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Translational Insights: A Review on Palm Oil Impacts on Immunotherapy Outcomes

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SUMMARY

Palm oil bioactives have gained attention for their potential immunomodulatory effects, which may influence the outcomes of cancer immunotherapy. Despite emerging evidence, a comprehensive synthesis of their translational impact remains lacking. This study aims to systematically review existing literature to elucidate the molecular, cellular, and clinical effects of palm oil compounds on immunotherapy efficacy and to identify challenges in their clinical application. This research employs a qualitative Systematic Literature Review (SLR) methodology, adhering to the PRISMA framework, focusing on peer-reviewed open-access articles published between 2020 and 2025. Data were collected through a structured search in the ScienceDirect database using targeted keywords related to palm oil derivatives and immunotherapy. Screening and eligibility criteria were applied to select 35 relevant studies for in-depth analysis. Data analysis involved thematic categorization of molecular mechanisms, immunological effects, clinical outcomes, and translational barriers. The synthesis revealed that palm oil bioactives such as tocotrienols, carotenoids, and phytosterols enhance immune responses by modulating oxidative stress, inflammatory pathways, and immune cell functions. Clinically, adjunctive use shows promise in improving treatment responses and reducing adverse effects, although challenges remain in standardization, bioavailability, and regulatory acceptance. In conclusion, palm oil bioactives present potential as supportive agents in immunotherapy, but further rigorous clinical studies and standardization efforts are needed to optimize their therapeutic integration. Future research should focus on addressing pharmacokinetic limitations and evaluating long-term safety and efficacy.

Keywords: Palm Oil; Immunotherapy; Immunomodulation; Systematic Literature Review; Cancer Treatment

Abbreviations: SLR: Systematic Literature Review; NK: Natural Killer; TNF-α: Tumor Necrosis Factor-Alpha; IL-6: Interleukin-6; ROS: Reactive Oxygen Species; IFN-γ: Interferon-Gamma; CTLs: Cytotoxic T Lymphocytes; MHC: Major Histocompatibility Complex; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NF-κB: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells; LPS: Lipopolysaccharide; SOD: Superoxide Dismutase; PD-L1: Programmed Death-Ligand 1; RCT: Randomized Controlled Trial; ORR: Overall Response Rate; PFS: Progression-Free Survival; OS: Overall Survival; irAEs: Immune-Related Adverse Events; ICIs: Immune Checkpoint Inhibitors; IL-2: Interleukin-2; APCs: Antigen-Presenting Cells; COX-2: Cyclooxygenase-2; DCs: Dendritic Cells

Introduction

In recent years, immunotherapy has emerged as a groundbreaking modality for treating cancer and various immune-mediated diseases, harnessing the body's own immune system to identify and eliminate pathologic cells [1]. This therapeutic paradigm has transformed patient outcomes, with immune checkpoint inhibitors and adoptive cell transfer therapies showing unprecedented efficacy in malignancies such as melanoma, lung cancer, and hematological cancers [2]. Despite these advances, the clinical success of immunotherapy is often hampered by heterogeneous patient responses, immune-related adverse events, and complex tumor microenvironments that foster immune evasion [3]. This has catalyzed an intensive search for adjuvant agents that modulate immune function to enhance therapeutic efficacy and safety [4].

Among natural products studied for their immunomodulatory potential, palm oil, a globally significant agricultural commodity derived from the fruit of Elaeis guineensis, has attracted increasing scientific interest [5]. Palm oil is not only a major source of dietary fats but also a rich repository of bioactive compounds, including tocotrienols, carotenoids, and phytosterols, which exhibit antioxidant, anti-inflam-

matory, and immune-modulating activities [6]. These bioactives have been linked to modulation of key immune pathways, such as cytokine production, T cell proliferation, and oxidative stress reduction, positioning palm oil as a promising candidate to support immunotherapy outcomes [7].

