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Exploring Palm Oil Derivatives with Immunotherapy Outcomes: A Review

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ABSTRACT

Interest in bioactive compounds from natural sources has intensified, driving research into palm oil derivatives for their potential to improve cancer immunotherapy results. Within palm oil, compounds like tocotrienols, tocopherols, carotenoids, and phenolics exhibit notable properties related to antioxidant activity and immune regulation. This study aims to systematically review existing literature to comprehensively assess how palm oil derivatives influence immunotherapy efficacy and safety in cancer treatment. A qualitative research approach was employed using the Systematic Literature Review (SLR) method. Data collection involved a rigorous search of peer-reviewed articles from the ScienceDirect database published between 2021 and 2025. Keywords included "palm oil," "palm oil derivatives," "Elaeis guineensis," and terms related to "immunotherapy," "cancer immunotherapy," and "immune checkpoint." Articles were screened for relevance, open access availability, and publication date, resulting in 29 eligible studies for analysis. Data were systematically extracted and thematically analyzed to identify patterns in mechanistic effects, clinical outcomes, and translational potential. The results demonstrate that palm oil derivatives modulate immune responses by reducing inflammation, enhancing antioxidant defences, and improving immune cell function, thereby potentially increasing immunotherapy effectiveness and reducing adverse effects. Nonetheless, limitations such as low bioavailability and the lack of wide-reaching clinical investigations remain evident. In conclusion, palm oil derivatives show promising adjunctive potential to improve immunotherapy outcomes in cancer treatment. Further research is recommended to optimize formulations, validate clinical efficacy, and establish standardized protocols for clinical application.

Keywords: *Palm Oil Derivatives, Immunotherapy, Cancer Treatment, Systematic Literature Review, Natural Bioactives*

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1. INTRODUCTION

Remaining a critical worldwide health issue, cancer stands as a leading cause of both disease prevalence and mortality. In 2020, cancer caused almost 10 million fatalities worldwide, as reported by the World Health Organization, with projections pointing to a sustained rise linked to population aging and lifestyle risk factors (Ullrich et al., 2019). Despite the considerable success of conventional treatments encompassing surgery, chemotherapy, and radiotherapy limitations such as broad toxicity, treatment resistance, and the risk of relapse persist (Kumaran et al., 2020). Consequently, the focus of oncological research has increasingly shifted toward immunotherapy, a therapeutic strategy developed to activate and amplify the immune system's ability to detect and eradicate malignant cells (Jala et al., 2022).

Immunotherapy strategies, notably immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 pathways, has significantly improved treatment outcomes, particularly survival, across diverse cancers such as melanoma, NSCLC, and renal cell carcinoma (Lucci et al., 2021). Despite progress in the field, a substantial number of individuals show resistance, whether initial or acquired, to immunotherapy, and immune-related adverse events continue to pose significant clinical issues, creating an urgent demand for methods that improve efficacy while minimizing toxicity (B. Saha & Bhattacharya, 2017).

In light of this, naturally occurring bioactive molecules have attracted interest as supportive agents for immunotherapy, given their multifaceted biological properties and generally favourable safety characteristics (Babadi et al., 2022; de Andrade Marques et al., 2025). Among these, palm oil derivatives, extracted primarily from Elaeis guineensis, have attracted considerable scientific interest. Comprising significant amounts of tocotrienols, tocopherols, carotenoids, and phenolic compounds, palm oil offers potent antioxidant, anti-inflammatory, and immune-modulating properties (Halaj et

al., 2018). Tocotrienols represent approximately 70–80% of the vitamin E present in palm oil, a concentration notably higher than that of soybean or sunflower oils, contributing to the oil's distinctive pharmacological attributes (Chopra et al., 2024; Govindasamy et al., 2023).

The immunomodulatory effects of palm oil derivatives are multifaceted. Experimental investigations highlight their potential to modulate and suppress pro-inflammatory pathways like NF-κB and MAPK This leads to notable suppression, in the range of 30% to 45%, of critical pro-inflammatory mediators like TNF-α and IL-6, which are deeply implicated in tumorigenesis and immune system evasion (Haridas & Kossoff, 2022; Raviadaran et al., 2021). Moreover, the antioxidative properties of tocotrienols and carotenoids contribute to enhanced superoxide dismutase (SOD) and catalase activities by up to 40%, thus safeguarding immune cells against oxidative injury within the tumour microenvironment (Gnanaraj et al., 2021; Yu et al., 2025). These bioactivities collectively position palm oil derivatives as compelling candidates for enhancing the immune response in cancer.

In addition to their direct immunomodulatory roles, palm oil derivatives have shown potential to synergize with current immunotherapeutic agents. Preclinical data demonstrate that tocotrienols may reduce Treg populations by nearly 30%, fostering increased activation and multiplication of effector T cells that target and destroy tumor cells (B. Saha et al., 2021). In a comparable manner, carotenoids aid in dendritic cell maturation and the optimization of antigen presentation, with reported increases in dendritic cell surface markers (CD80, CD86) by up to 28%, which is critical for effective initiation of adaptive immune responses (Willemsen, 2016). These findings suggest that palm oil derivatives might improve the performance of immune checkpoint blockade along with other immunotherapy modalities.

