of RPO than isolated-compound studies [29]. Pulmonary fibrosis remains a proof-of-concept indication. Contemporary evidence

does not demonstrate that RPO or palm TRF modifies established human pulmonary fibrosis, and the large difference between experimental dosing and clinically achievable exposure remains a major translational limitation. The current literature therefore supports mechanistic plausibility rather than clinical efficacy in this domain [29,66].

Anticancer Activity and Adjunct Oncology

The anticancer literature is extensive mechanistically but relatively immature clinically. Tocotrienol isoforms have demonstrated effects on proliferation, apoptosis, autophagy, angiogenesis, metastasis, immune checkpoints, cell-cycle control, and stress-response pathways. Systematic analysis of endoplasmic-reticulum stress indicates that tocotrienols can activate unfolded-protein-response pathways and promote cancer-cell death, but the underlying evidence identified in that analysis was essentially in vitro [38]. Recent reviews of γ- and δ-tocotrienol in colorectal cancer similarly describe modulation of apoptosis, metastasis, telomerase-related biology, cell-cycle progression, and interactions with established anticancer therapies. Nevertheless, the preponderance of cell studies compared with animal and human evidence illustrates the large translational gap [23,50,64]. Specific molecular studies add detail. β-Tocotrienol has been reported to suppress PD-L1-associated tumour signalling through JAK2/STAT3-related mechanisms, whereas δ-tocotrienol has been shown to disrupt PD-L1 glycosylation and reverse aspects of PD-L1-mediated immune suppression in experimental models. γ-Tocotrienol can influence autophagy through the GSK3β/β-catenin pathway in gastric-cancer models [55,56,68]. The most clinically informative contemporary oncology study is a randomized Phase II investigation of δ-tocotrienol added to FOLFOXIRI for metastatic colorectal cancer. The intervention did not significantly prolong the primary endpoint of time to first hospitalization or death. Some secondary observations, including fewer oxaliplatin dose reductions, suggested possible supportive or neuroprotective effects, but these findings are hypothesis-generating and cannot establish anticancer efficacy [44]. This negative primary endpoint is important because it demonstrates why laboratory anticancer activity cannot be treated as proof of clinical cancer efficacy. Current evidence supports continued investigation of tocotrienols as adjuncts, chemosensitizers, toxicity-modifying agents, or delivery-system components, while survival and tumour-control claims require successful prospective human trials [44,50,64]. Nanoformulation may partially address pharmacokinetic barriers. A 2025 palm-oil nanoemulsion improved tocotrienol stability and antioxidant activity and demonstrated greater cytotoxicity against melanoma cells than free tocotrienol while retaining substantially lower toxicity toward normal fibroblast cells under the experimental conditions. Although promising, these findings remain preclinical [8].

Integrative Mechanistic Architecture

Because the disease-specific literature repeatedly converges on a limited set of biological processes, Figure 2 provides an interpretive map linking the principal RPO bioactive classes to recurrent intracellular pathways and the biomedical applications in which those pathways are discussed. The map is intended to clarify conceptual convergence across heterogeneous studies rather than to imply that each compound acts on every pathway or that mechanistic modulation necessarily predicts clinical benefit (Figure 2).

