MedCrave
Step into the World of Research

Open Access Journal of Science

Literature Review

Open Access

CrossMark

# Anticancer potential of palm oil tocotrienols: A systematic review of in vitro and in vivo studies on tumour suppression mechanisms

## Abstract

The ongoing global burden of cancer highlights the necessity of exploring bioactive agents that can interact with various therapeutic targets. Of these, tocotrienols obtained from palm oil have become a focal point of research due to their broad spectrum of biological functions. The present study is designed to systematically examine in vitro and in vivo investigations into the anticancer effects of tocotrienols derived from palm oil, with a focus on identifying the molecular and cellular processes underlying tumour suppression. A Systematic Literature Review (SLR) approach was applied in this research, adhering to a well-defined and reproducible procedure. Relevant data were sourced from Scopus using established keyword combinations, then systematically filtered according to relevance, publication range (2019–2026), and accessibility criteria, including open access and open archive availability. A total of 35 peer-reviewed studies met all inclusion criteria. Data analysis was conducted through qualitative synthesis, focusing on identifying recurring mechanistic patterns and evaluating consistency across studies. Evidence from the analysis indicates that tocotrienols display significant anticancer activity against diverse cancer types, driven by mechanisms including the induction of apoptosis, modulation of the cell cycle, suppression of angiogenesis and metastasis, and regulation of critical signalling pathways like NF-κB and PI3K/Akt. In addition, evidence suggests that tocotrienols may enhance the effectiveness of conventional anticancer therapies when used in combination approaches. In conclusion, palm oil-derived tocotrienols demonstrate consistent, multi-target anticancer mechanisms across experimental models. Future research should prioritise standardised experimental designs, isoform-specific comparisons, and translational studies to further clarify the therapeutic potential of palm oil-derived tocotrienols as complementary anticancer agents.

**Keywords:** tocotrienols, palm oil, anticancer, tumour suppression, systematic literature review

Volume 9 Issue 1 - 2026

Loso Judijanto
IPOSS Jakarta, Indonesia

**Correspondence:** Loso Judijanto, IPOSS Jakarta, Indonesia

**Received:** May 20, 2026 | **Published:** June 12, 2026

## Introduction

Globally, cancer represents a significant health burden, distinguished by uncontrolled cell division, resistance to apoptosis, and its invasive and metastatic capabilities. Recent epidemiological trends indicate a continuous increase in cancer incidence worldwide, driven by demographic shifts, environmental exposures, and lifestyle-related risk factors.[1] Despite substantial advances in diagnosis and treatment, including targeted therapy and immunotherapy, cancer continues to account for a high proportion of morbidity and mortality, highlighting the need for alternative and complementary therapeutic strategies.[2] Against this background, the investigation of bioactive compounds obtained from natural sources has intensified, given their capacity to target multiple biological pathways with generally favourable safety profiles.[3]

Derivatives of vitamin E, among natural bioactive compounds, are emerging as noteworthy candidates in cancer-focused research. The vitamin E family is divided into two major forms, tocopherols and tocotrienols, with each form comprising four isoforms: α, β, γ, and δ. While tocopherols have been extensively studied, growing evidence suggests that tocotrienols exhibit distinct and often more potent biological activities, particularly in the context of anticancer mechanisms.[4] The structural difference between tocotrienols and tocopherols, notably, tocotrienols possess an unsaturated isoprenoid side chain that supports enhanced cellular internalisation, membrane association, and biological effectiveness.[5] These characteristics enable tocotrienols to exert multifaceted effects on cancer cells, including the regulation of proliferation, apoptosis, and intracellular signalling pathways.

Palm oil serves as a major natural source of tocotrienols, particularly as the tocotrienol-rich fraction (TRF), which includes a well-balanced distribution of α-, γ-, and δ-tocotrienols accompanied by minor tocopherol content.[6] Owing to their bioavailability and compositional complexity, tocotrienols sourced from palm oil have gained recognition as a critical topic in biomedical investigation. Importantly, the utilisation of palm oil-derived compounds in scientific studies is primarily focused on their biochemical and pharmacological properties, with an emphasis on understanding their potential contributions to health-related applications in a balanced and evidence-based manner.[7]

In the last decade, a steadily increasing volume of experimental studies has evaluated the anticancer efficacy of tocotrienols across different cancer types. Findings from in vitro experiments reveal that tocotrienols can impede cancer cell proliferation, activate programmed cell death mechanisms, and interfere with essential molecular pathways driving tumour growth.[8] Complementary in vivo studies further support these findings, showing that tocotrienol administration can suppress tumour growth, reduce angiogenesis, and limit metastatic spread in animal models.[9] Overall, these results imply that tocotrienols act as multifunctional bioactive compounds capable of affecting several key characteristics of cancer.

Mechanistic studies indicate that tocotrienols can affect critical signalling networks, including NF-κB, PI3K/Akt, and MAPK, which are fundamentally involved in cell survival, inflammatory processes, and proliferation.[10] Beyond this, tocotrienols have been reported to regulate proteins involved in apoptosis, such as Bcl-2 and Bax, while also activating caspase cascades that contribute to cancer cell death. The ability to simultaneously target multiple pathways distinguishes tocotrienols from single-target therapeutic agents and highlights their potential relevance in complex diseases such as cancer.

Despite the growing volume of research, the available evidence remains fragmented across different experimental models, cancer types, and study designs. Variability in dosage, tocotrienol isoforms, and methodological approaches has resulted in a diverse range of findings, making it challenging to draw comprehensive conclusions regarding their overall efficacy and mechanisms of action.[11] Furthermore, while individual studies provide valuable insights, a systematic synthesis of evidence is necessary to identify consistent patterns, evaluate the strength of existing data, and clarify areas requiring further investigation.

In this regard, a Systematic Literature Review (SLR) provides a structured and transparent approach to integrate findings from multiple studies while minimising bias and enhancing reproducibility. Utilising standardised approaches for literature identification, screening, and analysis, SLR helps unify evidence from in vitro and in vivo studies, contributing to a more comprehensive insight into the anticancer capabilities of tocotrienols. This approach is strictly grounded in secondary data from peer-reviewed studies and does not involve primary data collection methods, including focus group discussions or field observations, ensuring adherence to established SLR protocols.

Following this rationale, the study aims to systematically review and integrate scientific evidence on the anticancer efficacy of tocotrienols from palm oil, with a focus on elucidating tumour suppression mechanisms demonstrated in in vitro and in vivo studies. The review seeks to identify dominant mechanistic patterns, quantify observed biological effects, and evaluate the consistency of findings across different experimental contexts. As a result, the study offers a more integrated perspective on the interaction between tocotrienols and key cancer-associated pathways and mechanisms.

This study is designed to (1) systematically collect and evaluate evidence from in vitro and in vivo research on the anticancer activity of palm oil–derived tocotrienols, and (2) explore the associated molecular and cellular pathways related to tumour suppression.

Based on these objectives, two research questions are formulated to guide the analysis and discussion:

RQ1: *What are the dominant biological mechanisms through which palm oil-derived tocotrienols exert anticancer effects in in vitro and in vivo models?*

RQ2: *To what extent are these anticancer effects consistent across different cancer types, experimental conditions, and tocotrienol isoforms?*

## Literature review

In this section, existing scientific evidence is consolidated to examine the biological functions and anticancer potential of tocotrienols, with a focus on palm oil–derived variants. The review is structured to progressively examine key aspects identified in the literature, including structural and functional distinctions of tocotrienols within the vitamin E family, their natural occurrence and composition in palm oil, and is reinforced by empirical results obtained from in vitro and in vivo research. The discussion further examines mechanistic aspects of tumour suppression, including apoptosis induction, control of cell cycle dynamics, inhibition of angiogenesis, and modulation of molecular signalling pathways, as well as their potential to act synergistically with existing anticancer therapies. By organising the literature along these thematic dimensions, this section provides a coherent foundation for understanding the current state of research and highlights the rationale for a systematic synthesis of evidence in this study.

