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Review Article

From Oral Bioavailability to Intratumoral Exposure: Closing the Delivery Gap for Palm Tocotrienols in Cancer Therapy through Nanoemulsions, Lipid Nanocarriers, Tumor Targeting, and Translational Pharmacology—A Critical Review

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Abstract

Tocotrienols are naturally occurring vitamin E compounds with substantial experimental anticancer activity, including effects on proliferation, apoptosis, endoplasmic reticulum stress, autophagy, immune signaling, angiogenesis, metastasis, and chemosensitivity. However, this pharmacological promise has not produced a proportionately mature clinical oncology pipeline. This review argues that drug delivery represents a major, although not exclusive, translational bottleneck. Palm-derived tocotrienols are highly lipophilic compounds whose gastrointestinal absorption, systemic exposure, metabolism, tissue distribution, and tumor delivery are strongly influenced by formulation and isoform. The review critically distinguishes bioaccessibility, bioavailability, biodistribution, tumor accumulation, intratumoral penetration, intracellular release, and pharmacodynamic target engagement. Evidence for self-emulsifying drug-delivery systems, nanoemulsions, nanostructured lipid carriers, liposomes, polymer–lipid hybrid nanoparticles, and active-targeting approaches is evaluated alongside biological barriers including heterogeneous tumor vasculature, protein-corona formation, mononuclear-phagocyte-system sequestration, stromal resistance, and limited tumor penetration. A 2025 palm-oil nanoemulsion study provides timely proof of formulation-dependent enhancement of tocotrienol stability and anti-melanoma activity, but clinical evidence that nanoformulation improves intratumoral exposure or patient outcomes remains absent. Future development should therefore shift from dose-centered supplementation toward exposure-driven translational pharmacology integrating quantitative pharmacokinetics, tumor biodistribution, pharmacodynamic biomarkers, formulation safety, combination therapy, manufacturing reproducibility, and early-phase oncology trials.

Keywords: Tocotrienols, Palm oil, Cancer, Bioavailability, Nanoemulsions, Nanostructured lipid carriers, Tumor targeting, Pharmacokinetics, Nanomedicine, Drug delivery

JEL Classification: I10, I12, L65, O31, O32.

Introduction

Tocotrienols are members of the vitamin E family that have attracted sustained interest as potential anticancer agents. They share the chromanol head group of tocopherols but possess an unsaturated isoprenoid side chain containing three double bonds, a structural distinction that influences their membrane behavior, metabolism, tissue distribution, and biological activity. Palm oil is an especially important natural source because palm Tocotrienol-Rich Fraction (TRF) contains several tocotrienol isoforms together with varying proportions of tocopherols. During the past decade, experimental research has linked tocotrienols with suppression of cancer-cell proliferation, induction of apoptosis and autophagy, modulation of endoplasmic reticulum stress and the unfolded-protein response, inhibition of tumor-promoting signaling, and enhanced sensitivity to chemotherapy. Consequently, the biological plausibility of tocotrienols as oncology-relevant compounds is no longer based on a single antioxidant mechanism [1-5].

The principal translational question has therefore changed. Another review merely cataloguing anticancer pathways would add relatively little because recent literature already summarizes many molecular mechanisms and cancer models. A more consequential problem is why compounds displaying extensive experimental pharmacology have generated comparatively limited clinical development. Clinical studies demonstrate that tocotrienols can be administered to patients with cancer, but they have not yet established a consistently transformative therapeutic effect. In a randomized Phase II neoadjuvant breast-cancer study, addition of δ-tocotrienol did not significantly improve response rate, while a randomized Phase II trial in metastatic colorectal cancer did not significantly prolong the primary endpoint of time to hospitalization or death when δ-tocotrienol was added to FOLFOXIRI [6,7].

One plausible explanation is that the dose administered is not equivalent to the pharmacologically effective exposure achieved in the patient. Tocotrienols are poorly water-soluble lipophilic molecules whose oral absorption depends on solubilization, gastrointestinal lipid handling, food intake, formulation characteristics, transport through lipoprotein-associated pathways, metabolism, and isoform-specific disposition. A recent systematic review of human pharmacokinetic studies reported substantial differences among tocotrienol preparations and concluded that some annatto-derived δ-tocotrienol formulations generated greater systemic exposure than palm-derived TRF preparations studied under different conditions. Such comparisons demonstrate the importance of formulation and composition, but they should not be simplified into a conclusion that the palm source itself is pharmacologically inferior [8-10].

An unusually illustrative clinical observation emerged from the PPALM trial of Tocovid SupraBio combined with pentoxifylline in patients with chronic gastrointestinal toxicity after pelvic radiotherapy. Despite reportedly good treatment compliance, γ-tocotrienol could not be detected in serum in approximately 41% of treated participants. Although this study was not a trial of anticancer efficacy, the pharmacokinetic observation is directly relevant to oncology development because it demonstrates that prescribed oral dosing does not guarantee detectable systemic exposure in every patient. Failure to account for such exposure variability could obscure true pharmacodynamic relationships and help explain inconsistent clinical effects across tocotrienol trials [11].

Formulation science has already shown that this limitation is modifiable. Self-Emulsifying Drug-Delivery Systems (SEDDS) can improve the solubilization and intestinal presentation of poorly water-soluble compounds, and human tocotrienol studies indicate that self-emulsifying preparations produce superior or more consistent exposure relative to conventional oily preparations. A solid SEDDS formulation reported in 2022 achieved human tocotrienol exposure comparable with a commercially available self-emulsifying preparation while providing the pharmaceutical advantages of a solid dosage form. These findings indicate that bioavailability is not a fixed intrinsic property of tocotrienols, it is partly an engineered characteristic of the final drug product [12,10]. The emergence of nanoformulation further expands this possibility. In 2025, Aththar, et al., incorporated tocotrienols into a palm-oil nanoemulsion and reported a mean particle diameter of approximately 64.8 nm, good storage characteristics, sustained release, enhanced antioxidant activity, and greater cytotoxic activity against B16F0 melanoma cells than free tocotrienols. The nanoemulsion produced an IC_{50} of approximately 45.07 μg/mL compared with 78.75 μg/mL for free tocotrienols, while toxicity against NIH-3T3 comparator cells remained considerably lower. These results are an important proof of formulation-dependent enhancement, although they remain in vitro evidence and do not establish improved tumor targeting, animal pharmacokinetics, intratumoral accumulation, or clinical efficacy [13].

The central argument of this review is therefore that the translational problem should be conceptualized as a delivery-to-effect continuum, rather than simply a bioavailability problem. A formulation must first stabilize and release the tocotrienol payload, facilitate intestinal absorption or parenteral disposition, generate adequate systemic exposure, avoid excessive off-target sequestration, reach malignant tissue, penetrate the tumor microenvironment, release the compound intracellularly, and achieve sufficient concentrations to engage relevant pharmacological targets. Nanomedicine research has repeatedly shown that successful completion of an earlier step does not guarantee success at a later step, and that improved plasma exposure or tumor accumulation can fail to produce improved therapeutic outcome [14-17]. Accordingly, this critical qualitative review evaluates how formulation may overcome the delivery bottleneck of palm tocotrienols in cancer therapy. It distinguishes bioaccessibility, bioavailability, biodistribution, tumor targeting, intratumoral penetration, cellular uptake, payload release, and pharmacodynamic target engagement, evaluates self-emulsifying

systems, nanoemulsions, nanostructured lipid carriers, liposomes, and polymer-lipid hybrid systems, examines the limitations of passive and active tumor targeting, and proposes a bench-to-bedside development framework in which formulation improvement is judged ultimately by tumor pharmacology and patient-relevant outcomes rather than by particle size or plasma exposure alone.