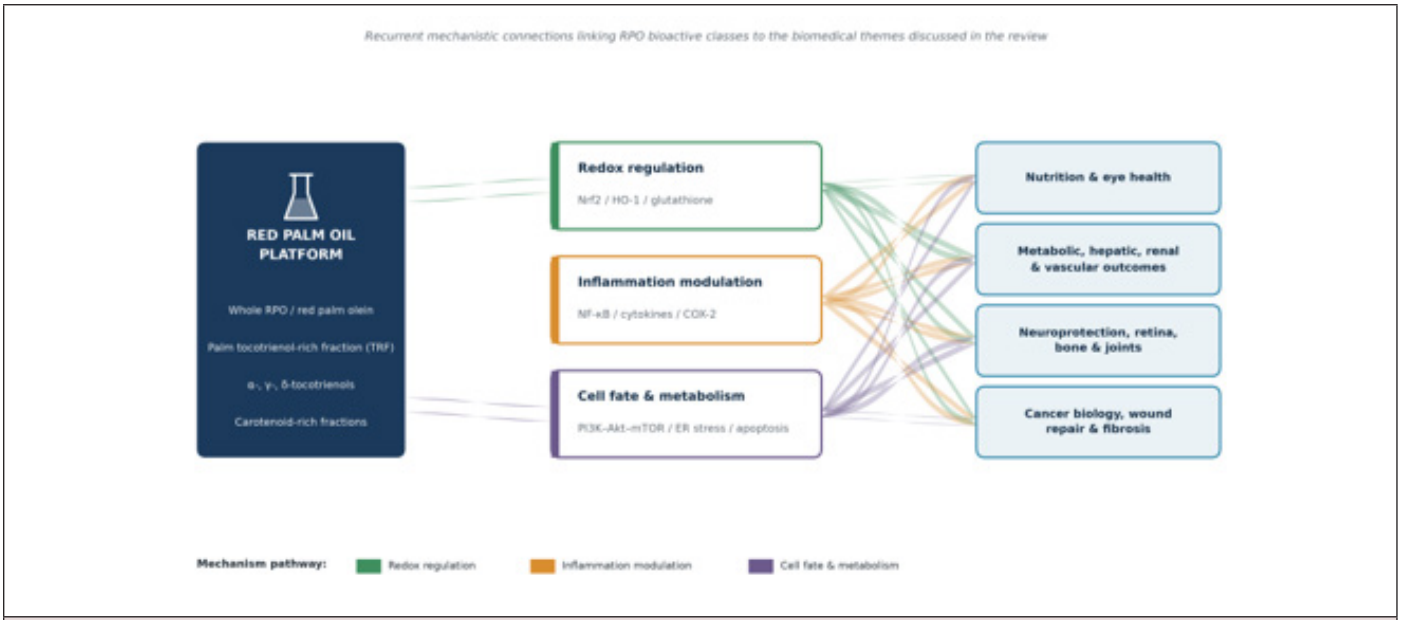

Figure 2: Bioactive–mechanism–biomedical application map. Source: author's qualitative synthesis. The map illustrates recurrent mechanistic connections rather than a claim that every compound acts on every pathway or that pathway modulation necessarily produces clinical benefit. The literature most frequently connects RPO carotenoids and tocotrienols with redox defence, NF-κB-related inflammation, apoptosis, metabolic signalling, and tissue protection [3,38,66].

Discussion and Critical Analysis

From Nutritional Oil to Biomedical Platform

The evidence reviewed demonstrates that RPO can no longer be evaluated solely as a dietary source of fat. Its retained carotenoids and tocotrienols create multiple levels of biomedical functionality. At the simplest level, RPO provides provitamin-A carotenoids, producing a direct nutrient-replacement mechanism that has now generated randomized human evidence. At a second level, concentrated palm-derived tocotrienols act as pharmacologically active nutraceuticals capable of modulating oxidative, inflammatory, neurological, metabolic, and signalling pathways. At a third level, RPO is increasingly functioning as an input for engineered delivery systems designed to enhance stability, absorption, or targeted biological activity [30,57,58]. These levels should not be conflated. Nutritional correction of vitamin A deficiency requires a different evidentiary standard and mechanism from the proposed use of tocotrienol as an adjunct anticancer compound. Similarly, demonstrating that a nanoemulsion kills melanoma cells does not establish therapeutic efficacy in melanoma patients. A principal contribution of this review is therefore to apply a translational lens to a literature that often uses "health benefit", "therapeutic effect", and "biomedical potential" interchangeably [8,44,59].

An Interpretive View of Translational Maturity

Figure 3 organizes the literature along a translational continuum, from mechanistic exploration to replicated clinical implementation. It is used here as a qualitative heuristic for asking how far a biomedical claim has travelled, not as a formal hierarchy produced through standardized quantitative appraisal scoring (Figure 3).