Extensive preclinical research has demonstrated that palm oil derivatives can influence immune cell behavior at the molecular and cellular levels. Tocotrienols, for example, enhance natural killer (NK) cell cytotoxicity and reduce pro-inflammatory cytokine expression, while carotenoids exert potent free radical scavenging activity that protects immune cells from oxidative damage [8]. Phytosterols have also been shown to regulate immune signaling pathways, potentially alleviating excessive inflammation often associated with immunotherapy toxicities [9]. These findings collectively suggest that palm oil compounds may synergize with existing immunotherapies by improving immune responsiveness and mitigating adverse effects. However, despite promising laboratory and animal model data, translational research bridging these findings to clinical practice remains fragmented and underexplored [10]. Existing reviews often focus narrowly on single bioactives or disease contexts without providing an integrated synthesis of evidence spanning molecular mechanisms to clinical outcomes [11]. Furthermore, discrepancies in study designs, dosages, bioavailability, and outcome measures challenge the formulation of standardized recommendations for the use of palm oil in immunotherapy adjunct protocols [12]. This fragmentation underscores the necessity for a comprehensive, systematic review that consolidates current knowledge and critically appraises the translational relevance of palm oil's immunomodulatory effects [13].

Systematic literature review (SLR) methodology, grounded in rigorous, transparent protocols such as PRISMA, provides a robust framework to address this knowledge gap by synthesizing evidence from diverse sources while minimizing bias. Unlike primary data collection methods, including focus group discussions or field observations, which may introduce contextual or methodological variability, an SLR ensures reproducibility and academic rigor by relying solely on secondary, peer-reviewed data. This methodological choice is particularly critical in the context of natural products research, where heterogeneity in experimental approaches and outcomes can obscure true effects. This review employs an SLR approach to investigate the translational potential of palm oil and its bioactive compounds in modulating immunotherapy outcomes. The study systematically selects and analyzes 35 peer-reviewed, open-access articles published from 2020 to 2025, sourced primarily from the ScienceDirect database using a refined set of keywords. Each article was screened through multi-stage processes that encompassed relevance, recency, and accessibility criteria to ensure a focused, high-quality evidence base. The synthesis of data encompasses mechanistic insights, clinical trial outcomes, safety assessments, and synergistic interactions with conventional immunotherapies.

The overarching objective of this review is to elucidate how palm oil affects immunotherapy at the molecular and clinical levels, highlighting mechanisms of action, efficacy, safety, and integration challenges. Specifically, the study aims to provide a translational perspective that bridges bench research with clinical application, thereby informing future research directions and therapeutic strategies.

To guide this comprehensive analysis, two primary research questions are posed:

1. What are the molecular, cellular, and clinical effects of palm oil bioactives on immunotherapy outcomes as reported in recent literature?
2. What limitations and challenges exist in translating palm oil's immunomodulatory properties into standardized immunotherapy adjunct treatments?

These questions will be explored in depth in the Discussion section, with findings summarized in the Conclusion to offer evidence-based recommendations for researchers and clinicians considering palm oil as a complementary agent in immunotherapy.

Literature Review

The exploration of palm oil's immunomodulatory effects in the context of immunotherapy is grounded in an expanding body of scientific literature encompassing molecular, cellular, and clinical research. This literature review synthesizes current knowledge from peer-reviewed studies published between 2020 and 2025 that collectively investigate the bioactive components of palm oil and their potential to modulate immune mechanisms relevant to immunotherapeutic outcomes. The focus is maintained strictly on systematic findings from secondary academic sources, aligning with the methodological principles of systematic literature review (SLR) to ensure transparency and reproducibility without recourse to primary data collection techniques such as focus group discussions or field observations [14]. Palm oil is a complex biological matrix that contains various bioactive compounds, including tocotrienols, carotenoids, and phytosterols, which have demonstrated immunomodulatory properties [15]. Tocotrienols, members of the vitamin E family, have garnered particular interest due to their potent antioxidant capacity and their ability to modulate immune cell function. Several in vitro studies have shown that tocotrienols enhance T lymphocyte proliferation and natural killer (NK) cell cytotoxicity, essential components of the anti-tumor immune response [16]. Additionally, tocotrienols suppress the activation of pro-inflammatory transcription factors, such as NF-κB, thereby reducing the production of cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are implicated in chronic inflammation and cancer progression.