Literature Review: Conceptual and Theoretical Foundations

Tocotrienol Chemistry and Pharmacological Relevance

The vitamin E family comprises four tocopherols and four tocotrienols, conventionally designated α, β, γ, and δ according to methylation patterns on the chromanol ring. Tocotrienols differ from tocopherols primarily through the presence of an unsaturated isoprenoid side chain. This structural difference affects physicochemical behavior and biological disposition, including membrane interactions and metabolic processing. α-Tocopherol is preferentially retained through hepatic α-tocopherol transfer protein, whereas non-α vitamin E forms, including tocotrienols, are generally more susceptible to metabolism and elimination. Consequently, biological potency observed in cells cannot be interpreted independently of pharmacokinetic exposure in vivo [9,1]. Palm-derived TRF is particularly relevant to translational development because it provides an industrially scalable natural mixture of tocotrienol isoforms. Human trials reviewed by Looi, et al., show that palm TRF has already been administered across multiple clinical contexts, supporting a substantial safety and human-exposure foundation. Nevertheless, considerable heterogeneity exists in dose, formulation, treatment duration, and measured endpoints. This heterogeneity reinforces the need to specify whether an oncology study uses purified α-, γ-, or δ-tocotrienol, a palm TRF mixture, or another source, because these should not be considered pharmacologically interchangeable products [18,8].

Anticancer Mechanisms as Justification for Delivery Optimization

The rationale for investing in tocotrienol delivery would be weak if the underlying anticancer biology were unconvincing. However, recent evidence provides multiple mechanistic reasons to regard tocotrienols as pharmacologically interesting oncology payloads. Reviews of breast cancer describe antiproliferative, pro-apoptotic, antiangiogenic, anti-invasive, and signaling effects, while systematic evaluation of endoplasmic reticulum stress demonstrates that tocotrienols can activate the unfolded-protein response and ER-stress-associated cell death pathways in cancer models [2,4]. Tocotrienol action also appears isoform- and context-dependent. β-Tocotrienol has been reported to suppress PD-L1 expression through modulation of JAK2/STAT3 signaling, linking tocotrienol pharmacology with both tumor-intrinsic signaling and antitumor immune regulation. δ-Tocotrienol has demonstrated antiproliferative and pro-apoptotic effects in hepatocellular-carcinoma models, accompanied by mitochondrial alterations and autophagy-related responses. Contemporary prostate-cancer literature likewise distinguishes biological effects among vitamin E forms rather than treating them as a single class [19-21].

Combination therapy may be especially relevant. Tocotrienols can influence NF-κB, Akt/mTOR, STAT, apoptotic, survival, and other pathways involved in chemotherapy resistance, and contemporary reviews describe preclinical chemosensitization to agents including taxanes and platinum-containing drugs. Earlier experimental work also showed that γ-tocotrienol could enhance docetaxel-related effects in resistant prostate-cancer models, while newer comparative research continues to indicate isoform-dependent chemosensitization. These observations suggest that a clinically useful tocotrienol formulation may ultimately be developed as an adjunct rather than as a stand-alone cytotoxic agent [22,23].

The important translational implication is that delivery should be matched to the biological mechanism. If synergy depends on sustained inhibition of a survival pathway during chemotherapy exposure, transient plasma peaks may be inferior to controlled release. If efficacy depends on intracellular ER stress or PD-L1-associated signaling, tumor accumulation without intracellular release may be insufficient. Thus, formulation engineering should follow a pharmacodynamic hypothesis rather than assuming that any increase in exposure will produce the desired anticancer outcome.

Bioaccessibility, Bioavailability, Biodistribution, and Tumor Targeting

Four terms frequently become conflated in discussions of nutraceutical delivery. Bioaccessibility describes the fraction of a compound that becomes available for absorption after release from a formulation and processing in the gastrointestinal environment. For lipophilic tocotrienols, this includes incorporation into lipid phases and mixed micellar structures. Bioavailability refers more specifically to the fraction and rate at which the administered compound reaches systemic circulation. SEDDS primarily addresses these early gastrointestinal and systemic steps [10]. Biodistribution begins after systemic entry and describes where drug-related material travels within the body. Plasma AUC provides only one dimension of systemic exposure, it does not reveal how much tocotrienol reaches liver, spleen, kidney, brain, muscle, tumor stroma, or malignant cells. Nanocarriers can profoundly alter biodistribution because their size, surface chemistry, charge, protein interactions, lipid composition, and clearance pathways differ from those of free small molecules [24,25]. Tumor targeting is an even more demanding concept. It requires preferential or therapeutically meaningful delivery to malignant tissue relative to non-target tissues, but even this does not guarantee efficacy. A carrier may accumulate around tumor blood vessels without penetrating deeply, remain confined in stromal or macrophage compartments, or fail to release sufficient free tocotrienol inside cancer cells. Accordingly, tumor accumulation, tumor penetration,

cellular internalization, and pharmacodynamic target engagement should be measured as distinct steps rather than collapsed under the generic term "targeting" [26-28].

Figure 1 shows that the principal conceptual contribution of this review is the separation of the successive delivery stages that are often incorrectly treated as synonymous. The figure makes clear that increasing oral absorption is only an early step and that clinically meaningful anticancer activity ultimately requires target engagement within malignant tissue (Figure 1).

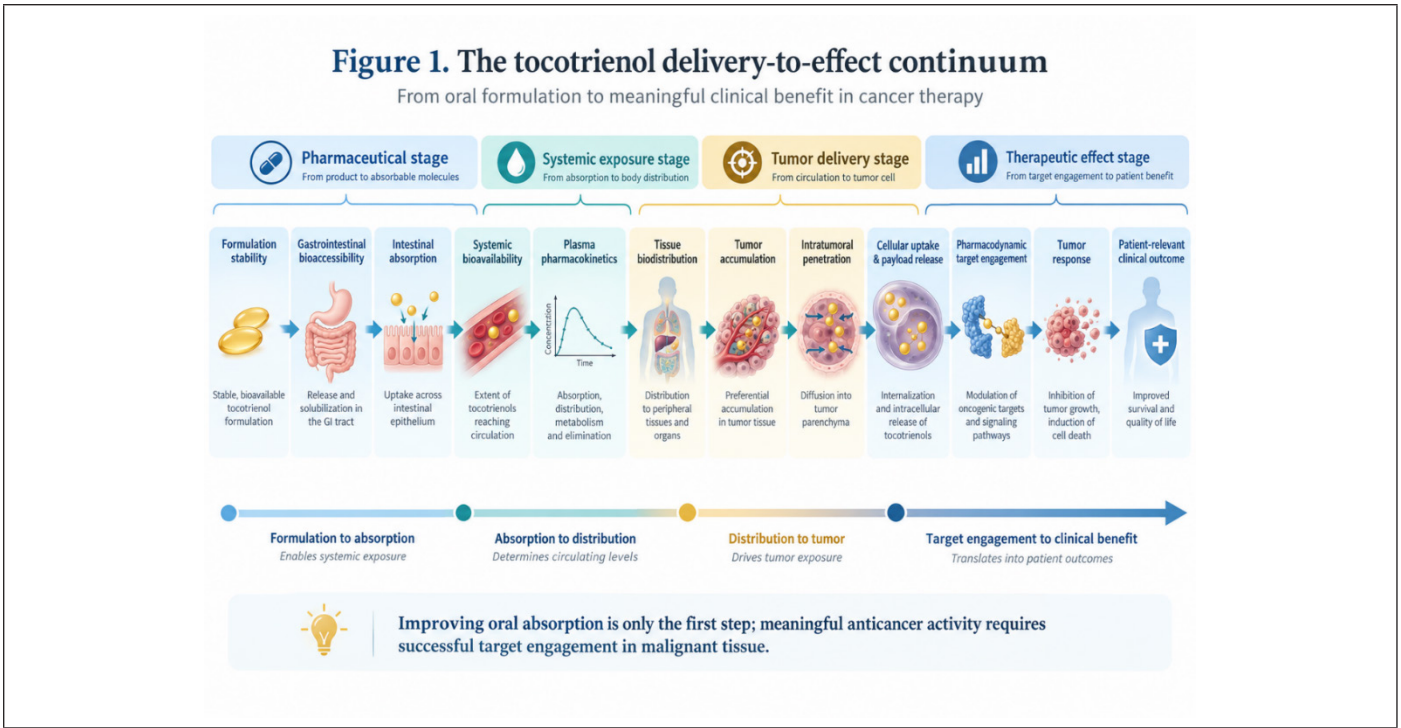

Figure 1: The tocotrienol delivery-to-effect continuum.

