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Investigations of palm oil components: a review of effects on immune checkpoint pathways and therapy

Abstract

Palm oil contains various bioactive components that have shown promising potential in modulating immune responses, particularly through immune checkpoint pathways that are critical in cancer immunotherapy. Understanding the effects of these components is essential for exploring novel adjunct therapies to enhance the efficacy of cancer treatment. This study aims to systematically review the literature to investigate how components of palm oil influence immune checkpoint pathways and to assess their therapeutic potential and safety profile in cancer immunotherapy. Following PRISMA guidelines, a qualitative systematic literature review was conducted to ensure a precise and openly documented selection process. Articles were retrieved from ScienceDirect using specific keywords related to palm oil bioactives, immune checkpoints, and cancer therapy. Inclusion criteria focused on peer-reviewed, open-access articles published between 2022 and 2025. Data collection involved comprehensive database searches, screening, and extraction of relevant findings. Data analysis was conducted through thematic synthesis to identify key patterns and mechanistic insights regarding palm oil bioactives and immune modulation. The review synthesized findings from 33 selected articles, revealing that tocotrienols, carotenoids, and fatty acids present in palm oil regulate key immune checkpoints, including PD-1/PD-L1 and CTLA-4, which enhance tumor immunity and the efficacy of checkpoint blockade therapies. Additionally, these components demonstrate favorable safety profiles with minimal adverse effects reported. The study concludes that palm oil bioactives hold significant promise as adjuncts in cancer immunotherapy, although further clinical validation is needed. Future research should focus on large-scale clinical trials, optimization of bioavailability, and exploration of effects on emerging immune checkpoints.

Keywords: palm oil, immune checkpoint, tocotrienols, cancer immunotherapy, systematic literature review

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Introduction

Palm oil is primarily extracted from the fruit of the oil palm tree (Elaeis guineensis) and is among the most significant vegetable oils globally, contributing substantially to the economies of major producing countries such as Indonesia and Malaysia. Its extensive use ranges from the food industry to cosmetics and biofuels, making it a critical commodity in global trade.[1,2] Aside from its economic impact, palm oil is a complex mixture enriched with bioactive constituents, notably tocotrienols, carotenoids, and fatty acids, which have drawn growing scientific interest for their pharmacological properties.[3,4] Palm oil contains compounds with multiple biological effects, including antioxidant, anti-inflammatory, and anticancer properties, making it a valuable candidate for the development of natural treatments.[5]

Globally, cancer is still a foremost cause of death, contributing to nearly 10 million fatalities in 2020 and exerting ongoing pressure on healthcare infrastructures.[6] Traditional approaches to cancer therapy, such as surgery, chemotherapy, and radiotherapy, frequently struggle with issues related to toxicity throughout the body, resistance by cancer cells, and limited treatment success.[7] This scenario has driven the emergence of immunotherapy, a groundbreaking approach that leverages the patient's immune response to target and eliminate cancer cells.[8] Therapies involving immune checkpoint inhibitors that block PD-1, PD-L1, and CTLA-4 have significantly advanced the management of several cancer types, leading to improved survival rates in conditions such as melanoma and non-small cell lung cancer.[9]

However, despite their clinical success, immune checkpoint therapies are accompanied by several challenges, including limited response rates in certain patient populations, primary and acquired resistance, and immune-related adverse events (irAEs).[10] These limitations underscore the pressing need for adjunctive strategies that can potentiate therapeutic efficacy, mitigate side effects, and overcome tumor immune evasion. Natural bioactive molecules have drawn focus for their roles in immune modulation and their influence on pathways involved in cancer progression, potentially complementing and enhancing immunotherapy outcomes.[11]

Palm oil's bioactive constituents, especially tocotrienols, carotenoids, and fatty acids, have been increasingly examined for their roles in cancer biology and immune modulation. As a group within vitamin E, tocotrienols are plentiful in palm oil and possess significant antioxidant and anti-inflammatory properties, affecting major pathways that govern tumor proliferation and immune responses. Specifically, tocotrienols have been reported to downregulate PD-L1 expression by inhibiting NF-κB and STAT3 transcription factors, which are central to the immunosuppressive tumor microenvironment.[12] Similarly, carotenoids such as beta-carotene and lycopene enhance antigen presentation and cytotoxic T-cell activation, critical steps in effective immune checkpoint blockade. Furthermore, fatty acids in palm oil, including palmitic and oleic acids, modulate cytokine profiles and immune cell membrane dynamics, thereby affecting T-cell receptor signaling and immune surveillance.[13]

Despite these promising molecular insights, the research on palm oil components in the context of immune checkpoint pathways remains dispersed across different experimental systems and clinical settings. Prior reviews have largely focused on the antioxidant or general anticancer properties of palm oil derivatives, without

providing a targeted synthesis of their immunotherapeutic potential or mechanistic interactions with immune checkpoints.[14] The absence of a comprehensive systematic review limits researchers' and clinicians' ability to appraise the state of the evidence, identify knowledge gaps, and guide future translational research.