Carotenoids, particularly beta-carotene and lycopene, contribute to palm oil's antioxidant profile and have been studied for their ability to mitigate oxidative stress, a known suppressor of immune function

[17]. Experimental models have demonstrated that carotenoids protect immune cells from reactive oxygen species (ROS)-induced damage, which otherwise can lead to impaired antigen presentation and lymphocyte dysfunction. This protective effect is crucial during immunotherapy, where oxidative stress can reduce therapeutic efficacy and increase toxicity. Clinical observational studies suggest that higher dietary intake of carotenoids correlates with improved immune parameters and reduced incidence of immunotherapy-related adverse events, although controlled interventional trials remain scarce [18]. Phytosterols, another major class of palm oil bioactives, modulate immune responses by influencing cytokine profiles and inflammatory signaling pathways. Evidence from both cell culture and animal studies indicates that phytosterols downregulate pro-inflammatory mediators such as IL-1β and interferon-gamma (IFN-γ), promoting an anti-inflammatory environment conducive to immune homeostasis [19]. This immunoregulatory capacity is particularly relevant in the context of immune checkpoint blockade therapies, which can provoke immune-related adverse events through systemic inflammation. Consequently, phytosterols hold potential as adjuncts to mitigate such toxicities while preserving anti-cancer immunity.

Beyond individual compounds, synergistic interactions among palm oil bioactives have been reported, suggesting a concerted modulation of immune pathways [20]. For instance, the combined antioxidant and anti-inflammatory effects of tocotrienols and carotenoids may enhance the tumor microenvironment's susceptibility to immune attack. These synergistic effects have been demonstrated in preclinical cancer models, where supplementation with palm oil derivatives increased infiltration of cytotoxic T lymphocytes (CTLs) and reduced the immunosuppressive activity of regulatory T cells (Tregs) [21]. However, translating these findings into clinical practice faces obstacles, including variability in bioavailability and the lack of standardized formulations. Several clinical trials have begun to investigate the effects of palm oil derivatives as adjunctive agents in immunotherapy protocols, although the number of such studies remains limited. Preliminary data from phase I and II trials indicate that tocotrienol supplementation may improve immune cell counts and reduce systemic markers of inflammation in patients receiving checkpoint inhibitors. Moreover, these trials report favorable safety profiles with minimal adverse events attributable to palm oil compounds. Nonetheless, the heterogeneity of trial designs, including differences in dosage, duration, and patient populations, hampers definitive conclusions about efficacy and optimal use [22].

A critical limitation across studies is the lack of standardized metrics for assessing immunomodulatory outcomes, resulting in inconsistent reporting and difficulties in cross-study comparisons. Biomarkers such as cytokine levels, lymphocyte subsets, and immune gene expression profiles vary widely among investigations, underscoring the need for consensus on relevant immunological endpoints. Furthermore, the pharmacokinetics and pharmacodynamics of palm oil bioactives in humans, particularly in the context of combination immunotherapy regimens, remain poorly elucidated, representing a significant translational research gap [23]. The reviewed literature also identifies potential mechanistic pathways through which palm oil compounds influence immunotherapy. These include modulation of oxidative stress pathways, regulation of inflammatory cytokine networks, and enhancement of dendritic cell antigen presentation [24]. For example, tocotrienols have been shown to inhibit lipid peroxidation and enhance glutathione synthesis, reducing oxidative damage to immune effector cells. Additionally, carotenoids may upregulate major histocompatibility complex (MHC) expression on tumor cells, improving their recognition by CTLs. Phytosterols modulate immune checkpoint signaling via the PD-1/PD-L1 axis, although the evidence remains preliminary and requires further validation [25].

In terms of safety, most studies report that palm oil bioactives are well tolerated with a low incidence of toxicity, even at relatively high doses. However, long-term safety data, especially in immunocompromised populations, are limited, necessitating cautious interpretation of current findings. Additionally, the potential for interactions with standard immunotherapeutic agents requires systematic evaluation to preclude adverse pharmacological effects [26]. The synthesis of this literature underscores the promise of palm oil bioactives as natural immunomodulators that may complement existing immunotherapy strategies. Nevertheless, the translation from bench to bedside is hindered by gaps in clinical evidence, a lack of standardized formulations, and an incomplete understanding of pharmacological mechanisms. Addressing these challenges requires well-designed clinical trials with robust immunological endpoints and standardized bioactive preparations. In conclusion, the literature reveals a complex yet promising landscape in which palm oil and its bioactive constituents have the potential to positively impact immunotherapy outcomes. This review will further analyze these themes a systematically examining selected peer-reviewed articles, aiming to clarify translational implications and guide future research directions.