Figure 1 illustrates why pharmacological development should not terminate at Cmax or AUC. A formulation may substantially improve systemic bioavailability while simultaneously increasing hepatic sequestration or failing to enter a poorly perfused tumor. Conversely, a delivery platform producing only modest changes in plasma concentration could theoretically improve efficacy if it substantially increases tumor-to-plasma distribution, intracellular accumulation, or duration of target engagement. This multistage framework is consistent with contemporary precision-delivery literature emphasizing systemic, microenvironmental, and cellular barriers as separable determinants of therapeutic performance [24,29,25].

Passive Targeting and the Changing EPR Paradigm

The Enhanced Permeability and Retention (EPR) effect has historically provided the conceptual foundation for passive tumor targeting. The classic model proposes that abnormally permeable tumor vasculature permits nanoparticle extravasation while inefficient lymphatic drainage promotes retention. This principle has supported enormous investment in nanocarrier development, yet clinical translation has been less reliable than early preclinical models suggested. Contemporary reviews emphasize substantial heterogeneity in vascular permeability across tumor types, individual lesions, disease stages, metastatic sites, and patients [30,14]. Recent work has further questioned whether passive interendothelial leakage alone adequately explains nanoparticle tumor entry. Nguyen, et al., contrasted the traditional EPR model with active transport and retention mechanisms involving endothelial transport and interactions with tumor components. The emerging view is not that the EPR phenomenon is irrelevant, but that nanoparticle delivery is biologically more complex and less universal than simplistic formulations imply [29,31]. This matters for tocotrienols because a hypothetical palm-tocotrienol nanoparticle cannot be assumed to "target cancer" merely because it is nanosized. Its delivery will depend on vascular biology, tumor type, particle properties, host clearance, and tissue-specific mechanisms. A formulation that produces excellent accumulation in a highly permeable murine xenograft may behave very differently in a fibrotic pancreatic tumor, diffuse metastatic disease, or human breast carcinoma.

Method

This study used a critical qualitative literature-review design with a mechanistic, pharmaceutical, and translational orientation.

The approach was chosen because the evidence base combines heterogeneous types of knowledge, including tocotrienol chemistry, in vitro anticancer studies, clinical supplementation trials, human pharmacokinetics, formulation studies, cancer nanomedicine, tumor biology, toxicology, and regulatory science. Such evidence is more appropriately integrated through structured narrative synthesis than through a pooled quantitative effect estimate [32,33]. Literature identification focused on peer-reviewed journal articles published between 2020 and 2026, with priority given to PubMed/MEDLINE-indexed literature and records verified through journal or publisher platforms. Search concepts included combinations of "tocotrienol," "palm tocotrienol," "cancer," "pharmacokinetics," "bioavailability," "self-emulsifying drug delivery," "nanoemulsion," "lipid nanoparticle," "nanostructured lipid carrier," "liposome," "polymer-lipid hybrid," "tumor targeting," "EPR effect," "protein corona," "biodistribution," "tumor penetration," "nanotoxicity," and "clinical translation." Citation chaining and cross-checking of relevant contemporary reviews were used to identify mechanistically important primary studies. This search strategy was intended to achieve conceptual breadth rather than the exhaustive retrieval expected in a systematic review [34].

Evidence was interpreted using four levels. The first comprised direct studies of tocotrienols incorporated into advanced delivery systems with cancer-related endpoints. The second comprised tocotrienol formulation and human pharmacokinetic evidence without direct tumor-delivery measurement. The third included tocotrienol oncology studies demonstrating biological or clinical rationale without advanced delivery systems. The fourth consisted of transferable cancer-nanomedicine evidence concerning biodistribution, active targeting, protein corona, tumor penetration, safety, manufacturing, and clinical translation. The review is explicitly not a systematic literature review or meta-analysis. No PRISMA flow diagram, formal risk-of-bias scoring system, or pooled effect estimate is presented. The purpose is instead to construct a critical translational synthesis while clearly distinguishing direct tocotrienol evidence from platform-level extrapolation.

Results: Thematic Findings

Bioavailability is a Genuine but Formulation-Sensitive Bottleneck

Available human pharmacokinetic evidence supports the proposition that tocotrienol exposure is highly formulation-dependent. Lipophilicity limits aqueous dispersion, and oral uptake is influenced by gastrointestinal lipid processing and the presence of dietary fat. Following absorption, tocotrienols enter lipoprotein-mediated transport pathways, while hepatic metabolism and lower affinity for α-tocopherol transfer protein contribute to their comparatively rapid disposition. Differences among isoforms further complicate interpretation of total tocotrienol concentrations [9,8]. Sharif, et al., reported that annatto-derived tocotrienols, particularly δ-tocotrienol in the studies included in their systematic review, could achieve higher pharmacokinetic exposure than palm-derived TRF preparations. This finding is important but should not be interpreted as a controlled demonstration of biological inferiority of palm tocotrienols. Formulation type, dose, isoform composition, fed state, study population, and analytical methods can all influence observed exposure. Future comparisons should therefore be formulation-matched and dose-normalized rather than source-based alone [8]. Clinical heterogeneity is more than a theoretical issue. In the PPALM trial, γ-tocotrienol remained undetectable in a substantial proportion of treated participants despite reported adherence. Such findings indicate that conventional dose assignment can create substantial exposure misclassification: two patients taking the same capsule regimen may not experience the same pharmacological treatment. Oncology development should therefore routinely include measured exposure rather than assuming compliance is equivalent to pharmacokinetic delivery [11].

SEDDS Demonstrates that Oral Tocotrienol Exposure can be Engineered

Self-emulsifying drug-delivery systems offer a relatively mature approach to the oral-delivery problem. SEDDS mixtures generate fine emulsions after contact with gastrointestinal fluid, improving the apparent solubilization of lipophilic payloads and reducing dependence on spontaneous aqueous dissolution. They may also increase passive intestinal permeability and reduce variability caused by food-dependent solubilization. For tocotrienols, these characteristics are particularly attractive because the active compound itself is oily and highly lipophilic [10]. The 2022 human study by Lee, et al., demonstrated that oily tocotrienols could be converted into a solid self-emulsifying dosage form with improved oral pharmacokinetic performance. Solidification can additionally address practical weaknesses of liquid SEDDS, including handling, capsule compatibility, physical stability, and manufacturing convenience. The study reinforces an important principle for oncology translation: drug delivery can substantially change the exposure generated by the same underlying tocotrienol payload [12].

