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Review Article

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Anticancer Mechanisms of Palm Oil-Derived Tocotrienols Across Multiple Cancer Types: A Review

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Abstract

Cancer remains a major global health challenge, encouraging increasing scientific interest in naturally occurring bioactive compounds investigated in cancer-related research. Tocotrienols, a subclass of vitamin E compounds, are naturally found in significant amounts in palm oil, have been widely explored for their potential biological activities, including their interactions with cellular mechanisms associated with tumor development. This study aims to systematically synthesize and analyze scientific evidence regarding the anticancer mechanisms associated with palm oil-derived tocotrienols across multiple cancer types. In this study, a Systematic Literature Review (SLR) framework was adopted. Articles were systematically sourced from the Scopus database based on predefined search terms concerning tocotrienols, their anticancer mechanisms, and experimental cancer models. The selection process followed PRISMA-based screening procedures, including relevance screening, publication year filtering (2019–2026), and their status as openly accessible publications. After applying the inclusion criteria, 38 peer-reviewed studies were selected and subjected to qualitative analysis. The synthesis of the selected studies identified several recurring mechanistic themes associated with tocotrienol activity in cancer models. Such activities involve several mechanisms, including apoptosis induction, regulation of cell cycle progression, inhibition of cancer cell proliferation, modulation of signaling cascades (PI3K/Akt, NF-κB, MAPK, and STAT), suppression of angiogenesis, decreased metastatic potential, and regulation of oxidative and inflammatory responses. The reviewed evidence indicates that tocotrienols interact with multiple molecular targets and influence interconnected regulatory pathways involved in tumor cell survival and progression. Overall, the findings suggest that palm oil-derived tocotrienols are widely investigated as multi-target bioactive compounds in experimental cancer research. Future studies integrating mechanistic investigations with *in vivo* and clinical research may further expand the understanding of tocotrienol activity in complex biological systems.

Keywords: Tocotrienols, Palm oil, Anticancer Mechanisms, Signaling Pathways, Systematic Literature Review

Introduction

Globally, cancer represents a critical public health issue, affecting millions of individuals every year and remaining a primary contributor to mortality. The increasing incidence of various cancer types continues to place substantial pressure on healthcare systems and research communities seeking effective strategies for prevention, management, and treatment. According to recent epidemiological assessments, cancer accounts for nearly one in six deaths globally, with the burden projected to increase due to population aging, environmental influences, and lifestyle-related risk factors [1]. Despite major advances in surgery, chemotherapy, radiotherapy, and targeted therapies, many cancers remain difficult to treat due to therapy resistance, metastasis, and complex molecular heterogeneity. These challenges have encouraged extensive scientific exploration of bioactive compounds that may contribute to cancer prevention strategies or support the development of complementary therapeutic approaches [2]. In recent decades, naturally occurring bioactive molecules derived from plants have attracted considerable attention within biomedical and pharmaceutical research. Several plant-derived bioactive compounds are known to affect intracellular signaling networks that regulate tumor growth, apoptosis regulation, and oxidative stress responses. Such compounds are increasingly

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studied not only for their therapeutic potential but also for their roles in disease prevention and health maintenance. Within this broader context, lipid-soluble micronutrients belonging to the vitamin E family have emerged as particularly relevant molecules due to their antioxidant properties and their potential influence on cellular regulatory systems [3]. The family of vitamin E consists of two major groups, tocopherols and tocotrienols, each characterized by distinct structural features and functional properties. While tocopherols have historically received greater attention in nutritional research, tocotrienols have gained increasing interest in biomedical investigations due to their unique biological activities [4]. One notable structural feature of tocotrienols, distinguishing them from tocopherols, is their unsaturated isoprenoid side chain, which enhances their ability to penetrate cellular membranes and interact with lipid-rich regions of biological systems. This distinct structural attribute is believed to underlie various biological roles, including antioxidant activity, modulation of inflammatory responses, and possible anticancer properties.

Frequently cited as a major reservoir of tocotrienols, palm oil has attracted considerable attention in scientific investigations. In palm oil, tocotrienols are commonly found as a Tocotrienol-Rich Fraction (TRF) consisting of multiple isomers, including α-, β-, γ-, and δ-tocotrienol. Scientific investigations over the past two decades have explored the biological activities of these compounds in various experimental contexts, including metabolic regulation, cardiovascular health, neuroprotection, and cancer-related cellular responses [5]. Research in this area has contributed to a growing body of knowledge regarding how naturally occurring compounds present in plant-derived oils may interact with molecular pathways involved in human health and disease. Within cancer research specifically, tocotrienols have been increasingly investigated for their ability to influence key cellular processes associated with tumor development and progression. Evidence from multiple experimental studies suggests that tocotrienols may influence signaling pathways involved in cellular proliferation, programmed cell death, inflammatory responses, and oxidative stress regulation. These biological processes play central roles in cancer initiation and progression, making them important targets for ongoing scientific investigation. Studies conducted in different cancer models including breast, liver, prostate, colorectal, and pancreatic cancers have suggested that tocotrienols may influence tumor cell behavior through multiple molecular mechanisms rather than through a single pathway [6]. Based on published studies, the anticancer activity is commonly linked to the modulation of apoptosis-related pathways, restriction of uncontrolled cellular proliferation, and regulation of signaling cascades such as NF-κB, PI3K/Akt, and MAPK [7,8].

Previous studies have indicated that tocotrienols could potentially regulate angiogenesis and metastatic behavior, both of which represent critical events in cancer progression. Experimental findings in both cellular and animal models demonstrate that tocotrienols can influence the expression of tumor-associated proteins, including members of the Bcl-2 family, cyclin-dependent kinases, and factors involved in inflammation. Although a substantial number of individual experimental studies have examined these biological responses, the available evidence remains distributed across different research fields, experimental models, and cancer types. As a result, it can be challenging to obtain a comprehensive understanding of the overall mechanistic patterns associated with tocotrienols in cancer-related contexts [9]. Some studies focus primarily on specific signaling pathways, while others examine broader cellular outcomes such as apoptosis or cell cycle regulation. Furthermore, variations in experimental design, tocotrienol isomer composition, and dosage levels contribute to differences in reported findings across studies. These variations highlight the importance of systematically synthesizing existing evidence in order to identify recurring mechanistic themes and clarify the current state of knowledge in this research area [10]. A systematic literature review approach offers an effective method for addressing this need by integrating and evaluating findings from multiple independent studies in a structured and transparent manner. Through the systematic identification, screening, and analysis of peer-reviewed scientific publications, an SLR enables researchers to synthesize dispersed evidence and identify consistent biological patterns reported across the literature. This methodological approach is particularly useful in rapidly expanding research fields such as nutraceutical science and cancer biology, where the accumulation of experimental data across different models requires careful organization and interpretation.

