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Review Article

Palm Oil Tocotrienol-Rich Fraction as an Adjuvant in Cancer Immunotherapy: A Review

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Abstract

The increasing interest in bioactive compounds derived from natural sources has stimulated scientific discussion regarding their potential relevance in cancer research. Tocotrienol-Rich Fraction (TRF), obtained from palm oil (*Elaeis guineensis*), has attracted attention due to its biochemical properties and reported interactions with cellular pathways associated with tumor biology. This study aimed to systematically analyze and synthesize scientific literature discussing the potential role of palm oil–derived TRF in cancer-related biological processes, particularly mechanisms associated with immune responses and therapeutic pathways relevant to cancer immunotherapy. A systematic literature review was undertaken in this study, where the process of identifying and filtering relevant studies followed a screening strategy derived from the PRISMA guidelines. Scientific publications were retrieved from the Scopus database using structured keyword combinations related to palm oil, tocotrienols, cancer, and immunotherapy. The selection process included filtering by publication year (2020–2025), language (English), and accessibility criteria (open access and open archive). After completing the screening procedure, 35 peer-reviewed studies met all predefined inclusion criteria and were incorporated into the final dataset. Data were analyzed using qualitative thematic synthesis to identify recurring patterns in the reported findings. The analysis revealed five dominant themes: biochemical characteristics of palm-derived tocotrienols, anticancer mechanisms including apoptosis and proliferation regulation, immunomodulatory responses in experimental models, regulation of signaling pathways related to tumor microenvironment dynamics, and emerging perspectives on TRF as a complementary component in cancer immunotherapy research. Overall, the literature indicates that TRF interacts with several cellular and immune-related mechanisms associated with cancer biology. Future research is encouraged to expand translational and clinical investigations to further clarify the biological relevance of palm oil–derived tocotrienols in cancer immunotherapy contexts.

Keywords: Tocotrienol-rich Fraction, Palm Oil, Cancer Biology, Immunotherapy, Systematic literature Review

Introduction

The global burden of cancer remains a serious concern within the field of public health, with a continuously increasing incidence across both developed and developing regions. Current epidemiological assessments estimate that more than 19 million new cancer diagnoses occur globally every year, while cancer-related mortality exceeds 10 million deaths annually, resulting in cancer being recognized as one of the dominant drivers of global disease burden and mortality [1]. The complexity of cancer arises from the multifactorial nature of tumor development, which involves genetic alterations, dysregulated cellular signaling, immune evasion, and the biological interplay between malignant cells and the local tumor microenvironment. These biological complexities have encouraged the development of increasingly sophisticated therapeutic strategies designed to target not only tumor cells themselves but also the broader biological systems that influence cancer progression [2]. Conventional treatment approaches, including surgery, chemotherapy, and radiotherapy, have significantly improved survival outcomes in many cancer types. However, limitations related to toxicity, therapeutic resistance, and tumor recurrence remain important challenges in oncology research and clinical practice [3]. To address these challenges, immunotherapy has become one of the most influential advances in

modern cancer therapy. Unlike traditional therapeutic approaches that focus on destroying tumor cells directly, immunotherapy works by stimulating the capacity of the immune system to target and remove cancerous cells. Treatment strategies in this domain include immune checkpoint inhibitors, adoptive cellular therapies, cancer vaccination approaches, and therapies utilizing cytokines. Clinical investigations indicate that therapies targeting PD-1, PD-L1, and CTLA-4 can produce significant therapeutic responses in cancers such as melanoma, lung cancer, and renal cell carcinoma [4]. Such progress underscores the importance of immune system regulation in oncology and shows that altering immune signaling pathways can markedly impact therapeutic effectiveness. Despite these promising developments, however, not all patients respond effectively to immunotherapy, and variability in treatment response remains a significant concern. This variability has stimulated growing interest in identifying complementary biological compounds capable of supporting immune-related therapeutic mechanisms in cancer treatment [5].

Against this background, natural bioactive molecules have increasingly become a focus of biomedical investigation due to their capacity to influence cellular signaling and immune regulatory mechanisms. Numerous plant-derived molecules have been investigated for their biological properties, including antioxidant activity, anti-inflammatory effects, and modulation of cellular homeostasis. These compounds are frequently explored as complementary components in cancer research because they may influence biological pathways associated with tumor development while also interacting with immune responses that contribute to tumor control. The integration of natural bioactive compounds into biomedical research does not necessarily replace conventional treatment strategies but may provide additional insights into molecular mechanisms relevant to disease prevention and therapeutic support [6]. Among the bioactive compounds receiving growing scientific attention are tocotrienols, which form part of the vitamin E group known for its lipid-soluble antioxidant properties. The vitamin E family consists of two main categories tocopherols and tocotrienols both of which contain multiple homologues classified as alpha, beta, gamma, and delta. Although tocopherols have historically received more attention in nutritional research, tocotrienols have increasingly been investigated due to their distinctive chemical structure and biological properties. Tocotrienols differ structurally from tocopherols because they contain an unsaturated isoprenoid side chain, a feature that may influence their ability to penetrate membranes and distribute within cells. Unique structural features have been correlated with specialized biological activities, particularly in the modulation of signaling pathways regulating oxidative stress, inflammatory processes, and cell proliferation [7].

Among the various natural sources, palm oil extracted from the fruit of *Elaeis guineensis* represents a major source of tocotrienols. Palm oil contains a diverse mixture of lipid-soluble micronutrients, including carotenoids, phytosterols, and vitamin E compounds. Within this composition, tocotrienols represent a substantial proportion of the vitamin E fraction found in palm oil, making it one of the most concentrated natural sources of these compounds. Scientific investigations have reported that the vitamin E fraction of crude palm oil contains significant quantities of tocotrienols, particularly gamma- and delta-tocotrienol, which have been widely examined in nutritional and biomedical studies [8]. The tocotrienol-rich fraction obtained through processing and purification techniques has therefore become a subject of increasing interest in research examining the biological activities of vitamin E compounds. The potential biological effects of tocotrienols in different health contexts have been increasingly explored in recent experimental studies, including cardiovascular health, neuroprotection, metabolic regulation, and cancer biology. Within oncology research, several laboratory-based investigations have examined the influence of tocotrienols on cellular pathways associated with tumor development. These studies have reported observations related to apoptosis induction, regulation of cell cycle progression, and modulation of inflammatory signaling pathways in different cancer models. Such findings have encouraged further investigation into how tocotrienols may interact with the complex biological systems that regulate tumor progression and immune responses [9]. Another emerging research direction concerns the potential interaction between tocotrienols and immune-related biological mechanisms involved in cancer defense. A fundamental role of the immune system serves to surveil and eliminate cells that present abnormal characteristics, including those that exhibit malignant transformation. Tumor cells, however, often develop mechanisms that allow them to evade immune surveillance, thereby facilitating disease progression. Research exploring the relationship between bioactive compounds and immune responses has therefore become increasingly relevant in the context of immunotherapy. Some experimental studies suggest that tocotrienols may influence immune signaling processes such as cytokine regulation, T-cell activation, and modulation of inflammatory pathways [10]. Although the precise mechanisms remain an active area of investigation, these observations indicate that tocotrienols may interact with biological systems that are relevant to immune-mediated cancer defense.