However, SEDDS primarily solves the front end of the delivery continuum. Improved intestinal absorption does not inherently solve tumor biodistribution. Once tocotrienols enter systemic circulation, their lipoprotein association, metabolism, protein interactions, and tissue partitioning become dominant determinants. Thus, SEDDS is best viewed as strong evidence that the bioavailability bottleneck is engineerable, not as evidence that oral formulation alone will solve oncology delivery.

Palm-Oil Nanoemulsion Provides Direct Formulation Proof-of-Concept

The 2025 study by Aththar, et al., represents the most directly relevant contemporary formulation study for the present review. Tocotrienols incorporated into a palm-oil-based nanoemulsion showed favorable nanoscale characteristics, with a reported mean

particle diameter of approximately 64.8 ± 8 nm and a polydispersity index of 0.288. The formulation retained relatively stable particle dimensions during accelerated storage and showed controlled tocotrienol release of approximately 78% over 54 hours [13].

Biological performance also improved. Nanoemulsified tocotrienol demonstrated greater antioxidant activity than free tocotrienol in chemical assays and significantly stronger cytotoxicity against B16F0 melanoma cells. The reported IC_{50} fell from approximately 78.75 µg/mL for free tocotrienol to 45.07 µg/mL for nanoemulsified tocotrienol, whereas NIH-3T3 cells retained considerably lower sensitivity. Additional experiments demonstrated increased late apoptosis and G1-phase arrest [13]. The implications should nevertheless be stated carefully. Improved cytotoxicity in cultured cells can result from greater dispersion, increased interaction with cell membranes, altered uptake, or release characteristics. None of these establishes preferential delivery to tumors in vivo. The formulation has not yet demonstrated improved plasma pharmacokinetics, reduced liver or splenic sequestration, superior tumor-to-plasma concentration ratios, deeper tumor penetration, or better survival in an animal tumor model. Thus, the study provides proof of formulation enhancement, not yet proof of tumor targeting.

Figure 2 emphasizes that the delivery bottleneck consists of several sequential biological barriers rather than a single solubility problem. The figure also identifies the stages that are improved by SEDDS or nanoemulsion technology and the later stages that remain largely untested for palm tocotrienols (Figure 2).

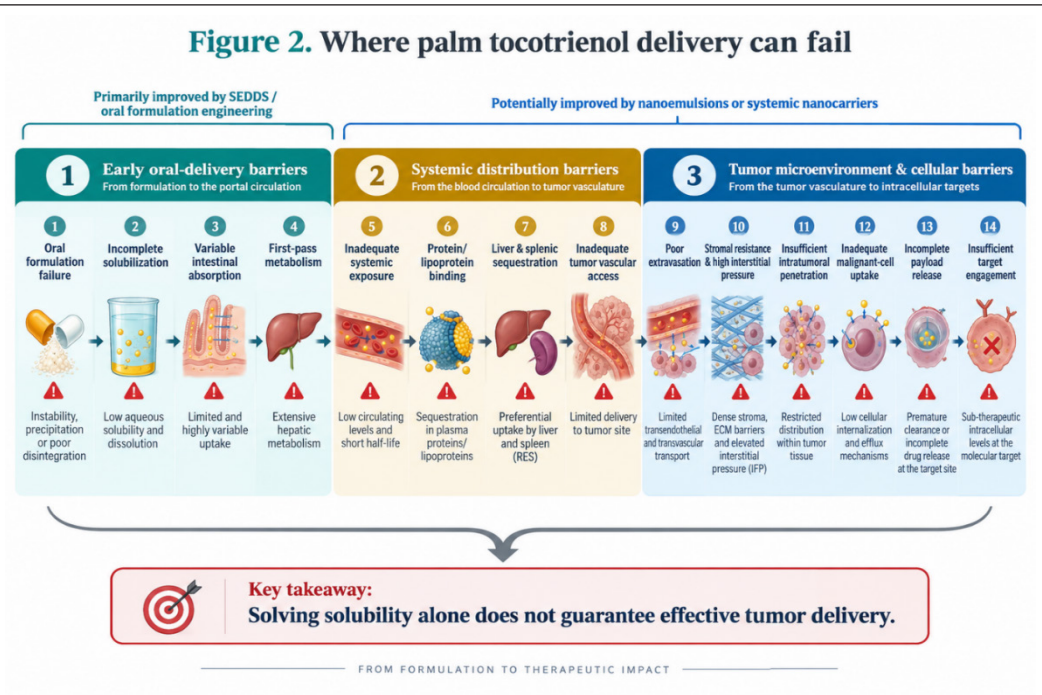

Figure 2: Where palm tocotrienol delivery can fail.

The figure demonstrates why solving only the earliest barriers may not translate into superior oncology outcomes. SEDDS principally improves solubilization and absorption, whereas nanoemulsions and systemic nanocarriers may additionally modify circulation and biodistribution. After systemic administration, however, carriers face protein-corona formation, phagocytic recognition, vascular heterogeneity, tumor extracellular matrix, interstitial pressure, and cellular internalization barriers. These barriers are recognized across contemporary cancer nanomedicine and should be incorporated prospectively into tocotrienol-formulation development [35,29,28,25].

Nanostructured Lipid Carriers as a Logical Tocotrienol Platform

Nanostructured Lipid Carriers (NLCs) are second-generation lipid nanoparticles typically combining solid and liquid lipids to create a less ordered internal matrix than conventional solid lipid nanoparticles. This architecture can increase accommodation of hydrophobic payloads, reduce drug expulsion during storage, support controlled release, and permit surface functionalization. Such properties are conceptually well matched to tocotrienols because the active molecules are highly lipophilic and compatible with lipid phases [36,37]. In cancer nanomedicine, NLCs have been used to improve delivery of hydrophobic chemotherapeutics and natural products, and can be engineered for passive or ligand-mediated targeting. The platform may also permit co-loading of tocotrienols with another antineoplastic agent, potentially synchronizing intratumoral exposure when synergy is mechanistically justified.

However, increased formulation complexity introduces challenges in reproducibility, payload ratio, drug-release synchronization, stability, and regulatory characterization [38]. For palm tocotrienols, the first meaningful NLC studies should therefore move beyond particle characterization. They should directly compare free TRF, SEDDS-TRF, non-targeted NLC-TRF, and targeted NLC-TRF under matched dose conditions, followed by plasma PK, liver/spleen distribution, tumor concentrations, spatial intratumoral distribution, and pharmacodynamic biomarkers. Without this sequence, better encapsulation efficiency would remain a pharmaceutical achievement rather than an oncology-development milestone.

Liposomes Offer Clinically Mature Design Principles

Liposomes have a major advantage over more experimental delivery platforms: multiple liposomal products have already established the clinical feasibility of lipid-vesicle drug delivery. Their phospholipid bilayers can accommodate lipophilic compounds while aqueous compartments can carry hydrophilic agents. PEGylation can prolong circulation, while antibodies, peptides, or other ligands can be added for targeting. Stimulus-responsive systems can further modify release under acidic, enzymatic, thermal, or externally triggered conditions [39,40]. (PubMed) A 2025 review of liposomal vehicles for tumor targeting further emphasizes that clinical translation depends on matching vesicle composition, targeting strategy, release behavior, and tumor biology rather than relying on liposomal architecture alone [41]. Tocotrienols could theoretically be incorporated into the lipid bilayer, where their lipophilic character may favor high loading. This is particularly interesting for combination therapy because a liposome could potentially co-deliver tocotrienol with another anticancer agent while altering relative tissue exposure. Research on phytochemical-loaded liposomes has repeatedly identified poor bioavailability and nonspecific distribution as major barriers that liposomal delivery may help overcome [42]. Nevertheless, liposomal precedent should not be confused with guaranteed success for tocotrienols. Bilayer incorporation could influence membrane stability and release kinetics, while the antioxidant properties of tocotrienols might interact with oxidation-sensitive phospholipids. Formulation design must therefore establish the proportion of encapsulated tocotrienol that remains carrier-associated in circulation, how quickly active compound is released in tumors, and whether carrier retention prevents rather than facilitates intracellular access.