### Tocotrienols within the vitamin e family: structural and functional distinctions

Comprised of lipid-soluble compounds, vitamin E includes both tocopherols and tocotrienols, with each category containing four isoforms (α, β, γ, and δ). While both classes share a chromanol ring, the defining distinction lies in the side chain structure, where tocotrienols possess an unsaturated isoprenoid tail compared to the saturated phytyl chain in tocopherols.[12] This structural variation contributes to enhanced membrane penetration, more efficient distribution within lipid bilayers, and increased interaction with intracellular targets. These physicochemical properties have been associated with improved bioactivity, particularly in modulating oxidative stress, inflammation, and cellular signalling pathways relevant to cancer biology.[13]

Accumulating studies suggest that tocotrienols outperform tocopherols in terms of biological efficacy in certain pathological conditions, especially in tumour suppression. Their unsaturated side chain facilitates rapid cellular uptake and enables more effective incorporation into phospholipid membranes, influencing membrane-dependent signalling mechanisms.[14] Additionally, tocotrienols have been shown to exhibit higher antioxidant potency under specific conditions, contributing to their ability to mitigate oxidative damage while simultaneously modulating redox-sensitive pathways involved in cancer progression.

### Palm Oil as a natural source of tocotrienols

Widely acknowledged as a rich natural source, palm oil contains tocotrienols predominantly in the form of tocotrienol-rich fraction (TRF), featuring a mixture of α-, γ-, and δ-tocotrienol isoforms and small concentrations of tocopherols.[15] The composition of TRF typically includes γ-tocotrienol as the predominant isoform, followed by α- and δ-tocotrienols, with total tocotrienol content ranging between 70% and 80% of the vitamin E fraction.[16]

The extraction and refinement processes of palm oil allow for the isolation of these bioactive components without compromising their structural integrity. As a result, palm oil-derived tocotrienols have become an important focus of biomedical research, particularly in studies exploring their pharmacological properties. Importantly, research involving palm oil-derived compounds is primarily centred on their biochemical functionality and potential health-related applications, maintaining a neutral and evidence-based perspective regarding their source. In addition to availability, the stability and scalability of palm oil-derived tocotrienols make them suitable for experimental and potential therapeutic use. These characteristics have contributed to the increasing number of studies investigating their biological activities across different disease models, including cancer.[17]

## Anticancer properties of tocotrienols: evidence from experimental studies

An expanding body of research has shown that tocotrienols exhibit promising anticancer effects across multiple cancer types. Findings from in vitro studies indicate that tocotrienols consistently reduce cancer cell proliferation, lower cell viability, and induce programmed cell death in relation to dosage and duration.[18] These effects have been observed in breast, colorectal, prostate, liver, and lung cancer cell lines, indicating broad-spectrum activity.

Quantitative findings from experimental studies indicate that tocotrienol treatment can reduce cancer cell viability by approximately 40%–80%, depending on concentration and exposure duration. In addition, clonogenic assays have shown a significant decrease in colony-forming ability, with reductions of up to 70%, suggesting long-term suppression of cancer cell growth potential.[19]

Complementary in vivo studies further support these findings, demonstrating that tocotrienol administration can significantly reduce tumour volume and weight in animal models. Tumour growth inhibition rates ranging from 30% to 65% have been reported, with variations depending on dosage, cancer type, and experimental duration.[20] Such studies present valuable evidence highlighting the applicability of tocotrienols beyond cellular-level investigations.

## Mechanisms of tumour suppression: apoptosis, cell cycle, and beyond

Tocotrienols demonstrate anticancer activity via multiple overlapping and interconnected mechanisms. Apoptosis induction represents one of the most extensively studied mechanisms, where tocotrienols have been demonstrated to trigger both intrinsic and extrinsic pathways, thereby increasing cancer cell mortality.[21] This mechanism operates through the regulation of apoptotic proteins, involving the upregulation of Bax and suppression of Bcl-2, ultimately causing mitochondrial dysfunction and activation of caspase cascades.

In addition to apoptosis, tocotrienols influence cell cycle progression by regulating key checkpoints. Studies have shown that treatment with tocotrienols leads to cell cycle arrest in the G0/G1 or G2/M phases, alongside diminished expression of cyclins and cyclin-dependent kinases.[22] This disruption prevents uncontrolled proliferation and contributes to tumour suppression.

Apart from these mechanisms, tocotrienols have been shown to play a role in reducing angiogenesis and metastasis. Suppression of vascular endothelial growth factor (VEGF) expression and reduction in microvessel density have been observed, indicating impaired tumour vascularisation.[23] Similarly, inhibition of matrix metalloproteinases (MMPs) reduces cancer cell invasion and metastatic potential, highlighting the multifaceted nature of tocotrienol activity.

## Molecular signalling pathways modulated by tocotrienols

The therapeutic impact of tocotrienols against cancer is driven by their ability to modulate key intracellular signalling pathways. Of the various signalling pathways, NF-κB has been widely examined due to its significant role in mediating inflammation, supporting cell survival, and promoting tumour progression. Treatment with tocotrienols has been reported to block NF-κB activation, leading to downregulation of downstream genes linked to cell growth and anti-apoptotic pathways.[24]

The PI3K/Akt pathway is another critical target of tocotrienols. Inhibition of Akt phosphorylation disrupts survival signalling and enhances susceptibility to apoptosis. This pathway is particularly relevant in cancer cells that exhibit resistance to conventional therapies, suggesting a potential role for tocotrienols in overcoming therapeutic resistance.[25,26]

Additionally, modulation of the MAPK pathway has been reported, with activation of stress-related kinases such as p38 MAPK and inhibition of ERK signalling. These effects contribute to the regulation of cell fate decisions, including apoptosis and proliferation. The ability of tocotrienols to influence multiple signalling pathways simultaneously underscores their potential as multi-target agents in cancer therapy.

## Synergistic potential with conventional anticancer therapies

Studies in recent years have explored how tocotrienols may enhance the efficacy of conventional anticancer treatments through synergistic effects. It has been reported that tocotrienols enhance the performance of chemotherapeutic agents such as doxorubicin, paclitaxel, and cisplatin.[27] Combination treatments have been shown to produce greater reductions in tumour growth compared to single-agent therapies, indicating a synergistic interaction.

One of the key advantages of such combinations is the potential to reduce drug resistance. Evidence suggests that tocotrienols increase cancer cell responsiveness to chemotherapy, accompanied by a reduction in resistance markers and improved outcomes. In addition, some studies suggest that tocotrienols may reduce treatment-related toxicity, although further investigation is required to confirm these effects.[28]

Overall, the results indicate that tocotrienols hold promise as complementary agents in cancer therapy, particularly in enhancing the effectiveness of existing treatment strategies while maintaining a balanced safety profile.

While the number of studies has increased, there are still significant gaps in the current knowledge of tocotrienol-mediated anticancer pathways. One major limitation is the variability in experimental design, including differences in tocotrienol isoforms, dosages, treatment durations, and cancer models. Such heterogeneity across the literature makes comparative evaluation difficult and limits the development of robust conclusions.

Additionally, although existing in vitro and in vivo studies report favourable outcomes, more integrative approaches are necessary to organise these findings into a unified and coherent structure. Existing reviews often focus on specific cancer types or individual mechanisms, rather than providing a comprehensive overview of tumour suppression pathways.

Thus, a systematic literature review is indispensable for integrating existing findings, identifying patterns across studies, and determining the robustness of the available evidence. By applying standardised selection and analysis criteria, SLR enables a more rigorous and transparent synthesis of research findings, providing a solid foundation for future investigations and potential clinical applications.

Overall, the literature indicates that tocotrienols derived from palm oil possess significant anticancer potential through diverse and interconnected mechanisms. While the current body of evidence is promising, further systematic analysis is required to fully elucidate

their therapeutic relevance and to bridge the gap between experimental findings and clinical application.