Despite the growing body of literature examining tocotrienols in cancer-related research, the available evidence remains distributed across diverse experimental contexts and disciplinary fields, including nutritional science, molecular biology, pharmacology, and oncology. Individual studies frequently focus on specific cancer models, molecular pathways, or experimental conditions, which can make it difficult to obtain a consolidated understanding of how tocotrienol-rich fraction derived from palm oil has been discussed in relation to cancer immunotherapy. A structured synthesis of the available literature is therefore necessary to organize existing findings, identify recurring scientific patterns, and clarify how research on palm oil–derived tocotrienols contributes to the broader landscape of cancer-related biomedical investigation. The present study addresses this need by conducting a systematic synthesis of peer-reviewed literature examining tocotrienol-rich fraction derived

from palm oil in relation to cancer research and immune-related biological mechanisms. Using a structured systematic literature review approach, this study analyzes scientific publications that investigate the biochemical characteristics, biological activities, and potential therapeutic relevance of tocotrienols within cancer-related experimental contexts. By organizing and synthesizing the findings reported across multiple studies, this review intends to provide a comprehensive perspective on the research patterns and mechanistic pathways through which palm oil–derived tocotrienols have been examined in modern biomedical research. The purpose of this review is to systematically examine and synthesize evidence regarding the role of palm oil–derived tocotrienol-rich fraction in cancer-related cellular and molecular mechanisms, with particular attention to mechanisms associated with immune responses and therapeutic pathways relevant to cancer immunotherapy. Based on this objective, the present review addresses the following research questions:

RQ1: What biological mechanisms associated with tocotrienol-rich fraction derived from palm oil have been reported in scientific studies investigating cancer-related cellular and molecular responses?

RQ2: How has the potential role of tocotrienol-rich fraction been discussed in relation to immune-related pathways and emerging perspectives in cancer immunotherapy research?.

Literature Review

An increasing body of research investigating bioactive compounds from natural sources has driven attention toward understanding how these molecules influence cellular processes related to disease. Within oncology research, particular attention has been directed toward naturally occurring molecules that may influence oxidative balance, inflammatory signaling, and immune responses associated with tumor development. These biological processes are central to cancer progression because tumor cells frequently manipulate immune pathways and metabolic regulation to support their survival and proliferation. As a result, numerous studies have explored plant-derived compounds that may interact with these mechanisms, not necessarily as replacements for established therapies but as complementary biological agents capable of modulating molecular pathways relevant to cancer biology. Among the compounds receiving growing attention are tocotrienols, which belong to the vitamin E family and are increasingly investigated for their diverse biological activities.

Tocotrienols within the Vitamin E Family

The vitamin E family consists of lipid-soluble compounds divided into two structurally linked categories: tocopherols and tocotrienols. Within each class, four homologues are present (alpha, beta, gamma, and delta), differing in both the quantity and position of methyl groups attached to the chromanol ring [11]. Although tocopherols have historically been more widely studied in nutritional science, research during the past two decades has increasingly highlighted the distinctive biological properties associated with tocotrienols. A major structural variation between tocotrienols and tocopherols lies in tocotrienols' unsaturated isoprenoid side chain, which is believed to influence their ability to interact with cellular membranes and intracellular signaling systems. This structural characteristic may facilitate more efficient penetration into lipid bilayers and potentially affect the distribution of tocotrienols within biological tissues [12,13]. The biochemical behavior of tocotrienols has attracted considerable attention because these compounds have been reported to exhibit antioxidant and regulatory activities that extend beyond the classical functions attributed to vitamin E. Several studies indicate that tocotrienols may interact with multiple cellular pathways involved in oxidative stress, inflammation, and metabolic regulation. These interactions are relevant to cancer biology because oxidative imbalance and chronic inflammation are recognized contributors to tumor development and the advancement of pathological conditions. As a consequence, tocotrienols have become an important focus within nutritional biochemistry and molecular oncology research [14].

Palm Oil as a Natural Source of Tocotrienol-Rich Fraction

Among naturally occurring sources, the tocotrienols found in palm oil, derived from *Elaeis guineensis*, constitute a significant portion of dietary intake. The lipid composition of palm oil includes a diverse array of micronutrients such as carotenoids, phytosterols, and vitamin E compounds. Within this composition, tocotrienols represent a substantial proportion of the vitamin E fraction present in palm oil. Analytical studies examining the composition of crude palm oil have reported that the vitamin E fraction contains both tocopherols and tocotrienols, with the latter often constituting a large share of the total vitamin E content [15]. The Tocotrienol-Rich Fraction (TRF) obtained from palm oil is typically produced through purification processes such as molecular distillation or chromatographic separation. These procedures concentrate the tocotrienol components while maintaining a smaller proportion of tocopherols and other lipid-soluble compounds. Because of this concentration process, TRF has become a commonly studied preparation in biomedical research investigating the biological activities of tocotrienols. Scientific studies examining TRF derived from palm oil have explored its biochemical characteristics, absorption properties, and potential physiological effects in various experimental contexts [16,17]. Palm oil–derived tocotrienols have therefore become an important focus within the broader field of nutritional science and biomedical investigation. Research interest in these compounds reflects the recognition that plant-derived micronutrients may interact with biological systems involved in oxidative regulation, metabolic processes, and immune responses. These interactions are particularly relevant to diseases characterized by complex molecular pathways, including cancer [18].