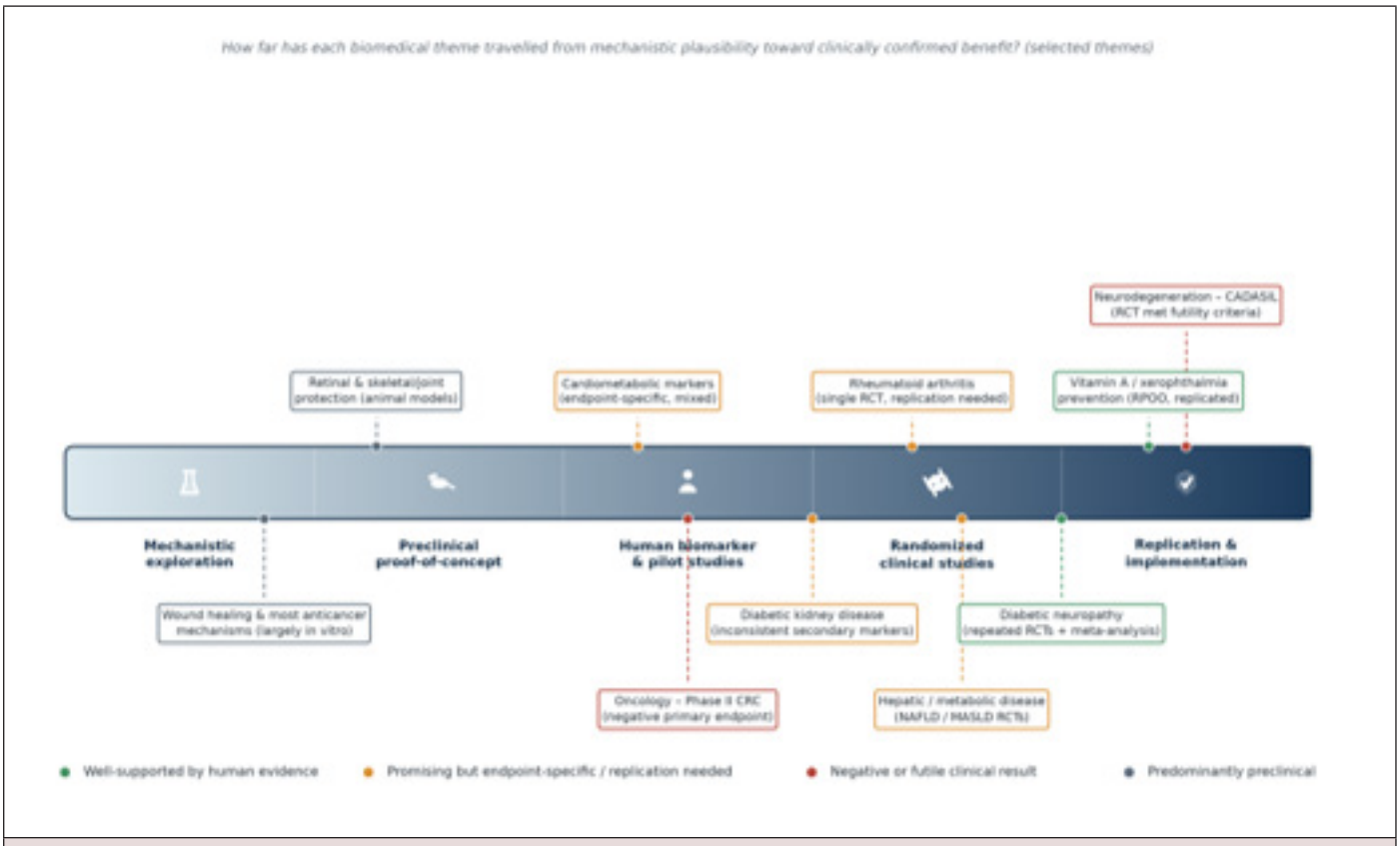

Figure 3: Interpretive translational continuum for RPO and palm-derived bioactives. Source: author's qualitative synthesis. Cell studies illuminate mechanisms, animal models establish biological proof-of-concept, human biomarker studies indicate exposure and physiological response, randomized trials test causal clinical effects, and replicated studies are needed before routine implementation. The continuum is therefore an interpretive reading aid rather than a formal evidence-grading scale.

Within this interpretive continuum, the most direct whole-RPO evidence is concentrated in nutritional and ocular applications. The RPOO studies in vitamin-A-deficient children are notable because compositional rationale, biomarker response, and clinically relevant ocular outcomes align. Even here, the literature distinguishes prevention from treatment: prevention of xerophthalmia appears clearer than reversal of established xerophthalmia [59,60]. Palm TRF has been investigated clinically across a broader set of applications. Diabetic neuropathy is supported by repeated improvements in nerve-conduction outcomes and is reinforced by secondary synthesis, making it one of the more mature non-nutritional themes in the literature. Diabetic kidney disease shows renal-function signals, but effects on albuminuria and mechanistic biomarkers remain inconsistent. Hepatic disease has generated several randomized studies, yet larger independent and multinational replication remains limited [14,24,34,39,41].

Rheumatoid arthritis represents an important emerging indication because the reported outcome involved disease activity rather than only biochemical markers. Nevertheless, a single relatively small RCT does not establish a new adjunct treatment standard. Replication with larger populations, longer follow-up, prespecified medication strata, and radiographic or functional outcomes will be required [67].

Mechanistic Convergence and Biological Plausibility

The most consistent mechanistic theme is regulation of oxidative stress. RPO and tocotrienols can increase endogenous antioxidant capacity and reduce lipid peroxidation in numerous models. However, interpreting these substances simply as "antioxidants" understates the available evidence. Nrf2, NF-κB, inflammatory cytokines, COX-2, iNOS, PI3K/Akt/mTOR, TGF-β/Smad, apoptosis-related proteins, ER-stress responses, and immune-checkpoint signalling appear repeatedly across disease models [1,3,38,56]. This convergence provides biological plausibility but also introduces an interpretive risk. Signalling networks such as NF-κB and PI3K/Akt are ubiquitous, so an intervention that modifies them in vitro is not automatically selective or therapeutically useful in humans. Dose, tissue exposure, treatment duration, baseline disease state, formulation, and interactions with conventional medication can all determine whether pathway modulation produces benefit, no effect, or toxicity [3,38,66]. The relatively good safety profile of tocotrienol in contemporary clinical trials is reassuring, but safety should not be inferred from natural origin. Continued pharmacokinetic and toxicity research is necessary, particularly for high-dose isolated isomers and novel nanocarriers whose tissue distribution may differ fundamentally from dietary RPO [15,53].

Why Bioavailability May Determine Clinical Success

Poor or variable bioavailability is one plausible explanation for discrepancies between strong preclinical findings and weaker clinical effects. Tocotrienols are highly lipophilic, and circulating exposure depends on formulation, food intake, intestinal transport, and release kinetics. Recent pharmacokinetic analyses further indicate that concentration-dependent absorption and rapid elimination can restrict systemic retention, while formulation-based strategies can improve but not fully eliminate these intrinsic barriers [32,37,53]. Encapsulation technologies directly address this problem. Microencapsulation can protect RPO carotenoids and vitamin E from degradation, nanoliposomes can improve encapsulation and oxidative stability, nanoemulsions and self-emulsifying systems can increase aqueous dispersion and oral exposure, and proniosomal gels can provide sustained topical delivery of palm TRF. These approaches strengthen the pharmaceutical rationale for RPO-derived bioactives, although improved formulation performance should not be equated with improved clinical outcomes until pharmacokinetic and efficacy studies confirm the connection [7,18,26,32,46]. The translational implication is substantial. Future trials should not treat "tocotrienol dose" as the only exposure variable, chemical composition, isomer ratio, delivery system, fed or fasting state, plasma pharmacokinetics, and tissue distribution should be reported consistently. Without these data, two apparently similar 400-mg interventions may represent materially different biological exposures, making cross-study comparison and replication difficult [32,37,53].