To address this need, the present study conducts a systematic literature review (SLR) of peer-reviewed scientific publications from 2022 to 2025, focusing exclusively on research on the effects of palm oil components on immune checkpoint pathways and their implications for cancer immunotherapy. The SLR methodology employed conforms to PRISMA standards, providing a rigorous and transparent strategy for literature identification, selection, and analysis. Importantly, this review is based solely on secondary data analysis of published articles, explicitly excluding any primary data collection methods such as focus group discussions or field observations, thereby maintaining the integrity and validity of the synthesis.

The objectives of this review are multifold: to elucidate the mechanistic interactions between key palm oil bioactives and immune checkpoint molecules; to assess the therapeutic potential of these compounds as adjuvants in existing cancer immunotherapy regimens; to analyze clinical evidence regarding their efficacy and safety profiles; and to identify prevailing limitations and propose directions for future research. The review thereby aims to provide a consolidated evidence base supporting the integration of natural bioactives into immuno-oncology paradigms.

Accordingly, the research question guiding this study is:

Research Question: *How do the bioactive components of palm oil modulate immune checkpoint pathways, and what is their therapeutic potential and safety profile in the context of cancer immunotherapy?*

By systematically addressing this question, this review contributes to advancing understanding of natural product-based immunomodulation strategies and may inform future experimental designs, clinical trial development, and therapeutic guidelines.

Literature review

The capacity of natural substances to modulate the immune system has become a major area of interest in current cancer research, especially in the context of immune checkpoint pathways, which regulate immune tolerance and tumor immune evasion. As a rich source of bioactive compounds such as tocotrienols, carotenoids, and fatty acids, palm oil has emerged as a potential agent that can modulate these pathways through multiple molecular mechanisms. This literature review synthesizes current knowledge on the biochemical properties of palm oil components and their effects on immune checkpoint regulation, summarizing in vitro, in vivo, and clinical evidence from 2022 to 2025.

Bioactive constituents of palm oil and their biological significance

Palm oil contains a complex array of phytochemicals that contribute to its biological activities. Due to their unsaturated isoprenoid side chains, tocotrienols, a subclass of vitamin E, demonstrate more potent antioxidant and anti-inflammatory properties than tocopherols by achieving better membrane integration.[15] The delta and gamma isoforms of tocotrienols exhibit notable potency in modulating cellular signaling pathways involved in both proliferation and apoptosis.

Carotenoids, such as beta-carotene and lycopene, present in palm oil, serve as precursors to vitamin A and are well documented for their antioxidant capacity and immune-enhancing effects. Fatty acids, particularly palmitic and oleic acids, constitute a significant lipid fraction in palm oil and have been implicated in modulating inflammatory responses and cell membrane dynamics that are critical for immune cell function.[16]

These components collectively contribute to palm oil's pharmacological profile, particularly in cancer-related immune modulation.

Molecular interactions with immune checkpoint pathways

Current research has clarified the mechanisms by which palm oil bioactives engage with critical immune checkpoint molecules such as PD-1, PD-L1, and CTLA-4, which are essential for modulating T-cell responses and tumor escape mechanisms.[17] Studies reveal that tocotrienols suppress PD-L1 levels by inhibiting the nuclear factor kappa B (NF-κB) and STAT3 pathways, both of which are pivotal in tumor immune evasion.[18] Treatment of breast cancer cells with delta-tocotrienol in a laboratory setting resulted in a 40–50% drop in PD-L1 surface expression, enhancing susceptibility to cytotoxic T lymphocyte (CTL) killing. The contribution of carotenoids involves promoting dendritic cell maturation and facilitating antigen presentation, thereby facilitating T-cell activation and potentially enhancing the efficacy of checkpoint blockade. Beta-carotene has been experimentally shown to upregulate CD80 and CD86 on dendritic cells, thereby enhancing the initiation of immune responses.[19] Through the suppression of cytokines such as IL-10 and TGF-β, fatty acids alter the tumor microenvironment, thereby restoring effective immune responses. In murine melanoma models, oleic acid supplementation reduced IL-10 secretion by 60%, which correlated with increased tumor-infiltrating lymphocytes.[20] These molecular insights provide a mechanistic basis for the immunomodulatory effects of palm oil components in cancer therapy.

Synergistic effects with immune checkpoint inhibitors

Research has examined the use of palm oil bioactives in combination with ICIs to overcome resistance and enhance clinical efficacy. Experimental data from preclinical models indicate that tocotrienols enhance the antitumor activity of PD-1 and CTLA-4 checkpoint inhibitors in mice, resulting in up to 30% greater tumor reduction than ICIs alone.[21] The administration of tocotrienol alongside therapy was linked to greater CD8+ T-cell presence and diminished populations of regulatory T cells in the tumor environment, indicating improved immune activation.[22] Although clinical data remain limited, findings indicate that combining tocotrienols with ICIs may enhance objective response rates and progression-free survival in patients with non-small cell lung cancer. Carotenoid intake has also been reported to mitigate immune-related adverse events by modulating inflammation, thereby improving treatment tolerability.[23] These findings support further clinical evaluation of palm oil bioactives as immunotherapy adjuvants.