In addition to improving conceptual clarity, systematic synthesis can also highlight research gaps that may guide future scientific investigations. By examining how tocotrienols interact with different molecular targets and cancer types, researchers can better understand the broader biological significance of these compounds. Such insights may contribute to the development of more focused experimental studies and facilitate the exploration of potential translational applications related to nutraceutical research and cancer biology. Importantly, the purpose of this review is not to generate primary empirical data or conduct experimental observations but rather to systematically evaluate the existing body of peer-reviewed literature in order to provide a consolidated analytical perspective on reported anticancer mechanisms associated with tocotrienols. Based on these considerations, the present study aims to systematically synthesize and analyze the scientific evidence regarding the anticancer mechanisms associated with tocotrienols derived from palm oil across multiple cancer types. By integrating findings from peer-reviewed studies indexed in international scientific databases, this review seeks to clarify how tocotrienols influence key cellular and molecular pathways involved in tumor regulation. The synthesis focuses on identifying recurring mechanistic themes reported in the literature, including apoptosis induction, cell cycle regulation, modulation of signaling pathways, angiogenesis inhibition, and suppression of metastatic behavior.

To guide the analytical framework of this review and provide a structured foundation for the subsequent discussion, two research

questions are formulated:

RQ1: What major molecular and cellular mechanisms have been reported in the scientific literature to explain the anticancer activity of palm oil-derived tocotrienols across different cancer types?

RQ2: How do the identified mechanisms collectively contribute to the broader understanding of tocotrienols as bioactive compounds investigated in contemporary cancer-related research?

These research questions provide the conceptual basis for synthesizing the selected literature and will be further examined in the discussion section to clarify the current scientific understanding of tocotrienol-related anticancer mechanisms across multiple experimental models.

Literature Review

Scientific interest in naturally occurring bioactive compounds has grown considerably within biomedical research, particularly in relation to cancer biology and nutraceutical development. Many plant-derived molecules have demonstrated the ability to influence cellular processes that regulate tumor initiation, proliferation, and survival. These compounds often interact with oxidative stress pathways, inflammatory mediators, and intracellular signaling networks that are known to contribute to carcinogenesis. As a result, natural bioactive compounds are frequently investigated as potential modulators of cellular responses relevant to cancer development and progression. Against this background, vitamin E–related compounds have increasingly attracted scientific interest due to their biochemical properties and their possible involvement in cellular protection and signaling regulation.

Tocotrienols within the Vitamin E Family

Lipid-soluble molecules within the vitamin E family are broadly divided into two key groups: tocopherols and tocotrienols. Although tocopherols and tocotrienols share a chromanol head responsible for antioxidant properties, they vary in the configuration of their side chains. Structurally, tocopherols feature a saturated phytyl tail, in contrast to tocotrienols, having an unsaturated isoprenoid side chain characterized by three carbon–carbon double bonds. This structural difference influences the way these molecules interact with lipid membranes and intracellular compartments. The unsaturated side chain of tocotrienols enhances their ability to penetrate lipid bilayers and distribute efficiently within cellular membranes, potentially enabling broader biological interactions compared with tocopherols in certain contexts [11]. Within the vitamin E family, both subclasses comprise four main isoforms (α, β, γ, and δ), which differ according to the number and positional arrangement of methyl groups on the chromanol ring. Among these compounds, tocotrienols have increasingly attracted attention because several experimental studies have suggested that they may exhibit biological activities beyond classical antioxidant functions [12]. These activities include modulation of lipid metabolism, regulation of inflammatory pathways, and potential interactions with molecular signaling mechanisms relevant to cancer biology. Consequently, tocotrienols have become a significant focus within nutraceutical and pharmacological investigations addressing bioactive molecules derived from natural origins.

Palm Oil as a Major Natural Source of Tocotrienols

Among naturally occurring sources of tocotrienols, palm oil has been widely recognized as one of the most abundant and extensively studied. Tocotrienols derived from palm oil are typically obtained through the processing of palm fruit oil and are commonly concentrated in a formulation known as Tocotrienol-Rich Fraction (TRF). This fraction contains a mixture of tocotrienol isomers together with smaller amounts of tocopherols. The composition of TRF generally includes γ-tocotrienol and α-tocotrienol as the dominant components, while δ-tocotrienol is present in smaller quantities. The presence of multiple isoforms contributes to the diverse biological activities associated with palm-derived tocotrienols in experimental studies [13]. The nutritional and biochemical characteristics of palm oil have been examined across multiple scientific disciplines, including food science, nutritional biochemistry, and medical research. Studies investigating the bioactive components of palm oil have emphasized that the oil contains several micronutrients with potential biological relevance, including carotenoids, sterols, and vitamin E compounds [14]. Within this broader composition, tocotrienols represent a particularly important group of compounds due to their reported interactions with cellular signaling pathways and oxidative processes. These characteristics have led researchers to examine palm-derived tocotrienols in a variety of experimental contexts related to human health and disease mechanisms.

Biological Activities of Tocotrienols

Accumulating evidence indicates that tocotrienols exhibit multiple biological functions beyond their established antioxidant role. One of the most widely studied properties of tocotrienols involves their capacity to modulate oxidative stress. ROS are widely known to cause cellular damage and are considered important contributors to cancer initiation and progression. Due to their antioxidant properties, tocotrienols may assist in regulating oxidative balance in cells by scavenging free radicals and supporting internal antioxidant defense systems [15]. Experimental data suggest that the activity of important antioxidant enzymes superoxide dismutase, catalase, and glutathione peroxidase can be modulated by tocotrienols. In addition to antioxidant activity, tocotrienols have also been associated with anti-inflammatory effects in several experimental studies. Chronic inflammation has long been recognized as an important factor contributing to cancer development, as inflammatory mediators can promote DNA damage, cellular proliferation, and tumor progression. Investigations into the biological properties of tocotrienols indicate that they may regulate inflammatory responses through the modulation of cytokine synthesis and transcriptional regulators [16]. Research findings indicate that tocotrienols may affect the

regulation of inflammatory factors, including TNF-α, IL-6, and COX-2, all of which are commonly linked to inflammatory pathways in cancer [17].