Qualitative Biomedical Evidence Landscape

Figure 4: Qualitative biomedical evidence landscape. Source: author's synthesis. Vitamin-A-related applications, diabetic neuropathy, diabetic kidney disease, hepatic/metabolic disorders, and rheumatoid arthritis have generated human interventional research, whereas retinal neuroprotection, skeletal protection, pulmonary fibrosis, wound healing, and most anticancer mechanisms remain dominated by experimental studies. Neurodegenerative disease occupies an intermediate and internally inconsistent position, with extensive mechanistic literature but limited or negative clinical confirmation.

Figure 4 condenses the dominant pattern of literature discussed in this review by showing where each biomedical theme is concentrated-human intervention studies, preclinical research, or a mixture of both-and the cautious interpretation that follows from that pattern. It is intended as a qualitative orientation device rather than a formal evidence-grading framework (Figure 4).

This qualitative gradient should shape the language used to describe RPO-derived biomedical applications. Terms such as "clinically supported" require convincing and reproducible human outcomes, whereas "promising", "potential", and "preclinical" are more appropriate for applications represented mainly by cultured cells, animal models, or early formulation work. This terminology is intended to promote interpretive caution rather than impose a formal evidence-grading system [11,28,44].

Anticancer Potential: Strong Mechanisms, Weak Clinical Confirmation

Anticancer research illustrates this issue most clearly. Tocotrienols modulate numerous cancer-related pathways and can sensitize malignant cells to established therapies in experimental systems. Reviews describe interactions with apoptosis, cell-cycle checkpoints, ER stress, autophagy, metastasis, inflammatory pathways, and immune-checkpoint biology [23,38,50,64]. Yet the Phase II colorectal-cancer trial provides an important corrective: δ-tocotrienol did not significantly improve the primary endpoint when added to intensive chemotherapy. A signal relating to oxaliplatin dose reduction may justify further supportive-care research, but the trial cannot be used to claim that tocotrienol improves cancer survival or tumour control [44]. Consequently, future oncology research should focus on clearly defined roles such as chemosensitization, mitigation of treatment-related neurotoxicity, immunomodulation, targeted nano-delivery, or tumour-specific pharmacokinetics. Broad claims of "anticancer activity" are less informative than indication-specific and mechanism-specific trials, particularly when clinical endpoints remain neutral despite extensive preclinical signalling evidence [44,50,64].

Neuroprotection: Translational Lessons from Negative Evidence

The neuroprotection literature provides another important lesson. TRF repeatedly improves oxidative and inflammatory measures in experimental neural models, protects retinal neurons, and affects disease-related proteins, however, the negative CADASIL trial indicates that these mechanisms may not reverse or slow established human small-vessel disease. This contrast reinforces the importance of separating mechanistic plausibility from demonstrated disease modification [11,22,65]. Several explanations may account for this translational gap. Antioxidant or membrane-protective interventions may be more effective before irreversible structural injury, central-nervous-system exposure may be inadequate, and neurodegenerative disorders involve multiple pathogenic drivers that are unlikely to be modified by a single nutraceutical pathway. Future studies should therefore stratify participants by disease stage, incorporate pharmacokinetic measurements, and prioritize prespecified imaging, functional, and patient-centred outcomes [37,53,65].

Safety, Source Attribution, and Interpretive Limitations

Several interpretive issues require attention. First, studies frequently use commercial tocotrienol preparations with different compositions, while botanical origin is not always described adequately. Second, part of the literature is supported by palm-oil-related organizations or nutraceutical manufacturers, making transparent conflict-of-interest reporting and independent replication especially important. Third, this qualitative review is intentionally selective and interpretive: it connects conceptually important literature rather than calculating a complete study census or pooled effect estimate, so absence of a study from the narrative should not be interpreted as evidence that it does not exist [28,53]. Positive-publication bias is also plausible because natural-product research often prioritizes successful mechanistic outcomes. A critical qualitative synthesis should therefore give explicit attention to null and negative findings and should resist allowing a large preclinical literature to overshadow contradictory human results. The RPOO cardiometabolic trial, lipid meta-analysis, mixed metabolic findings, negative CADASIL trial, and colorectal-cancer primary endpoint demonstrate the value of this balanced reading [11,27,44, 64,69,]. Fourth, doses used in rodents and cells cannot be directly extrapolated to humans. Preclinical studies should provide exposure data where possible, while human-equivalent dose calculations should not be treated as substitutes for pharmacokinetic validation. This distinction is especially important for lipophilic tocotrienols, for which absorption, elimination, and tissue exposure can vary substantially with formulation and administration conditions [37,53].

Research Priorities

Future research should first standardize intervention characterization. Each trial should report palm source, extraction process, tocotrienol isomer profile, tocopherol concentration, carotenoid composition, oxidation status, excipients, and delivery technology. Such reporting would improve reproducibility and reduce ambiguity between whole-RPO effects, palm-TRF effects, isolated-isomer effects, and formulation-dependent changes in exposure [28,37]. Second, pharmacokinetic and pharmacodynamic work should precede large efficacy trials. Plasma and, where feasible, tissue concentrations should be related to biological outcomes. Novel nano- and micro-delivery systems are particularly suitable for such translational studies because formulation changes can materially alter exposure [8,46,58]. Third, clinical research should prioritize patient-important outcomes rather than relying predominantly on biochemical surrogates. For diabetic neuropathy this means pain, functional impairment, nerve conduction, and quality of life, for kidney disease, long-term eGFR decline and kidney failure, for liver disease, imaging or histological progression, for neurodegeneration, cognition, disability, and imaging progression, and for oncology, progression-free survival, toxicity, quality of life, and treatment completion. This shift would help distinguish biologically interesting changes from outcomes

that matter directly to patients [14,24,44]. Fourth, head-to-head studies should distinguish the complete RPO matrix from purified fractions. Whole RPO may produce interactive effects through carotenoids, tocotrienols, tocopherols, fatty acids, and other minor components, whereas purified isoforms permit more precise dosing and mechanistic inference. Direct comparison would clarify whether biomedical activity depends on the food matrix, a concentrated palm fraction, a particular isomer, or a delivery-system effect [28,30,57].