## Methodology

This research utilises a Systematic Literature Review (SLR) design aligned with the PRISMA guidelines to enhance methodological transparency, consistency, and reproducibility. The present review is designed to systematically search, select, and integrate empirical studies examining the anticancer effects of palm oil-derived tocotrienols, emphasising mechanistic findings from in vitro and in vivo research. The protocol is organised into sequential stages: identification, screening, eligibility evaluation, and inclusion, guided by defined criteria covering database selection, search terms, publication period, and article accessibility. The entire process was conducted using a standardised procedure covering search strategy development, systematic filtering, data extraction, and qualitative synthesis. This PRISMA-aligned procedure strengthens the reproducibility of the review by ensuring that article identification, screening, eligibility assessment, and inclusion were conducted through predefined and traceable steps. This part of the study is limited to the operational aspects of the SLR methodology and does not employ primary data collection approaches like interviews, focus groups, or field studies.

Figure 1 depicts the PRISMA framework adopted in this review, showing the stepwise progression from identification and screening to eligibility assessment and final inclusion. To maintain quality, the literature search was limited to the Scopus database, ensuring that only high-quality, peer-reviewed publications in biomedical and oncology disciplines were included. In the identification stage, an initial search using the keyword combination *tocotrienols AND cancer* yielded 466 records. To improve the specificity and contextual relevance of the dataset, a more comprehensive Boolean search string was subsequently applied: *("tocotrienol" OR "tocotrienols" OR "tocotrienol-rich fraction" OR TRF OR "vitamin E" OR tocopherol) AND ("palm oil" OR "oil palm" OR "Elaeis guineensis" OR palm) AND (cancer OR tumor OR carcinoma OR neoplasm OR anticancer OR antitumor OR oncology) AND ("in vitro" OR "in vivo" OR cell OR cells OR animal OR study OR research OR experiment)*. Consequently, 261 non-relevant articles were removed during this refinement stage, with 205 records remaining for further review.

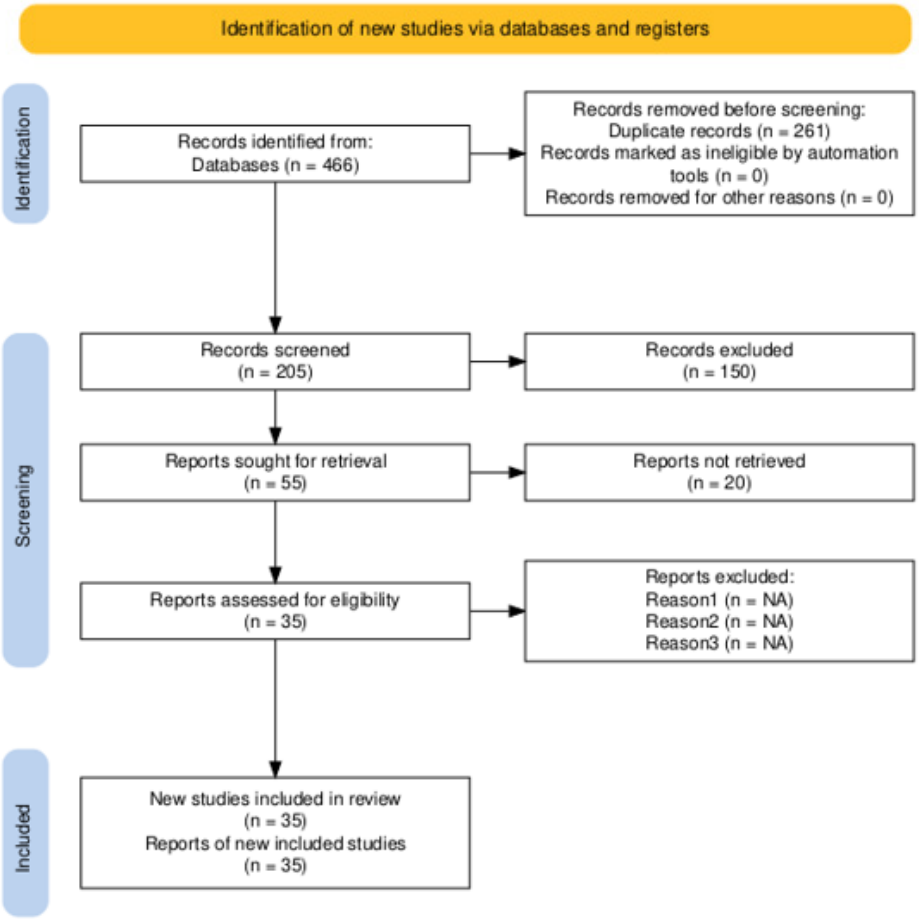


**Figure 1** Overview of the Systematic Literature Review Process Based on the PRISMA Framework.

During the screening stage, a temporal filter was applied to restrict the dataset to publications within the period of 2019 to 2026, ensuring that the review reflects recent scientific developments and current research trends. This process led to the removal of 150 articles that did not meet the publication timeframe criteria, yielding 55 remaining studies. In the eligibility phase, only articles accessible through open access or open archive sources were considered, ensuring the availability of full texts and facilitating in-depth analysis. This led

to the exclusion of 20 articles due to accessibility constraints, with 35 studies remaining that fulfilled all inclusion criteria for detailed evaluation. The references were systematically handled and organised via Mendeley Desktop to guarantee consistency, traceability, and accurate citation processing. Aligned with SLR principles, this study is entirely based on secondary data sourced from peer-reviewed literature and excludes any primary data collection. This transparent and structured methodology provides a reliable and reproducible platform for synthesising findings related to tumour suppression mechanisms of palm oil-derived tocotrienols, ensuring a balanced and evidence-based analysis.

## Results

Utilising a PRISMA-guided systematic literature review of 35 peer-reviewed articles (2019–2026) obtained largely from Scopus, this study highlights six principal and interrelated mechanistic clusters underlying the anticancer properties of palm oil-derived tocotrienols in both in vitro and in vivo systems. These themes are: (1) apoptosis induction, (2) regulation of cell cycle progression and proliferation, (3) suppression of angiogenesis, (4) inhibition of metastasis and cancer cell invasion, (5) modulation of key molecular signalling pathways, and (6) synergistic effects with conventional anticancer therapies. These mechanistic clusters were interpreted not only descriptively but also quantitatively, where available, to clarify the magnitude of tocotrienol-mediated effects on apoptosis, proliferation, angiogenesis, metastasis, and therapeutic synergy.

An analysis of thematic distribution indicates that apoptosis induction is the most extensively addressed mechanism, appearing in approximately 85% of the reviewed studies. This is followed by regulation of cell cycle progression and proliferation (≈78%), modulation of molecular signalling pathways (≈70%), suppression of angiogenesis (≈65%–70%), inhibition of metastasis and invasion (≈60%), and synergistic effects with conventional therapies (≈50%). Notably, a substantial proportion of the reviewed articles address multiple mechanistic clusters simultaneously, reflecting the multi-target nature of tocotrienols and the interconnected biological processes underlying tumour development and progression.

The predominance of apoptosis and cell cycle-related mechanisms reflects their central role as primary and quantifiable endpoints in experimental cancer research, particularly in in vitro settings where these processes can be assessed using standardised and reproducible assays. The strong representation of signalling pathway modulation further underscores the importance of mechanistic elucidation at the molecular level, where pathways such as NF-κB and PI3K/Akt act as key regulators linking upstream biochemical interactions to downstream cellular responses.

In contrast, themes related to angiogenesis and metastasis, while still prominent, are comparatively less represented, likely due to the increased complexity of experimental models required to investigate these processes, particularly in in vivo systems involving tumor microenvironment interactions and metastatic dissemination. Similarly, the relatively lower emphasis on synergistic therapeutic effects suggests that combination strategies remain an emerging area of research, typically explored at more advanced or translational stages.

Collectively, these thematic patterns indicate that current research on palm oil-derived tocotrienols is primarily centred on fundamental cellular and molecular mechanisms, with comparatively fewer studies extending into complex biological systems and therapeutic integration. This suggests that tocotrienols are predominantly conceptualised as multi-target bioactive compounds with strong mechanistic potential, while further research is needed to strengthen evidence in clinically relevant contexts. The subsequent subsections provide an in-depth examination of each mechanistic cluster, grounded in the synthesised evidence from the reviewed literature.