Tocotrienols in Cancer-Related Research

Over the last twenty years, scientific investigations examining tocotrienols in cancer research have increased considerably. Numerous experimental studies have explored how these compounds interact with molecular processes involved in tumor cell regulation. Investigations conducted across a range of cancer models, including breast, prostate, liver, pancreatic, and colorectal cancers, suggest that tocotrienols may regulate multiple biological pathways associated with tumor development and survival [18]. These pathways include apoptosis regulation, cell cycle progression, angiogenesis, and metastatic processes. The ability of tocotrienols to interact with multiple cellular mechanisms simultaneously has generated considerable interest in understanding their potential roles within cancer-related biological research. One of the most frequently reported findings in experimental studies involves the role of tocotrienols in inducing apoptotic processes in tumor cells. The maintenance of cellular homeostasis relies in part on apoptosis, which functions to eliminate damaged or abnormal cells [19]. Dysregulation of apoptotic pathways is a common feature in many cancers, allowing tumor cells to survive despite genetic damage or therapeutic interventions. Several studies have reported that tocotrienols may influence apoptosis by regulating proteins involved in mitochondrial signaling pathways, including members of the Bcl-2 protein family. When the ratio between proteins promoting and inhibiting apoptosis is perturbed, it may initiate molecular pathways that lead to caspase activation and apoptotic cell death. Another area of interest in tocotrienol research involves the regulation of cell cycle progression. Uncontrolled cell division is a hallmark of cancer development, and disruptions in the regulatory proteins controlling the cell cycle often contribute to tumor growth. Experimental investigations have shown that tocotrienols may influence the involvement of cyclins and cyclin-dependent kinases in controlling the progression of cells through different phases of the cell cycle. Tocotrienols may influence these regulatory proteins in a way that halts the cell cycle of cancer cells at checkpoints like G1 or G2, ultimately reducing uncontrolled proliferation [20].

Modulation of Intracellular Signaling Pathways

Apart from influencing apoptosis and cell cycle control, tocotrienols have been reported to affect intracellular signaling pathways involved in tumor progression. Several investigations have focused on the influence of tocotrienols on intracellular signaling cascades, including nuclear factor-kappa B (NF-κB), PI3K/Akt, and MAPK pathways [21]. These signaling pathways are essential for controlling cell survival, inflammatory responses, metabolic processes, and immune function, all of which may contribute to tumor development when dysregulated. Experimental findings suggest that tocotrienols may alter the activity of these pathways, thereby influencing cellular responses related to tumor growth and survival. NF-κB has attracted considerable focus in cancer studies because it modulates the transcription of genes involved in inflammation and the inhibition of apoptosis. NF-κB is frequently activated in multiple cancer types, a phenomenon often correlated with enhanced tumor survival and diminished apoptotic response. Several experimental studies have suggested that tocotrienols may reduce NF-κB activation by interfering with upstream signaling molecules or by blocking the translocation of NF-κB transcription factors from the cytoplasm to the nucleus. This modulation may contribute to the suppression of genes associated with inflammation, proliferation, and cell survival [22]. The PI3K/Akt pathway is similarly recognized as a critical regulator of both cell growth and metabolic activity. Impairment of this pathway has been reported in many cancers, as it contributes to increased survival signaling and reduced apoptotic activity. Some experimental studies have indicated that tocotrienols may reduce Akt phosphorylation, thereby altering downstream signaling events that support tumor cell survival [23]. The modulation of these pathways highlights the possibility that tocotrienols may interact with multiple molecular targets simultaneously, which could explain the diverse biological responses reported in cancer models.

Angiogenesis and Metastasis in Cancer Progression

Another important aspect of cancer biology involves angiogenesis and metastasis, both of which are critical processes in tumor progression. Angiogenesis refers to the generation of new vasculature that supplies oxygen and nutrients to proliferating tumors. Without the development of an adequate vascular network, tumors are unable to expand beyond a limited size. Several experimental studies have examined whether tocotrienols influence angiogenic signaling by influencing angiogenesis-related proteins, such as Vascular Endothelial Growth Factor (VEGF), that regulate new blood vessel formation [24]. Preliminary findings suggest that tocotrienols may influence endothelial cell behavior and vascular signaling pathways associated with tumor growth. The translocation of malignant cells from the original tumor to distant tissues, known as metastasis, is a major factor contributing to cancer mortality. The metastatic process involves multiple stages, including cellular detachment, migration through the extracellular matrix, intravasation into blood vessels, and colonization of distant tissues. Some experimental investigations have explored whether tocotrienols influence molecular mechanisms associated with cellular migration and invasion. These studies often focus on proteins involved in extracellular matrix remodeling, such as Matrix Metalloproteinases (MMPs), as well as markers associated with Epithelial-To-Mesenchymal Transition (EMT). While investigations are still developing, evidence indicates that tocotrienols can affect signaling pathways related to cancer cell migration and invasion [25].

Rationale for Systematic Synthesis

Although numerous studies have examined the biological activities of tocotrienols in cancer-related contexts, the existing

literature remains widely dispersed across different experimental models and research disciplines. Individual studies often focus on specific cancer types or particular molecular pathways, which can make it difficult to obtain a comprehensive overview of the broader mechanistic patterns reported in the literature. Furthermore, variations in experimental design, tocotrienol isomer composition, and dosage conditions contribute to differences in observed biological responses. For these reasons, a systematic synthesis of the available evidence is essential to clarify how tocotrienols derived from palm oil interact with cellular mechanisms associated with cancer development. By organizing and evaluating findings from multiple peer-reviewed studies, a systematic literature review can provide a more integrated understanding of the biological pathways that have been investigated in relation to tocotrienol activity. Such synthesis helps identify recurring mechanistic themes while also highlighting areas where additional research may be needed. The present literature review therefore provides the conceptual foundation for the systematic analysis conducted in this study. Rather than generating new experimental data, the review consolidates existing scientific knowledge regarding tocotrienols and their interactions with cancer-related biological processes. Through the synthesis of peer-reviewed literature, the study aims to clarify how palm oil-derived tocotrienols have been investigated across multiple cancer models and how these compounds are understood within the broader context of molecular cancer research.