Conclusion

Current evidence indicates that red palm oil should be viewed as a biologically active lipid matrix containing clinically and experimentally relevant carotenoids, tocotrienols, tocopherols, and other phytonutrients. Its clearest direct human biomedical application remains delivery of provitamin-A carotenoids, for which recent randomized evidence supports improvements in nutritional status and prevention of vitamin-A-deficiency-related ocular manifestations. Palm-derived tocotrienol-rich fractions substantially broaden the biomedical landscape. Randomized human evidence is now available for diabetic neuropathy, diabetic kidney disease, hepatic and metabolic disorders, rheumatoid arthritis, and selected cardiometabolic and ageing-related outcomes. Nevertheless, beneficial effects are endpoint-specific and are not consistently observed across lipid, inflammatory, metabolic, or disease-progression measures. Neuroprotective, retinal, skeletal, wound-healing, anti-fibrotic, and anticancer applications remain scientifically promising but predominantly preclinical. Particularly in oncology and neurodegeneration, impressive pathway modulation should not be equated with proven clinical efficacy. Negative or neutral randomized results are essential components of the evidence base and narrow the range of claims that can presently be supported. The most compelling mechanistic synthesis involves coordinated modulation of oxidative stress, Nrf2-dependent cytoprotection, NF-κB-related inflammation, apoptosis, metabolic signalling, ER stress, and tissue-remodelling pathways. Emerging nanoemulsions, nanoliposomes, and microencapsulation technologies may overcome important problems of stability and bioavailability and therefore represent a major translational frontier. Overall, this qualitative reading of the recent literature positions RPO and verified palm-derived bioactives as a promising platform spanning nutrition, nutraceuticals, adjunct therapeutics, and biomedical delivery systems. The literature is strongest where compositional plausibility is connected to human outcomes, and weakest where mechanistic abundance has not yet been matched by clinical confirmation. Future progress will depend on standardized preparations, rigorous pharmacokinetics, independent replication, adequately powered clinical trials, clinically meaningful endpoints, and transparent reporting of both beneficial and null findings. Rather than offering a definitive pooled estimate of efficacy, the contribution of this review is to show how diverse biomedical findings fit together, where they conflict, and which translational questions deserve priority.

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None.

Conflict of Interest

None.

References

1. Abdul Nasir NA, Shi Wei Tan, Daud Ahmad Bin Israf Ali, Huzwah Khaza ai, Jia Woei Wong, et al. (2020) Cellular uptake and anti-inflammatory effects of palm oil-derived delta (δ)-tocotrienol in microglia. Cellular Immunology 357: 104200.
2. Abdul Nasir NA, 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.
3. Ajuwon OR, Marnewick JL, Oguntibeju OO, Davids LM (2022) Red palm oil ameliorates oxidative challenge and inflammatory responses associated with lipopolysaccharide-induced hepatic injury by modulating NF-κB and Nrf2/GCL/HO-1 signaling pathways in rats. Antioxidants 11(8): 1629.
4. Al Baiaty FDR, Shareena Ishak, Faizah Mohd Zaki, Farin Masra, Dayang Anita Abdul Aziz, 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): 529.
5. Alhajaji R, Ahmed A Hassan, Manar Ahmad Al-Harahsheh, Reem Rabie Saber, Marina Amgad Soliman, et al. (2026) Effectiveness of vitamin E in the treatment of diabetic neuropathy: systematic review and meta-analysis. Hormones.
6. 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): 160.
7. Apriani EF, Mahdi Jufri, Tommy Julianto Bustami Effendi, Windy Keumala Budianti, et al. (2026) The effect of sucrose palmitate characteristics as a surfactant on the physical stability of red palm oil submicroemulsions. Journal of Advanced Pharmaceutical Technology & Research 17(2): 93-99.
8. Aththar AF, Farhana Raushani, Fransiska Christydira Sekaringtyas, Sjaikhurrizal El Muttaqien, Damai Ria Setyawati, et al. (2025) Palm oil nanoemulsion enhances tocotrienol stability, antioxidant, and selective anti-melanoma activity. Naunyn-Schmiedeberg's Archives of Pharmacology 398(12): 17415-17433.
9. Braun V, Clarke V (2021) Can I use TA? Should I use TA? Should I not use TA? Comparing reflexive thematic analysis and other pattern-based qualitative analytic approaches. Counselling and Psychotherapy Research 21(1): 37-47.
10. Casati L, Pagani F, Maggi R, Ferrucci F, Sibilia V (2020) Food for bone: evidence for a role for delta-tocotrienol in the physiological control of osteoblast migration. International Journal of Molecular Sciences 21(13): 4661.
11. Chabriat H, Lucie Biard, Stéphanie Guey, Nassira Alili, Carla Machado, et al. (2026) Tocotrienol-rich vitamin E complex in CADASIL (T3CAD): a randomised, double-blind, placebo-controlled trial. eClinicalMedicine 94: 103853.
12. Chen S, Ahmad B, Palanisamy UD, Abdul Hafid SR, Selvaduray KR, et al. (2026) Immunomodulatory effects of palm-derived tocotrienol-rich fraction in healthy volunteers following influenza vaccination: a randomised clinical trial. Nutrition Research, advance online publication.