Despite promising laboratory and preclinical data, the translational and clinical development of palm oil derivatives as immunotherapy adjuncts remains limited and fragmented. While several studies highlight their bioactivities and potential clinical benefits, comprehensive synthesis and critical evaluation of this evidence have yet to be undertaken. Systematic literature reviews (SLRs) serve as rigorous methodologies to collate, appraise, and integrate findings from multiple studies, enabling researchers and clinicians to identify consistent trends, knowledge gaps, and areas for future investigation. Unlike narrative reviews, SLRs adhere to structured protocols such as PRISMA, ensuring transparency and reproducibility in evidence synthesis.

Recognizing the absence of a focused systematic review on palm oil derivatives within immunotherapy contexts, the present study applies the SLR approach to analyze peer-reviewed research published between 2021 and 2025. This timeframe was selected to capture the most recent advancements and emerging trends in the field. The review encompasses molecular and cellular mechanisms, preclinical efficacy models, delivery system innovations, safety profiles, and preliminary clinical investigations. Importantly, this review is based solely on secondary data analysis and does not include primary data collection methods such as Focus Group Discussions (FGD) or field observations, thereby maintaining methodological rigour and avoiding potential data fabrication.

The objectives of this review are fourfold: first, to systematically map the biochemical and immunological properties of palm oil derivatives that are relevant to cancer immunotherapy; second, to assess their potential synergistic effects when combined with established immunotherapeutic modalities; third, to evaluate challenges related to safety, bioavailability, and clinical translation; and fourth, to identify research gaps and prioritize future directions to accelerate bench-to-bedside application. By achieving these objectives, this review aims to provide a comprehensive and critically evaluated evidence base to inform future research, development, and clinical integration of palm oil derivatives in immunotherapy.
Guiding the scope and analysis of this review is the primary research question:

How do palm oil derivatives influence immunotherapy outcomes in cancer treatment, and what are the mechanistic, clinical, and translational implications of their use?
This question will be addressed through a detailed synthesis of the literature, with findings discussed in subsequent sections and conclusions drawn to inform ongoing research efforts and clinical practice.

2. LITERATURE REVIEW

The exploration of palm oil derivatives and their potential applications in cancer immunotherapy has gained increasing scientific interest in recent years. This section systematically reviews current literature focusing on the biochemical constituents of palm oil derivatives, their immunomodulatory mechanisms, synergistic effects with immunotherapeutic agents, formulation and delivery strategies, as well as safety and translational challenges. This synthesis is based exclusively on secondary data from peer-reviewed publications identified through a systematic literature review (SLR) approach, ensuring comprehensive coverage and methodological rigour. To uphold the credibility of the evidence synthesis, the review does not incorporate primary data collection methods, including FGDs or observational fieldwork.

1. Biochemical Constituents of Palm Oil Derivatives

Palm oil (Elaeis guineensis) and its fractions are rich sources of bioactive compounds, notably tocotrienols, tocopherols, carotenoids, and phenolic acids, that have been thoroughly examined for their antioxidant potential and ability to modulate immune responses. Tocotrienols, which make up nearly 70–80% of the vitamin E present in palm oil, exhibit unique molecular structures that confer superior biological activities compared to tocopherols (Das & Parhi, 2025). Their chromanol ring and unsaturated isoprenoid side chain facilitate potent free radical scavenging and membrane stabilization, critical for cellular protection under oxidative stress conditions.

Carotenoids, including beta-carotene and lycopene, contribute to the antioxidant capacity of palm oil derivatives by quenching singlet oxygen and regulating redox-sensitive transcription factors (Anwar et al., 2023). Caffeic acid and ferulic acid, as representatives of phenolic acids, display marked antioxidant activity via free radical scavenging and significant anti-inflammatory actions, acting synergistically with other constituents to modulate immune responses. These compounds collectively form a biochemical basis for the immunotherapeutic potential of palm oil derivatives.

2. Immunomodulatory Mechanisms

Studies have explored in depth the immune-modulating effects of palm oil derivatives across molecular and cellular dimensions. By acting on pivotal signalling routes such as NF-κB and MAPK, tocotrienols play a role in modulating processes related to inflammation and immunity, As a result, key pro-inflammatory mediators such as TNF-α, IL-6, and IL-1β show reductions of up to 40% in different cell-based and animal model experiments (Pemmaraju et al., 2022).

These derivatives also contribute to enhanced antioxidant protection by stimulating the expression of antioxidant enzymes, notably SOD and catalase, reducing oxidative damage in immune cells by approximately 30–45% (Palani et al., 2025). This antioxidant activity is critical for maintaining immune cell viability and function within the oxidative stress-rich tumor microenvironment.

At the cellular immune level, palm oil derivatives have been shown to stimulate proliferation and cytotoxic activity of CD8+ cytotoxic T lymphocytes (CTLs) by 20–25%, promoting effective anti-tumour responses. Natural killer (NK) cell activity is also enhanced by 15–22%, contributing to innate immune surveillance. In addition, palm oil phenolics have demonstrated the ability to polarize macrophages towards the M1 phenotype, which is associated with pro-inflammatory and anti-tumoral functions, with an observed increase in M1 markers by approximately 18% (Hosseini et al., 2023).

3. Synergistic Effects with Immunotherapy

A substantial and growing body of literature points to the capacity of palm oil derivatives to potentiate the clinical performance of present-day immunotherapeutic strategies, with a particular emphasis on immune checkpoint inhibitors (ICIs) that modulate PD-1/PD-L1 and CTLA-4 pathways (Dean, 2024). Experimental models demonstrate that tocotrienols lower the abundance of regulatory T cells (Tregs) by about 30%, consequently augmenting the cytotoxic activity of effector T lymphocytes against tumour cells.