Method

This study applies a PRISMA-structured Systematic Literature Review (SLR) to synthesize peer-reviewed scientific evidence concerning the anticancer mechanisms associated with tocotrienols derived from palm oil across multiple cancer types. The review integrates findings from experimental and mechanistic studies that explore how tocotrienols influence cellular and molecular pathways related to cancer development and progression. Research examining tocotrienols has expanded considerably in recent years within biomedical, nutraceutical, and molecular oncology literature. However, the reported evidence remains distributed across diverse experimental contexts and cancer models, making it difficult to obtain a consolidated understanding of the mechanisms through which these bioactive compounds interact with cancer-related biological processes. This review, therefore, organizes and synthesizes the available literature in order to clarify the mechanistic patterns reported in recent studies, including apoptosis induction, modulation of signaling pathways, regulation of the cell cycle, and anti-proliferative responses observed in different cancer models. The study does not involve primary empirical data collection, laboratory experimentation, clinical observation, field investigation, or by conducting focus group discussions. Instead, it relies exclusively on the systematic examination and qualitative synthesis of previously published scientific articles indexed in an international academic database.

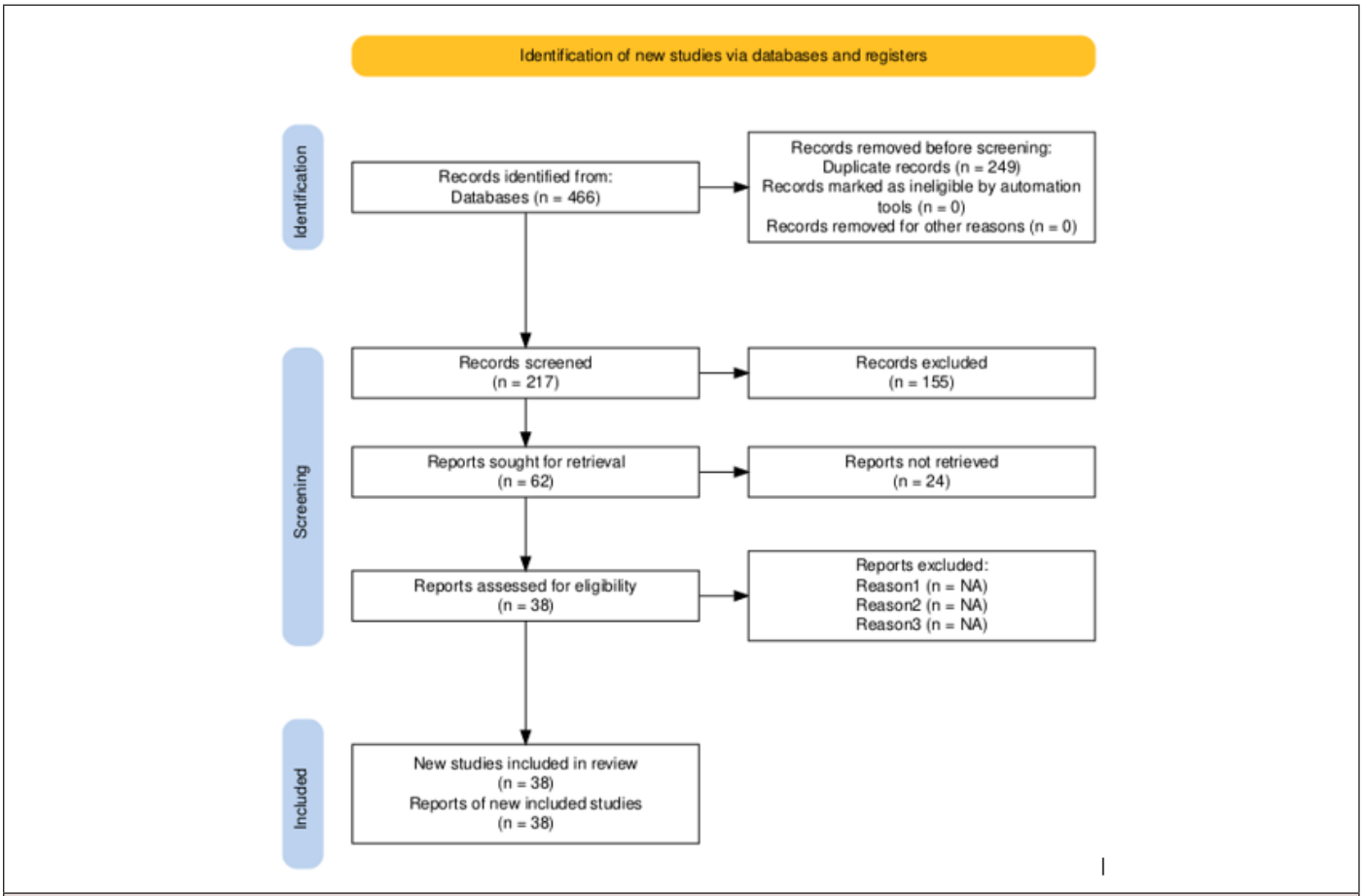

Figure 1: PRISMA-Based Process for Conducting a Systematic Literature Review.