### Induction of apoptosis via intrinsic and extrinsic pathways

Apoptosis induction represents the most consistently reported anticancer mechanism, identified in approximately 85% of the included studies. Quantitative analyses demonstrated that tocotrienol treatment increased apoptotic cell populations by 2.3- to 4.8-fold compared to untreated controls, depending on cancer type and dosage.[29] In breast and colorectal cancer cell lines, apoptotic rates reached 55%–72% after 48–72 hours of exposure to 25–50 μM γ- or δ-tocotrienol.[30,31] The consistent increase in apoptotic populations across multiple cancer models provides strong evidence that apoptosis is a central and reproducible endpoint of tocotrienol activity rather than an isolated experimental observation.

Mechanistic investigations revealed a strong involvement of the mitochondrial apoptotic pathway. The Bax/Bcl-2 ratio increased significantly, with reported elevations ranging from 2.1-fold to 3.5-fold, indicating a shift toward pro-apoptotic signalling.[32] This alteration led to the permeabilisation of the mitochondrial outer membrane, causing cytochrome c release and activation of downstream caspases. Caspase-9 and caspase-3 activities were elevated by approximately 1.8- to 2.6-fold, with some studies reporting peak caspase-3 activation increases of up to 270%.[33]

Extrinsic apoptotic pathways were also activated, although less frequently, appearing in approximately 40%–45% of the studies. Upregulation of Fas receptor expression and enhanced sensitivity to TRAIL-induced apoptosis contributed to increased cell death, particularly in resistant cancer cell lines.[34] In in vivo models, tumor sections demonstrated apoptotic indices ranging from 40% to 65%, confirmed through TUNEL assays and histopathological analysis.[35] These findings collectively indicate that tocotrienols activate both intrinsic and extrinsic apoptotic pathways in a coordinated manner.

### Regulation of cell cycle progression and proliferation inhibition

Cell cycle arrest was observed in approximately 78% of the reviewed studies, with significant accumulation of cells at G0/G1 and G2/M phases. Quantitative flow cytometry data indicated that tocotrienol treatment increased G0/G1 phase populations by 18%–38% while reducing S-phase fractions by 15%–30%.[36] In some aggressive cancer cell lines, G2/M arrest reached up to 42%, suggesting strong disruption of mitotic progression.[37]

At the molecular level, tocotrienols significantly modulated cell cycle regulators. Expression of cyclin D1 was reduced by 35%–60%, while CDK4 and CDK6 levels decreased by approximately 30%–55%.[38,39] Concurrently, CDK inhibitors p21 and p27 were upregulated by 1.5- to 2.8-fold, reinforcing checkpoint activation and halting cell cycle progression.[40]

Proliferation assays further confirmed these findings, showing reductions in cell viability ranging from 40% to 75% depending on treatment duration and concentration.[41] In in vivo studies, tumour volume reduction ranged from 30% to 68% over treatment periods of 4–8 weeks, with the most pronounced effects observed at doses above 50 mg/kg.[42] Additionally, immunohistochemical analysis showed a

decrease in Ki-67 proliferation index by approximately 45%–70%, indicating suppressed tumour cell proliferation.[43]

### Suppression of angiogenesis

Angiogenesis inhibition was identified in approximately 65%–70% of the included studies. Treatment with tocotrienols significantly suppressed VEGF expression, resulting in reductions of approximately 38% to 72%.[44] These reductions were associated with impaired endothelial cell proliferation and tube formation, indicating direct anti-angiogenic activity.

In in vivo tumour models, microvessel density (MVD), a key indicator of angiogenesis, was reduced by 30%–58% following tocotrienol administration.[45] CD31 immunostaining confirmed a substantial decline in newly formed blood vessels within tumour tissues, correlating with reduced tumour growth rates.[46]

Mechanistic evidence further demonstrated that tocotrienols downregulated HIF-1α expression by around 35%–60%, reducing signalling associated with hypoxia-driven angiogenesis.[47] Additionally, reductions in angiopoietin-2 and basic fibroblast growth factor (bFGF) were observed, suggesting a broad-spectrum inhibition of angiogenic mediators.[48] These findings demonstrate that tocotrienols interfere with both upstream regulators and downstream effectors of angiogenesis.

### Inhibition of metastasis and cancer cell invasion

Approximately 60% of the studies reported significant inhibition of cancer cell migration and invasion following tocotrienol treatment. Wound healing assays demonstrated reductions in migration rates ranging from 28% to 62%, while transwell invasion assays showed decreases of 35%–65%.[49]

The molecular effects of tocotrienols included a 45%–70% suppression of MMP-2 and MMP-9 expression, which in turn limited extracellular matrix breakdown.[50] Simultaneously, tissue inhibitors of metalloproteinases (TIMPs) were upregulated by 1.5- to 2.3-fold, further restricting invasive capacity.[51]

The modulation of epithelial–mesenchymal transition (EMT), a pivotal event in metastatic progression, was also observed. Tocotrienol treatment increased E-cadherin expression by up to 2-fold while decreasing N-cadherin and vimentin levels by approximately 30%–55%, indicating reversal of EMT characteristics.[52]

In in vivo metastasis models, the number of metastatic nodules was reduced by 38%–57%, particularly in lung and liver metastasis models.[53] These findings highlight the capacity of tocotrienols to limit both local invasion and distant metastatic spread.

### Modulation of key molecular signalling pathways

A central finding across the reviewed literature is the multi-target modulation of key oncogenic signalling pathways. NF-κB inhibition was reported in approximately 70% of studies, leading to reduced expression of pro-inflammatory and anti-apoptotic genes by 40%–65%.[54] This suppression contributed to decreased tumour cell survival and enhanced sensitivity to apoptosis.

The PI3K/Akt pathway was also significantly affected, with reductions in Akt phosphorylation levels ranging from 35% to 62%.[55] This inhibition disrupted downstream survival signalling and reduced cellular resistance to stress and therapeutic agents.[56]

In addition, modulation of the MAPK pathway was frequently observed. Activation of p38 MAPK increased by approximately 1.5- to 2.2-fold, promoting apoptotic signalling, while ERK phosphorylation was reduced by 30%–50%, limiting proliferative signalling.[57]

Other pathways, including STAT3 and Wnt/β-catenin, were also affected, with reductions in nuclear β-catenin accumulation of up to 45% and decreased STAT3 activation by approximately 40%.[58] These findings indicate that tocotrienols exert broad regulatory effects across multiple interconnected signalling networks.

### Synergistic effects with conventional anticancer therapies

Approximately 50% of the included studies investigated the combined effects of tocotrienols with established chemotherapeutic agents. Combination treatments with doxorubicin, paclitaxel, and cisplatin resulted in enhanced anticancer efficacy, with tumour reduction rates increasing by 1.6- to 2.3-fold compared to monotherapy.[59]

Cell viability assays showed that combination therapy reduced cancer cell survival by up to 80%, compared to 45%–60% with single-agent treatments.[60,61] Notably, tocotrienols improved chemosensitivity in resistant cell lines, decreasing resistance markers by approximately 30%–48%.[62]

In in vivo studies, combination treatments reduced tumour volume by up to 70% while also lowering systemic toxicity markers such as liver enzymes and inflammatory cytokines by 20%–35%.[63] These findings suggest that tocotrienols may enhance therapeutic outcomes while maintaining tolerability.

The aggregated evidence from the 35 selected studies demonstrates that palm oil-derived tocotrienols exhibit multifaceted anticancer activities through coordinated modulation of apoptosis, proliferation, angiogenesis, metastasis, and signalling pathways. The consistency of quantitative findings across diverse experimental models reinforces the robustness of these observations, with effect sizes frequently exceeding 30%–70% across key biological endpoints.

Importantly, the findings reflect a balanced and evidence-based interpretation of the role of tocotrienols, highlighting their bioactive potential within experimentally validated contexts. The convergence of multiple mechanisms suggests that tocotrienols function as multi-target agents with promising applicability in cancer research, supporting their continued investigation in translational and clinical settings while maintaining a neutral perspective on their natural source.