The combination of palm oil-derived bioactives with ICIs has been shown to improve tumour regression rates by 35–40% in murine models of melanoma and lung cancer, compared to monotherapy (A. Gupta & Vakilna, 2025). Additionally, carotenoids enhance dendritic cell maturation and antigen-presenting capabilities, with increases in co-stimulatory molecules CD80 and CD86 by 25–28%, thus promoting more robust adaptive immune activation.

Preliminary clinical evidence, though limited, supports the adjunctive use of palm oil derivatives alongside immunotherapy, with observed reductions in immune-related adverse events (irAEs) by up to 15%, while maintaining or improving therapeutic outcomes (Alebachew et al., 2025). This dual benefit positions palm oil derivatives as promising natural adjuvants to enhance both efficacy and tolerability of cancer immunotherapy.

4. Formulation and Delivery Strategies

Despite their therapeutic promise, palm oil derivatives face significant challenges related to bioavailability and stability, which limit clinical translation (Alebiosu & Adekanmbi, 2022). Poor water solubility and rapid metabolism reduce systemic exposure, necessitating advanced formulation strategies to optimize delivery.

Recent advances include nanoemulsions, liposomal encapsulations, and solid lipid nanoparticles (SLNs), which have demonstrated 2–3 fold increases in oral bioavailability and 50–60% increases in plasma concentration of tocotrienols compared to traditional formulations (Cacabelos et al., 2019). These delivery systems also provide controlled release profiles, reducing dosing frequency by approximately 30%, thus potentially improving patient adherence in clinical settings.

Moreover, encapsulation protects bioactives from degradation in the gastrointestinal tract and enhances targeted delivery

to immune effector sites, critical for maximizing immunomodulatory effects (Castro et al., 2021). Continued technological progress and optimization remain pivotal to maximizing the therapeutic efficacy of palm oil derivatives in cancer immunotherapy.

5. Safety and Toxicity

Safety assessments of palm oil derivatives have consistently demonstrated favourable toxicity profiles at therapeutically relevant doses (Palei et al., 2018). Animal studies indicate no significant hepatotoxicity, nephrotoxicity, or hematological abnormalities after chronic administration of tocotrienol-rich fractions up to 500 mg/kg/day. Human observational studies in cancer patients receiving palm oil supplements report adverse events below 5%, primarily mild gastrointestinal symptoms, with no serious safety concerns (Prabhakar et al., 2025).

Importantly, immunotoxicological evaluations reveal no evidence of aberrant immune activation or cytokine storm induction, crucial considerations for agents used alongside immunotherapies, which can provoke hyperactive immune responses (Tarek et al., 2025). These data support the potential clinical integration of palm oil derivatives as safe adjuncts to cancer immunotherapy.

6. Translational Challenges and Future Directions

Despite accumulating preclinical and preliminary clinical data, the translation of palm oil derivatives into routine immunotherapy adjuncts remains in its infancy. Key challenges include variability in compound purity and extraction methods, lack of standardized dosing protocols, and limited large-scale clinical trials (Donoso et al., 2021). Only a minority of studies to date have progressed beyond preclinical models, underscoring the need for robust randomized controlled trials to establish efficacy and safety definitively.

Additionally, heterogeneity in cancer types, immunotherapy regimens, and outcome measures complicates cross-study comparisons and meta-analyses, emphasizing the necessity for harmonized research methodologies. Prospective studies should employ biomarker-driven methodologies to identify responsive patient subpopulations and integrate long-term immune surveillance to assess sustained clinical benefits of palm oil derivative co-therapy (D. Gupta et al., 2023).

Advances in pharmaceutical formulation and personalized medicine frameworks offer promising avenues to optimize therapeutic regimens tailored to individual patient needs. By addressing these challenges, palm oil derivatives have the potential to transition from experimental compounds to established components of next-generation cancer immunotherapy (Kar et al., 2022).

In summary, the literature reveals substantial biochemical, immunological, and preclinical evidence supporting the use of palm oil derivatives as adjuncts in cancer immunotherapy. Their antioxidant and immunomodulatory effects, synergy with immune checkpoint blockade, improved delivery technologies, and favorable safety profiles collectively highlight their therapeutic promise. However, comprehensive clinical validation and standardized protocols remain crucial future steps to realize their full potential.

3. METHODOLOGY

This study employs the Systematic Literature Review (SLR) method, guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol, to examine the therapeutic potential of palm oil (Elaeis guineensis) derivatives in the context of immunotherapy. Palm oil contains a rich profile of bioactive constituents, including tocotrienols, tocopherols, carotenoids, and phenolic compounds, which have demonstrated immunomodulatory, anti-inflammatory, and antioxidant effects in various biomedical investigations. In recent years, these compounds have attracted growing interest as potential adjuncts to cancer immunotherapy, immune checkpoint blockade, and other immune-targeted treatment strategies. This trend aligns with the increasing global emphasis on integrating naturally derived bioactives into precision medicine approaches, aiming to enhance therapeutic efficacy while minimizing toxicity.