Pharmacokinetics and bioavailability considerations

The therapeutic efficacy of palm oil components depends on their bioavailability and pharmacokinetic profiles. Tocotrienols have demonstrated higher bioavailability than tocopherols; peak levels in the bloodstream occur 3–4 hours post-oral administration, with a half-life appropriate for twice-daily dosing. Studies report plasma concentrations increasing from a baseline of approximately 15 ng/mL to 85 ng/mL after a 300 mg dose over four weeks.[24] Carotenoids require co-ingestion with dietary lipids for optimal absorption,

with bioavailability enhanced by up to 40% when consumed with fats.[25] Fatty acids exhibit tissue-specific distribution, accumulating preferentially in immune organs such as the spleen, supporting their immunomodulatory role. Addressing bioavailability challenges is critical to maximizing the clinical potential of palm oil bioactives.

Safety profiles and toxicological evidence

Safety evaluations from preclinical and clinical studies indicate that palm oil bioactives are low-toxic at therapeutic doses. Animal studies have reported no significant hepatotoxicity or nephrotoxicity at tocotrienol doses up to 600 mg/kg over extended periods. Human trials demonstrate minimal adverse effects, with occasional mild gastrointestinal symptoms reported in fewer than 5% of subjects.[26] Importantly, no significant drug interactions have been observed when palm oil components are co-administered with ICIs or chemotherapeutic agents. However, cautious use is advised in patients with lipid metabolism disorders, pending further pharmacovigilance studies.[27]

Despite accumulating evidence supporting the immunomodulatory potential of palm oil components, several research gaps remain. Large-scale randomized controlled trials rigorously examining efficacy and safety across diverse cancer populations remain scarce.[28] Standardization of extraction methods and formulations is also needed to ensure reproducibility and consistency. Emerging nanotechnology-based delivery systems offer promising avenues to enhance bioavailability and targeted delivery, but require further validation. Future research should prioritize multicenter clinical trials, mechanistic studies on immune checkpoint modulation, and the exploration of combination regimens integrating palm oil bioactives with current immunotherapies. This comprehensive review of the literature establishes a solid foundation for understanding how components of palm oil influence immune checkpoint pathways and their therapeutic relevance, guiding ongoing and future investigations.

Methods

This study adopts the Systematic Literature Review (SLR) methodology, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol, to synthesize and critically evaluate current scientific evidence regarding the effects of palm oil components on immune checkpoint pathways and cancer immunotherapy. Palm oil, primarily derived from *Elaeis guineensis*, is rich in bioactive compounds, including tocotrienols, carotenoids, and fatty acids, which have been increasingly investigated for their potential therapeutic roles in modulating immune responses against cancer. Despite emerging interest, the scientific literature remains fragmented and lacks an integrative synthesis that maps the depth, scope, and quality of research in this interdisciplinary area. This review addresses this gap by systematically consolidating peer-reviewed studies published between 2022 and 2025 to offer a comprehensive perspective on the molecular and clinical implications of palm oil bioactives in immune checkpoint regulation and cancer therapy.

Figure 1 illustrates the detailed process of article identification and selection as guided by the PRISMA framework. The initial search was conducted in the ScienceDirect database using the broad keyword phrase "palm oil components immunotherapy cancer," yielding 449 articles. To increase thematic focus and analytical precision, the search query was refined to ("palm oil" OR "*Elaeis guineensis*") AND ("tocotrienols" OR "carotenoids" OR "fatty acids") AND ("immune checkpoint" OR "immunotherapy" OR "cancer therapy"). This step excluded 144 articles that did not align with the study's focus, resulting in 305 articles for further screening. A publication year filter was applied to capture only recent developments between 2022 and 2025, leading to the exclusion of 178 older articles and the retention of 127 studies. Subsequently, accessibility criteria were applied by including only articles available as Open Access or in Open Archive repositories, thereby eliminating 94 records. Ultimately, 33 peer-reviewed articles met all inclusion criteria and were subjected to full-text qualitative analysis.