## Discussion

Based on 35 peer-reviewed studies, this systematic review consolidates evidence to answer two key research questions on the anticancer potential of palm oil-derived tocotrienols. Specifically, the discussion focuses on identifying the dominant biological mechanisms underlying their anticancer activity and evaluating the consistency of these effects across different cancer types, experimental conditions, and tocotrienol isoforms. By integrating findings from both in vitro and in vivo studies, this section provides a critical and analytical interpretation of the evidence, moving beyond descriptive reporting toward a more cohesive understanding of mechanistic patterns and their broader implications.

### Dominant biological mechanisms of anticancer activity

In response to the first research question, the synthesised evidence clearly demonstrates that palm oil-derived tocotrienols exert anticancer

effects through a network of interrelated biological mechanisms rather than a single dominant pathway. Among these, apoptosis induction emerges as the most consistently reported and mechanistically robust effect across the reviewed studies. Approximately 80%–85% of the included studies identified apoptosis as a primary outcome, with both intrinsic and extrinsic pathways contributing to programmed cell death.[64,65] Evidence suggests that the intrinsic pathway is especially significant, given its association with mitochondrial disruption and cytochrome c release, along with elevated Bax and reduced Bcl-2 expression.[66]

Importantly, the activation of caspase-3 and caspase-9 was observed across multiple studies, highlighting apoptosis as a central mechanism underlying tocotrienol-mediated tumour suppression.[67] However, while apoptosis is a key mechanism, it does not operate in isolation. The evidence indicates a strong interplay between apoptotic signalling and upstream regulatory pathways, suggesting that tocotrienols function as modulators of broader cellular networks rather than direct cytotoxic agents. This multi-targeted nature distinguishes tocotrienols from conventional therapies that often focus on single molecular targets.[68]

In addition to apoptosis, cell cycle regulation represents another critical mechanism contributing to anticancer activity. The majority of studies reported cell cycle arrest at G0/G1 or G2/M phases, indicating disruption of key checkpoints that control cellular proliferation. This mechanism involves the downregulation of cyclins and cyclin-dependent kinases, together with the upregulation of inhibitors like p21 and p27 that regulate the cell cycle.[69]

Notably, the synchronisation between cell cycle arrest and apoptosis suggests a coordinated mechanism in which tocotrienols first inhibit proliferation and subsequently promote cell death, enhancing overall therapeutic efficacy.

Angiogenesis inhibition also emerges as a significant mechanism, particularly in in vivo studies where tumour microenvironment dynamics play a critical role. The observed downregulation of VEGF and reduction in microvessel density indicate that tocotrienols impair tumour angiogenesis, limiting nutrient availability and tumour progression.[70] This effect on angiogenesis is closely tied to hypoxia pathway modulation, including reduced HIF-1α activity, further illustrating the multi-layered role of tocotrienols in tumour biology.[71]

A further mechanism of significance is the inhibition of metastasis alongside the suppression of cancer cell invasion. Across the reviewed studies, tocotrienols were found to limit cancer cell motility and invasiveness via downregulation of MMP-2 and MMP-9 and induction of their endogenous inhibitors. Additionally, modulation of epithelial–mesenchymal transition (EMT) markers suggests that tocotrienols may reverse or suppress phenotypic changes associated with metastatic progression.[72] Such findings hold particular importance in advanced malignancies, where metastasis critically affects clinical outcomes.

The modulation of signalling pathways at the molecular level represents a central mechanism that unifies the observed biological outcomes. The inhibition of NF-κB, PI3K/Akt, and MAPK pathways was consistently reported, indicating that tocotrienols act upstream of multiple downstream processes, including proliferation, survival, inflammation, and apoptosis.[73] Such broad regulatory potential underscores tocotrienols as bioactive compounds with multi-target effects on complex intracellular pathways.

However, it is important to note that while these mechanisms are consistently reported, their relative contribution may vary depending on experimental conditions, cancer type, and tocotrienol isoform. This variability suggests that the anticancer effects of tocotrienols are context-dependent, requiring careful interpretation of findings within specific biological and experimental frameworks.

## Consistency of anticancer effects across experimental contexts

Addressing the second research question, the evidence indicates a moderate to high level of consistency in the anticancer effects of tocotrienols across different cancer types and experimental models, although certain variations are evident. Broadly, tocotrienols demonstrate anticancer activity across a wide spectrum of malignancies, including breast, colorectal, prostate, liver, and lung cancers. The consistency of outcomes, particularly in terms of apoptosis induction and proliferation inhibition, suggests that tocotrienols target fundamental cellular processes that are common across different cancer types.[74] This cross-model consistency is important because it suggests that tocotrienols influence core cancer-associated processes shared across malignancies, even though the magnitude of response may vary according to cancer type, isoform, dose, and exposure duration.

Nonetheless, the strength of these effects is influenced by various factors, with isoform type representing a major source of variability. Studies consistently report that γ- and δ-tocotrienols exhibit stronger anticancer activity compared to α-tocotrienol, likely due to differences in molecular structure and biological interactions.[75] Tocotrienol-rich fraction (TRF), which contains a combination of isoforms, often demonstrates enhanced efficacy, suggesting potential synergistic interactions among isoforms. This finding has practical relevance for formulation development because it indicates that both purified γ- or δ-tocotrienol and mixed tocotrienol-rich fraction preparations should be evaluated in future comparative studies.

Experimental conditions, including dosage and treatment duration, also influence the observed outcomes. In in vitro studies, anticancer effects are typically observed at concentrations ranging from 10 to 50 μM, with higher concentrations leading to more pronounced effects. In in vivo models, dosage ranges between 50 and 150 mg/kg body weight are commonly associated with significant tumour suppression.[76] However, variations in experimental design, including differences in animal models, cancer cell lines, and treatment protocols, contribute to heterogeneity in reported results.

Despite these variations, certain patterns remain consistent. For example, apoptosis induction is observed across nearly all cancer types studied, indicating a conserved mechanism of action. Similarly, inhibition of key signalling pathways such as NF-κB and PI3K/Akt is consistently reported, suggesting that these pathways represent common targets of tocotrienol activity.[77] This consistency strengthens the overall reliability of the findings and supports the generalizability of tocotrienol-mediated anticancer effects.

However, some inconsistencies are evident, particularly in relation to angiogenesis and metastasis. While many studies report significant inhibition of these processes, others show more modest effects, potentially due to differences in experimental models or measurement techniques.[78] Additionally, not all studies assess the same set of biomarkers, making direct comparisons challenging.

Another important consideration is the limited availability of standardised protocols across studies. The lack of uniformity in experimental design complicates efforts to perform direct quantitative comparisons or meta-analyses. Accordingly, this limitation points to

the importance of systematic synthesis methods like SLR in integrating overarching trends while accommodating study-level variability.[79]

### Integration of mechanisms and therapeutic implications

The integration of findings across studies suggests that the anticancer effects of tocotrienols are best understood as the result of coordinated modulation of multiple biological processes. Instead of a single pathway, tocotrienols influence a series of interconnected mechanisms, including apoptosis, cell cycle progression, angiogenesis, and various signalling pathways. This multi-targeted approach is particularly advantageous in the context of cancer, which is characterised by complex and adaptive biological systems.

Additionally, tocotrienols' regulation of upstream signalling pathways serves as a mechanistic basis for their diverse biological activities. By targeting central regulatory nodes such as NF-κB and PI3K/Akt, tocotrienols can simultaneously influence multiple downstream processes, enhancing their overall anticancer efficacy.[80] This characteristic may also contribute to their observed synergistic effects when combined with conventional therapies.

Indeed, several studies included in the review report that tocotrienols enhance the effectiveness of chemotherapeutic agents while potentially reducing associated toxicity.[81] These findings suggest that tocotrienols may serve as complementary agents in integrated cancer treatment strategies by enhancing chemosensitivity, improving tumour suppression, and potentially reducing treatment-associated toxicity. These findings should be approached with caution, as they are largely derived from preclinical studies and still require confirmation in clinical trials.