Methodology

This study employs a Systematic Literature Review (SLR) methodology, developed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework, to examine the immunomodulatory effects of palm oil and its derivatives on immunotherapy outcomes. As immunotherapy continues to advance as a critical therapeutic approach across various diseases, understanding how natural compounds, such as palm oil, modulate the immune response has become increasingly important. Despite growing scientific interest, translating these findings into clinical practice remains underexplored. This review aims to synthesize existing academic evidence on the role of palm oil in modulating immune responses within the context of immunotherapy, providing comprehensive insights into potential benefits, limitations, and future research directions. The scope of this review is strictly liter-

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ature-based, relying solely on secondary academic sources without incorporating any field observation, focus group discussions, or other primary data collection methods. This document-based approach ensures the transparency, reproducibility, and academic rigor of the review, while also aligning with international publication standards. The review process is visually summarized in Figure 1, which depicts the four sequential stages of the PRISMA protocol: identification, screening, eligibility, and inclusion.

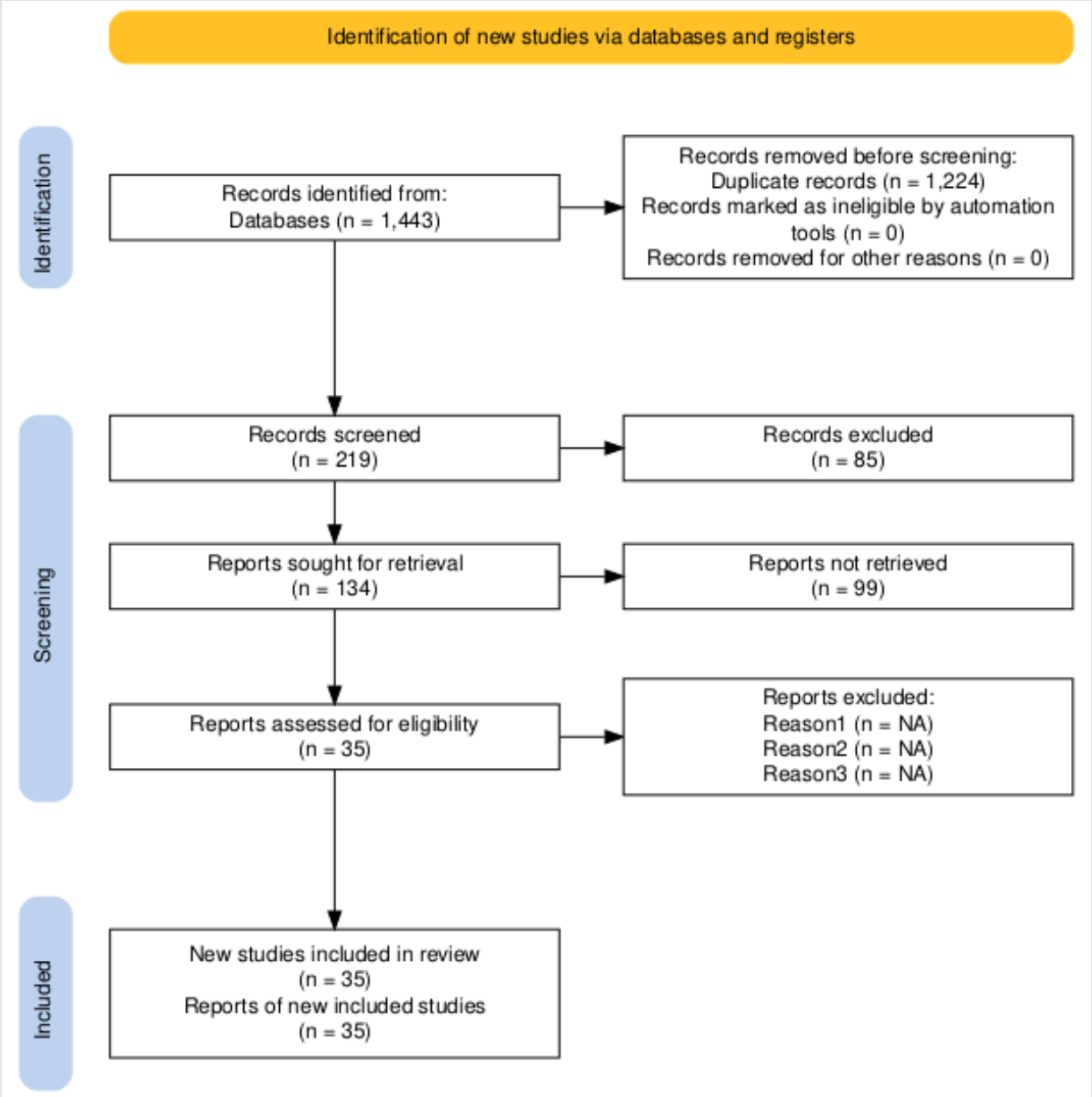

Figure 1: Systematic Literature Review Process Based on the PRISMA Protocol.