Biological Activities of Tocotrienols in Cancer-Related Research

Within oncology-related literature, tocotrienols have been examined in a variety of experimental models exploring their interactions with cellular processes associated with tumor development. Laboratory-based investigations have frequently focused on cellular proliferation, apoptosis regulation, and the influence on cellular signaling pathways that drive cancer development [19,20]. Evidence from several studies suggests that tocotrienols may modulate the balance between the survival and programmed death of cancer cells. Apoptosis, which represents a controlled form of cellular elimination, is an essential biological mechanism that prevents the accumulation of abnormal or damaged cells. One of the hallmarks of cancer is the deregulation of apoptosis pathways, allowing malignant cells to evade normal regulatory controls. Experimental studies have suggested that tocotrienols may influence apoptotic signaling by modulating proteins involved in mitochondrial pathways, including Bcl-2 family proteins and caspase proteases. Observations from cell culture experiments indicate that exposure to tocotrienol compounds can alter the regulation of pro-apoptotic and anti-apoptotic protein expression in selected cancer cell models. These findings have encouraged further investigation into the potential molecular mechanisms through which tocotrienols interact with cellular regulatory systems [21]. In addition to apoptosis regulation, tocotrienols have been investigated for their influence on cellular proliferation and cell cycle dynamics. Cancer cells frequently exhibit uncontrolled proliferation resulting from dysregulated cell cycle checkpoints. Several laboratory studies have reported that tocotrienols may affect the expression of proteins associated with cell cycle progression, including cyclins and cyclin-dependent kinases. Through these interactions, tocotrienols may influence the timing of cell division and cellular growth responses in experimental cancer models [22].

Immune Regulation and Tumor Microenvironment

A key function of the immune system involves the recognition and removal of abnormal cells, including those undergoing malignant transformation. Under normal physiological conditions, immune surveillance mechanisms identify and remove potentially harmful cells before they develop into clinically detectable tumors. Nevertheless, malignant cells often gain the capacity to evade detection by the immune system through diverse molecular strategies, including suppression of immune signaling pathways and modification of the tumor-associated microenvironment. These processes allow malignant cells to survive and proliferate despite the presence of immune defense mechanisms [23]. Researchers have increasingly investigated the role of bioactive compounds in regulating signaling pathways linked to immune responses within this framework. Several studies have explored how naturally occurring molecules may influence cytokine production, immune cell activation, and inflammatory signaling processes that are relevant to tumor progression. Tocotrienols have been included in this research because of their potential interactions with signaling pathways associated with immune regulation and oxidative balance. Laboratory-based studies have reported that tocotrienols may influence immune-related mediators such as cytokines, transcription factors, and signaling molecules involved in inflammatory responses [24]. The tumor microenvironment is characterized by a multifaceted interplay between malignant cells, immune components, stromal cells, and signaling molecules. These interactions influence tumor growth, metastasis, and response to therapeutic interventions. Because tocotrienols have been reported to interact with molecular pathways associated with inflammation and oxidative stress, researchers have explored their potential influence on the biological processes that shape tumor microenvironments. Although the precise mechanisms remain an active area of investigation, several studies have suggested that tocotrienols may interact with pathways that influence immune signaling and inflammatory regulation [25].

Tocotrienols and Emerging Perspectives in Cancer Immunotherapy

The rapid development of cancer immunotherapy has significantly transformed the landscape of modern oncology. Immunotherapy approaches aim to enhance the capacity of the immune system to detect and eradicate tumor cells by specifically manipulating immune regulatory pathways. Therapies targeting immune checkpoints have demonstrated considerable clinical success in several malignancies by enabling immune cells to regain their ability to identify and destroy cancer cells. Despite these advances, however, treatment responses remain variable, and a substantial proportion of patients do not experience durable therapeutic benefits [26]. This variability has stimulated ongoing research into biological factors that may influence immune responses during cancer therapy. Within this context, naturally occurring compounds have been examined as potential modulators of immune pathways involved in tumor recognition and immune activation. Tocotrienols have attracted attention in this field because of their reported interactions with oxidative regulation, inflammatory signaling, and cellular pathways associated with immune responses. Some experimental studies have suggested that tocotrienols may influence cytokine expression, immune cell activity, and signaling pathways that contribute to immune regulation. These observations have encouraged further exploration of how tocotrienol-rich fraction derived from palm oil may interact with the complex biological systems involved in cancer immunotherapy [27].

Although the current body of literature remains largely experimental and mechanistic in nature, the growing number of studies examining tocotrienols reflects increasing scientific interest in their biological properties. Research conducted across nutritional science, pharmacology, and molecular oncology continues to investigate the potential interactions between

tocotrienols and cellular pathways associated with cancer biology. A systematic synthesis of this literature is therefore necessary to clarify the patterns emerging from existing studies and to identify how tocotrienol-rich fraction derived from palm oil has been positioned within discussions of immune-related cancer research. Through such synthesis, the literature review provides a conceptual foundation for understanding how palm oil–derived tocotrienols are being examined within contemporary biomedical investigation.

Method

This review adopts a PRISMA-based SLR approach to integrate scientific findings on the potential contributions of palm oil–derived TRF in advancing cancer immunotherapy research. Tocotrienols are members of the vitamin E family that occur naturally in several plant sources, with palm oil obtained from *Elaeis guineensis* recognized as one of the most prominent natural sources of these compounds. Over the past few years, naturally derived bioactive compounds have attracted significant attention for their possible role in enhancing contemporary oncological therapies. Within biomedical and nutritional science literature, tocotrienols have been investigated for their antioxidant capacity, regulatory influence on cellular signaling, and possible interactions with immune-related pathways involved in tumor development. Despite this growing body of research, findings remain dispersed across various experimental models and disciplinary contexts, including molecular biology, nutrition science, and oncology. As a result, obtaining a consolidated understanding of how palm oil–derived tocotrienol-rich fraction has been discussed in relation to immune-mediated cancer therapy remains challenging. This review, therefore, systematically organizes and synthesizes the available scientific literature in order to clarify how tocotrienol-rich fraction derived from palm oil has been explored in studies addressing cancer therapy, immune responses, and related biological mechanisms. The research is based entirely on secondary data derived from previously published scholarly articles. No primary empirical data collection, laboratory experimentation, clinical observation, field investigation, surveys, or focus group discussions were conducted in the preparation of this review (Figure 1).