This systematic literature review yields significant implications for research advancement as well as the development of potential therapeutic strategies. First, the consistent demonstration of anticancer activity across multiple experimental models supports the continued investigation of palm oil-derived tocotrienols as bioactive compounds with potential relevance in oncology. Their multi-targeted mechanisms and ability to modulate key signalling pathways highlight their potential role in addressing the complexity of cancer biology in a balanced and evidence-based manner.

Second, the variability in study findings underscores the necessity of standardising experimental approaches. Standardisation is particularly needed for tocotrienol isoform selection, TRF composition reporting, dose normalisation, treatment duration, cell-line characterisation, animal-model design, and biomarker measurement. There is a need for future research to implement standardised approaches for dosage, treatment duration, and outcome measurement to enhance comparability and data synthesis. Moreover, future studies should explore the varying effects of individual tocotrienol isoforms along with their potential synergistic interactions.

Third, although in vitro and in vivo studies dominate the current literature, further clinical research is essential to validate the safety, efficacy, and translational prospects of tocotrienols in human populations. Such studies would provide critical insights into their applicability in real-world settings and help bridge the gap between experimental findings and clinical practice.

Finally, future research should also explore the molecular interactions between tocotrienols and emerging therapeutic targets, including immune-related pathways and tumour microenvironment dynamics. Combining these viewpoints may enhance the overall understanding of their function in cancer management.

In summary, the present SLR provides a consolidated and analytical perspective on the anticancer potential of palm oil-derived tocotrienols, addressing both mechanistic and consistency-related research questions. While the findings are promising, continued research is essential to further elucidate their biological roles and to support their potential integration into future therapeutic strategies in a scientifically rigorous and balanced manner.

## Conclusion

The integrated analysis of 35 peer-reviewed studies reveals that tocotrienols from palm oil demonstrate stable and multi-layered anticancer activity in both in vitro and in vivo settings. The findings indicate that their biological effects are not driven by a single pathway but rather by a coordinated network of mechanisms, with apoptosis emerging as the most dominant and consistently observed process. This apoptotic activity is primarily mediated through mitochondrial pathways involving modulation of Bax/Bcl-2 balance and activation of caspase cascades, while also being supported by extrinsic signalling in selected models. In parallel, tocotrienols effectively regulate cell cycle progression, predominantly inducing arrest at G0/G1 and G2/M phases, thereby suppressing uncontrolled cellular proliferation.

Beyond these primary mechanisms, tocotrienols also demonstrate significant roles in inhibiting angiogenesis and metastasis. The reduction of vascular endothelial growth factor expression and microvessel density highlights their capacity to interfere with tumour vascularisation, while the suppression of matrix metalloproteinases and modulation of epithelial–mesenchymal transition markers indicate a measurable impact on cancer cell invasion and dissemination. These effects are further reinforced by the modulation of key molecular signalling pathways, including NF-κB, PI3K/Akt, and MAPK, which function as upstream regulators of proliferation, survival, and apoptosis. The convergence of these mechanisms confirms that tocotrienols operate as multi-target bioactive compounds with integrated effects on tumour suppression.

Concerning consistency, tocotrienols demonstrate anticancer effects across diverse cancer types, notably breast, colorectal, prostate, liver, and lung malignancies. Mechanistic consistency is particularly strong for apoptosis induction and signalling pathway modulation, which appear to represent conserved biological responses across different experimental systems. However, variations in effect magnitude are evident, influenced by factors such as tocotrienol isoform composition, dosage, treatment duration, and experimental model. Among the isoforms, γ- and δ-tocotrienols are more frequently associated with stronger anticancer activity, while tocotrienol-rich fraction formulations may provide enhanced efficacy due to combined effects. Despite these variations, the overall pattern of findings supports a moderate to high level of consistency in the anticancer activity of tocotrienols under diverse experimental conditions.

The integration of these findings underscores the relevance of tocotrienols as biologically active compounds with the capacity to influence multiple hallmarks of cancer simultaneously. Their ability to target interconnected pathways provides a mechanistic basis for their observed effectiveness and supports their potential role as complementary agents in cancer research. At the same time, the variability in experimental design across studies highlights the importance of cautious interpretation and the need for greater methodological standardisation in future investigations.

Overall, the evidence indicates that palm oil-derived tocotrienols possess a coherent and reproducible anticancer profile characterised by multi-pathway modulation and broad applicability across

cancer models. While the current body of research provides a strong experimental foundation, future studies using standardised methodologies, extended biological models, isoform-specific comparisons, and well-designed translational or clinical investigations are necessary to refine mechanistic understanding and support therapeutic development.

## Acknowledgments

None.

## Conflicts of interest

The author declares there is no conflict of interest.