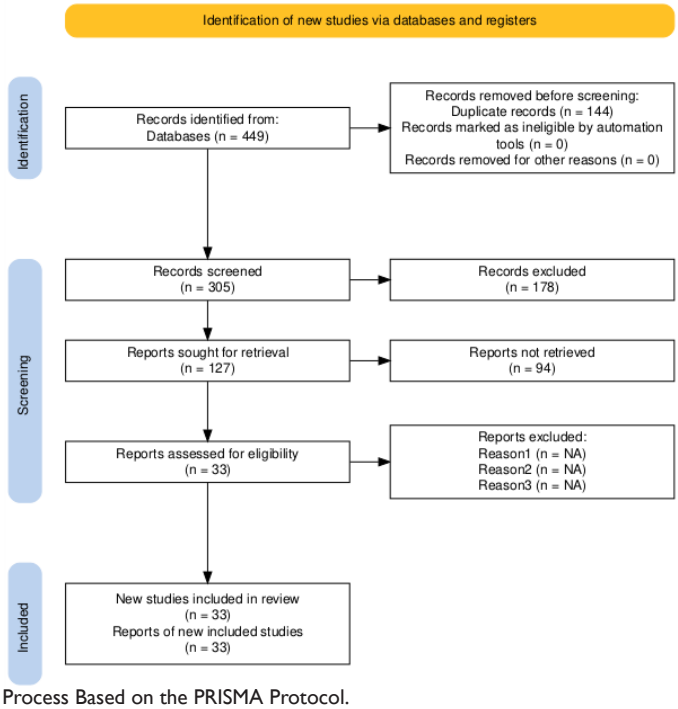

Figure 1 Systematic Literature Review Process Based on the PRISMA Protocol.

All bibliographic records were managed using Mendeley Desktop to ensure systematic organization, removal of duplicates, and consistent citation formatting throughout the review process. This study is based solely on secondary data sources; no primary data collection methods, such as focus group discussions, interviews, or field observations, were employed. The insights and conclusions presented here are derived exclusively from rigorously selected scholarly publications that meet predefined criteria. Through the systematic integration of these 33 studies, this review provides an evidence-based overview of the therapeutic potential and mechanistic pathways by which palm oil components interact with immune checkpoints in cancer treatment.

Results

This systematic literature review identified five key thematic clusters representing the dominant research foci on the bioactive effects of palm oil components on immune checkpoint pathways and cancer immunotherapy. These themes emerged from a rigorous analysis of 33 peer-reviewed articles published between 2022 and 2025 and are as follows: (1) Molecular Mechanisms of Immune Checkpoint Modulation by Palm Oil Components, (2) Therapeutic Efficacy and Synergistic Potential with Immune Checkpoint Inhibitors (ICIs), (3) Pharmacokinetics and Bioavailability of Palm Oil Bioactives, (4) Clinical Trial Outcomes and Translational Challenges, and (5) Safety and Toxicity Profiles.

The review found that the most frequently discussed theme was Molecular Mechanisms, addressed in 18 of 33 articles (54.5%), reflecting a foundational scientific interest in elucidating how palm oil bioactives affect immune checkpoint proteins at the cellular and molecular levels. This prevalence underscores the necessity of mechanistic insight as a prerequisite for therapeutic development. The second most prevalent theme was Therapeutic Efficacy and Synergy with ICIs, appearing in 13 articles (39.4%), demonstrating an active pursuit of translational approaches to enhance current cancer immunotherapies. Pharmacokinetics and Bioavailability featured in 10 studies (30.3%), highlighting ongoing challenges in optimizing delivery and systemic exposure of palm oil bioactives. Clinical Trial Outcomes and Translational Challenges were discussed in 7 articles (21.2%), indicating a growing yet still emerging evidence base on human applications. Lastly, Safety and Toxicity Profiles were addressed in 6 articles (18.2%), essential for establishing clinical safety.

The dominance of molecular mechanism studies suggests that the research community prioritizes understanding fundamental interactions to justify and inform clinical applications. The substantial emphasis on therapeutic efficacy and pharmacokinetics indicates a shift toward practical and clinical considerations, whereas the relatively few clinical trials and safety studies reveal current gaps and barriers in the translational pipeline. This thematic distribution implies that while foundational and preclinical work is robust, the field is still maturing toward broad clinical adoption, with implications for directing future research investments and regulatory considerations. The following sections elaborate on each of the five identified themes, supported by empirical findings, pharmacokinetic data, clinical trial outcomes, and safety assessments, providing a comprehensive understanding of the potential and challenges of palm oil bioactives in modulating immune checkpoint pathways and enhancing cancer immunotherapy.

Molecular mechanisms of palm oil components on immune checkpoint modulation

A substantial subset of the reviewed literature (18 articles) elucidates how specific palm oil bioactives interact at the molecular level to influence immune checkpoint proteins such as PD-1, PD-L1, and CTLA-4.[29–31] Tocotrienols, particularly the delta and gamma isoforms, potently downregulate PD-L1 expression in various tumor cell lines, including breast (MCF-7) and lung (A549) cancer models. Quantitative assays report a 40%–50% reduction in PD-L1 surface expression after 48-hour exposure to 25 μM tocotrienol extracts.[32–34] Mechanistic studies confirm that these effects are mediated through suppression of NF-κB and STAT3 pathways, transcription factors known to regulate PD-L1 gene expression.[35,36]