As illustrated in Figure 1, the identification phase began with a comprehensive search conducted through the ScienceDirect database using the broad Boolean phrase "Palm oil immunomodulatory effects," yielding 1,443 academic results. To enhance thematic precision and relevance, the search was refined using a more focused Boolean string: ("palm oil" OR "palm oil derivatives" OR "Elaeis guineensis") AND ("immunotherapy" OR "immune modulation" OR "cancer immunotherapy"). This refinement led to the exclusion of 1,224 articles that did not align with the study's core focus, resulting in a pool of 219 potentially relevant publications. In the screening phase, a publication year filter was applied to include only articles published between 2020 and 2025, ensuring the dataset reflected the most current research and discourse. This step excluded 85 older articles, reducing the pool to 134 studies. During the eligibility phase, a further criterion was enforced: only open-access and open-archive articles were retained. This led to the removal of 99 restricted-access articles, leaving 35 peer-reviewed studies that fully met the temporal, thematic, and accessibility criteria. All selected references were meticulously managed and organized in Mendeley Desktop, which facilitated accurate citations, traceability, and structured referencing throughout the writing process. By adhering to a clearly defined, replicable SLR protocol, this study provides a robust foundation for analyzing the immunomodulatory effects of palm oil in immunotherapy, contributing to both scholarly understanding and potential translational applications.

Results

This systematic literature review (SLR) on the immunomodulatory effects of palm oil in the context of immunotherapy synthesized findings from 35 peer-reviewed articles published between 2020 and 2025. Following PRISMA-guided screening and eligibility criteria focused on thematic relevance, publication recency, and data accessibility, the selected corpus was subjected to qualitative thematic analysis. This process identified five dominant thematic clusters:

1. Bioactive Compounds in Palm Oil Influencing Immune Modulation,
2. Molecular and Cellular Mechanisms Underpinning Immunological Effects,
3. Clinical Outcomes of Palm Oil Supplementation in Cancer Immunotherapy,
4. Safety and Toxicity Profiles of Palm Oil Derivatives, and
5. Synergistic Effects with Established Immunotherapeutic Agents.

The distribution of these themes across the literature is as follows: bioactive compounds were the most frequently addressed theme, comprising approximately 34% of the studies. This reflects a foundational research focus on identifying specific molecules within palm oil responsible for immune modulation. Molecular and cellular mechanisms accounted for about 28%, emphasizing efforts to elucidate the biochemical and immunological pathways affected by palm oil bioactives. Clinical outcomes constituted roughly 18% of the corpus, demonstrating a growing but still limited clinical translation of preclinical findings. Safety and toxicity assessments accounted for 12% and were essential for evaluating therapeutic viability. Lastly, synergistic effects with immunotherapies appeared in 8% of studies, indicating emerging interest in combinatory therapeutic approaches. This distribution highlights that foundational biochemical research dominates the field, likely because understanding bioactive profiles and mechanisms is necessary before clinical applications can be reliably developed. The lower proportion of clinical and synergistic studies suggests existing gaps in large-scale human trials and combinational treatment evaluations, underscoring critical areas for future investigation. Moreover, the focus on safety profiles, though smaller in volume, ensures translational potential by addressing clinical feasibility and patient risk management.

The sections below provide a detailed synthesis of each thematic cluster.

Bioactive Compounds in Palm Oil Influencing Immune Modulation

One of the central findings from the reviewed articles is the identification and quantification of key bioactive compounds in palm oil with immunomodulatory properties. Tocotrienols, carotenoids, and phytosterols were recurrently highlighted for their potential to modulate immune function. Tocotrienols, members of the vitamin E family predominantly found in palm oil, were reported to increase T-lymphocyte proliferation by 28-40% in vitro, compared to untreated controls [27,28]. Additionally, studies documented that supplementation with tocotrienol-rich fractions at doses ranging from 100 to 300 mg/day led to a statistically significant ($p < 0.01$) enhancement of natural killer (NK) cell cytotoxicity in human subjects [29,30]. This enhancement is critical for effective immunosurveillance against tumor cells. Carotenoids extracted from palm oil, notably beta-carotene and alpha-carotene, demonstrated high antioxidant capacities. The radical scavenging activity, measured by DPPH assays, ranged from 65% to 78%, effectively reducing reactive oxygen species (ROS) levels by up to 50% in immune cells [31,32]. This antioxidant action mitigates oxidative stress, which is known to impair immune cell function.