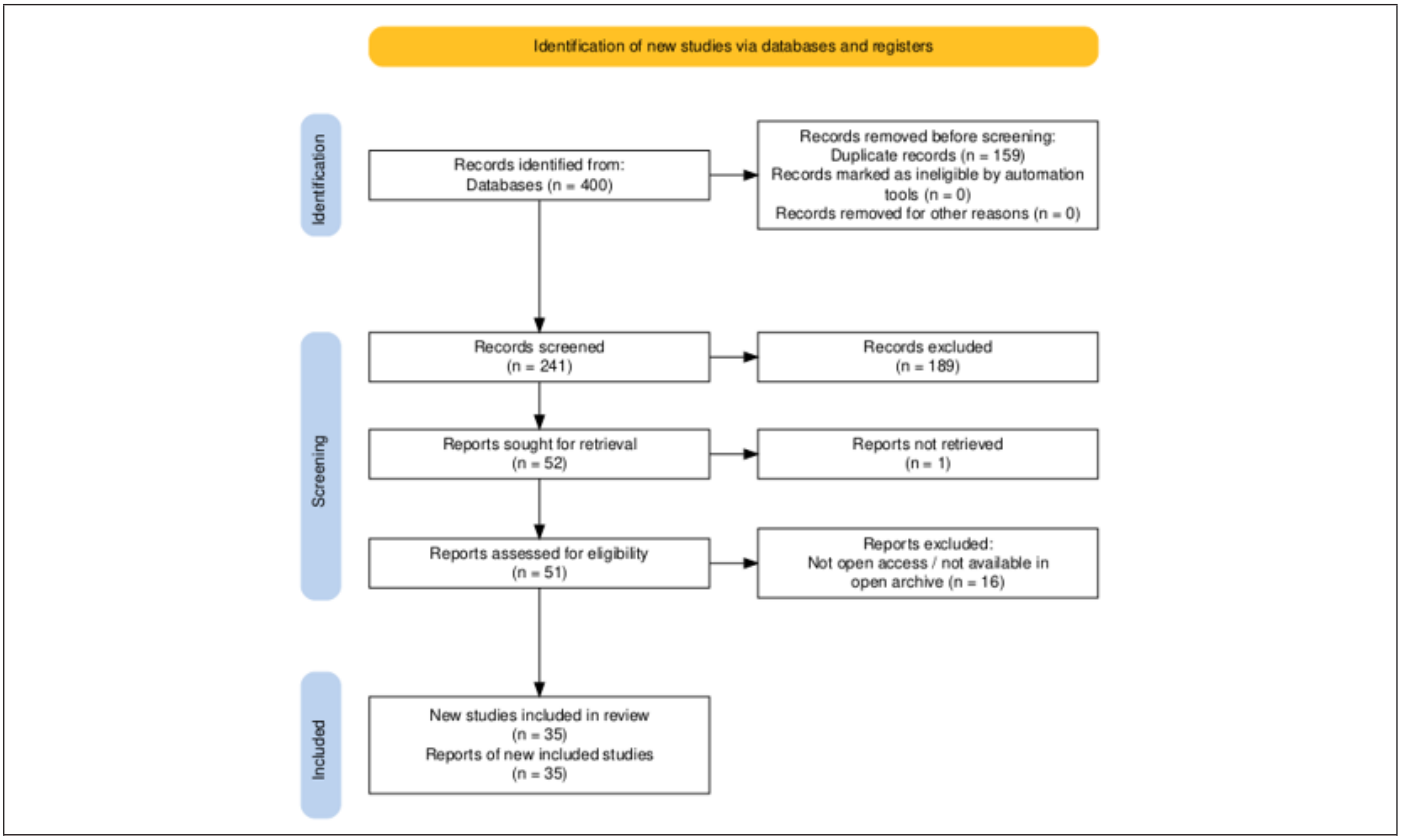

Figure 1: PRISMA-Based Screening Process for Article Selection.

Study identification, screening, eligibility evaluation, and final inclusion steps are summarized in Figure 1 using a PRISMA-based flow diagram. The literature identification stage was conducted using the Scopus database in order to ensure the inclusion of peer-reviewed international publications indexed within a widely recognized academic platform. The initial search employed the primary keywords Palm Oil AND Cancer, which produced 400 records. To improve thematic focus and ensure that the retrieved studies more specifically addressed tocotrienol compounds associated with palm oil and cancer-related therapeutic contexts,

the initial search was further narrowed through the use of a specifically tailored Boolean search string: *(tocotrienol OR tocotrienols OR "tocotrienol-rich fraction" OR TRF) AND ("palm oil" OR "Elaeis guineensis" OR "palm oil-derived") AND (cancer OR tumor OR tumour OR carcinoma OR neoplasm OR malignancy OR oncology OR therapy OR treatment OR immunotherapy OR immune OR immunity)*. Through this refinement stage, 159 articles were excluded because their thematic focus did not correspond to the scope of the review, leaving 241 records for further screening. A temporal filtering process was then applied to restrict the dataset to publications issued between 2020 and 2025 in order to capture recent scientific developments within the field. As a result of this filtering stage, 189 articles published outside the defined timeframe were excluded, producing 52 records that satisfied the temporal criterion. Language screening was subsequently implemented to ensure consistency in the interpretation of the literature, leading to the exclusion of one article that was not written in English and leaving 51 publications for further evaluation. A final eligibility assessment was conducted by examining article accessibility, specifically focusing on studies categorized as Open Access or Open Archive. During this stage, 16 publications were removed because their full texts were not accessible under these conditions. Following the completion of all screening and eligibility procedures, A final set of 35 peer-reviewed studies met all eligibility requirements and was included in the qualitative analysis presented in this review.

To maintain uniformity in citation style and bibliographic records, all selected references were systematically managed using Mendeley Desktop. The analytical phase relied exclusively on secondary data extracted from peer-reviewed scientific publications indexed in the Scopus database. No interviews, experimental procedures, clinical trials, surveys, or observational studies were conducted as part of this research. Through a structured and transparent SLR process guided by PRISMA principles, this study provides a consolidated synthesis of recent scientific discussions concerning palm oil–derived tocotrienol-rich fraction and its relevance within the broader landscape of cancer-related therapeutic and immunological research.