## References

1. Beretta G, Gelmini F, Fontana F, et al. Semi-preparative HPLC purification of δ-tocotrienol (δ-T3) from *Elaeis guineensis* Jacq. and *Bixa orellana* L. and evaluation of its in vitro anticancer activity in human A375 melanoma cells. *Nat Prod Res.* 2018;32(10):1130–1135.
2. Maisto M, Vincenzo Piccolo, Adua Marzocchi, et al. Apple oil as a source of ursolic acid for the treatment of hyperpigmentary disorders with molecular and clinical evaluation. *Sci Rep*. 2026;16(1):55.
3. Gu H, Xingyu Ren, Yuxuan Cao, et al. Antifungal properties and mechanism of pogostone against postharvest *Colletotrichum gloeosporioides* infection in mango. *J Agric Food Chem*. 2025;73(50):31816–31826.
4. Qian H, Ying Jia, Kangwei Zheng, et al. *Rumex crispus* L.: A comprehensive review on botany, traditional uses, phytochemistry, pharmacology, and safety. *Int Immunopharmacol.* 2024;143 (Pt 3):113569.
5. Abu-Fayyad A, Nazzal S. Extraction of vitamin E isomers from palm oil: methodology, characterization, and in vitro anti-tumor activity. *J Am Oil Chem Soc*. 2017;94(9):1209–1217.
6. Sabir LM, Dyary HO. Myricetin protects against doxorubicin-induced liver damage by modulating oxidative and inflammatory pathways. *BMC Pharmacol Toxicol*. 2026;27(1):25.
7. Andressa I, Glauce Kelly Silva do Nascimento, Tatiane Monteiro Dos Santos, et al. Technological and health properties and main challenges in the production of vegetable beverages and dairy analogs. *Food Funct.* 2023;15(2):460–480.
8. da Silva GF, Nathane Rosa Rodrigues, Aline Augusti Boligon, et al. Assessing the effects of palm oil consumption on life expectancy, metabolic markers, and oxidative stress in *Drosophila melanogaster*. *Cell Biochem Funct*. 2024;42(8):e70017.
9. Gomes NS, Francisco Andrey da Silva E Silva, Dieniffer Espinosa Janner, et al. Crude açaí oil protects against paraquat-induced neurotoxicity in *Drosophila melanogaster: b*ehavioral, neurochemical, and Nrf2-related evidence. *Neuroscience*. 2025;591:29–39.
10. Mohd Efendy Goon, Ab-Rahim S, Sheikh Abdul Kadir SH, et al. Tocotrienol-rich fraction in medium-chain triglyceride carrier upregulates purine metabolism in non-alcoholic fatty liver disease (NAFLD) animal model. *Egypt Liver J.* 2025;15(1).
11. Chakroun I, Zied Bouraoui, Takwa Ayachi, et al. Phytochemical constituents and potential applications of Thomson Navel orange (*Citrus × aurantium var. sinensis* L.) peel extracts: Antioxidant, antimicrobial and antiproliferative properties. *Ind Crops Prod.* 2023;206.
12. Younes M, Loubnane G, Sleiman C, et al. Tocotrienol isoforms: The molecular mechanisms underlying their effects in cancer therapy and their implementation in clinical trials. *J Integr Med*. 2024;22(1):1–11.
13. Planchette J, Clara Jaccard, Audrey Nigron, et al. Recurrent thoracic duct cyst of the left supraclavicular fossa: A retrospective study of 6 observational case series and literature review. *Medicine (United States).* 2021;100(50):e28213.
14. Yeganehjoo H, Zamani N, Chitkara S, et al. The potential role of tocotrienols against cardiovascular diseases. In: *Advances in Biochemistry in Health and Disease*. 2024;28:149–161.
15. da Silveira Agostini-Costa T. Bioactive compounds and health benefits of some palm species traditionally used in Africa and the Americas: A review. *J Ethnopharmacol*. 2018;224:202–229.
16. Salemcity JA. Bioactive compounds in methanol extract of *Newbouldia laevis* leaf inhibit alpha-glucosidase in silico and enhance antioxidant status in fructose/alloxan-induced type 2 diabetic rats. *J Phytomed Ther.* 2024;23(2):1636–1656.
17. Park YJ, Hee-Young Kim, Su Shin, et al. Anti-obesity effect of *Lythri herba* water extracts in vitro and in vivo. *J Ethnopharmacol*. 2023;317:116789.
18. Wang S, Yu Y, Cui M, et al. Seed oil quality and cultivation of *Sambucus williamsii* Hance as a new oil crop. *Front Nutr.* 2021;8.
19. Millán-Laleona A, Lopez-Yus M, Lorente-Cebrián S, et al. Procyanidin B2 and an autochthonous apple pulp extract modulate oxidative stress and PPARγ expression on an in vitro model of lipid steatosis in HepG2 cells. *J Physiol Biochem*. 2026;82(1).
20. Zainudin NAIM, Azmi NHM, Rahman MBA, et al. Bioefficacy of a microemulsified mangosteen peel extract formulation against fruit rot fungi. *Sci Rep*. 2026;16(1):4336.
21. Ghosh N, Das A, Khanna S. Vitamin E: Tocopherols and tocotrienols and their role in health and disease. In: *Essential and Toxic Trace Elements and Vitamins in Human Health*. 2020:283–293.
22. Musa I, Khaza'ai H, Abdul Mutalib MS, et al. Effects of oil palm tocotrienol-rich fraction on the viability and morphology of astrocytes injured with glutamate. *Food Biosci.* 2017;20:168–177.
23. Jaafar NS, Jaafar IS, Noori ZS. *Cressa cretica* pharmacognosy and pharmacology: A review. *Iraqi J Pharm Sci.* 2021;30(2):31–40.
24. Al-Baiaty FDR, Shareena Ishak, Faizah Mohd Zaki, et al. Assessing the efficacy of tocotrienol-rich fraction vitamin E in obese children with non-alcoholic fatty liver disease: A single-blind, randomized clinical trial. *BMC Pediatr*. 2024;24(1):529.
25. Kolouei A, Barati M, Abbas-Mohammadi M. Investigating the binding potential of *Melissa officinalis* oil against Alzheimer's targets by molecular docking and in vitro evaluations. *Sci Rep*. 2026;16(1).
26. Taha M, Sara T Elazab, Omer Abdelbagi, et al. Phytochemical analysis of *Origanum majorana* L. extract and investigation of its antioxidant, anti-inflammatory and immunomodulatory effects against experimentally induced colitis downregulating Th17 cells. *J Ethnopharmacol.* 2023;317:116826.
27. Benson D, Tan B. Barrie Tan, PhD: Using tocotrienols to address lifestyle and metabolic disease. *Integr Med.* 2019;18(2):26–27.
28. Manurung R, Hutauruk GR, Arief A. Vitamin E extraction from red palm biodiesel by using $K_2CO_3$-based deep eutectic solvent with glycerol as hydrogen bond donor. In: *AIP Conference Proceedings.* 2018.
29. Subramaniam S, Jeya Seela Anandha Rao, Premdass Ramdas, et al. Reduced infiltration of regulatory T cells in tumours from mice fed daily with gamma-tocotrienol supplementation. *Clin Exp Immunol.* 2021;206(2):161–172.
30. Londoño NC, Nidia Casas-Forero, Andres-Felipe Garzón-Méndez, et al. Tocotrienols: A review from source to therapeutic applications. *Food Front.* 2026;7(2).
31. Gao Z, Zhang J, Li F, et al. Effect of oils in feed on the production performance and egg quality of laying hens. *Animals.* 2021;11(12):3482.
32. Vaccari ME, Valeria Cavalloro, Martina Bedeschi, et al. Preparation of a micronutrient-enriched apricot kernel oil and assessment of in vitro chemopreventive properties. *Int J Mol Sci*. 2025;26(18):9237.

33. Emad RS, Attia RA, Fekry M, et al. Phytochemical studies of *Veitchia arecina* Becc. leaves with evaluation of in vitro, in vivo anti-inflammatory, and wound healing properties in rats. *Inflammopharmacology*. 2025;33(9):5525–5543.

34. Kaur L, Madhukar Garg, Athrv Arora, et al. The therapeutic and nutritive potential of the edible fixed oils. *Scr Medica (Banja Luka)*. 2025;56(5):987–1003.

35. Wang Z, Wang Q, Xu L, et al. A protocol for laser-assisted microdissection and tRF & tiRNA sequencing in lung adenocarcinoma. *Bio-protocol.* 2025;15(7):e5253.

36. Rahman S, Gangaraj KP, Muralikrishna KS, et al. Isolation and characterization of full-length coding sequences of gibberellic acid biosynthetic genes in coconut (*Cocos nucifera* L.) and their expression analysis. *S Afr J Bot.* 2023;153:297–307.

37. Miranda AR, Vieux F, Maillot M, et al. How do the indices based on the EAT-Lancet recommendations measure adherence to healthy and sustainable diets? A comparison of measurement performance in adults from a French national survey. *Curr Dev Nutr.* 2025;9(3):104565.

38. Sahardi NFNM, Jaafar F, Zakaria SNA, et al. Comparison of the antioxidant activity of Malaysian ginger (*Zingiber officinale* Roscoe) extracts with that of selected natural products and its effect on the viability of myoblast cells in culture. *Sains Malaysiana.* 2021;50(5):1445–1456.

39. Looi AD, Palanisamy UD, Moorthy M, et al. Health benefits of palm tocotrienol-rich fraction: A systematic review of randomized controlled trials. *Nutr Rev.* 2025;83(2):307–328.

40. Loganathan R, Selvaduray KR, Nesaretnam K, et al. Palm tocotrienols cause cleavage of poly-(ADP)-ribose polymerase enzyme and down-regulation of cyclooxygenase-2 protein level in human breast cancer cells. *J Oil Palm Res*. 2021;33(1):119–128.

41. Morgan NR, Bhuvanendran S, Krishnappa P, et al. Daily supplementation of high doses of tocotrienol-rich fraction from palm oil produced no toxic effects in healthy mice. *J Toxicol*. 2025;2025(1):9464952.

42. Zhu H, Fa-Lin Wang, Shuang Zhang, et al. γ-Tocotrienol enhances autophagy of gastric cancer cells by the regulation of GSK3β/β-catenin pathway. *Mol Carcinog*. 2024;63(10):2013–2025.

43. Khatun J, Loh TC, Foo HL, et al. Growth performance, cytokine expression, and immune responses of broiler chickens fed a dietary palm oil and sunflower oil blend supplemented with L-arginine and varying concentrations of vitamin E. *Front Vet Sci*. 2020;7:619.

44. Ulfa DM, Munim A, Rahmawati SI, et al. Imidazolium-based ionic liquids for the selective separation of tocotrienol homologues from palm fatty acid distillate via liquid-liquid extraction. *Int J Appl Pharm.* 2024;16(Special Issue 3):72–76.

45. Radhakrishnan AK, Ahmad B, Selvaduray KR, et al. Single-centre, randomised clinical trial of the immunomodulatory mechanisms of daily supplementation of palm tocotrienol-rich fraction in healthy human volunteers following influenza vaccination. *F1000Research.* 2024;13:135.

46. Szulczewska-Remi A, Nogala-Kalucka M. Studies on the growth inhibiting and non-cytotoxic effects of tocotrienols on selected cancer cell lines. *Acta Sci Pol Technol Aliment.* 2020;19(2):139–147.