13. Chin KY (2024) Updates in the skeletal and joint protective effects of tocotrienol: a mini review. Frontiers in Endocrinology 15: 1417191.

14. Chuar PF, Yeek Tat Ng, Sonia Chew Wen Phang, Yan Yi Koay, J Ian Ho, et al. (2021) Tocotrienol-rich vitamin E (Tocovid) improved nerve conduction velocity in type 2 diabetes mellitus patients in a Phase II double-blind, randomized controlled clinical trial. Nutrients 13(11): 3770.

15. Damodaran T, Yahaya NS, Mordi MN (2025) Integrative toxicity assessment of tocotrienol-rich fraction from palm oil using in silico methods and zebrafish embryotoxicity model. Toxicology *in Vitro* 107: 106062.

16. Ekeuku SO, Muhamed Lahtif Nor Muhamad, Alya Aqilah Aminuddin, Fairus Ahmad, Sok Kuan Wong, et al. (2024) Effects of emulsified and non-emulsified palm tocotrienol on bone and joint health in ovariectomised rats with monosodium iodoacetate-induced osteoarthritis. Biomedicine & Pharmacotherapy 170: 115998.

17. Fatima S, Khan DA, Aamir M, Pervez MA, Fatima F (2023) δ-Tocotrienol in combination with resveratrol improves the cardiometabolic risk factors and biomarkers in patients with metabolic syndrome: a randomized controlled trial. Metabolic Syndrome and Related Disorders 21(1): 25-34.

18. Fong TT, Chaiku P, Nyam KL, Chu CC (2025) Development and evaluation of a proniosomal gel for palm tocotrienol-rich fraction topical delivery. Journal of Applied Pharmaceutical Science 15(12): 46-59.

19. Guo HF, Roslida Abd Hamid, Razana Mohd Ali, Sui Kiat Chang, Mohammed Habibur Rahman, et al. (2020) Healing properties of epidermal growth factor and tocotrienol-rich fraction in deep partial-thickness experimental burn wounds. Antioxidants 9(2): 130.

20. Guo HF, Razana Mohd Ali, Roslida Abd Hamid, Sui Kiat Chang, Mohammed Habibur Rahman, et al. (2022) Epidermal growth factor and tocotrienol-rich fraction cream formulation accelerates burn healing process based on its gene expression pattern in deep partial-thickness burn wound model. International Journal of Lower Extremity Wounds 21(4): 544-554.

21. Gupta L, Sood PK, Nehru B, Sharma S (2023) Ameliorative effect of palm oil in aluminum lactate induced biochemical and histological implications in rat brain. Biological Trace Element Research 201(6): 2843-2853.

22. Ismail M, Abdulsamad Alsalahi, Mustapha Umar Imam, Der Jiun Ooi, Huzwah Khaza ai, et al. (2020) Safety and neuroprotective efficacy of palm oil and tocotrienol-rich fraction from palm oil: a systematic review. Nutrients 12(2): 521.

23. Khalid AQ, Tabarek Najeeb Zaidan, Saatheeyavaane Bhuvanendran, Kasthuri B Magalingam, Shaza M Mohamedahmed, et al. (2025) Insights into the anticancer mechanisms modulated by gamma and delta tocotrienols in colorectal cancers. Nutrition Reviews 83(3): e1295-e1310.

24. Koay YY, Gerald Chen Jie Tan, Sonia Chew Wen Phang, J Ian Ho, Pei Fen Chuar, et al. (2021) A Phase IIb randomized controlled trial investigating the effects of tocotrienol-rich vitamin E on diabetic kidney disease. Nutrients 13(1): 258.

25. Kraus S, Matthias Breier, Weng Marc Lim, Marina Dabic, Satish Kumar, et al. (2022) Literature reviews as independent studies: guidelines for academic practice. Review of Managerial Science 16(8): 2577-2595.

26. Lee WJ, Tan CP, Sulaiman R, Hee YY, Chong GH (2020) Storage stability and degradation kinetics of bioactive compounds in red palm oil microcapsules produced with solution-enhanced dispersion by supercritical carbon dioxide: a comparison with the spray-drying method. Food Chemistry 304: 125427.

27. Li F, Biao Xu, Samira Soltanieh, Fernando Zanghelini, Ahmed Abu Zaid, et al. (2022) The effects of tocotrienols intake on obesity, blood pressure, inflammation, liver and glucose biomarkers: a meta-analysis of randomized controlled trials. Critical Reviews in Food Science and Nutrition 62(26): 7154-7167.

28. 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.

29. Lu Y, Yihan Zhang, Zhenyu Pan, Chao Yang, Lin Chen, et al. (2022) Potential therapeutic effects of tocotrienol-rich fraction and carotene against bleomycin-induced pulmonary fibrosis in rats via TGF-β/Smad, PI3K/Akt/mTOR and NF-κB signaling pathways. Nutrients 14(5): 1094.