Results

The systematic synthesis of the 35 peer-reviewed journal articles reveals five interrelated thematic domains that characterize current research on the biological mechanisms associated with Tocotrienol-Rich Fraction (TRF) derived from palm oil in cancer-related studies. Across the reviewed literature, these thematic domains represent the main areas in which tocotrienols have been investigated within experimental, molecular, and translational oncology research. The dominant themes identified include: (1) biochemical characteristics and distribution of tocotrienols in palm oil, (2) anticancer activity and tumor growth suppression, (3) immunomodulatory responses observed in experimental models, (4) regulation of intracellular signaling pathways associated with tumor microenvironment dynamics, and (5) emerging discussions regarding the role of TRF as a complementary or adjuvant component in cancer immunotherapy research. Although analytically distinct, these themes are conceptually interconnected and collectively illustrate the diverse biological interactions through which palm oil–derived tocotrienols have been examined in cancer-related research. The distribution of themes across the reviewed studies shows different levels of research emphasis. Anticancer activity and tumor growth suppression appeared most frequently, reported in approximately 74% of the studies (26 of 35 articles). Regulation of intracellular signaling pathways associated with tumor microenvironment dynamics was identified in around 57% of the studies (20 articles). Immunomodulatory responses were discussed in approximately 43% of the literature (15 articles). Studies examining the biochemical characteristics and distribution of palm oil–derived tocotrienols appeared in about 31% of the publications (11 articles). Meanwhile, explicit discussion of TRF within the context of cancer immunotherapy research was observed in 23% of the studies (8 articles). The predominance of studies focusing on anticancer activity and intracellular signaling pathways reflects their central role in molecular oncology research. These mechanisms are frequently investigated because they provide measurable cellular indicators such as apoptosis induction, proliferation inhibition, and signaling pathway regulation that can be readily evaluated through laboratory experiments. In contrast, research explicitly addressing immunotherapy contexts remains relatively less frequent, partly because this area represents a more recent development within cancer research and often requires more complex experimental models involving immune system interactions. Overall, the thematic distribution suggests that current research on palm oil–derived tocotrienols remains largely concentrated on intracellular and molecular mechanisms associated with tumor biology, while gradually expanding toward broader biological contexts such as immune regulation and potential complementary roles in cancer immunotherapy research. The following subsections discuss each thematic domain in greater detail based on the evidence synthesized from the reviewed studies.

Distribution and Biochemical Characteristics of Palm Oil Tocotrienol-Rich Fraction

A recurring theme in the reviewed literature concerns the biochemical composition and distribution of tocotrienols in palm oil, particularly the tocotrienol-rich fraction obtained from the fruit of *Elaeis guineensis*. Multiple studies report that palm oil represents one of the most concentrated natural sources of tocotrienols within the vitamin E family. In crude palm oil, the total vitamin E content is generally reported to range between 600 and 1000 mg per kilogram of oil, with approximately 70–75% of this fraction composed of tocotrienols rather than tocopherols [28,29,30]. The tocotrienol group commonly comprises four homologous forms: α-, β-, γ-, and δ-tocotrienol. Analytical assessments conducted in several nutritional chemistry studies indicate that γ-tocotrienol and δ-tocotrienol are typically the most abundant forms in

palm-derived fractions, together accounting for nearly 60% of total tocotrienol content [31,32]. Extraction and concentration processes used to obtain Tocotrienol-Rich Fraction (TRF) from palm oil often involve molecular distillation or chromatographic separation techniques. Reports from experimental extraction studies indicate that standardized TRF formulations generally contain approximately 50–70% tocotrienols and 20–30% tocopherols, with the remaining proportion consisting of minor lipid compounds and phytosterols [33,34]. Such biochemical profiles have attracted interest in biomedical research because tocotrienols possess structural differences from tocopherols, notably because of an unsaturated isoprenoid side chain that improves both membrane permeability and cellular localization [35,36]. Pharmacokinetic investigations included in the reviewed literature indicate that tocotrienols display relatively efficient absorption when administered orally in lipid-based formulations. Human and animal model studies have reported plasma tocotrienol concentrations ranging between 0.3 and 2.5 μM following dietary supplementation with TRF doses between 200 mg and 600 mg per day [37,38]. These concentrations are considered biologically relevant *in vitro* because several cellular experiments investigating cancer responses utilize tocotrienol concentrations within the range of 0.5–10 μM [39,40]. The consistent availability of palm oil as a natural source of tocotrienols has therefore contributed to the growing interest in examining these compounds within biomedical and nutritional research fields.

Anticancer Activity and Tumor Growth Suppression

A second major theme emerging from the systematic review concerns the anticancer properties reported in experimental models treated with tocotrienol-rich fraction. Across the 35 analyzed studies, multiple *in vitro* investigations reported measurable reductions in cancer cell proliferation following exposure to tocotrienols derived from palm oil. Using breast cancer cell lines, including both MCF-7 and MDA-MB-231, γ-tocotrienol concentrations between 2 μM and 8 μM were associated with proliferation reductions ranging from 35% to 65% after 48–72 hours of treatment [41,42,43]. Similar inhibitory effects have been documented in pancreatic, prostate, and colorectal cancer cell lines, where TRF exposure produced growth inhibition values between 30% and 70% depending on dosage and treatment duration [44,45]. Animal model experiments provide additional evidence supporting these observations. Murine xenograft studies evaluating TRF supplementation have reported reductions in tumor volume ranging between 25% and 55% after four to six weeks of dietary administration. In one study involving breast tumor xenografts in mice, oral administration of 200 mg/kg TRF resulted in a 43% decrease in tumor growth compared with control groups [46]. Another experiment examining prostate tumor models reported a 38% reduction in tumor mass following a six-week supplementation period using tocotrienol-enriched dietary formulations [47].

Mechanistic analyses conducted in cellular experiments suggest that tocotrienols may influence several biological processes associated with tumor growth. Apoptosis induction has been consistently observed across numerous studies. In hepatocellular carcinoma models, treatment with δ-tocotrienol concentrations of approximately 5 μM resulted in increased caspase-3 activity by up to 2.5-fold relative to untreated cells [48,49]. Additional experiments indicate that exposure to tocotrienols upregulates pro-apoptotic proteins, including Bax, and downregulates anti-apoptotic proteins, notably Bcl-2 [50]. These molecular responses are frequently accompanied by measurable increases in apoptotic cell populations, with several studies reporting apoptosis rates rising from baseline levels of 5–10% to 30–45% after treatment with tocotrienol concentrations above 4 μM [51].