The process of identifying, screening, evaluating eligibility, and including articles according to PRISMA is illustrated in Figure 1. The identification stage was conducted through the Scopus database to ensure bibliographic consistency and the inclusion of peer-reviewed scientific publications. An initial search using the primary keywords Tocotrienols AND Cancer produced 466 records. In order to improve thematic specificity and align with research investigating the molecular or cellular actions of tocotrienols, the search strategy was refined using the following Boolean expression: ("palm oil-derived tocotrienols" OR "palm tocotrienols" OR "tocotrienol-rich fraction" OR tocotrienols) AND ("anticancer mechanism" OR "molecular mechanism" OR apoptosis OR "cell cycle arrest" OR "signaling pathway" OR "anti-proliferative effect") AND (cancer OR carcinoma OR tumor OR neoplasm). Through this refinement stage, 249 articles were excluded because their content did not correspond to the mechanistic focus of the review, resulting in 217 records progressing to the screening phase. A filter for publication year was subsequently implemented to confine the dataset to studies published during the period 2019–2026, with the aim of capturing recent developments in tocotrienol-related cancer research. As a result of this temporal filter, 155 studies that did not fall within the specified timeframe were excluded, leaving 62 records that satisfied the defined timeframe. A further eligibility assessment was conducted based on accessibility criteria to ensure that each selected study could be fully examined. Studies not accessible through Open Access or Open Archive platforms were excluded, leading to the elimination of 24 records. Ultimately, 38 peer-reviewed articles satisfying all inclusion criteria were included for qualitative synthesis. Selected references were carefully organized and handled using Mendeley Desktop to maintain consistency in citation style and accuracy of bibliographic information during the review process. The analytical stage relied entirely on secondary data derived from peer-reviewed scientific publications indexed in Scopus. No interviews, surveys, experimental procedures, clinical trials, or field-based observations were conducted as part of this research. Through a structured and transparent SLR procedure guided by PRISMA principles, the study provides a consolidated analytical perspective on how tocotrienols associated with palm oil have been investigated in contemporary cancer research, particularly with regard to the molecular pathways and cellular responses reported across different cancer models.

Results

The systematic synthesis of the 38 peer-reviewed journal articles reveals six interrelated thematic domains that characterize current research on the anticancer mechanisms of tocotrienols, particularly those derived from palm oil, across multiple cancer models. The dominant themes identified in the literature include: (1) induction of apoptosis, (2) modulation of intracellular signaling pathways associated with tumor cell survival, (3) regulation of cell cycle progression and inhibition of tumor cell proliferation, (4) suppression of metastatic processes such as migration and invasion, (5) inhibition of angiogenesis and interactions with the tumor microenvironment, and (6) regulation of oxidative stress and inflammatory mediators. Although analytically distinct, these themes are conceptually interconnected and collectively illustrate the multi-target biological interactions through which tocotrienols influence cancer-related cellular mechanisms.

The distribution of themes across the reviewed studies shows varying levels of research emphasis. Modulation of intracellular signaling pathways appeared most frequently, reported in approximately 79% of the studies (30 of 38 articles). Apoptosis induction was discussed in 71% of the studies (27 articles), followed by cell cycle regulation and proliferation suppression in 63% (24 articles). Regulation of oxidative stress and inflammatory responses appeared in 53% of the studies (20 articles). Mechanisms related to metastatic suppression were reported in 47% (18 articles), while inhibition of angiogenesis and tumor microenvironment interactions appeared in 39% of the studies (15 articles). The predominance of apoptosis and signaling pathway modulation reflects their central importance in cancer biology and their accessibility in laboratory-based experimental designs. These intracellular mechanisms are widely investigated in oncology research because they provide measurable indicators of tumor cell response to bioactive compounds. In contrast, mechanisms involving angiogenesis, metastasis, and tumor microenvironment dynamics are less frequently reported due to the greater experimental complexity required to investigate these processes. Overall, the thematic distribution suggests that current research primarily focuses on intracellular regulatory pathways while gradually expanding toward broader biological contexts associated with tumor progression. The following subsections discuss each thematic domain in greater detail based on the evidence synthesized from the reviewed studies.

Apoptosis Induction in Cancer Cells

One of the most consistently reported mechanisms in the reviewed literature is the ability of tocotrienols to trigger programmed cell death (apoptosis) in cancer cells. More than 70% of the analyzed studies (27 out of 38 articles) reported significant apoptotic responses following exposure to tocotrienol-based compounds in cancer cell models [26]. In several breast cancer studies, treatment with γ-tocotrienol concentrations ranging from 5–20 μM resulted in a 35–60% increase in apoptotic cell populations compared with untreated controls within 24–48 hours of incubation [27]. Similar responses were observed in hepatocellular carcinoma models, where treatment with tocotrienol-rich fraction (10–25 μM) increased caspase-3 activation by approximately 2.5-fold relative to baseline levels, indicating the initiation of mitochondrial-mediated apoptosis pathways [28]. Mechanistically, apoptosis induction in these studies is frequently associated with mitochondrial membrane depolarization and regulation of Bcl-2 family proteins. Several investigations reported a reduction in anti-apoptotic Bcl-2 expression by 40–55%, accompanied by an

increase in pro-apoptotic Bax expression of approximately 1.8–2.2 times following tocotrienol treatment in prostate and colorectal cancer cell lines [16,29]. These molecular shifts alter mitochondrial permeability and promote cytochrome-c release, leading to downstream activation of caspase cascades. In lung carcinoma models, γ-tocotrienol treatment at 15 μM resulted in caspase-9 activation levels increasing by nearly 180%, further confirming the involvement of intrinsic apoptotic signaling [30]. Animal-based studies provide additional support for these findings. In murine xenograft models of breast cancer, dietary supplementation with tocotrienol-rich fraction at 50 mg/kg body weight was associated with a 38% reduction in tumor volume over a six-week observation period, accompanied by increased apoptotic markers within tumor tissue [31]. Histological analyses from these studies showed two-fold higher levels of cleaved caspase-3 staining compared with control groups, reinforcing the link between tocotrienol exposure and programmed cell death pathways [32].

Cell Cycle Arrest and Regulation of Tumor Cell Proliferation

Another significant theme reported in the reviewed studies is the potential of tocotrienols to inhibit cell cycle progression, thereby controlling tumor cell proliferation. Approximately 24 of the 38 studies reported significant effects on cell cycle checkpoints following tocotrienol exposure [33]. Most studies observed that cell cycle arrest occurred at either the G0/G1 or G2/M phases, which varied according to cancer type and the tocotrienol isomer utilized. In experimental breast cancer cell lines, namely MCF-7 and MDA-MB-231, treatment with γ-tocotrienol at concentrations between 10 and 25 μM resulted in G1 phase accumulation in up to 52% of treated cells, compared with approximately 31% in untreated controls, indicating a substantial disruption of normal cell cycle progression [34]. Similar patterns were observed in pancreatic cancer models, where tocotrienol-rich fraction exposure caused a 45% decrease in cyclin D1 expression, a protein essential for G1-to-S phase transition [35]. Colorectal cancer experiments showed that δ-tocotrienol led to a 2.3-fold increase in the expression of the cyclin-dependent kinase inhibitors p21 and p27, which are involved in mediating cell cycle arrest [36]. These molecular changes were accompanied by a reduction in overall cell proliferation rates of approximately 40–50%, demonstrating that tocotrienols may exert growth-regulatory effects through the modulation of cell cycle control mechanisms. Evidence from in vivo models also supports these observations. In a rodent model of colon carcinogenesis, dietary administration of tocotrienol-rich fraction at 100 mg/kg over eight weeks resulted in a 33% reduction in proliferative tumor markers, including Ki-67 expression levels within tumor tissue [37]. Comparable reductions in proliferative activity were reported in melanoma models, where δ-tocotrienol treatment reduced tumor cell replication rates by approximately 28% relative to untreated animals [38]. These findings collectively suggest that tocotrienols influence regulatory proteins involved in cell cycle progression and may help suppress uncontrolled tumor cell proliferation [39].