30. Madoromae H, Lertcanawanichakul M (2025) Red palm oil: nutritional composition, bioactive properties, and potential applications in health and cosmetics: a narrative review. Molecules 30(22): 4402.

31. Magalingam KB, Premdass Ramdas, Sushela Devi Somanath, Kanga Rani Selvaduray, Saatheeyavaane Bhuvanendran, et al. (2022) Tocotrienol-rich fraction and levodopa regulate proteins involved in Parkinson's disease-associated pathways in differentiated neuroblastoma cells. Nutrients 14(21): 4632.

32. Mohamad NV (2023) Strategies to enhance the solubility and bioavailability of tocotrienols using self-emulsifying drug delivery system. Pharmaceuticals 16(10): 1403.

33. Nainggolan M, Sinaga AGS (2021) Characteristics of fatty acid composition and minor constituents of red palm olein and palm kernel oil combination. Journal of Advanced Pharmaceutical Technology & Research 12(1): 22-26.

34. Ng YT, Sonia Chew Wen Phang, Gerald Chen Jie Tan, En Yng Ng, Nevein Philip Botross Henien, et al. (2020) The effects of tocotrienol-rich vitamin E (Tocovid) on diabetic neuropathy: a Phase II randomized controlled trial. Nutrients 12(5): 1522.

35. 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 & Function 16(5): 1847-1863.

36. Nurdin SU, Nurdjanah S, Triyandi R, Nurhadi B (2024) Antioxidant activity, glycemic response, and functional properties of rice cooked with red palm oil. Journal of Nutrition and Metabolism 2024: 3483292.

37. Ooi AG, Yuen KH, Chu CC, Wong JW (2026) Oral delivery of tocotrienols: addressing pharmacokinetic challenges with formulation-based strategies. Lipids, advance online publication.

38. Pang KL, Mai CW, Chin KY (2023) Molecular mechanism of tocotrienol-mediated anticancer properties: a systematic review of the involvement of endoplasmic reticulum stress and unfolded protein response. Nutrients 15(8): 1854.

39. Pervez MA, Dilshad Ahmed Khan, Shakeel Ahmed Mirza, Atiq Ur Rehman Slehria, Uzma Nisar, et al. (2022) Comparison of delta-tocotrienol and alpha-tocopherol effects on hepatic steatosis and inflammatory biomarkers in patients with non-alcoholic fatty liver disease: a randomized double-blind active-controlled trial. Complementary Therapies in Medicine 70: 102866.

40. Pervez MA, Dilshad Ahmed Khan, Sayed Tanveer Abbas Gilani, Safia Fatima, Aamir Ijaz, et al. (2023) Hepato-protective effects of delta-tocotrienol and alpha-tocopherol in patients with non-alcoholic fatty liver disease: regulation of circulating microRNA expression. International Journal of Molecular Sciences 24(1): 79.

41. Pervez MA, Khan DA, Slehria AUR, Ijaz A (2020) Delta-tocotrienol supplementation improves biochemical markers of hepatocellular

injury and steatosis in patients with nonalcoholic fatty liver disease: a randomized, placebo-controlled trial. Complementary Therapies in Medicine 52: 102494.

42. Phang SCW, Ahmad B, Abdul Kadir K, Palanisamy UDM (2023) Effects of tocotrienol-rich fraction supplementation in patients with type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Advances in Nutrition 14(5): 1159-1169.

43. Post C, Sarala R, Gatrell C, Prescott JE (2020) Advancing theory with review articles. Journal of Management Studies 57(2): 351-376.

44. Raunkilde L, Torben Frøstrup Hansen, Birgitte Mayland Havelund, Caroline Brenner Thomsen, Søren Rafael Rafaelsen et al. (2023) Delta tocotrienol as a supplement to FOLFOXIRI in first-line treatment of metastatic colorectal cancer: a randomized, double-blind, placebo-controlled phase II study. Acta Oncologica 62(9): 1066-1075.

45. Razali RA, Wan Zurinah Wan Ngah, Suzana Makpol, Daijiro Yanagisawa, Tomoko Kato, et al. (2025) Shifting perspectives on the role of tocotrienol vs. tocopherol in brain health: a scoping review. International Journal of Molecular Sciences 26(13): 6339.

46. Rodsamai T, Manat Chaijan, Prawit Rodjan, Arlee Tamman, Nassareen Supaweera, et al. (2025) Design and bioanalysis of nanoliposome loaded with premium red palm oil for improved nutritional delivery and stability. Foods 14(4): 566.

47. Sadikan MZ, Abdul Nasir NA, Agarwal R, Mohd Ismail N (2020) Protective effect of palm oil-derived tocotrienol-rich fraction against retinal neurodegenerative changes in rats with streptozotocin-induced diabetic retinopathy. Biomolecules 10(4): 556.

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

49. Sadikan MZ, Lidawani Lambuk, Nur Hidayah Reshidan, Nurliyana Ain Abdul Ghani, Azral Ismawy Ahmad, 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.

50. Sailo BL, Suravi Chauhan, Mangala Hegde, Sosmitha Girisa, Mohammed S Alqahtani, et al. (2025) Therapeutic potential of tocotrienols as chemosensitizers in cancer therapy. Phytotherapy Research 39(4): 1694-1720.