Polymer–Lipid Hybrid Nanoparticles

Polymer–lipid hybrid nanoparticles seek to combine complementary features of two carrier classes. A polymeric core may provide mechanical stability and sustained release, whereas an outer lipid or lipid–PEG layer can improve biocompatibility and enable surface functionalization. Reviews describe these systems as promising for hydrophobic small molecules, biological agents, imaging compounds, and combination therapies [43,44]. For tocotrienols, a hybrid system could theoretically reduce premature leakage while controlling release after tumor accumulation. A tocotrienol could be loaded into a hydrophobic polymeric or lipid-associated region, while surface ligands could be selected according to tumor biology. The major trade-off is increasing complexity. Each additional polymer, lipid, surfactant, targeting ligand, and stabilizer introduces a new quality attribute, toxicological variable, and manufacturing challenge. Complexity is justified only if it produces a quantitatively meaningful improvement in therapeutic index.

Active Tumor Targeting: Promising but Frequently Overstated

Active targeting commonly uses antibodies, antibody fragments, peptides, folate derivatives, aptamers, sugars, or other ligands that bind receptors expressed at relatively high levels on malignant or tumor-associated cells. In principle, such ligands can increase cellular recognition and internalization after the carrier reaches the tumor. Contemporary targeted-delivery research includes strategies directed toward receptors such as EGFR and many other cancer-associated surface molecules [27,26]. A critical distinction is that active targeting generally does not eliminate the need for favorable systemic biodistribution. A ligand cannot bind a receptor if the carrier is removed by the liver or spleen before reaching the tumor, and it cannot overcome poor perfusion merely by increasing receptor affinity. Active targeting often acts most strongly at the level of cellular binding and internalization after extravasation. This distinction is particularly important for tocotrienols because claims that a ligand "delivers tocotrienol selectively to cancer" would need direct quantitative validation in vivo. Biomimetic cell-membrane coatings represent a more elaborate targeting strategy. Cancer cell, platelet, erythrocyte, leukocyte, or hybrid membranes may provide immune-evasive or homotypic recognition properties. Such platforms have attracted considerable oncology interest, but standardization, membrane-source variability, manufacturing complexity, and biological reproducibility remain substantial challenges [45,46].

Protein Corona can Rewrite Nanoparticle Identity

When nanoparticles contact blood, proteins and other biomolecules adsorb to their surface and form a biomolecular corona. The biological system therefore "sees" a nanoparticle whose identity can differ considerably from the particle originally characterized in buffer. The corona can change effective size, surface charge, circulation, cell recognition, immune interactions, and targeting behavior. It can also cover targeting ligands and reduce receptor-specific binding [35]. (PubMed) More recent work also shows that protein-corona composition and its effects on pharmacokinetics and organ targeting can vary with patient-specific biological factors, strengthening the case for evaluating nanoformulations in clinically representative biological matrices [47]. This issue directly challenges in vitro evaluation of tocotrienol

nanocarriers. A formulation may demonstrate excellent cancer-cell uptake under serum-free or simplified culture conditions but lose that behavior when exposed to plasma proteins. Future tocotrienol nanoformulations should therefore be evaluated in biologically relevant protein environments, and the relationship between corona composition, macrophage uptake, tumor-cell internalization, and payload release should be characterized.

Biodistribution and Clearance Compete with Tumor Delivery

The mononuclear-phagocyte system constitutes another major barrier. Nanoparticles can accumulate in liver and spleen because of vascular structure, resident macrophages, opsonization, and carrier size or surface properties. This is not necessarily toxic and can sometimes be exploited therapeutically, but for solid-tumor delivery it may represent loss of active payload before the carrier reaches its intended target [25]. Carrier design therefore requires balance. Increasing hydrophilicity or PEGylation may prolong circulation but can reduce cellular uptake or induce other biological consequences. Smaller particles may penetrate tissue more readily but may clear differently or carry less payload. Larger particles may achieve higher loading yet exhibit poorer penetration. No single particle size or surface chemistry is universally optimal, which is why precision-nanoparticle research increasingly advocates matching carrier properties to the biology of the disease and drug [24,25].

Intratumoral Penetration is Distinct from Tumor Accumulation

Solid tumors frequently contain chaotic vasculature, dense extracellular matrix, cancer-associated fibroblasts, high interstitial pressure, hypoxic zones, necrotic regions, and spatially heterogeneous malignant populations. Consequently, nanoparticles measured in homogenized tumor tissue may be concentrated around vascular regions while penetrating poorly into the tumor core. This distinction is crucial because a high bulk-tumor concentration can coexist with inadequate drug delivery to the cells driving resistance or recurrence [28]. (PubMed) A 2025 review of deep-tumor nanocarrier penetration similarly identifies vascular, stromal, physicochemical, and cellular transport barriers as interacting constraints and highlights stimuli-responsive and surface-engineering strategies as potential routes to improve spatial drug delivery [48]. For tocotrienols, spatial pharmacology should therefore become an explicit endpoint. Future animal studies should quantify whether fluorescently or isotopically traceable carrier and tocotrienol payload reach the tumor rim, core, stromal compartments, macrophages, and malignant cells. Mass-spectrometry imaging or carefully validated surrogate techniques could distinguish total tumor accumulation from biologically useful intracellular exposure.

Figure 3 compares the major formulation platforms according to the particular delivery problem each is most capable of addressing. The comparison emphasizes that there is currently insufficient evidence to declare one platform superior for palm-tocotrienol oncology because the required head-to-head PK/PD studies have not yet been conducted (Figure 3).

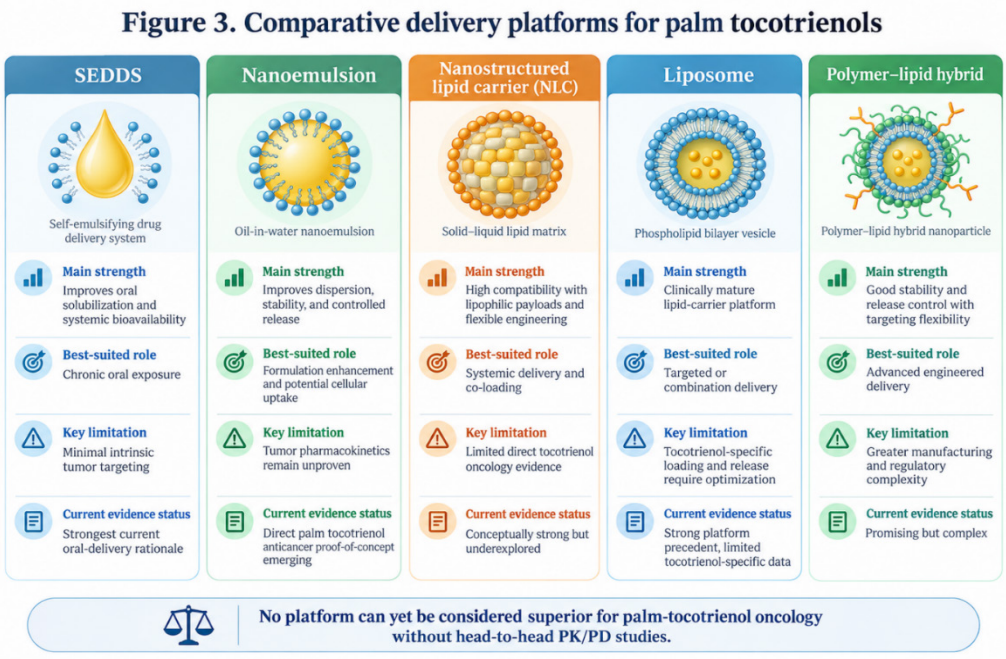

Figure 3: Comparative delivery platforms for palm tocotrienols.