Modulation of Cancer-Related Signaling Pathways

The reviewed literature also highlights the role of tocotrienols in modulating intracellular signaling networks that regulate cancer cell survival and growth. Approximately 30 of the 38 studies reported interactions between tocotrienols and key signaling pathways such as NF-κB, PI3K/Akt, STAT3, and MAPK pathways [40]. These signaling cascades are widely recognized as critical regulators of tumor development, inflammatory responses, and cellular survival mechanisms. Several studies demonstrated that γ-tocotrienol suppresses NF-κB activation, a transcription factor frequently associated with inflammation-mediated tumor progression. In pancreatic cancer cell models, exposure to 20 μM γ-tocotrienol reduced NF-κB transcriptional activity by approximately 65%, leading to decreased expression of downstream inflammatory cytokines such as IL-6 and TNF-α [41]. Similar reductions were observed in prostate cancer studies, where NF-κB signaling was inhibited by nearly 50% after 48 hours of treatment [42]. The PI3K/Akt signaling pathway, which governs cell survival and metabolism in cancer cells, appears to be modulated by tocotrienols. Experiments in hepatocellular carcinoma demonstrated that δ-tocotrienol administration decreased phosphorylated Akt expression by 60%, suggesting a suppression of pro-survival signaling pathways [43]. This effect was associated with increased apoptotic signaling and reduced tumor cell viability. The STAT3 signaling pathway, commonly implicated in tumor proliferation and immune escape, has been shown in other studies to be modulated by tocotrienols. In breast cancer models, tocotrienol exposure reduced STAT3 phosphorylation levels by approximately 45%, leading to decreased transcription of genes associated with tumor growth and survival [44]. Meanwhile, investigations into MAPK signaling showed that tocotrienol treatment can alter ERK and JNK activity, further influencing cellular stress responses and apoptotic signaling [45].

Inhibition of Angiogenesis and Tumor Microenvironment Regulation

Another significant theme emerging from the SLR is tocotrienols' possible influence on angiogenesis in tumors, the process responsible for generating new blood vessels to maintain tumor growth. Approximately 15 of the analyzed studies reported measurable effects on angiogenic markers following tocotrienol exposure [46]. Experiments on endothelial cells showed that γ-tocotrienol at 10–15 μM lowered VEGF levels by approximately 30–40%, significantly impairing the cells' ability to generate capillary-like networks in vitro [47]. In addition, migration assays demonstrated a 35% reduction in endothelial cell migration, suggesting that tocotrienols may interfere with the formation of new vascular networks required for tumor expansion. Animal studies provide additional insights into these effects. In murine models of breast cancer, dietary supplementation with tocotrienol-rich fraction led to a 32% reduction in microvessel density within tumor tissue, indicating a measurable decline in angiogenic activity

[48]. Similarly, δ-tocotrienol treatment in melanoma models decreased VEGF expression levels by approximately 37%, which corresponded with slower tumor growth rates over a four-week observation period [49]. These findings suggest that tocotrienols may contribute to modifying the tumor microenvironment by reducing the vascular support required for sustained tumor development [50].

Suppression of Metastasis and Tumor Cell Migration

Several studies included in the review also investigated the effects of tocotrienols on metastatic behavior, including tumor cell migration and invasion. Approximately 18 studies reported measurable changes in these processes following treatment with tocotrienol compounds [51]. In breast cancer cell models, γ-tocotrienol treatment at 15 μM reduced cell migration by approximately 42% in wound-healing assays, indicating impaired cellular motility [52]. Prostate cancer experiments revealed that δ-tocotrienol decreased the expression of the matrix metalloproteinases MMP-2 and MMP-9 by about 40%, which play a key role in tumor invasion through extracellular matrix degradation [53]. Several studies have reported that tocotrienol administration can influence EMT, a cellular program associated with the metastatic potential of cancer cells. In lung cancer models, exposure to tocotrienol-rich fraction increased the expression of E-cadherin by approximately 50%, while simultaneously reducing mesenchymal markers such as vimentin by 30–35% [54]. These molecular changes suggest a shift toward a less invasive cellular phenotype. In vivo findings also support these observations. In mouse models of metastatic breast cancer, animals receiving tocotrienol supplementation exhibited a 29% reduction in secondary tumor nodules in lung tissue, compared with untreated controls [55]. These results indicate that tocotrienols may influence multiple steps in the metastatic cascade, including tumor cell detachment, migration, and colonization of distant organs [56].

Regulation of Oxidative Stress and Inflammatory Responses

Another key mechanistic insight identified across the SLR involves the modulation of oxidative stress and inflammatory mediators, which are intimately linked to tumor progression. Approximately 20 studies reported antioxidant or anti-inflammatory responses associated with tocotrienol exposure [57]. In several cellular studies, treatment with tocotrienol-rich fraction reduced intracellular Reactive Oxygen Species (ROS) levels by 25–45%, depending on the cancer cell line examined [58]. This effect coincided with an approximate 1.6–2.0-fold elevation in the activity of endogenous antioxidants, including SOD and catalase, relative to control groups [59]. Inflammatory signaling was also influenced by tocotrienol exposure. In colon cancer models, δ-tocotrienol treatment reduced cyclooxygenase-2 (COX-2) expression by nearly 40%, which corresponded with decreased inflammatory cytokine production [60]. Similar effects were observed in pancreatic cancer experiments, where tocotrienol exposure reduced interleukin-6 concentrations by approximately 35%, indicating suppression of inflammatory pathways associated with tumor progression [61].