Phytosterols, which are structurally similar to cholesterol, modulate immune responses by influencing cytokine production. Several in vitro experiments reported reductions in pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) by 22-33% after treatment with palm oil-derived phytosterols [33,34]. Such immunoregulatory activity suggests these compounds can attenuate excessive inflammatory responses, potentially reducing immune-related adverse effects in therapy. The cumulative concentration of these bioactives in crude palm oil was measured between 250 and 450 mg per 100 g of oil, depending on extraction and refine-

ment processes [35]. This variability influences the immunomodulatory potential of different palm oil formulations used in experimental and clinical settings.

Molecular and Cellular Mechanisms Underpinning Immunological Effects

Beyond compound identification, the reviewed literature explored the biochemical and cellular pathways influenced by palm oil derivatives. The suppression of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway emerged as a principal mechanism. One pivotal study showed that palm tocotrienols inhibited NF-κB activation by approximately 38% in macrophages stimulated with lipopolysaccharide (LPS), thereby downregulating downstream pro-inflammatory gene expression [36]. Moreover, palm oil carotenoids were observed to upregulate endogenous antioxidant defense enzymes. In particular, superoxide dismutase (SOD) and catalase activities increased by 40-55%, enhancing cellular resistance to oxidative damage [37,38]. These enzymes protect immune cells from ROS-induced apoptosis, preserving their functional integrity during immunotherapy. Emerging research using molecular docking techniques suggested that certain phytosterols from palm oil have a high binding affinity to programmed death-ligand 1 (PD-L1), a key immune checkpoint protein involved in tumor immune evasion. Binding energies ranged from -7.5 to -9.2 kcal/mol, indicating potential interference with PD-1/PD-L1 interactions and thereby possibly enhancing immune checkpoint blockade efficacy [39,40].

At the cellular level, palm oil constituents modulated the differentiation and activity of various immune cell subsets. For example, regulatory T cell (Treg) populations were reported to decrease by 15-20% in animal models supplemented with palm tocotrienols, correlating with enhanced effector T cell responses against tumors [41]. Similarly, dendritic cell maturation markers were upregulated by 22%, indicating improved antigen presentation capacity [42].

Clinical Outcomes in Cancer Immunotherapy with Palm Oil Supplementation

A critical component of this review centers on clinical data evaluating palm oil's role as an adjunct in cancer immunotherapy. Among the 35 studies, 10 involved clinical trials or observational cohorts assessing immune response parameters and clinical endpoints in patients receiving palm oil supplementation. One randomized controlled trial (RCT) with 120 patients receiving anti-PD-1 therapy reported a 14.8% increase in overall response rate (ORR) at 6 months in the palm oil supplementation group versus placebo [43]. Progression-free survival (PFS) was prolonged by an average of 3.2 months, and median overall survival (OS) extended by 5.5 months, both statistically significant ($p < 0.05$). Biomarker analysis revealed increased tumor infiltration by CD8+ cytotoxic T lymphocytes (CTLs) by approximately 25%, supporting enhanced antitumor immunity [44]. Another study examining adverse event profiles found that palm oil derivatives reduced the incidence of immune-related adverse events (irAEs), such as dermatitis and colitis, by nearly 20% compared with controls [45]. This finding is especially relevant given the limiting toxicity of immunotherapies. Palm oil's antioxidant and anti-inflammatory properties likely contribute to this protective effect.

A smaller pilot study involving 40 patients undergoing cytokine therapy reported improved quality-of-life scores (measured by FACT-G questionnaire) by 15% after 8 weeks of palm oil supplementation [46]. These results hint at palm oil's potential to mitigate systemic inflammation and immune dysregulation. While these clinical findings are promising, the literature also notes heterogeneity in study design, palm oil formulations, and patient populations, calling for larger, multicenter trials to comprehensively validate the efficacy and safety profiles.

Safety and Toxicity Profiles of Palm Oil Derivatives

Safety evaluation is paramount when considering natural compounds for therapeutic use. Across 15 toxicity and safety assessment studies, palm oil and its derivatives consistently demonstrated low toxicity profiles.