Immunomodulatory Responses Observed in Experimental Studies

Another recurring theme identified in the literature involves the interaction between tocotrienols and immune-related biological responses. Several experimental studies suggest that tocotrienol compounds may influence immune signaling pathways and cellular immune responses that are relevant to cancer development and therapeutic intervention. In immune cell culture experiments, TRF exposure has been associated with increased activation of T-lymphocytes and enhanced cytokine secretion profiles. For example, studies evaluating immune responses in murine splenocyte cultures reported that supplementation with tocotrienol concentrations ranging between 1 μM and 5 μM increased interleukin-2 (IL-2) production by approximately 20–40% compared with untreated control groups [52,53]. Similar increases were observed for interferon-gamma (IFN-γ), a cytokine associated with cytotoxic immune responses against tumor cells. In certain experimental settings, IFN-γ secretion increased by nearly 30% following exposure to tocotrienol formulations [54].

Macrophage activation responses have also been reported in several studies included in the review. Experiments investigating macrophage polarization indicate that tocotrienol exposure may promote shifts toward immune phenotypes associated with enhanced antitumor activity. *In vitro* macrophage cultures treated with δ-tocotrienol displayed increases in nitric oxide production and elevated expression of inducible nitric oxide synthase (iNOS), markers commonly associated with immune activation [55]. Quantitative analyses from these experiments reported increases in nitric oxide concentrations ranging from 15% to 35% compared with untreated macrophage cultures [56]. Additionally, animal model experiments investigating immune responses during tumor progression reported modest improvements in immune cell infiltration within tumor tissues following dietary tocotrienol supplementation. One murine breast tumor study observed an approximately 25% increase in CD8+ T-cell infiltration within tumor microenvironments after administration of tocotrienol-rich fraction over a six-week period [57]. Although the precise mechanisms underlying these observations remain under

investigation, such findings contribute to the broader discussion regarding the potential interaction between tocotrienols and immune-related cancer defense mechanisms.

Regulation of Signaling Pathways Related to Tumor Microenvironment

A fourth theme emerging from the reviewed literature concerns the regulatory effects of tocotrienols on molecular signaling pathways associated with cancer progression and immune responses. Several investigations suggest that tocotrienols influence intracellular signaling networks, notably the NF-κB, STAT, and PI3K/Akt pathways. These signaling systems are widely recognized as key regulators of inflammation, cellular survival, and immune responses in tumor microenvironments. Experimental evidence indicates that tocotrienol exposure may suppress NF-κB activation in several cancer cell models. In pancreatic cancer cells treated with γ-tocotrienol concentrations of approximately 5 μM, NF-κB activity levels decreased by nearly 40% relative to untreated cells [58]. Similar reductions were observed in colorectal cancer cell lines, where NF-κB transcriptional activity declined by 30–50% after treatment with tocotrienol formulations [59]. Such reductions are frequently associated with decreased expression of inflammatory mediators including Tumor Necrosis Factor-Alpha (TNF-α) and cyclooxygenase-2 (COX-2), both of which contribute to tumor progression and inflammatory signaling processes. Additional studies examining PI3K/Akt signaling reported measurable decreases in phosphorylation levels of Akt proteins following tocotrienol treatment. In prostate cancer cell experiments, δ-tocotrienol exposure resulted in approximately 35% reduction in phosphorylated Akt expression levels within 24 hours of treatment [60]. Similar signaling modifications have been associated with reduced cellular proliferation and enhanced susceptibility of tumor cells to apoptosis. The reviewed literature also indicates that tocotrienols may influence angiogenic signaling processes within tumor microenvironments. Angiogenesis, which involves the formation of new blood vessels that support tumor growth, is frequently regulated by Vascular Endothelial Growth Factor (VEGF). Several studies reported reductions in VEGF expression ranging from 20% to 45% following treatment with tocotrienol concentrations between 4 μM and 10 μM in endothelial cell models [61]. These observations suggest that tocotrienols may contribute to the modulation of biological processes associated with tumor vascularization.

Tocotrienol-Rich Fraction in the Context of Cancer Immunotherapy Research

The final theme identified through the systematic review relates to the emerging discussion of tocotrienol-rich fraction as a potential complementary component within cancer immunotherapy research. Although the majority of the analyzed studies focused on molecular or cellular mechanisms, several publications have explored the possibility that tocotrienols could interact with therapeutic strategies aimed at enhancing immune responses against tumor cells. In experimental models combining tocotrienol supplementation with conventional anticancer treatments, researchers have reported improvements in treatment response indicators. For instance, one animal model study reported that combining TRF supplementation with chemotherapeutic treatment produced a 20% greater reduction in tumor volume compared with chemotherapy alone [62]. Additional experimental reports describe enhanced immune signaling responses when tocotrienols were used alongside immune-related therapeutic approaches, although these findings remain preliminary and require further validation through clinical investigation. Across the 35 reviewed studies, the discussion surrounding tocotrienols in immunotherapy contexts generally emphasizes their potential role in supporting immune regulation, oxidative balance, and cellular signaling processes associated with tumor biology. The evidence suggests that tocotrienols derived from palm oil are being actively investigated within nutritional science, molecular oncology, and biomedical research. While the current literature remains largely experimental, the growing number of studies exploring tocotrienol-related mechanisms indicates continued scientific interest in understanding how these naturally occurring compounds may interact with complex biological pathways relevant to cancer treatment strategies.

Discussion

The systematic literature synthesis conducted in this study examined scientific publications investigating the biological and immunological relevance of Tocotrienol-Rich Fraction (TRF) derived from palm oil within the broader context of cancer-related research. Based on the analysis of the selected thirty-five peer-reviewed articles, several recurring thematic patterns emerged regarding the cellular responses, molecular pathways, and immune-related mechanisms associated with TRF. The discussion presented in this section addresses the two research questions formulated in the introduction by integrating and interpreting the findings reported across the reviewed literature. Rather than introducing new empirical data, the discussion interprets patterns identified from previously published studies in order to clarify how palm oil–derived tocotrienols have been positioned within contemporary biomedical research concerning cancer biology and immunotherapy.

1.1. Biological Mechanisms Associated with Tocotrienol-Rich Fraction in Cancer-Related Cellular Responses (RQ1)

The first research question focuses on identifying biological mechanisms associated with TRF that have been reported in studies examining cancer-related cellular and molecular processes. The body of literature suggests that studies on palm oil–derived tocotrienols commonly address four major mechanistic domains: oxidative stress regulation, apoptosis induction, modulation of cellular signaling pathways, and inhibition of uncontrolled cellular proliferation. These mechanisms represent central biological

processes involved in tumor development and progression and therefore form the basis of many experimental investigations examining the ability of natural compounds to act against cancer. One of the most frequently reported mechanisms in the literature involves the ability of tocotrienols to influence oxidative balance within cellular systems. Oxidative stress is recognized as a key contributor to genomic instability, DNA damage, and tumor initiation. Reactive Oxygen Species (ROS) generated during metabolic processes can accumulate and interfere with normal cellular signaling pathways, ultimately promoting carcinogenic transformation if not adequately regulated. Several experimental studies have reported that tocotrienols exhibit antioxidant properties capable of interacting with oxidative pathways by mitigating oxidative stress and strengthening the cell's endogenous antioxidant systems. Studies in cell models indicate that TRF can decrease ROS accumulation and upregulate antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, highlighting its potential in preserving redox homeostasis [63,64].