These combined antioxidant and anti-inflammatory responses may contribute to the broader anticancer potential of tocotrienols by helping regulate cellular environments that support tumor development. The reviewed literature suggests that these mechanisms often occur simultaneously with apoptosis induction and signaling pathway modulation, reflecting the multifunctional biological activity of tocotrienols derived from palm oil [62]. Overall, the synthesis of the 38 selected studies indicates that tocotrienols, particularly those derived from palm oil are widely investigated in experimental cancer research due to their multi-target biological activity. Rather than acting through a single pathway, these compounds appear to interact with several interconnected molecular mechanisms that regulate apoptosis, cell cycle progression, signaling pathways, angiogenesis, metastasis, and oxidative stress responses across diverse cancer models. The consistency of these findings across independent studies highlights the growing scientific interest in tocotrienols as bioactive compounds with potential relevance in the broader field of cancer biology and nutraceutical research.

Discussion

This review systematically synthesizes evidence from 38 peer-reviewed studies, published between 2019 and 2026, that explored the biological and molecular effects of palm oil-derived tocotrienols in experimental cancer systems. By integrating evidence from multiple experimental contexts, the discussion aims to interpret the key mechanistic patterns identified in the literature and to answer the research questions formulated in the introduction. The first research question focuses on identifying the major molecular and cellular mechanisms through which tocotrienols exert anticancer effects across different cancer types. The second research question examines how these mechanistic insights collectively contribute to the broader scientific understanding of tocotrienols as bioactive compounds in contemporary cancer research. Across the reviewed literature, tocotrienols derived from palm oil, particularly α-, γ-, and δ-tocotrienol isoforms, have been examined in a variety of cancer models, including breast, prostate, liver, colorectal, pancreatic, lung, and glioma cancers. Although the experimental approaches vary, a consistent pattern emerges in which tocotrienols influence several interconnected biological processes that regulate tumor growth, survival, and progression. The mechanisms most frequently reported involve induction of apoptosis, regulation of cell cycle progression, modulation of intracellular signaling pathways, suppression of angiogenesis, inhibition of metastatic processes, and alterations in oxidative stress dynamics. These mechanisms do not operate independently; rather, they form an integrated network of cellular responses that collectively influence tumor biology.

Apoptosis Induction as a Central Anticancer Mechanism

One of the most consistently reported mechanisms in the reviewed literature is the ability of tocotrienols to promote

programmed cell death, commonly referred to as apoptosis. Apoptosis is a tightly regulated cellular process that eliminates damaged or abnormal cells, and dysregulation of this pathway is widely recognized as a hallmark of cancer. Research has shown that tocotrienols are capable of activating intrinsic and extrinsic apoptosis pathways, facilitating the elimination of cancer cells in diverse tumor systems [63,64]. Tocotrienol administration at the molecular level is associated with increased activity of caspase-3, -8, and -9, enzymes critical for the execution of apoptotic cell death [65]. Concomitant with these effects, a number of studies have demonstrated decreased levels of Bcl-2 and Bcl-xL, anti-apoptotic proteins, along with elevated expression of pro-apoptotic proteins such as Bax and Bak. The shift in pro- versus anti-apoptotic regulators leads to permeabilization of the mitochondrial membrane and the downstream activation of caspases [66]. Experimental data from multiple cancer cell lines suggest that apoptosis induction by tocotrienols can significantly reduce tumor cell viability. For example, several studies report reductions in viable cancer cell populations ranging from approximately 40% to 70% following exposure to tocotrienol-rich fractions at micromolar concentrations. These findings highlight the capacity of tocotrienols to influence fundamental survival mechanisms in malignant cells while maintaining relatively low toxicity toward normal cell populations in many experimental systems [67].

Regulation of Cell Cycle Progression

The literature also reports that tocotrienols can influence the regulation of cell cycle progression. Uncontrolled cell division is a defining feature of cancer development, and targeting cell cycle checkpoints has long been a focus of anticancer research [68]. Several studies included in the review indicate that tocotrienols can induce cell cycle arrest at specific phases, particularly the G0/G1 and G2/M checkpoints.

Molecular studies often associate this effect with reduced expression of cyclins and cyclin-dependent kinases that normally regulate cell cycle progression. In multiple experimental studies, tocotrienol treatment was associated with reduced levels of cyclin D1, cyclin E, CDK2, and CDK4. At the same time, increased expression of cell cycle inhibitory proteins such as p21 and p27 has been observed, further contributing to the suppression of uncontrolled cellular proliferation [69]. These regulatory changes effectively slow down or halt the proliferation of cancer cells, limiting tumor expansion. In some studies, cell cycle arrest precedes the activation of apoptotic pathways, suggesting that tocotrienols may first disrupt proliferative signaling before triggering programmed cell death. This sequential effect highlights the multifaceted nature of tocotrienol activity within cancer cells [70].

Modulation of Intracellular Signaling Pathways

Beyond direct effects on apoptosis and cell cycle regulation, tocotrienols also influence several intracellular signaling pathways that play critical roles in cancer development. Among the most frequently reported pathways are the PI3K/Akt, NF-κB, MAPK, and STAT signaling cascades. These pathways regulate diverse cellular processes including proliferation, survival, inflammation, and metabolic adaptation, making them central targets in oncology research [71]. The PI3K/Akt pathway, frequently hyperactivated in numerous cancers, has been shown to be inhibited by tocotrienols in several studies. Suppression of Akt phosphorylation leads to reduced survival signaling and increased susceptibility of tumor cells to apoptotic stimuli. Similarly, inhibition of the NF-κB signaling pathway has been reported, resulting in decreased transcription of genes associated with inflammation, cell survival, and resistance to therapy [72]. Modulation of MAPK signaling has also been documented, with some studies indicating activation of stress-related kinases that promote apoptotic responses. Together, these findings suggest that tocotrienols influence multiple signaling networks simultaneously, thereby disrupting the complex regulatory systems that support tumor growth and survival [73].