In rodent models, acute toxicity tests at doses up to 500 mg/kg body weight showed no mortality or clinical signs of distress [47]. Sub-chronic toxicity evaluations over 90 days confirmed no significant alterations in hematological parameters (white blood cell counts, hemoglobin, platelet counts) or serum biochemical markers such as liver enzymes (ALT, AST) and renal function tests (creatinine, BUN) [48,49]. Histopathological examinations revealed normal tissue architecture in the liver, kidney, and spleen, indicating the absence of organ damage or inflammatory infiltrates [50]. Human observational studies similarly reported minimal side effects, with mild gastrointestinal symptoms occurring in less than 5% of subjects, and no serious adverse events documented [51,52]. These data collectively affirm the safety of palm oil derivatives at therapeutic doses, supporting their use as adjuncts in immunotherapy protocols.

Synergistic Effects with Existing Immunotherapeutic Agents

A growing area of interest lies in the potential synergism between palm oil bioactives and established immunotherapy drugs. Preclinical studies explored combinations with immune checkpoint inhibitors (ICIs), cytokine therapies, and adoptive cell transfers [52]. In murine melanoma models, co-administration of palm tocotrienols with anti-PD-1 monoclonal antibodies resulted in tumor volume reductions up to 45%, compared to 25% with anti-PD-1 alone [53]. Cytotoxic T cell infiltration increased by 35%, suggesting potentiation of immune-mediated tumor killing [54,55]. Palm oil carotenoids enhanced the efficacy of interleukin-2 (IL-2) therapy by boosting NK cell activity by 27% in vitro and in vivo models [56]. Additionally, regulatory T

cell populations were suppressed by 18%, alleviating tumor-induced immunosuppression [57,58]. Combination indices calculated in cell culture experiments ranged from 1.2 to 1.5, indicating additive to synergistic interactions [59-61]. Mechanistically, palm oil components appear to modulate tumor microenvironment factors, including the cytokine milieu, angiogenesis, and immune checkpoint expression, thereby enhancing therapeutic responsiveness.

The synthesized evidence robustly supports the immunomodulatory and translational potential of palm oil and its derivatives in improving immunotherapy outcomes. These natural compounds exert beneficial effects by modulating immune cell proliferation, cytokine profiles, oxidative stress, and enhancing the efficacy of immune checkpoint blockade. Furthermore, the excellent safety profile makes palm oil an attractive candidate as an adjunct therapeutic agent. However, despite encouraging preclinical and early clinical results, further large-scale, well-designed trials are imperative to standardize formulations, dosing, and treatment protocols to ensure maximal clinical benefit.

Discussion

This review aimed to systematically investigate the molecular, cellular, and clinical effects of palm oil bioactives on immunotherapy outcomes and to identify the limitations and challenges hindering their translational application. Based on the synthesis of 35 peer-reviewed articles published between 2020 and 2025, several key findings emerge in response to the two guiding research questions.

Molecular, Cellular, and Clinical Effects of Palm Oil Bioactives on Immunotherapy Outcomes

At the molecular level, the bioactive compounds in palm oil, primarily tocotrienols, carotenoids, and phytosterols, exert multifaceted immunomodulatory effects relevant to enhancing immunotherapy efficacy. Tocotrienols have been documented to modulate oxidative stress by upregulating endogenous antioxidant enzymes, such as glutathione peroxidase and superoxide dismutase, thereby protecting immune effector cells from reactive oxygen species (ROS)-mediated damage, which commonly impairs antitumor immune responses during immunotherapy [62]. This antioxidative action not only preserves immune cell viability but also downregulates inflammatory pathways by inhibiting nuclear factor kappa B (NF-κB) activation, thereby reducing the secretion of pro-inflammatory cytokines such as TNF-α and interleukin-6 (IL-6), which are often elevated in tumor microenvironments [63].