The most appropriate platform depends on the therapeutic objective. If the primary goal is chronic oral exposure, SEDDS may be more rational than an elaborate intravenous carrier. If the objective is rapid tumor-specific delivery during chemotherapy, a parenteral lipid nanocarrier may offer greater control over biodistribution. If tocotrienol is intended to sensitize tumor cells to a second drug, co-delivery could be advantageous only when the timing and intracellular exposure ratios are pharmacodynamically justified. Platform selection should therefore be indication- and mechanism-specific rather than driven by novelty alone [49,38].

Existing Oncology Trials Provide an Important Reality Check

The clinical tocotrienol literature remains small but is valuable precisely because it constrains overly optimistic extrapolation from cell studies. In the neoadjuvant breast-cancer Phase II trial by Kjær et, al., 80 women were randomized to standard neoadjuvant treatment with or without δ-tocotrienol. No significant difference in treatment response or serious adverse events was found between the groups. The study illustrates that strong preclinical anticancer rationale does not automatically translate into improved response when tocotrienol is simply added to standard therapy [6]. The metastatic colorectal-cancer study by Raunkilde, et al., similarly tested δ-tocotrienol with FOLFOXIRI. The intervention did not significantly prolong the primary endpoint of time to hospitalization or death, although fewer oxaliplatin dose reductions occurred in the tocotrienol arm, suggesting a possible supportive or neuroprotective effect requiring further investigation. These results do not demonstrate that delivery was responsible for lack of efficacy, but they reinforce the need to connect dose with exposure, target engagement, and tumor pharmacology [7]. The PPALM trial contributes a different lesson. Its detection of inadequate serum γ-tocotrienol exposure in a substantial proportion of participants suggests that pharmacokinetic failure can occur even when adherence is acceptable. Together, these clinical observations support a future development strategy in which patients are not categorized merely by assigned dose but also by measured systemic and, wherever feasible, tumor exposure [11].

Discussion and Analysis

Is Bioavailability the Central Translational Bottleneck?

The available evidence supports bioavailability as an important bottleneck, but it does not justify treating it as the sole explanation for limited clinical progress. Human pharmacokinetic variability, SEDDS-related improvements, and the PPALM observations demonstrate that oral delivery can fail before adequate systemic exposure is achieved. However, cancer therapy requires a much longer chain of successful events. A patient can have high plasma concentrations without adequate tumor penetration, and a tumor can accumulate nanoparticles without receiving enough intracellular free tocotrienol to alter cancer biology. The concept of a single "bioavailability problem" should therefore be replaced by a sequential bottleneck model. In this model, oral bioavailability is the first major hurdle for conventional supplementation, whereas biodistribution, tumor access, cellular delivery, and pharmacodynamics become progressively more important as systemic exposure improves. The dominant bottleneck may differ among formulations and patients. This interpretation aligns with broader cancer-nanomedicine experience. Despite decades of successful preclinical engineering, only a fraction of anticancer nanomedicines has generated transformative clinical outcomes. Contemporary analyses argue that increased tumor drug concentration alone does not guarantee better efficacy and that some successful nanomedicines have delivered their greatest clinical advantage through altered toxicity rather than dramatic enhancement of tumor-cell killing [16,14].

The Plasma-Exposure Fallacy

A major risk in tocotrienol development is assuming that improved plasma AUC constitutes successful translation. AUC is extremely useful because it confirms that formulation changes systemic exposure, allows dose normalization, and permits PK/PD modeling. It should therefore be measured routinely. But plasma concentration is an intermediate endpoint rather than the therapeutic endpoint. The relevant oncology question is whether a formulation increases the tumor concentration–time profile of pharmacologically available tocotrienol while maintaining acceptable exposure in normal tissues. Even tumor concentration can be insufficient if most of the measured compound remains trapped in extracellular carrier, tumor-associated macrophages, or necrotic tissue. Ideally, development should progress from plasma PK to whole-tissue biodistribution, spatial intratumoral analysis, cell-specific uptake, and molecular target engagement.

This transition is precisely where many nanomedicines struggle. Reviews of clinical translation repeatedly identify mismatches between simplified preclinical models and heterogeneous human tumor biology, as well as insufficient integration of biodistribution, pharmacodynamics, manufacturability, and patient selection [50,51,15,17]. (PubMed) A recent review of cancer-nanomedicine translation likewise identifies tumor heterogeneity, complex nano-bio interactions, scale-up, production cost, and regulatory uncertainty as major reasons why promising preclinical systems do not routinely become approved therapies [52].

The Nanometer Fallacy

A related error is equating nanoscale particle size with therapeutic superiority. A particle diameter between approximately 50 and 150 nm may be pharmaceutically interesting, but nanometer size is not itself a biological mechanism. Likewise, high encapsulation efficiency, narrow polydispersity, or favorable zeta potential are necessary formulation-quality characteristics but do not establish tumor targeting. The 2025 palm nanoemulsion study is valuable because it goes beyond particle characterization and demonstrates improved biological activity. Nevertheless, even this

should be regarded as the beginning rather than the completion of translational evidence. The next developmental step must establish in vivo pharmacokinetics and tumor distribution, followed by efficacy in appropriate animal models. Only after those studies demonstrate exposure–response relationships would clinical testing of a nanoformulated product becomes pharmacologically persuasive [13].

Figure 4 challenges the common assumption that nanoparticles automatically target malignant cells through the EPR effect. It depicts tumor delivery as a competitive journey in which protein corona formation, hepatic and splenic clearance, vascular transport, stromal penetration, and cellular uptake collectively determine how much tocotrienol reaches a cancer-cell target (Figure 4).