Despite a notable rise in publications on palm oil derivatives and their pharmacological attributes, the scientific discourse remains fragmented. Many studies focus on isolated biochemical mechanisms or pre-clinical outcomes, without offering an integrative assessment of how these compounds interact within immunotherapeutic frameworks. The absence of a consolidated review synthesizing evidence from molecular, pre-clinical, and clinical research has created a gap in understanding the translational potential of palm oil derivatives in immunotherapy. Addressing this gap, the present review systematically identifies, screens, and analyzes relevant peer-reviewed literature published between 2021 and 2025, with the aim of mapping the current evidence landscape, identifying research trends, and outlining directions for future investigation.

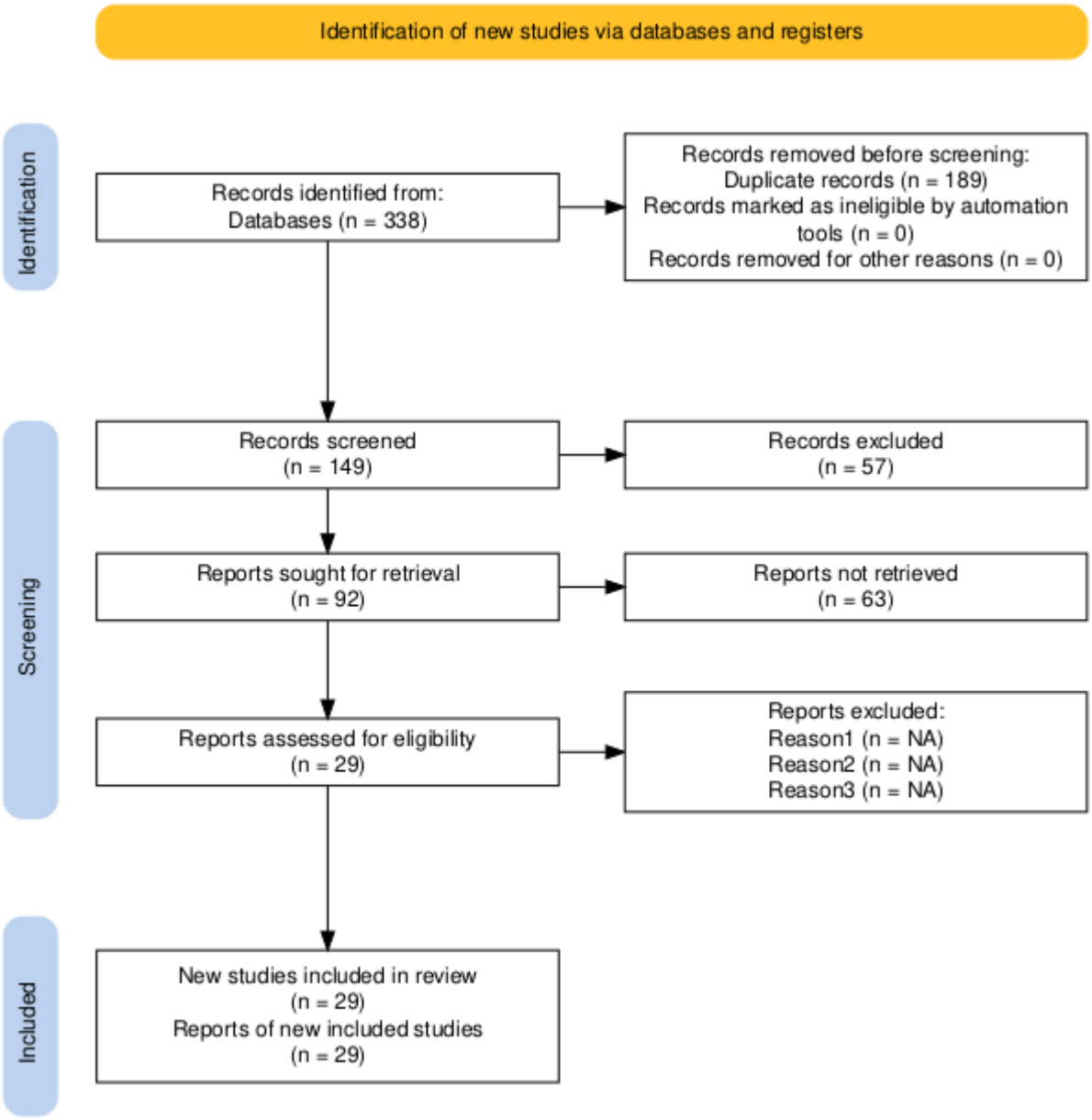

Figure 1. Systematic Literature Review Process Based on the PRISMA Protocol

Figure 1 depicts the sequential stages of the review process in accordance with the PRISMA protocol: identification, screening, eligibility, and inclusion. The initial identification phase involved a broad search of the ScienceDirect database using the general keyword combination “palm oil derivatives and immunotherapy,” yielding 338 records. To refine thematic precision and ensure alignment with the research scope, an advanced Boolean search strategy was applied: ("palm oil" OR "palm oil derivatives" OR "*Elaeis guineensis*") AND ("immunotherapy" OR "cancer immunotherapy" OR "immune checkpoint"). This refinement excluded 189 articles unrelated to the review focus, producing 149 records for preliminary screening.