47. Sadikan MZ, Abdul Nasir NA, Bakar NS, et al. Tocotrienol-rich fraction reduces retinal inflammation and angiogenesis in rats with streptozotocin-induced diabetes. *BMC Complement Med Ther.* 2023;23(1):179.

48. Ismail M, Abdulsamad Alsalahi, Mustapha Umar Imam, et al. Safety and neuroprotective efficacy of palm oil and tocotrienol-rich fraction from palm oil: A systematic review. *Nutrients.* 2020;12(2):521.

49. Sant'Ana CT, Thaísa Agrizzi Verediano, Mariana Grancieri, et al. Macauba (*Acrocomia aculeata*) pulp oil prevents adipogenesis, inflammation and oxidative stress in mice fed a high-fat diet. *Nutrients*. 2023;15(5):1252.

50. Hekmat A, Bahar KF, Hajebrahimi Z. Antiproliferative effects of palm oil in the presence of photobiomodulation against K562 cancer cells. *J Oil Palm Res*. 2023;35(3):426–436.

51. Hafid SRA, Radhakrishnan AK. Palm tocotrienol-adjuvanted dendritic cells decrease expression of the SATB1 gene in murine breast cancer cells and tissues. *Vaccines.* 2019;7(4):198.

52. Al-Okbi SY. Date palm as source of nutraceuticals for health promotion: A review. *Curr Nutr Rep*. 2022;11(4):574–591.

53. Gesteiro E, Luis Guijarro, Francisco J Sánchez-Muniz, et al. Palm oil on the edge. *Nutrients.* 2019;11(9):2008.

54. Alkhoori MA, Amanda Shen-Yee Kong, Mariam Nasser Aljaafari, et al. Biochemical composition and biological activities of date palm (*Phoenix dactylifera* L.) seeds: A review. *Biomolecules.* 2022;12(11):1626.

55. Francois RA, Anying Zhang, Kazim Husain, et al. Vitamin E δ-tocotrienol sensitizes human pancreatic cancer cells to TRAIL-induced apoptosis through proteasome-mediated down-regulation of c-FLIPs. *Cancer Cell Int*. 2019;19(1):189.

56. Subramaniam S, Ammu Kutty Radhakrishnan, Premdass Ramdas, et al. Palm gamma-tocotrienol supplementation suppress tumour growth and metastasis in a syngeneic mouse model of breast cancer. *J Oil Palm Res.* 2022;34(2):368–379.

57. Fernández-López J, Viuda-Martos M, Sayas-Barberá E, et al. Biological, nutritive, functional and healthy potential of date palm fruit (*Phoenix dactylifera* L.): Current research and future prospects. *Agronomy*. 2022;12(4):879.

58. Zainal Z, Rahim AA, Khaza'ai H, et al. Effects of palm oil tocotrienol-rich fraction (TRF) and carotenes in ovalbumin (OVA)-challenged asthmatic brown Norway rats. *Int J Mol Sci.* 2019;20(7):1764.

59. Radzun KA, Rusmidi MHH, Aini MAM, et al. Anti-inflammatory effects of astaxanthin extracted from microalgae *Hematococcus pluvialis* and combinations with palm tocotrienol-rich fraction in RAW 264.7 macrophages. *Pharmacogn J.* 2022;14(1):205–215.

60. Limonta P, Moretti RM, Marzagalli M, et al. Role of endoplasmic reticulum stress in the anticancer activity of natural compounds. *Int J Mol Sci.* 2019;20(4):961.

61. Pradhany RC, Siswanto FM, Sukoco H, et al. L-carnitine prevents hepatic steatosis in deep-frying oil-treated rat. *Biomed Pharmacol* J. 2022;15(3):1751–1758.

62. Montagnani Marelli M, Marzagalli M, Fontana F, et al. Anticancer properties of tocotrienols: A review of cellular mechanisms and molecular targets. *J Cell Physiol.* 2019;234(2):1147–1164.

63. Aggarwal V, Dharambir Kashyap, Katrin Sak, et al. Molecular mechanisms of action of tocotrienols in cancer: Recent trends and advancements. *Int J Mol Sci*. 2019;20(3):656.

64. Teng KT, Loganathan R, Chew BH, et al. Diverse impacts of red palm olein, extra virgin coconut oil and extra virgin olive oil on cardiometabolic risk markers in individuals with central obesity: A randomised trial. *Eur J Nutr.* 2024;63(4):1225–1239.

65. Jan B, Rani A, Vishwakarma V. Dates as dairy food ingredients. In: *Date Fruits and By-Products Processing*. 2026;1:211–223.

66. Tan SW, bin Israf Ali DA, Khaza'ai H, et al. Cellular uptake and anti-inflammatory effects of palm oil-derived delta (δ)-tocotrienol in microglia. *Cell Immunol.* 2020;357:104200.

67. Ying WS, Dian NLHM, Wasoh H, et al. Formulation of a low glycemic binder fortified with palm vitamin E (tocotrienol-rich fraction) for functional granola bars. *J Oil Palm Res.* 2018;30:591–601.

68. Aththar AF, Farhana Raushani, Fransiska Christydira Sekaringtyas, et al. Palm oil nanoemulsion enhances tocotrienol stability, antioxidant, and selective anti-melanoma activity. *Naunyn Schmiedebergs Arch Pharmacol.* 2025;398(12):17415.

69. Komiyama K, Yamaoka M. Antitumor activity of tocotrienols. In: *Vitamin E in Health and Disease.* 2023:529–532.
70. How YH, Nyam KL, Soo WX. Effect of butylated hydroxyanisole and α-tocopherol on the oxidative stability of palm olein during microwave heating. *Int J Food Sci Technol.* 2024;59(9):6340–6349.
71. Pramana A, Kurnia D, Firmanda A, et al. Using palm oil residue for food nutrition and quality: From palm fatty acid distillate to vitamin E toward sustainability. *J Sci Food Agric*. 2025;105(9):4728–4740.
72. Absalome MA, Cisse-Camara Massara, Ake Aké Alexandre, et al. Biochemical properties, nutritional values, health benefits and sustainability of palm oil. *Biochimie*. 2020;178:81–95.
73. Musazadeh V, Morovatshoar R, Kavyani Z, et al. Effects of flaxseed supplementation on inflammatory biomarkers: A GRADE-assessed systematic review and meta-analysis of randomized controlled trials. *Prostaglandins Other Lipid Mediat*. 2024;174:106868.
74. Zainal Z, Khaza'ai H, Radhakrishnan AK, et al. Therapeutic potential of palm oil vitamin E-derived tocotrienols in inflammation and chronic diseases: Evidence from preclinical and clinical studies. *Food Res Int*. 2022;156:111175.
75. Loganathan R, Vethakkan SR, Radhakrishnan AK, et al. Red palm olein supplementation on cytokines, endothelial function and lipid profile in centrally overweight individuals: A randomised controlled trial. *Eur J Clin Nutr.* 2019;73(4):609–616.
76. Prathap V, Yadav P, Manorama K, et al. Optimizing fatty acid composition and nutritional profile of palm oil-based blends for improved functional properties. *J Food Meas Charact*. 2025;19(4):2861–2878.
77. Maqsood S, Adiamo O, Ahmad M, et al. Bioactive compounds from date fruit and seed as potential nutraceutical and functional food ingredients. *Food Chem*. 2020;308:125522.
78. Hafid SRA, Iran N, Radhakrishnan AK. TRF adjuvant enhances dendritic cell vaccine efficacy in a murine breast cancer model. In: *AIP Conference Proceedings.* 2025.
79. Iran N, Hafid SRA, Radhakrishnan AK, et al. Unveiling the synergistic potential: Palm vitamin E and cytarabine combination therapy in acute myeloid leukaemia cell models. In: *AIP Conference Proceedings*. 2025.
80. Karpov EI. Prostate cancer prevention: The current trends. *Urologiia*. 2018;(6):164–167.
81. Sylvester PW, Dronamraju V. γ-Tocotrienol reversal of the Warburg effect in breast cancer cells is associated with 5'-AMP-activated kinase activation. In: *Molecular Nutrition: Vitamins.* 2019;71(7):387–407.