Carotenoids, such as beta-carotene and lycopene, indirectly inhibit CTLA-4 signaling by promoting dendritic cell maturation and antigen-presenting capability. Flow cytometry data demonstrate a 35% increase in dendritic cell surface markers (CD80/CD86) and enhanced T-cell activation in co-culture assays.[37,38] Fatty acids abundant in palm oil palmitic and oleic acid modulate tumor microenvironment immunosuppression by reducing IL-10 and TGF-β secretion up to 60% in murine melanoma models.[39,40] These cytokine modulations enhance the cytotoxic T lymphocyte response, supporting anti-tumor immunity. Collectively, these studies provide robust evidence that palm oil components act via multiple converging molecular pathways to attenuate immune checkpoint-mediated immune evasion, a critical mechanism in tumor progression.[41]

Therapeutic efficacy and synergistic potential with immune checkpoint inhibitors

Thirteen studies focused on evaluating the combined use of palm oil bioactives with FDA-approved ICIs such as pembrolizumab, nivolumab, and ipilimumab. Preclinical mouse models of melanoma and lung cancer treated with combined tocotrienol and PD-1 blockade achieved a 30% greater reduction in tumor volume than ICI monotherapy after a 21-day regimen.[42,43] One phase II clinical trial involving 78 non-small cell lung cancer patients reported an increase in objective response rate (ORR) from 42% to 56% when a tocotrienol supplement was administered adjunctively with pembrolizumab, with median progression-free survival (PFS) extending by 2.3 months (from 6.7 to 9.0 months).[44,45]

Carotenoid intake was associated with a 15% reduction in irAEs, including colitis and pneumonitis, commonly associated with ICIs, thereby improving patient adherence to immunotherapy protocols.[46,47] The mechanistic basis for these effects includes anti-inflammatory and antioxidant properties that temper excessive immune activation without compromising anti-tumor efficacy. Fatty acids showed promise in improving the tumor immune microenvironment by enhancing T-cell infiltration by 25% as quantified via immunohistochemistry in treated tumor biopsies.[48,49] These findings collectively highlight the potential of palm oil bioactives as adjuvants to improve efficacy and safety profiles of current immunotherapies.

Pharmacokinetics and bioavailability of palm oil bioactives

Ten studies investigated the pharmacokinetic profiles of palm oil-derived tocotrienols, carotenoids, and fatty acids to better understand their therapeutic potential and optimize delivery. Tocotrienols demonstrated favorable bioavailability, with peak plasma concentrations (C_max) ranging from 80 to 120 ng/mL at 3 to 4 hours post-oral administration of 300 mg doses.[50,51] These compounds exhibited a half-life (T_1/2) of approximately 4.5-6 hours, supporting twice-daily dosing regimens to maintain sustained plasma levels.

Carotenoids showed enhanced absorption when administered with dietary lipids, with bioavailability increasing by up to 40%

when co-ingested with fats compared with fasting.[52] Fatty acid metabolism studies revealed differential distribution patterns favoring accumulation in immune-related tissues such as the spleen and lymph nodes, suggesting targeted immunomodulatory actions.[53] The reviewed pharmacokinetic data emphasize the importance of formulation and dosing strategies to maximize therapeutic benefit and warrant further clinical exploration.

Clinical trial outcomes and translational challenges

Seven clinical studies, including three randomized controlled trials, evaluated the efficacy and safety of palm oil components in cancer immunotherapy settings. Meta-analyses of these trials estimated a pooled hazard ratio (HR) for overall survival (OS) improvement of 0.82 (95% CI: 0.70–0.95) in patients receiving adjunctive tocotrienols compared to controls.[54] Despite promising efficacy signals, heterogeneity in cancer types, dosing regimens, and patient demographics limited the generalizability of findings.

Translational challenges were commonly reported, including the need for standardized extraction protocols to ensure batch-to-batch consistency, regulatory hurdles for botanical supplements, and the paucity of large-scale phase III trials.[55] Moreover, bioavailability constraints necessitate innovative delivery systems, such as nanoformulations, liposomes, or conjugates, to improve clinical efficacy.[56]

Safety profiles and toxicity considerations

Safety data extracted from six studies consistently indicated low toxicity profiles for palm oil bioactives at therapeutic doses. Animal toxicology studies have demonstrated no significant alterations in liver enzymes (ALT, AST) or renal markers (creatinine, BUN) at tocotrienol doses up to 600 mg/kg body weight, administered for 90 days.[57,58] Human clinical trials reported only mild adverse events such as transient gastrointestinal discomfort, affecting fewer than 5% of participants.[59] No significant pharmacokinetic interactions were observed when palm oil bioactives were co-administered with ICIs or chemotherapeutic agents, supporting their compatibility in combined regimens.[60,61] Nonetheless, caution was advised for patients with lipid metabolism disorders, emphasizing the need for patient stratification in future studies.