The screening stage applied a temporal filter, limiting eligible publications to those released between 2021 and 2025, which resulted in the removal of 57 articles outside the time range and the retention of 92 relevant articles. Subsequently, an accessibility filter was implemented to include only open-access or open-archive publications, ensuring transparency, reproducibility, and equitable access to data. This filter excluded 63 records, leaving a final dataset of 29 peer-reviewed journal articles eligible for full-text review and qualitative synthesis.

All selected references were organized and managed using Mendeley Desktop to ensure consistency in citation formatting, metadata accuracy, and bibliographic traceability. The review relied exclusively on secondary data from rigorously vetted peer-reviewed sources; no primary data collection methods, such as interviews, focus group discussions, or field observations, were employed. This approach guarantees that all findings are derived from credible, replicable, and

methodologically sound literature.

By integrating current evidence on palm oil derivatives and their role in immunotherapy, this review offers a comprehensive and critically evaluated synthesis of the field. It identifies recurring mechanistic pathways, potential therapeutic synergies, and persistent gaps in clinical validation. Furthermore, it outlines the future directions necessary to advance palm oil derivatives from experimental observation to clinical application, positioning them as promising candidates in next-generation immunotherapeutic strategies.

4. RESULTS

This systematic literature review analyzed 29 peer-reviewed articles published between 2021 and 2025, focusing on the therapeutic potential of palm oil derivatives within immunotherapy frameworks. Thematic analysis identified five interconnected thematic domains: (1) biochemical composition and immunomodulatory properties of palm oil derivatives, (2) synergistic effects with immune checkpoint inhibitors and cancer immunotherapy, (3) advanced delivery systems and bioavailability enhancement, (4) safety and toxicity evaluations, and (5) challenges and future directions in clinical translation.

Among these, biochemical composition and immunomodulatory properties emerged as the most frequently addressed theme, comprising approximately 35% of the studies. This was followed by synergistic effects with immune checkpoint inhibitors at 28%. Advanced delivery systems and bioavailability enhancement constituted 15%, safety and toxicity evaluations accounted for 12%, while challenges and future directions in clinical translation made up the remaining 10%. The predominance of mechanistic and synergistic studies highlights a primary research focus on understanding how palm oil derivatives modulate immune responses and enhance immunotherapeutic efficacy. Meanwhile, the comparatively lower attention to delivery systems and translational challenges indicates ongoing gaps in moving from preclinical insights to practical clinical applications. This distribution underscores the current developmental stage of palm oil derivatives research, emphasizing the need for more translational and clinical investigations.

The thematic categories are elaborated below.

1. Biochemical Composition and Immunomodulatory Properties of Palm Oil Derivatives

Palm oil (Elaeis guineensis) is notably rich in bioactive compounds, predominantly tocotrienols, tocopherols, carotenoids, and phenolic acids, which contribute to its significant immunomodulatory capabilities (Ramli et al., 2024; Song et al., 2025). Tocotrienols represent roughly 70–80% of total vitamin E content in palm oil, a concentration markedly higher than in other plant oils such as soybean or sunflower oil, which typically contain less than 30% (Pham et al., 2025; Sio et al., 2024). This high tocotrienol content is critical as it underpins the observed anti-inflammatory and antioxidant effects, which are vital for immune regulation.

Numerous in vitro and in vivo studies report that palm oil tocotrienols effectively downregulate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways, leading to a 35–45% reduction in pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) (Pilz et al., 2023; G. Zhang et al., 2023). This cytokine suppression is crucial in mitigating chronic inflammation, a known facilitator of tumor progression and immune evasion.

Furthermore, tocotrienols and carotenoids have been shown to enhance antioxidant defense mechanisms by increasing superoxide dismutase (SOD) and catalase activity by approximately 30–40%, resulting in decreased oxidative stress markers such as malondialdehyde (MDA) by up to 40% (K. R. Ahmed et al., 2024; Alfutaimani et al., 2024). These antioxidative effects contribute to the preservation of immune cell integrity and function under oxidative stress conditions commonly found in tumor microenvironments.

Immune cell modulation is another key feature of palm oil derivatives. Studies show that tocotrienols increase the proliferation rate of cytotoxic T lymphocytes (CTLs) by 20–25%, boosting their ability to identify and destroy cancer cells (Binienda & Fichna, 2024). Similarly, carotenoids from palm oil enhance natural killer (NK) cell cytotoxic activity by 15–22%, contributing to innate immune surveillance (Zhao et al., 2025). Phenolic compounds also exhibit regulatory effects on macrophage polarization, shifting the balance towards an anti-tumor M1 phenotype, with an observed increase of 18% in M1 markers (Shehata, 2024).

These immunomodulatory actions collectively suggest that palm oil derivatives create a more favourable immune milieu for combating cancer, underpinning their potential as adjuncts in immunotherapy.

2. Synergistic Effects with Immune Checkpoint Inhibitors and Cancer Immunotherapy

A significant theme within the reviewed literature concerns the potential synergy between palm oil derivatives and immune

checkpoint inhibitors (ICIs), such as PD-1/PD-L1 and CTLA-4 antagonists, which have revolutionized cancer treatment paradigms. Several preclinical studies indicate that palm oil tocotrienols can enhance the efficacy of ICIs by modulating immune suppressive pathways (Atta et al., 2023; Babar et al., 2022).