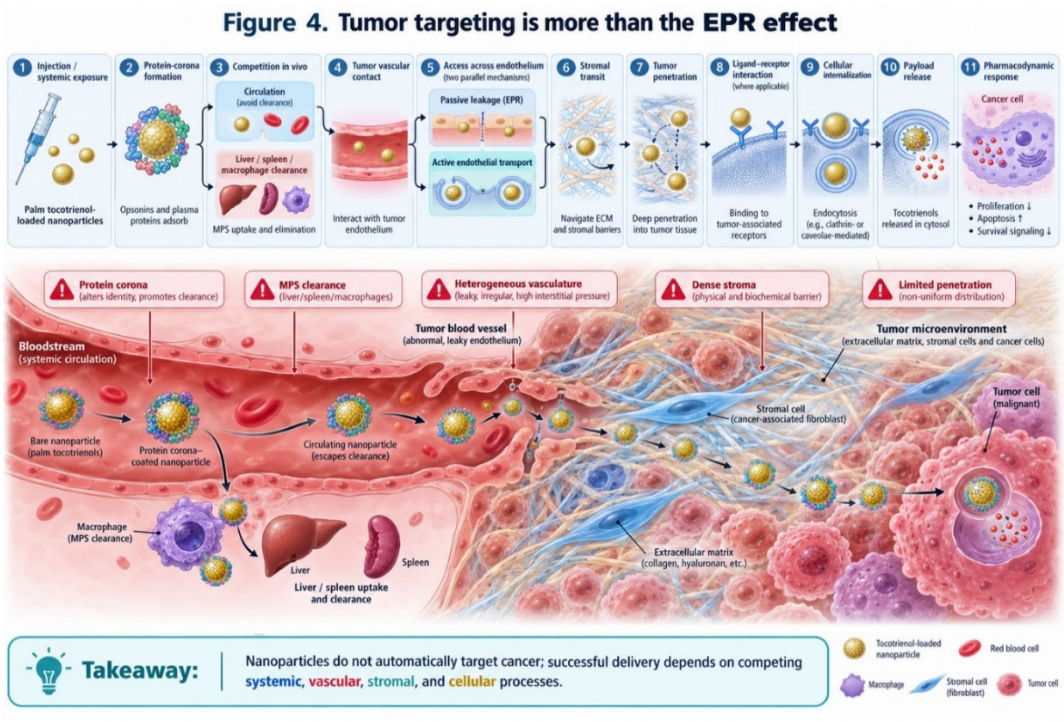

Figure 4: Tumor targeting is more than the EPR effect.

The Figure highlights the difference between passive and active targeting. Ligand attachment may improve recognition and internalization, but the carrier must first survive circulation and reach the tumor. The biological identity of the carrier can be modified by the protein corona, while abnormal vasculature and tumor matrix can prevent uniform penetration. These factors help explain why delivery strategies that perform well in simplified cell culture can underperform in animals or patients [35,30,29,27].

Palm Versus Annatto Should not become a False Binary

The comparative pharmacokinetic literature sometimes invites a simplistic conclusion that annatto-derived tocotrienols are superior to palm-derived tocotrienols. This would be premature. Annatto products frequently contain a substantially different isoform profile from palm TRF, and the formulations used in human pharmacokinetic studies are not necessarily equivalent. Different doses, excipients, self-emulsification properties, fed conditions, and analytical schedules may all influence measured exposure.

A more productive research question is whether palm-derived tocotrienols can be reformulated to achieve exposure comparable to, or better than, other tocotrienol preparations while preserving the biological advantages of their isoform mixture. The successful use of self-emulsifying systems demonstrates that formulation can change this comparison substantially. Head-to-head studies should therefore control total dose, isoform dose, formulation type, food intake, and sampling schedule before attributing pharmacokinetic differences to botanical source [8,10].

Combination Therapy may be the most Rational Oncology Pathway

Tocotrienols may be more promising as chemosensitizing, toxicity-modifying, or pathway-modulating adjuncts than as stand-alone cytotoxic agents. The clinical colorectal study already illustrates the feasibility of combining δ-tocotrienol with intensive chemotherapy, while contemporary mechanistic literature describes modulation of pathways associated with drug resistance [7,23]. Formulation creates both opportunities and risks in this context. Co-encapsulation of tocotrienol and chemotherapy could synchronize delivery, but biological synergy may require a specific temporal sequence. For example, pretreatment with tocotrienol may need to alter survival signaling before chemotherapy

exposure, whereas simultaneous release could be less effective. Conversely, uncontrolled prolonged release might antagonize therapies whose mechanism depends on oxidative damage. PK/PD modeling is therefore essential before selecting co-encapsulation simply because it is technically possible. Nanocarriers have already been explored clinically as a means of modifying chemotherapeutic pharmacology and toxicity. The experience of liposomal and other nanoscale anticancer products demonstrates that altered distribution can improve the therapeutic index even when tumor targeting is imperfect. Tocotrienol formulation should therefore seek clinically meaningful advantages such as enhanced target engagement, reduced required dose, improved combination tolerability, or reversal of resistance rather than pursuing "targeted nanotherapy" as an end in itself [53,49].

Nanotoxicology Cannot be Treated as an Afterthought

Although many lipid-based carriers use materials regarded as biocompatible, nanoscale formulations can produce biological behaviors that differ from their bulk components. Particle size, surface charge, aggregation, persistence, complement activation, immune-cell interactions, organ accumulation, and degradation products can influence toxicity. A tocotrienol formulation cannot therefore rely solely on the historical safety of oral vitamin E or palm TRF [54,55]. Safety assessment should incorporate conventional toxicology together with nanomedicine-specific pharmacology. Important endpoints include hematological and biochemical toxicity, hepatic and splenic accumulation, immunogenicity, complement activation, histopathology, inflammation, carrier clearance, and repeat-dose effects. These evaluations are especially important if an oral nutraceutical is converted into a parenteral nanosystem, because route of administration fundamentally changes tissue exposure.

The principle should be "safe by design." Carriers should be simplified wherever possible, and every component should have a clear functional justification. Adding a targeting ligand, polymer, imaging probe, or stimulus-responsive component may improve experimental sophistication but also increases manufacturing and toxicological uncertainty. Clinical translation tends to favor systems whose added complexity produces a measurable therapeutic advantage [54,56].

Manufacturing and Regulation are Part of Pharmacology

A formulation that cannot be manufactured reproducibly at scale is not a viable drug product. Nanocarrier size distribution, encapsulation efficiency, free-drug fraction, lipid oxidation, payload degradation, surface-ligand density, release kinetics, sterility, endotoxin levels, and storage stability can all influence in vivo behavior. Consequently, critical quality attributes must be linked to pharmacological performance from the early stages of development [57]. Scale-up can alter the very parameters that produced efficacy in the laboratory. Mixing energy, microfluidic flow, sonication, solvent removal, raw-material purity, and sterilization may change particle properties. For natural-source payloads such as palm TRF, additional standardization is needed because variation in isoform composition could become a pharmacological source of batch variability. Regulatory uncertainty remains another challenge. Nanomedicines combine conventional drug-product requirements with additional characterization of complex delivery structures. Reviews of nanomedicine regulation emphasize the need for robust physicochemical characterization, reproducible manufacturing, validated analytical methods, relevant preclinical models, and early dialogue with regulators [58,57].

A Bench-to-Bedside Roadmap for Palm Tocotrienol Oncology

The first developmental decision should concern the payload itself. Researchers must decide whether the intended active ingredient is standardized palm TRF or a purified palm-derived isoform. If a mixture is used, exact tocotrienol and tocopherol composition should be defined and controlled. If a purified isoform is selected, the decision should be justified by both anticancer potency and pharmacokinetic behavior. The second stage is formulation optimization. Relevant parameters include tocotrienol loading, chemical stability, particle size, polydispersity, zeta potential, free-drug fraction, release kinetics, gastrointestinal behavior for oral systems, serum stability for parenteral systems, and reproducibility. Optimization should not be based exclusively on maximum encapsulation efficiency because excessively stable encapsulation can impair payload release. The third stage is comparative pharmacokinetics. Free tocotrienol, established oral formulations, and the new delivery system should be tested at dose-normalized exposures. Cmax, Tmax, AUC, elimination half-life, metabolite formation, and interindividual variability should be measured. For parenteral systems, carrier-associated and free tocotrienol should ideally be distinguished. The fourth stage is biodistribution and tumor pharmacology. Studies should quantify tumor-to-plasma and tumor-to-normal-organ ratios and distinguish total drug from pharmacologically available drug where feasible. Spatial distribution should be measured rather than relying only on homogenized tumor concentrations. Tumor biopsies, lipidomics, mass-spectrometry imaging, fluorescence imaging with appropriate validation, or radiolabeled tracing could be used depending on the formulation.