Quantitative observations reported in several laboratory investigations suggest that exposure to tocotrienol compounds may reduce oxidative stress markers by measurable proportions in experimental cancer models. For instance, some *in vitro* studies reported reductions of intracellular oxidative markers ranging from approximately 20% to 40% following treatment with tocotrienol preparations at concentrations between 10 and 50 μM. These reductions were associated with improved regulation of mitochondrial function and stabilization of cellular oxidative balance [65]. Although these findings originate primarily from controlled laboratory experiments, they illustrate how tocotrienol compounds interact with biological systems involved in cancer development.

Another major mechanism frequently discussed in the literature concerns the activation of programmed cell death in malignant cells. Programmed cell death, or apoptosis, plays a vital role in maintaining tissue equilibrium and controlling the accumulation of aberrant cells. Cancer cells frequently evade apoptosis through alterations in regulatory proteins such as Bcl-2, Bax, and caspases, thereby enabling continuous growth and proliferation. Numerous experimental studies investigating tocotrienols have examined how these compounds interact with apoptotic pathways in cancer cell models. Experimental evidence suggests that tocotrienols may influence apoptosis through mitochondrial signaling pathways. Following treatment with TRF, laboratory investigations have documented elevated pro-apoptotic protein expression alongside reduced anti-apoptotic regulator levels in various malignant cell lines. Some studies reported increases in caspase-3 activation of up to two-fold compared with untreated controls, indicating enhanced apoptotic signaling following treatment with tocotrienol compounds [66,67]. Other studies documented increased Bax/Bcl-2 ratios in breast, prostate, and colorectal cancer cell models following tocotrienol exposure, suggesting a shift toward apoptotic regulation in malignant cells [68].

In addition to apoptosis, the reviewed studies frequently examined the influence of tocotrienols on cell cycle regulation. Cancer progression is closely associated with dysregulated cell cycle control mechanisms that allow tumor cells to proliferate without normal regulatory constraints. Several experimental studies have reported that tocotrienol compounds may induce cell cycle arrest at specific checkpoints, particularly the G1 and G2/M phases of the cell cycle. Observations from laboratory studies indicate that treatment with TRF may reduce the proportion of proliferating cancer cells by approximately 30% to 50% in certain experimental models, reflecting reduced cellular replication rates following tocotrienol exposure [69,70].

These cell cycle effects have been associated with modulation of cyclin-dependent kinases and regulatory proteins such as cyclin D1, p21, and p27. Changes in the expression of these molecules have been reported in several *in vitro* studies investigating the cellular response to tocotrienols. Such findings suggest that tocotrienols may interact with molecular regulators that control the transition between different stages of the cell cycle, thereby influencing the proliferation dynamics of cancer cells [71]. The literature also emphasizes the regulation of intracellular signaling pathways, which play pivotal roles in the progression of tumors. Networks like PI3K/Akt, NF-κB, and MAPK regulate critical cellular processes, including survival, inflammatory responses, and metabolic adjustments. Dysregulation of these pathways is frequently observed in malignant cells and contributes to tumor growth and resistance to therapy. Several experimental investigations have reported that tocotrienols may interact with these signaling systems by suppressing pathway activation or altering downstream molecular responses [72]. For example, some studies observed reduced activation of NF-κB signaling following treatment with tocotrienol compounds, leading to decreased expression of inflammatory mediators and survival-related genes. In certain experimental models, reductions in NF-κB transcriptional activity of approximately 25% to 35% were reported following TRF exposure. Such observations suggest that tocotrienols may influence inflammatory signaling networks that contribute to tumor development and progression [73].

Similarly, investigations examining the PI3K/Akt pathway have reported reductions in phosphorylation activity following treatment with tocotrienols in several cancer cell models. Because the PI3K/Akt signaling cascade is critical for enhancing cellular survival and preventing apoptosis, targeting this pathway is of significant interest in oncology studies [74]. The ability of tocotrienols to influence this signaling cascade has therefore attracted considerable attention within the biomedical literature. Collectively, these mechanistic findings indicate that TRF derived from palm oil interacts with multiple cellular pathways involved in cancer biology. Rather than targeting a single molecular mechanism, tocotrienols appear to influence a network of biological processes related to oxidative balance, apoptosis regulation, and cellular proliferation. This multi-target interaction profile has contributed to increasing scientific interest in tocotrienols as biologically active compounds within

cancer-related research. Tocotrienol-Rich Fraction and Immune-Related Pathways in Cancer Immunotherapy Research (RQ2). The second research question addresses how TRF has been discussed within the scientific literature in relation to immune-related pathways and emerging perspectives in cancer immunotherapy. The rapid expansion of immunotherapy research has transformed modern oncology by highlighting the importance of immune system interactions in tumor recognition and elimination. Therapeutic strategies such as immune checkpoint inhibitors, adoptive cell therapy, and cancer vaccines aim to strengthen immune responses against malignant cells. However, the effectiveness of these therapies can be influenced by complex biological factors including tumor microenvironment conditions, inflammatory signaling, and immune suppression mechanisms. Within this evolving research landscape, several studies have explored how bioactive compounds may influence immune-related biological pathways relevant to cancer therapy [75,76]. Tocotrienols have been included in this research due to their reported interactions with inflammatory signaling, oxidative regulation, and immune-related mediators. Although most available studies remain experimental rather than clinical, the literature indicates that tocotrienols may influence immune signaling networks involved in tumor development. One important area of investigation concerns the relationship between tocotrienols and cytokine regulation. Cytokines play a fundamental role in coordinating immune responses and mediating communication between immune cells. Several experimental studies examining TRF have reported changes in cytokine expression patterns following tocotrienol exposure in laboratory models. Studies have documented that tocotrienol administration is associated with diminished pro-inflammatory cytokine levels, notably TNF-α and IL-6 [77]. Quantitative observations from experimental studies suggest that levels of inflammatory cytokines may decrease by approximately 20% to 30% in certain cellular models following tocotrienol treatment. These reductions were associated with decreased activation of inflammatory signaling pathways that contribute to tumor-promoting microenvironments [78]. Although such findings require further validation in clinical contexts, they provide insight into how tocotrienols may influence immune-related signaling systems involved in cancer progression.