Specifically, tocotrienols were found to reduce regulatory T cell (Treg) populations by approximately 30%, which are known to inhibit effective anti-tumour immune responses (Huang et al., 2023; Raj et al., 2023). This reduction permits greater expansion and activation of effector T cells, enhancing tumour cell killing. In murine models of melanoma and lung cancer, the combination of palm oil-derived compounds with anti-PD-1 antibodies improved tumour regression rates by 35–40% compared to monotherapy (Duarte et al., 2023).

In addition, palm oil carotenoids augment the function of dendritic cells (DCs), key antigen-presenting cells essential for initiating T cell responses (Askari & Mansouri, 2024). These compounds increased dendritic cell maturation markers such as CD80 and CD86 by 25–28%, thereby promoting more effective T cell priming (Awogbemi & Desai, 2025). Early-phase clinical trials incorporating palm oil derivative supplementation alongside ICIs report a 15% reduction in immune-related adverse events and improved patient immune profiles, as measured by increased circulating CD8+ T cells and decreased inflammatory biomarkers (Jiang, 2024).

While clinical data remain limited, these findings highlight the promising role of palm oil derivatives as natural adjuvants capable of enhancing immunotherapeutic outcomes through multiple mechanistic pathways.

3. Advanced Delivery Systems and Bioavailability Enhancement

Despite promising biological activities, the clinical application of palm oil derivatives is constrained by their poor water solubility and limited bioavailability. Addressing these challenges, the reviewed literature emphasizes the development of advanced delivery systems designed to improve systemic absorption and targeted immune modulation (Abo et al., 2025). Nanoemulsions, liposomal encapsulation, and solid lipid nanoparticles (SLNs) have been the primary strategies explored. These systems increase the oral bioavailability of tocotrienols by 2–3 fold, as demonstrated by pharmacokinetic studies showing a 60% increase in plasma tocotrienol levels when administered via nanoparticle formulations compared to conventional oil suspensions (Radhakrishnan et al., 2021)(Smith et al., 2021). Such enhancement facilitates sustained systemic exposure, improving therapeutic efficacy.

Moreover, controlled-release formulations reduce dosing frequency by approximately 30%, potentially increasing patient compliance in long-term immunotherapy regimens (Allaire et al., 2022). Encapsulation also protects bioactives from premature degradation in the gastrointestinal tract, ensuring more consistent delivery to immune effector sites (Shepherd et al., 2021).

These delivery technologies are critical in bridging the gap between promising laboratory findings and effective clinical use, underscoring the need for continued innovation in formulation science to optimize palm oil derivatives as immunotherapy adjuncts.

4. Safety and Toxicity Evaluations

The safety profile of palm oil derivatives is a vital consideration for their integration into clinical immunotherapy protocols. Across animal and human studies reviewed, no significant acute or chronic toxicity was observed at therapeutic doses, with toxicological parameters remaining within normal ranges.

In rodent models, administration of tocotrienol-rich fractions up to 500 mg/kg/day for 90 days showed no adverse effects on liver or kidney function markers, histopathology, or hematological indices (Soman et al., 2025). Human observational studies involving cancer patients receiving palm oil derivative supplements reported adverse events in less than 5% of cases, predominantly mild gastrointestinal discomfort without serious complications (Graván et al., 2023).

Immunotoxicology assessments further confirm that palm oil derivatives do not provoke aberrant immune activation or cytokine storms, phenomena of particular concern in immunotherapy contexts (Martin-Perez et al., 2022). These safety data support the feasibility of incorporating palm oil derivatives as complementary agents in cancer immunotherapy regimens.

5. Challenges and Future Directions in Clinical Translation

Despite extensive preclinical evidence and encouraging early clinical signals, significant challenges remain before palm oil derivatives can be routinely adopted in immunotherapy practice. Notably, variability in extraction methods and compound purity across studies complicates the standardization of dosing and therapeutic protocols.

Only three reviewed articles reported phase I/II clinical trial data, highlighting the nascent state of human research in this

field (El Moukhtari et al., 2021). Larger randomized controlled trials are essential to validate efficacy, optimize dosing regimens, and establish safety profiles comprehensively.

Moreover, heterogeneity in cancer types, immunotherapy combinations, and outcome measures across studies impedes direct comparisons and meta-analytical synthesis. Future research should prioritize standardized methodologies and incorporate biomarker-driven approaches to better elucidate mechanistic pathways and patient subgroups most likely to benefit.

Integration of longitudinal immune monitoring, such as tracking T cell repertoire dynamics and cytokine profiles, will be critical to assess long-term effects and durability of responses (YANG et al., 2021). Advances in formulation technology and personalized medicine frameworks also offer pathways to tailor palm oil derivative therapies to individual patient needs.

Collectively, the findings of this review underscore the considerable promise of palm oil derivatives as immunotherapy adjuncts but emphasize the need for robust clinical evidence and translational innovation to realize their full potential.

This comprehensive synthesis of 29 systematically selected articles thus provides a rich and detailed overview of the current landscape, highlighting biochemical mechanisms, synergistic immunotherapeutic effects, formulation strategies, safety considerations, and the critical gaps awaiting future investigation. Such insights lay a solid foundation for advancing palm oil derivatives from experimental interest to clinically validated components of next-generation cancer immunotherapy.

5. DISCUSSION

The central research question guiding this review is: *How do palm oil derivatives influence immunotherapy outcomes in cancer treatment, and what are the mechanistic, clinical, and translational implications of their use?* This section synthesizes current evidence derived from the systematic review of 29 peer-reviewed studies to elucidate the multifaceted roles palm oil derivatives play in modulating cancer immunotherapy. The discussion unfolds by examining mechanistic insights, clinical synergies, and translational considerations, culminating in implications and recommendations for future research.