51. Sari DK, Nurhadi Ibrahim, Nina Herlina, Nurfida Khairina Arrasyid, Ridha Dharmajaya, et al. (2024) The effects of red palm oil, Koja bay leaves, and passion fruit seeds formulation on antioxidant activity, antihyperlipidemia, BDNF, and lipase enzyme activity on Sprague-Dawley rats. Journal of Experimental Pharmacology 16: 271-284.

52. Shaikh SA, Varatharajan R, Muthuraman A (2022) Palm oil derived tocotrienol-rich fraction attenuates vascular dementia in type 2 diabetic rats. International Journal of Molecular Sciences 23(21): 13531.

53. Sharif M, Dilshad Ahmed Khan, Kulsoom Farhat, Mudassar Noor, Mohammad Asghar Khan, et al. (2023) Pharmacokinetics and bioavailability of tocotrienols in healthy human volunteers: a systematic review. Journal of the Pakistan Medical Association 73(3): 603-610.

54. Sharif R, Mah Kit Wai, Ooi Theng Choon, Sitti Rahma Abdul Hafid, Tze Yan Lee, et al. (2025) Tocotrienol-enriched beverage enhances psychological well-being, antioxidant defense, and genomic stability in older adults: a randomized controlled trial. Nutrients 17(13): 2179.

55. Sun Z, Shutao Yin, Chong Zhao, Lihong Fan, Hongbo Hu, et al. (2022) Inhibition of PD-L1-mediated tumor-promoting signaling is involved in the anti-cancer activity of β-tocotrienol. Biochemical and Biophysical Research Communications 617(Pt 2): 33-40.

56. Sun Z, Xuan Ma, Chong Zhao, Lihong Fan, Shutao Yin, et al. (2024) Delta-tocotrienol disrupts PD-L1 glycosylation and reverses PD-L1-mediated immune suppression. Biomedicine & Pharmacotherapy 170: 116078.

57. Tan CH, Chao Jie Lee, Sze Ning Tan, Dickson Tik Sang Poon, Cheryl Yi Ern Chong, et al. (2021) Red palm oil: a review on processing, health benefits and its application in food. Journal of Oleo Science 70(9): 1201-1210.

58. Tan CH, Kalvin Meng Jun Chuo, Lee Sin Chang, Serene En Hui Tung, Risanti Situmorang, et al. (2026) Recent advancements in red palm oil nanoemulsion systems: a comprehensive review of formulations, characterization, and functional applications. Journal of the Science of Food and Agriculture 106(9): 5112-5124.

59. Tan PY, Radhika Loganathan, Kim Tiu Teng, Syahirah Nadiah Mohd Johari, Soo Ching Lee, et al. (2024) Supplementation of red palm olein-enriched biscuits improves levels of provitamin A carotenes, iron, and erythropoiesis in vitamin A-deficient primary schoolchildren: a double-blinded randomised controlled trial. European Journal of Nutrition 63(3): 905-918.

60. Tan PY, Chuan Chun Lim, Katherine Boon Hwei Seng, Radhika Loganathan, Yvonne Ai Lian Lim, et al. (2025) Red palm olein supplementation as a potential preventive solution for xerophthalmia among vitamin A-deficient primary schoolchildren: a cluster randomized controlled trial. European Journal of Clinical Nutrition 79(9): 928-936.

61. Teh SS, Mah SH, Lau HLN, Teng KT, Loganathan R (2021) Antioxidant potential of red palm-pressed mesocarp olein. Journal of Oleo Science 70(12): 1719-1729.

62. Teng KT, Loganathan R, Chew BH, Khang TF (2024) Diverse impacts of red palm olein, extra virgin coconut oil and extra virgin olive oil on cardiometabolic risk markers in individuals with central obesity: a randomised trial. European Journal of Nutrition 63(4): 1225-1239.

63. Trugilho L, Lívia Alvarenga, Ludmila Cardozo, Bruna Paiva, Jessyca Brito, 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 2025: 8482883.

64. Younes M, Loubnane G, Sleiman C, Rizk S (2024) Tocotrienol isoforms: the molecular mechanisms underlying their effects in cancer therapy and their implementation in clinical trials. Journal of Integrative Medicine 22(1): 1-11.

65. Yunita E, Nasaruddin ML, Ramli NZ, Yahaya MF, Damanhuri HA (2025) Scoping review: the role of tocotrienol-rich fraction as a potent neuroprotective agent. International Journal of Molecular Sciences 26(16): 7691.

66. Zainal Z, Khaza ai H, Radhakrishnan AK, 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.

67. Zainal Z, Othman AZ, Abdul Rahim A, Meganathan P, Radhakrishnan AK (2025) Reduction of disease activity in rheumatoid arthritis by tocotrienol-rich fraction supplementation: a randomized, double-blind, placebo-controlled trial. European Journal of Nutrition 64(5): 227.

68. Zhu H, Fa Lin Wang, Shuang Zhang, Li Xue, Guang Qiang Gao, et al. (2024) γ-Tocotrienol enhances autophagy of gastric cancer cells by the regulation of GSK3β/β-Catenin pathway. Molecular Carcinogenesis 63(10): 2013-2025.

69. Zuo S, Guiping Wang, QuanLe Han, Hongling Xiao, Heitor O Santos, et al. (2020) The effects of tocotrienol supplementation on lipid profile: a meta-analysis of randomized controlled trials. Complementary Therapies in Medicine 52: 102450.