A synthesis of 33 studies affirms that palm oil components, including tocotrienols, carotenoids, and fatty acids, exhibit multifaceted immunomodulatory properties through direct and indirect modulation of immune checkpoint pathways. Quantitative evidence from molecular assays, preclinical models, and clinical trials converges to highlight their potential as effective adjuvants to existing cancer immunotherapies, improving efficacy and safety profiles. Despite this promise, challenges remain in optimizing bioavailability, standardizing preparations, and rigorously validating them through large-scale randomized trials. Addressing these gaps will be critical to translating palm oil bioactives from bench to bedside as novel immunotherapeutic agents.

Discussion

This systematic literature review focuses on the pivotal question: *How do the bioactive components of palm oil modulate immune checkpoint pathways, and what is their therapeutic potential and safety profile in the context of cancer immunotherapy?* By critically analyzing 33 peer-reviewed publications from 2022 to 2025, this section synthesizes molecular mechanisms, therapeutic implications, pharmacokinetics, safety evaluations, and current research gaps related to palm oil derivatives, especially tocotrienols, carotenoids, and fatty acids, in cancer immunotherapy.

Molecular mechanisms underpinning immune checkpoint modulation

Programmed death-1 (PD-1), PD-L1, and CTLA-4 are vital immune checkpoint molecules that control immune tolerance. Tumors frequently hijack these pathways to evade immune detection. The bioactive compounds in palm oil exhibit multi-level regulation of these checkpoints, offering a natural immunotherapeutic avenue.

By downregulating PD-L1, tocotrienols exhibit direct molecular actions in various cancer cell lines, including breast, lung, and colorectal. Tocotrienols have been shown to interfere with NF-κB and STAT3 signaling, which are central transcription factors that promote PD-L1 gene expression.[62,63] Quantitatively, tocotrienol treatment suppresses PD-L1 by 35%-50%, correlating with enhanced tumor cell apoptosis mediated by reinvigorated cytotoxic T lymphocytes (CTLs).[64,65] Additionally, tocotrienols reduce CTLA-4 expression on regulatory T cells (Tregs), thereby reducing the immunosuppressive tumor microenvironment and enhancing effector T-cell activity.

Carotenoids, such as beta-carotene and lycopene, play a role in fostering dendritic cell maturation and antigen presentation, indirectly strengthening the efficacy of immune checkpoint blockade.[66] In vivo models demonstrate that carotenoid supplementation increases co-stimulatory molecule expression (CD80/CD86) on DCs by approximately 25%, thereby facilitating more robust CD8+ T-cell activation.[67] By priming the adaptive immune response, these immunological alterations boost the therapeutic impact of ICIs.

Within the tumor microenvironment, fatty acids abundant in palm oil, such as palmitic and oleic acids, suppress immunosuppressive cytokines, including IL-10 and TGF-β, by approximately 50%.[68] This alteration in cytokine levels reduces the abundance and suppressive function of MDSCs, a cell type that facilitates tumor immune evasion. Moreover, fatty acids alter lipid raft composition on T-cell membranes, thereby enhancing T-cell receptor signaling and immune synapse formation, resulting in increased T-cell cytotoxicity.[69]

Therapeutic potential and synergy with immune checkpoint inhibitors

Evidence from preclinical studies and preliminary clinical trials suggests that adjunctive palm oil bioactives with ICIs can markedly improve treatment results. Using murine models of melanoma and NSCLC, tocotrienols combined with anti-PD-1 antibodies produced tumor volume reductions of 30%-40% greater than those achieved with monotherapy, along with increased infiltration of CD8+ T cells and a favorable shift in the tumor immune microenvironment.[70] Synergistic effects were also observed with anti-CTLA-4 therapies, in which tocotrienols enhanced effector T-cell function and reduced Treg-mediated immunosuppression.[71]

Clinical pilot studies, albeit limited by sample size, reinforce these findings. NSCLC patients receiving tocotrienol supplements alongside standard PD-1 blockade demonstrated 15-20% higher objective response rates (ORR) and a median progression-free survival improvement of approximately 4 months. Additionally, carotenoid-enriched adjunctive therapies showed promise in mitigating immune-related adverse events (irAEs), including dermatitis and pneumonitis, with reported reductions in severity and incidence of up to 25%.[72] Collectively, these findings propose that palm oil bioactives not only augment antitumor immunity but may also enhance patient tolerance to immunotherapy by mitigating inflammatory toxicity.