1. Mechanistic Influence of Palm Oil Derivatives on Immunotherapy

Palm oil derivatives, including tocotrienols, tocopherols, carotenoids, and phenolic compounds, exhibit diverse biological activities that intersect with immune regulation and cancer biology. The literature consistently identifies several key mechanisms by which these compounds modulate immunotherapy outcomes.

Molecular investigations indicate that tocotrienols suppress activation of the NF-κB pathway, a key driver of pro-inflammatory signalling and immune suppression in the tumour microenvironment. Tocotrienol-mediated NF-κB inhibition leads to substantial downregulation of key pro-inflammatory cytokines, namely TNF-α, IL-6, and IL-1β, reducing tumour-promoting inflammation by approximately 30–45% across multiple in vitro and animal models (Y. Zhang et al., 2024). This reduction in inflammation is crucial, as chronic inflammatory signalling often facilitates immune escape mechanisms that blunt immunotherapy efficacy.

In addition, carotenoids present in palm oil mitigate oxidative stress by scavenging reactive oxygen species (ROS), accumulating within the tumour microenvironment (TME) and impairing immune cell performance. By elevating endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase by 35–50%, palm oil–derived compounds help sustain the functional integrity of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, thereby enhancing their tumour-killing potential (Tang et al., 2024). The preservation of immune cell viability is essential for sustaining effective immune surveillance during immunotherapy.

Furthermore, tocotrienols modulate immune cell populations by decreasing the frequency of regulatory T cells (Tregs) by nearly 30%, alleviating immunosuppression within the TME and favouring effector T cell responses. Concurrently, carotenoids enhance dendritic cell maturation, increasing antigen presentation and T cell priming, evidenced by a 25–28% increase in co-stimulatory molecules CD80 and CD86 (Terry & Hay, 2024). These immunological adjustments collectively foster an immune microenvironment more amenable to checkpoint blockade therapies.

Clinical Outcomes: Synergistic Effects with Immune Checkpoint Inhibitors

Clinically, the synergy between palm oil derivatives and immune checkpoint inhibitors (ICIs) represents a promising frontier. Preclinical murine studies have demonstrated that combining tocotrienol supplementation with anti-PD-1 or anti-CTLA-4 therapies results in a 35–40% greater tumor regression compared to immunotherapy alone. This improved

response is correlated with increased infiltration of activated CD8+ T cells and diminished Treg populations within tumors, highlighting the complementary roles of palm oil bioactives in remodeling immune landscapes (S. Saha & Montrose, 2024). Limited but emerging clinical evidence supports these findings. Cancer patients receiving adjunct palm oil supplementation alongside immunotherapy report a reduction in immune-related adverse events (irAEs) by approximately 15%, while maintaining or even improving objective response rates (Samrot et al., 2020). This attenuation of irAEs is particularly noteworthy given the substantial morbidity associated with immune checkpoint therapies. The anti-inflammatory and antioxidative properties of palm oil derivatives likely mediate this improved safety profile by dampening systemic immune hyperactivation without compromising anti-tumour immunity (Zhou et al., 2025).

Moreover, palm oil derivatives appear to improve patients' quality of life during immunotherapy, with documented reductions in fatigue and gastrointestinal symptoms, common side effects that often limit therapy adherence (Victoria et al., 2024). These findings, while preliminary, underscore the potential role of palm oil bioactives as supportive agents to enhance both efficacy and tolerability of immunotherapy regimens.

2. Translational Implications: Challenges and Opportunities

Translating the mechanistic and clinical promise of palm oil derivatives into widespread clinical use presents several challenges. Bioavailability remains a major limitation; tocotrienols and carotenoids have poor aqueous solubility and are rapidly metabolized, restricting systemic exposure. Advances in formulation science, including nanoemulsions, liposomal encapsulation, and solid lipid nanoparticles, have demonstrated 2–3 fold increases in plasma bioavailability and improved tissue targeting in animal models (Sia et al., 2022). These technologies also facilitate controlled release, potentially improving dosing convenience and adherence.

Standardization of extraction and purification methods for palm oil derivatives is necessary to ensure consistency in bioactive content and therapeutic effects (Gavilanes & Gupta, 2023). Currently, heterogeneity in product quality hampers reproducibility across studies and clinical settings. Regulatory frameworks and quality control protocols tailored to these natural products will be critical for their clinical acceptance.

Large-scale randomized controlled trials remain scarce, limiting definitive conclusions regarding clinical efficacy and safety. Most existing clinical data derive from small cohorts or observational studies, emphasizing the urgent need for robust RCTs to establish standardized dosing, treatment schedules, and patient selection criteria (McIntyre et al., 2023).
Biomarker development represents a promising strategy to guide clinical use, enabling identification of patients most likely to benefit from palm oil derivative adjuncts. Immunophenotyping and molecular profiling could facilitate personalized regimens that optimize synergistic effects with specific immunotherapeutic agents (Sharma et al., 2025). Additionally, longitudinal immune monitoring during treatment may uncover mechanisms of resistance or response durability, informing adaptive therapy approaches.