The fifth stage is pharmacodynamic confirmation. The relevant marker depends on the proposed anticancer mechanism: proliferation indices, apoptosis, autophagy, ER-stress markers, PD-L1 signaling, Akt/mTOR activity, NF-κB activity, or chemotherapy-sensitization markers may all be appropriate in different settings. The important requirement is to demonstrate that the formulation increases exposure and that increased exposure produces the predicted molecular effect.

The sixth stage involves combination therapy. Scheduling, dose ratios, and toxicity should be optimized using mechanistic PK/PD models rather than empirical combination alone. Patient-

derived organoids, three-dimensional tumor models, and carefully selected in vivo systems can help bridge cell-culture findings to clinical application. The seventh stage is translational safety and manufacturing. Repeated-dose toxicology, immune effects, biodistribution, clearance, formulation degradation, and manufacturing reproducibility should be addressed before large oncology efficacy experiments. This sequence reduces the risk that investigators optimize antitumor activity around a carrier that ultimately cannot be manufactured or safely administered. Finally, early human development should prioritize target engagement rather than efficacy alone. A Phase 0 or early Phase I study could test whether the formulation achieves the expected systemic and tumor exposure and whether tumor biopsies demonstrate pharmacodynamic activity. Only after these questions are answered should large efficacy-oriented studies be pursued. This approach is consistent with broader recommendations to make cancer nanomedicine more mechanism-driven and clinically translatable [51,15,17].

Figure 5 summarizes the proposed bench-to-bedside pathway and provides a practical development architecture for future palm-tocotrienol oncology programs. Its central principle is that progression to the next stage should depend on quantitative evidence that the preceding delivery barrier has actually been overcome (Figure 5).

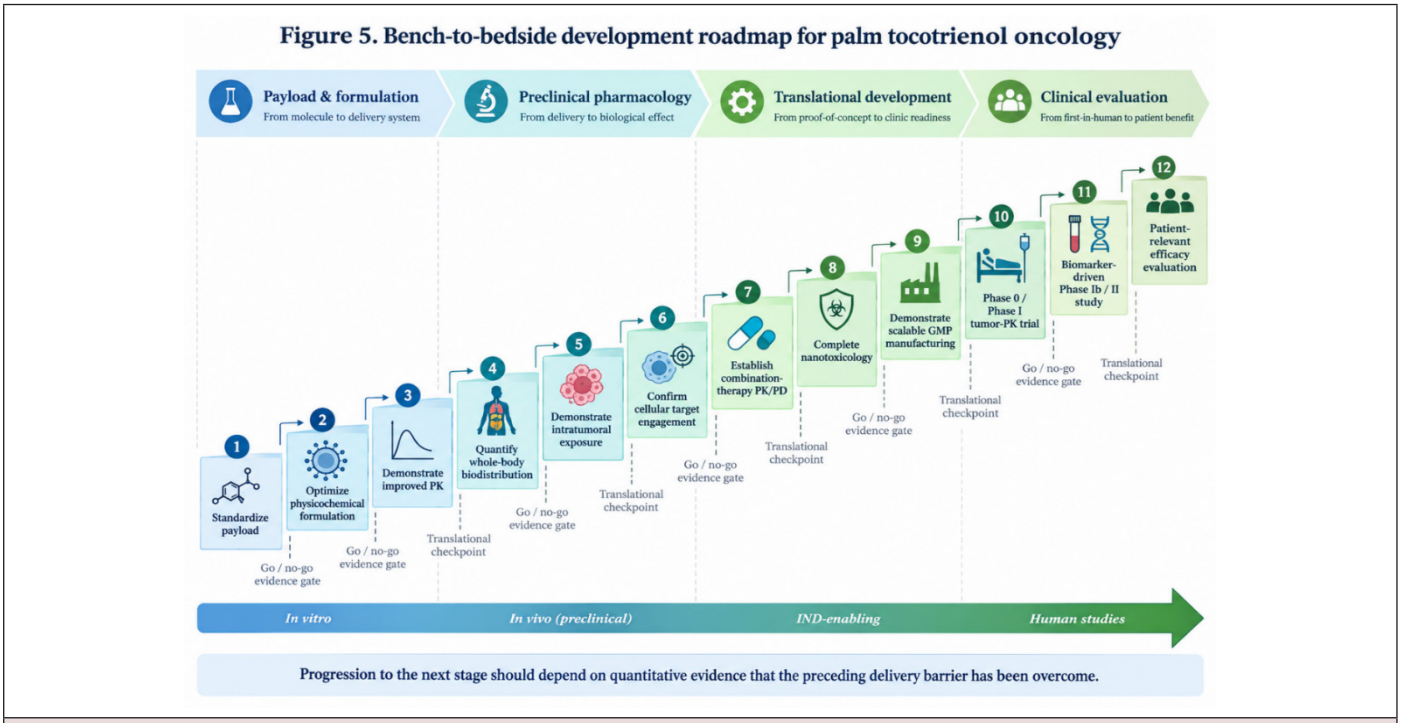

Figure 5: Bench-to-bedside development roadmap for palm tocotrienol oncology.

This staged framework differs from the conventional approach in which successful cell cytotoxicity is followed directly by increasingly complex nanoparticle engineering and eventual efficacy testing. Instead, each development gate asks a specific translational question: does the formulation increase exposure, does exposure reach the tumor, does tumor exposure reach malignant cells, does it alter the intended pathway, and does this produce a therapeutic advantage without unacceptable toxicity? Such an evidence chain is more likely to identify early whether a tocotrienol formulation has genuine clinical potential [50,14,17,25].

Conclusion

Palm tocotrienols possess a substantial experimental anticancer evidence base, but their clinical development should no longer be framed principally as a question of whether tocotrienols possess anticancer activity. The more useful question is whether therapeutically relevant concentrations can be delivered reproducibly to malignant tissue in patients. Available evidence demonstrates that tocotrienol pharmacokinetics are strongly formulation dependent. Self-emulsifying systems can improve oral exposure, while the 2025 palm-oil nanoemulsion study provides direct proof that formulation can improve tocotrienol stability and anticancer activity in a melanoma cell model. These advances are important, but neither higher plasma exposure nor stronger in vitro cytotoxicity demonstrates effective tumor targeting.

The delivery bottleneck should therefore be understood as a continuum extending from pharmaceutical availability and gastrointestinal bioaccessibility through systemic bioavailability, biodistribution, tumor accumulation, intratumoral penetration, cellular uptake, payload release, and pharmacodynamic target engagement. Improving one stage does not guarantee success

at the next. This distinction is especially important because tumor vasculature, protein corona, macrophage sequestration, stromal architecture, and interstitial pressure can substantially alter nanoparticle behavior in vivo. SEDDS, nanoemulsions, nanostructured lipid carriers, liposomes, and polymer–lipid hybrids all offer plausible advantages, but current evidence is insufficient to declare any platform superior for palm-tocotrienol oncology. The most appropriate system will depend on route of administration, intended cancer indication, tocotrienol isoform or TRF composition, combination partner, desired exposure pattern, and pharmacodynamic mechanism.

Future research should therefore shift from dose-driven supplementation to exposure-driven oncology pharmacology. The critical milestones are standardized payload composition, head-to-head formulation comparisons, quantitative PK, tumor biodistribution, spatial intratumoral measurements, target-engagement biomarkers, rational combination therapy, nanotoxicological assessment, reproducible manufacturing, and early human tumor-PK studies. Palm tocotrienols should advance toward oncology not because they can be made into nanoparticles, but because an optimized formulation can ultimately demonstrate that more pharmacologically active tocotrienol reaches the right malignant cells at the right concentration, for the right duration, with an improved therapeutic index.

Acknowledgement

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Conflict of Interest

None.

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