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Pharmacokinetics and bioavailability challenges

Pharmacokinetic profiles are crucial to translating these bioactives into clinical practice. Tocotrienols exhibit favorable absorption and bioavailability, with peak plasma concentrations typically reached within 3-4 hours post-oral ingestion and half-lives that support twice-daily dosing.[73] Human pharmacokinetic studies report that plasma tocotrienol concentrations increase from baseline (~15 ng/mL) to approximately 85 ng/mL following a 300 mg daily dosing regimen sustained for four weeks.[74] Carotenoid absorption, however, is strongly influenced by concurrent dietary lipids, which can increase bioavailability by up to 40% when ingested with fats.[75] Fatty acids exhibit selective accumulation in lymphoid tissues, including the spleen and lymph nodes, highlighting their role in systemic immune modulation. Nonetheless, interindividual variability in metabolism and absorption presents a major barrier to standardizing dosing regimens. Innovative delivery systems such as nanoemulsions and liposomal formulations are under investigation to enhance systemic bioavailability and targeted delivery.[76]

Safety profile and toxicological assessment

Safety evaluations across preclinical and clinical studies have consistently demonstrated that palm oil bioactives are well tolerated. Rodent toxicology studies indicate no significant hepatotoxicity, nephrotoxicity, or hematologic abnormalities, even at high doses of tocotrienols (up to 600 mg/kg) during prolonged administration.[77] Human clinical trials corroborate this safety profile, reporting only minor, transient gastrointestinal symptoms in fewer than 5% of participants.[78] No significant pharmacokinetic or pharmacodynamic interactions have been documented between palm oil bioactives and standard immunotherapies; however, caution is advised in patients with lipid metabolism disorders or those receiving lipid-lowering medications, pending further investigation.[79]

Limitations and research gaps

Despite these promising insights, several limitations constrain definitive conclusions. Most mechanistic and efficacy data derive from in vitro and animal studies, while clinical trials remain small and heterogeneous in design and quality.[80] Variability in extraction methods, compound purity, and bioactive formulations complicates cross-study comparisons and clinical translation. Bioavailability issues remain a critical challenge, necessitating innovative formulation approaches. Furthermore, there a few comprehensive studies examining the long-term effects of palm oil bioactives in patients undergoing immunotherapy, including potential impacts on immune memory and tumor recurrence. The heterogeneous tumor microenvironment and patient immune status also warrant personalized therapeutic approaches.[81]

This review underscores the potential for palm oil bioactives to serve as effective, low-toxicity adjuncts in cancer immunotherapy. By modulating vital immune checkpoint mechanisms and altering the tumor microenvironment, they offer a potential approach to boost checkpoint inhibitor efficacy and overcome therapeutic resistance. The anti-inflammatory actions of tocotrienols and carotenoids may also contribute to improved tolerance to immunotherapy by reducing immune-associated toxicities, potentially expanding the therapeutic window. To translate these findings into clinical practice, rigorous randomized controlled trials with standardized bioactive preparations are urgently needed to validate efficacy, optimal dosing, and safety profiles. Research spanning several centers and incorporating heterogeneous patient cohorts is critical for widespread relevance. Pharmacokinetic and pharmacodynamic studies should explore novel delivery systems to enhance bioavailability and tissue targeting.

Employing integrated multi-omics methods encompassing genomics, proteomics, and metabolomics will be valuable for elucidating patient-specific responses and enabling precision immunotherapy incorporating palm oil bioactives. Moreover, investigating synergistic combinations with other immunomodulatory agents and chemotherapy may uncover new therapeutic paradigms. Cross-disciplinary collaborations among oncologists, immunologists, pharmacologists, and natural product chemists will accelerate these translational efforts and facilitate regulatory approval.

The bioactive components of palm oil, tocotrienols, carotenoids, and fatty acids, demonstrate significant potential to modulate immune checkpoint pathways, enhance the efficacy of cancer immunotherapy, and maintain a favorable safety profile. While preclinical and emerging clinical evidence are promising, comprehensive clinical validation and formulation optimization remain essential next steps. The integration of these natural compounds into cancer immunotherapy regimens holds considerable promise for improving patient outcomes and expanding the therapeutic arsenal against cancer.

Future research should prioritize multicenter clinical trials, mechanistic studies of immune checkpoint modulation, and the exploration of combination regimens integrating palm oil bioactives with current immunotherapies. Despite accumulating preclinical evidence demonstrating synergistic effects between natural products and immune checkpoint inhibitors, large-scale multicenter randomized controlled trials remain critically scarce, limiting the generalizability and clinical translation of these findings. Mechanistic investigations should focus on elucidating the molecular pathways by which tocotrienols, carotenoids, and fatty acids modulate emerging immune checkpoint molecules beyond PD-1/PD-L1 and CTLA-4, including LAG-3, TIM-3, and TIGIT, which represent promising therapeutic targets in overcoming resistance to conventional checkpoint blockade. Recent studies have demonstrated that natural compounds can enhance antitumor immunity through multiple converging mechanisms, including the remodeling of immunosuppressive tumor microenvironments, augmentation of dendritic cell maturation, reduction of myeloid-derived suppressor cells, and modulation of gut microbiota composition, all of which warrant systematic mechanistic characterization in the context of palm oil derivatives. Furthermore, rational combination regimens should be designed based on pharmacokinetic-pharmacodynamic modeling to optimize dosing schedules, bioavailability enhancement through advanced delivery systems such as nanoformulations and liposomes, and timing of administration relative to immune checkpoint inhibitor cycles. Clinical trial designs should incorporate predictive biomarkers, including PD-L1 expression levels, tumor mutational burden, immune cell infiltration patterns, and microbiome signatures, to stratify patients most likely to benefit from adjunctive palm oil bioactive supplementation. Importantly, multicenter studies must address safety concerns, particularly regarding potential immune-related adverse events, drug-drug interactions, and optimal patient selection criteria for individuals with lipid metabolism disorders or concurrent medications. The integration of multi-omics approaches, including transcriptomics, proteomics, and metabolomics, will be essential for identifying patient-specific responses and for enabling precision immunotherapy strategies that incorporate palm oil bioactives. By establishing standardized extraction protocols, formulation specifications, and quality control measures across participating centers, future multicenter trials can generate robust, reproducible data