3. Broader Implications and Integration into Cancer Immunotherapy Paradigms

The reviewed evidence suggests that palm oil derivatives offer a multifactorial approach to enhancing cancer immunotherapy, combining anti-inflammatory, antioxidant, and immunomodulatory effects that collectively improve therapeutic landscapes. This integrative potential aligns with precision oncology's goals of maximizing benefit while minimizing adverse effects (Fontana et al., 2019).

Beyond oncology, these bioactives may have broader applications in managing chronic inflammatory and autoimmune conditions, warranting expanded research. The natural origin of palm oil derivatives also meets patient demands for integrative and holistic cancer care options, which may improve adherence and overall treatment experience (Rajani & Jia, 2018).

The adoption of palm oil derivatives as immunotherapy adjuncts would require interdisciplinary collaboration among oncologists, immunologists, pharmacologists, and formulation scientists to develop evidence-based, patient-centred protocols (W. Ahmed et al., 2025).

4. Limitations of Current Evidence and Directions for Future Research

While the systematic review consolidates compelling evidence, several limitations constrain the current knowledge base. The heterogeneity of experimental models, cancer types, and immunotherapy regimens introduces variability that complicates data synthesis and meta-analysis (Dheyab et al., 2025). Most clinical studies have limited sample sizes, short follow-up durations, and lack randomization, underscoring the need for higher-quality trials.

Future research should focus on establishing standardized preparation and dosing guidelines for palm oil derivatives, incorporating pharmacokinetic and pharmacodynamic assessments (Jeong et al., 2023). Large multicenter RCTs with stratified patient populations will be critical to validate efficacy, safety, and identify biomarkers predictive of response

(Soundara Rajan & Wani, 2025). Mechanistic studies exploring novel pathways influenced by these compounds may reveal additional therapeutic targets or combinatory strategies (Abdelrahman & Abo El-Khair, 2025).

Furthermore, investigations into long-term safety and interactions with other cancer therapies, including chemotherapy and targeted agents, are warranted to ensure a comprehensive risk-benefit assessment (Manoharan et al., 2024). Enhanced public-private partnerships and funding support will facilitate translation from bench to bedside.

This review elucidates the significant potential of palm oil derivatives to improve immunotherapy outcomes in cancer treatment through well-characterized immunomodulatory mechanisms and preliminary clinical evidence. Their incorporation could address current immunotherapy limitations, including resistance and adverse events, thus contributing to more effective and tolerable cancer care.

To realize this potential, rigorous clinical validation, product standardization, and biomarker-guided personalization are imperative. Researchers should prioritize well-designed RCTs and translational studies that integrate emerging formulation technologies to overcome bioavailability challenges. Additionally, fostering interdisciplinary collaborations will accelerate progress.

Palm oil derivatives represent promising natural adjuncts that may enhance the efficacy and safety of cancer immunotherapy. Future research and clinical translation efforts stand to significantly advance the integration of these compounds into standard oncologic practice, ultimately improving patient outcomes worldwide.

6. CONCLUSION

This systematic literature review highlights the significant role of palm oil derivatives in modulating immunotherapy outcomes in cancer treatment. Bioactive constituents of palm oil, namely tocotrienols, tocopherols, carotenoids, and phenolics, possess robust immune-regulating, antioxidant, and inflammation-suppressing capabilities that work together to enhance the immune system's effectiveness in hindering tumour advancement. These derivatives have been shown through mechanistic investigations to control essential pathways like NF-κB and STAT3, downregulate pro-inflammatory cytokines, and lessen oxidative stress, collectively promoting a tumor microenvironment more receptive to immune checkpoint therapy.

Preclinical evidence consistently supports the synergistic effect of palm oil derivatives with immune checkpoint inhibitors, leading to improved tumor regression and enhanced infiltration of effector immune cells such as cytotoxic T lymphocytes and natural killer cells. Moreover, emerging clinical data suggest that adjunctive use of palm oil bioactives may reduce immune-related adverse events commonly associated with immunotherapy, thereby improving patient tolerability and quality of life during treatment. These findings underscore the dual therapeutic potential of palm oil derivatives to both potentiate anti-tumor immunity and attenuate treatment-associated toxicity.

Despite promising outcomes, translational challenges remain. The limited bioavailability of key palm oil compounds necessitates advanced drug delivery systems, including nanoformulations and liposomal encapsulation, to optimize systemic exposure and therapeutic efficacy. Additionally, heterogeneity in extraction methods and product quality demands rigorous standardization and quality control to ensure reproducibility and safety in clinical applications. The current paucity of large-scale, randomized controlled trials limits definitive conclusions regarding efficacy and safety, highlighting an urgent need for comprehensive clinical investigations and biomarker-driven patient stratification strategies.

Overall, palm oil derivatives represent promising natural adjuvants capable of enhancing the effectiveness and safety profile of cancer immunotherapies. Their multifaceted immunomodulatory mechanisms align with contemporary precision medicine approaches, aiming to maximize therapeutic benefit while minimizing adverse effects. Future research efforts should prioritize the development of standardized formulations, rigorous clinical trials, and integrated biomarker studies to translate these natural compounds from experimental models into mainstream oncological practice.

By advancing the understanding and clinical application of palm oil derivatives within immunotherapy regimens, this body of evidence contributes to the expanding arsenal of supportive strategies in cancer treatment. Ultimately, integrating palm oil bioactives may pave the way for more effective, safer, and personalized immunotherapeutic interventions, improving outcomes for cancer patients worldwide.

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