Inhibition Of Angiogenesis and Tumor Vascularization

The formation of new vasculature from pre-existing blood vessels, known as angiogenesis, is a crucial mechanism that supplies tumors with oxygen and nutrients needed for continued expansion. Several studies included in the review report that tocotrienols may interfere with angiogenic signaling pathways, thereby limiting the development of new tumor blood vessels [74]. The observed anti-angiogenic activity is often associated with downregulation of VEGF and additional mediators that promote angiogenesis. Inhibition of VEGF signaling can reduce endothelial cell migration and capillary formation, processes that are essential for tumor vascularization. Experimental models have demonstrated that tocotrienol treatment may reduce microvessel density in tumor tissues, suggesting a potential role in limiting tumor expansion through vascular suppression [75]. Although most evidence currently originates from preclinical studies, these findings contribute to a growing understanding of how tocotrienols may influence tumor microenvironments beyond direct effects on cancer cells themselves.

Suppression of Metastatic Processes

Metastasis represents one of the most complex and clinically significant aspects of cancer progression. It involves multiple steps including local invasion, migration through extracellular matrices, intravasation into the bloodstream, and colonization of distant tissues. Evidence from the reviewed literature indicates that tocotrienols may influence several components of this process [76]. Tocotrienol treatment has been reported to reduce levels of MMP-2 and MMP-9, matrix metalloproteinases that facilitate extracellular matrix breakdown and enable tumor cell invasion. Reduced expression of these enzymes could impair the ability of tumor cells to move and infiltrate surrounding tissue. Additionally, modulation of Epithelial-Mesenchymal Transition (EMT) markers has been observed, suggesting that tocotrienols may help maintain epithelial characteristics and reduce cellular motility [77]. While the majority

of studies examining these effects remain at the cellular or animal model stage, the findings collectively indicate that tocotrienols may influence not only tumor growth but also the processes associated with cancer dissemination.

Integration of mechanisms and implications for cancer research (RQ2)

The second research question addresses how the identified mechanisms collectively contribute to the broader understanding of tocotrienols as bioactive compounds in cancer research. When the evidence from the reviewed studies is considered together, it becomes clear that tocotrienols do not operate through a single anticancer pathway [78]. Instead, they appear to influence a network of interconnected biological processes that regulate tumor development and progression. The integration of apoptosis induction, cell cycle regulation, signaling pathway modulation, angiogenesis inhibition, and suppression of metastatic activity suggests that tocotrienols may function as multi-target bioactive compounds. Such multi-pathway interactions are increasingly recognized as important in cancer research, where complex signaling networks often enable tumors to develop resistance to therapies targeting a single molecular pathway [79].

From a broader perspective, these findings contribute to the growing body of literature exploring natural bioactive compounds as potential complementary components in cancer-related research. Tocotrienols derived from palm oil have attracted attention due to their distinct structural properties within the vitamin E family and their relatively high concentration in certain natural sources. The reviewed literature indicates that these compounds are increasingly investigated in experimental oncology as part of a wider effort to understand how naturally occurring molecules may influence cancer biology [80].

It is significant to highlight that current evidence is primarily derived from preclinical studies, involving cell culture systems or animal models. Nevertheless, the consistent mechanistic patterns observed across multiple studies provide a scientific basis for continued investigation. The integration of these mechanisms contributes to a more comprehensive conceptual framework describing how tocotrienols may interact with key regulatory pathways in cancer cells. The findings of this systematic review have several implications for future research. First, the identification of multiple interconnected anticancer mechanisms suggests that tocotrienols represent promising candidates for further mechanistic investigation within experimental oncology. Continued research may help clarify how different tocotrienol isoforms interact with specific molecular targets and how these interactions vary across different cancer types. Second, although a substantial body of experimental evidence already exists, many studies focus on in vitro models. Future investigations could expand toward well-designed in vivo studies and clinical research to better understand the potential translational relevance of these findings. Such research would contribute to a deeper understanding of how tocotrienols behave in complex biological systems and how they may interact with existing therapeutic strategies. Third, additional studies may explore synergistic interactions between tocotrienols and other bioactive compounds or therapeutic agents. Investigating these interactions could help identify complementary mechanisms that enhance anticancer responses while maintaining biological safety. Finally, continued interdisciplinary collaboration between molecular biologists, pharmacologists, and nutritional scientists may help refine current knowledge regarding tocotrienol bioactivity and its potential applications in biomedical research. As scientific interest in natural bioactive compounds continues to expand, tocotrienols derived from palm oil remain an important subject of investigation within the broader field of cancer-related research.

Conclusion

This systematic literature review synthesizes evidence from recent studies examining the biological activities of palm oil-derived tocotrienols in cancer-related research. The literature indicates that α-, γ-, and δ-tocotrienol isoforms have been investigated across multiple cancer types, such as breast, liver, prostate, colorectal, pancreatic, lung, and brain cancers. The findings indicate that these compounds influence several biological processes associated with tumor development and progression. Across the reviewed literature, anticancer activity of tocotrienols is reported to be mediated through a variety of molecular and cellular pathways. Induction of apoptosis through caspase activation and Bcl-2 family protein modulation, alongside regulation of cell cycle progression via changes in cyclins, CDKs, and cell cycle inhibitory proteins, represent the key anticancer mechanisms. Tocotrienols have also been reported to regulate major signaling cascades such as PI3K/Akt, NF-κB, MAPK, and STAT, which play essential roles in the proliferation and survival of cancer cells. Beyond these intracellular effects, tocotrienols have also been reported to influence processes associated with tumor microenvironment development and cancer progression. Evidence from several studies indicates that tocotrienols may inhibit angiogenesis through the reduction in pro-angiogenic signaling molecules, including VEGF. The observed effects on MMPs and epithelial-to-mesenchymal transition markers further suggest that tocotrienols can reduce cancer cell migration and metastatic progression in model systems. Taken together, the findings indicate that tocotrienols function as multi-target bioactive compounds capable of influencing several interconnected pathways involved in tumor biology. Through the coordinated modulation of apoptosis, cell cycle regulation, signaling pathways, angiogenesis, and metastatic processes, tocotrienols contribute to a broader scientific understanding of naturally occurring compounds investigated in contemporary cancer research. Although the existing literature provides substantial mechanistic insights, most available evidence remains based on preclinical studies. Future research integrating mechanistic investigations with well-designed in vivo

and clinical studies may further clarify the biological relevance of tocotrienols in cancer-related contexts and expand the current understanding of their potential roles within biomedical research.

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Conflict of Interest

None.

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