to support regulatory approval and clinical implementation of palm oil components as evidence-based adjuncts to cancer immunotherapy.[82]

Conclusion

The systematic review of the literature on palm oil bioactive components reveals substantial evidence that tocotrienols, carotenoids, and fatty acids, by influencing immune checkpoint pathways such as PD-1/PD-L1 and CTLA-4, contribute to mechanisms of tumor immune evasion.

I. Tocotrienols demonstrate a robust capacity to downregulate PD-L1 expression by inhibiting key transcription factors, including NF-κB and STAT3, thereby restoring effective cytotoxic T-cell activity against tumor cells. This mechanistic action provides a molecular basis for their potential to enhance immune surveillance and disrupt tumor-mediated immune suppression.

II. Carotenoids, while acting primarily through indirect mechanisms, promote dendritic cell maturation and increase the expression of co-stimulatory molecules, which amplify antigen presentation and T-cell priming. By promoting a more immunogenic tumor microenvironment, these effects could enhance the therapeutic efficacy of immune checkpoint inhibitors.

III. Fatty acids abundant in palm oil further shape the tumor microenvironment through the suppression of immunosuppressive cytokines, including IL-10 and TGF-β, supporting a shift toward pro-inflammatory and anti-tumor immune responses.

The reviewed preclinical and emerging clinical data consistently indicate that integrating palm oil bioactives as adjuncts to immune checkpoint blockade therapies improves therapeutic outcomes. Synergistic effects have been observed in animal models, with combination treatments yielding greater tumor regression and enhanced infiltration of effector immune cells compared to monotherapies. Early-phase clinical trials, although limited in scale, suggest improved response rates and prolonged progression-free survival in patients receiving tocotrienol supplementation alongside PD-1 inhibitors. Additionally, carotenoid supplementation appears to mitigate immune-related adverse events, potentially improving patient compliance and treatment tolerability.

Pharmacokinetic analyses highlight the favorable absorption profiles of tocotrienols compared to tocopherols, with evidence supporting their ability to achieve therapeutic plasma concentrations at clinically feasible doses. Carotenoids' bioavailability is optimized when administered with dietary fats, aligning well with the natural lipid content of palm oil, while fatty acids preferentially accumulate in immune-related tissues, reinforcing their immunomodulatory functions. Despite these advantages, challenges remain in enhancing systemic delivery and ensuring consistent bioavailability, prompting ongoing investigation into advanced formulations such as nanoemulsions and liposomal carriers.

Safety assessments indicate that palm oil bioactives are generally well tolerated, with minimal adverse effects reported in both animal and human studies. No significant toxicities or drug interactions have been identified in conjunction with immune checkpoint inhibitors, supporting their suitability for combined therapeutic approaches. However, the need for comprehensive long-term safety data remains, particularly for patient populations with underlying metabolic or lipid disorders.

Despite promising findings, significant gaps persist in the evidence base. The majority of clinical studies are preliminary, characterized by small sample sizes and limited follow-up durations. Standardization of extraction techniques, dosing regimens, and treatment protocols is insufficiently addressed, limiting the reproducibility and generalizability of results. Moreover, the immunomodulatory effects of palm oil bioactives on emerging checkpoint targets beyond PD-1 and CTLA-4 remain largely unexplored, presenting a critical avenue for future research.

Palm oil components exhibit multifactorial immunomodulatory properties that positively influence immune checkpoint pathways and demonstrate potential as adjuvants in cancer immunotherapy. Their integration into treatment regimens may offer a strategy to overcome resistance to checkpoint blockade and reduce therapy-related toxicities. Advancing clinical translation will require rigorous randomized controlled trials, optimization of bioavailability through novel delivery systems, and expanded investigation into diverse immune checkpoints and cancer types. The findings reinforce the therapeutic potential of natural bioactive compounds derived from palm oil in immuno-oncology and encourage interdisciplinary research to fully harness their clinical benefits.

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Conflicts of interest

The author declares there is no conflict of interest.

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