Another area of research involves the interaction between tocotrienols and immune cell activity [79]. A range of immune cells, such as macrophages, dendritic cells, T lymphocytes, and natural killer cells, populate the tumor microenvironment. These immune components play essential roles in identifying abnormal cells and initiating immune responses against tumors. Some experimental studies have suggested that tocotrienol compounds may influence the activity of immune cells involved in tumor surveillance mechanisms.

For example, laboratory experiments have reported increased activation of certain immune cell markers following exposure to tocotrienols in controlled experimental conditions. Observations from these studies indicated enhanced immune signaling responses and increased production of immune-related mediators involved in antitumor responses [80]. Such findings suggest that tocotrienols may interact with immune regulatory pathways that contribute to tumor recognition and elimination. Research examining the tumor microenvironment has also explored how tocotrienols may influence interactions between cancer cells and surrounding immune cells. The tumor microenvironment is characterized by complex networks of signaling molecules, immune cells, and stromal components that collectively shape tumor progression and therapeutic responses. Some studies suggest that modulation of inflammatory signaling by tocotrienols may influence microenvironmental conditions that affect immune activity within tumor tissues [81]. These observations have led researchers to discuss the potential relevance of TRF within emerging perspectives on cancer immunotherapy. While current evidence does not suggest that tocotrienols function as standalone immunotherapeutic agents, several studies propose that they may contribute to supportive biological processes that influence immune responses during cancer treatment. The possibility that natural compounds could interact with immune pathways involved in tumor regulation has therefore become an area of ongoing scientific interest.

The synthesis of the reviewed literature indicates that tocotrienol-rich fraction derived from palm oil has been examined in numerous experimental studies investigating cellular and molecular responses related to cancer biology. The findings consistently highlight interactions between tocotrienols and key biological mechanisms including oxidative regulation, apoptosis induction, and signaling pathway modulation. These mechanisms are closely associated with processes that influence tumor development and cellular proliferation. In addition, emerging research examining immune-related pathways suggests that tocotrienols may interact with signaling networks involved in inflammation and immune regulation. Although most available studies remain preclinical in nature, the growing body of literature indicates increasing scientific interest in understanding how naturally occurring compounds may contribute to broader biological processes relevant to cancer therapy. The implications of these findings highlight the importance of continued investigation into the molecular interactions associated with tocotrienol compounds. As research exploring cancer immunotherapy continues to expand, further studies may examine how TRF interacts with immune signaling pathways in more complex biological systems. Future investigations may also explore clinical contexts in which tocotrienol-based compounds could be examined alongside established therapeutic strategies. In addition, future research could benefit from integrating experimental, translational, and clinical approaches in order to clarify the biological significance of tocotrienol-related mechanisms observed in laboratory models. Longitudinal studies, clinical trials, and advanced molecular analyses may provide deeper insights into how tocotrienol compounds interact with tumor microenvironments

and immune regulatory pathways. By exploring these mechanisms, the scientific community can better elucidate the potential impact of palm oil–derived tocotrienols on contemporary cancer research and the advancement of immunotherapeutic strategies.

Conclusion

The synthesis of the reviewed literature indicates that the Tocotrienol-Rich Fraction (TRF) derived from palm oil has been widely investigated in experimental cancer research for its interactions with cellular and molecular pathways associated with tumor development. The analyzed studies consistently report several biological mechanisms related to cancer-related cellular responses, including the regulation of oxidative stress, induction of apoptosis, modulation of cell-cycle progression, and alteration of intracellular signaling pathways that influence cellular survival and proliferation. Research indicates that tocotrienol administration can modulate oxidative stress by decreasing intracellular ROS and promoting the activity of antioxidant defense enzymes. In addition, multiple studies have reported that tocotrienols interact with mitochondrial apoptotic pathways through the regulation of proteins such as Bax, Bcl-2, and caspase enzymes, thereby supporting controlled elimination of abnormal cells in experimental cancer models. Beyond apoptotic regulation, several investigations indicate that TRF may influence cell-cycle control by modulating regulatory proteins associated with cyclin-dependent kinases and checkpoint mechanisms, particularly during the G1 and G2/M phases. These interactions have been associated with reduced proliferation of cancer cells in laboratory models. The reviewed literature also highlights that tocotrienols interact with major intracellular signaling networks involved in cancer biology, including NF-κB, PI3K/Akt, and MAPK pathways, which play central roles in inflammation, survival signaling, and metabolic regulation. Such observations suggest that TRF may influence multiple interconnected molecular processes that contribute to tumor-related cellular responses. In addition to these cellular mechanisms, the literature increasingly discusses the potential relevance of TRF in immune-related biological processes. Several experimental studies have explored how tocotrienols interact with cytokine signaling and inflammatory mediators that regulate communication between immune cells and tumor cells. Reported findings indicate that tocotrienol exposure may influence the expression of cytokines and inflammatory regulators associated with immune responses in the tumor microenvironment. These interactions are relevant because immune signaling pathways play a crucial role in tumor recognition and immune-mediated elimination of abnormal cells.

The reviewed studies also describe potential interactions between tocotrienols and immune cell activity within the tumor microenvironment. Experimental observations suggest that tocotrienol compounds may influence signaling mechanisms related to immune surveillance and cellular communication among immune cells such as macrophages, dendritic cells, and lymphocytes. Although current evidence does not indicate that TRF functions as a standalone immunotherapeutic intervention, the literature consistently positions tocotrienol-rich fraction as a biologically active compound capable of interacting with immune-related pathways associated with tumor regulation. Overall, the synthesized findings demonstrate that palm oil–derived tocotrienol-rich fraction is associated with multiple biological mechanisms relevant to cancer research, including oxidative stress modulation, apoptosis induction, regulation of cellular proliferation, and interaction with key signaling pathways. At the same time, emerging studies highlight its potential involvement in immune-related processes that shape tumor microenvironment dynamics. These observations illustrate how TRF has been examined within contemporary biomedical literature as a natural bioactive compound with potential relevance to broader discussions in cancer biology and immunotherapy research.

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None.

Conflict of Interest

None.

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