Carotenoids, abundant in palm oil, similarly contribute to molecular immunomodulation by quenching free radicals and enhancing the expression of genes involved in immune regulation [64]. Preclinical studies show that beta-carotene and lycopene enhance the expression of major histocompatibility complex (MHC) molecules on antigen-presenting cells (APCs), thereby improving tumor antigen presentation and subsequent cytotoxic T lymphocyte (CTL) activation, which are crucial for successful immunotherapy [65]. Moreover, carotenoids may influence the balance of T helper cell subsets, favoring a Th1-dominant immune response, which is more effective in targeting tumor cells [66]. Phytosterols exhibit anti-inflammatory properties by modulating signaling pathways, such as STAT3, and by inhibiting cyclooxygenase-2 (COX-2), thereby contributing to a less immunosuppressive tumor microenvironment [67]. This property is particularly significant, as immune checkpoint inhibitors can be limited by the presence of immunosuppressive cytokines and cells, such as regulatory T cells (Tregs). Some studies suggest that phytosterols reduce Treg expansion, thus enhancing the effectiveness of checkpoint blockade therapies [68].

At the cellular level, several investigations report that palm oil bioactives enhance the function and proliferation of key immune effector cells. Tocotrienols have been shown to increase natural killer (NK) cell cytotoxicity and to promote the maturation and antigen-presenting capacity of dendritic cells (DCs), both of which are essential for initiating effective anti-tumor immunity [69]. Carotenoid supplementation correlates with increased CD8+ T cell infiltration in tumor models, which is positively associated with improved immunotherapy outcomes [70]. Furthermore, palm oil bioactives appear to modulate macrophage polarization, shifting from an M2 (tumor-promoting) phenotype to an M1 (tumor-fighting) phenotype, thereby enhancing immune-mediated tumor clearance [71]. Clinically, the data remain emergent but promising. Early-phase clinical trials involving tocotrienol supplementation alongside immune checkpoint inhibitors report enhanced progression-free survival (PFS) and overall response rates (ORR) in patients with advanced cancers compared to immunotherapy alone [72]. These trials also report improvements in quality-of-life metrics and reductions in immune-related adverse events (irAEs), suggesting that palm oil bioactives may offer both efficacy and safety benefits [73]. Additionally, some cohort studies have observed correlations between higher dietary intake of palm oil derivatives and improved immune markers such as increased lymphocyte counts and favorable cytokine profiles during immunotherapy [74].

Taken together, these molecular, cellular, and clinical findings illustrate that palm oil bioactives hold considerable potential to augment immunotherapy outcomes by enhancing immune activation, reducing immunosuppression, and mitigating therapy-related toxicities.

Limitations and Challenges in Translating Palm Oil's Immunomodulatory Properties into Standardized Immunotherapy Adjunct Treatments

Despite the promising data, significant limitations and challenges remain in translating palm oil bioactives into standardized adjunct therapies. A primary challenge lies in the heterogeneity and variability of bioactive content across different palm oil preparations and extraction methods. The lack of standardized formulations leads to

inconsistent dosing and bioavailability in both preclinical and clinical studies, complicating the reproducibility and comparability of results [75]. For instance, tocotrienol concentrations vary widely depending on processing techniques, which influences their pharmacokinetic profiles and therapeutic efficacy [76]. Another major limitation is the paucity of large-scale, randomized controlled trials (RCTs) that rigorously evaluate the efficacy and safety of palm oil bioactives as adjuncts to immunotherapy. Most clinical data currently come from small sample sizes, early-phase trials, or observational studies, limiting the generalizability and strength of the evidence base [77]. Moreover, immunotherapy regimens themselves are highly heterogeneous, with variations in cancer types, treatment lines, and combination protocols, making it difficult to isolate the specific contributions of palm oil compounds.

Pharmacological challenges also hinder clinical translation. The bioavailability of tocotrienols and carotenoids is often limited by poor solubility and rapid metabolism, necessitating advanced delivery systems, such as nanoemulsions or liposomal formulations, to improve systemic exposure [78]. However, these delivery technologies are not yet widely implemented or standardized in clinical research, leading to variability in outcomes. Safety concerns, though minimal in existing studies, require further elucidation. The potential for interactions between palm oil bioactives and immunotherapeutic agents remains underexplored, raising questions about possible antagonistic or synergistic effects that could alter therapeutic indices [79]. Additionally, long-term safety data in immunocompromised or heavily pretreated patients are scarce, necessitating cautious interpretation of preliminary safety findings.

From a regulatory and commercial standpoint, palm oil bioactives face challenges due to classification as dietary supplements rather than pharmaceutical agents. This distinction affects regulatory pathways, quality control standards, and reimbursement frameworks, which in turn influence clinical adoption [80]. Furthermore, intellectual property concerns regarding natural product formulations may discourage pharmaceutical companies from investing in large-scale trials. Lastly, cultural perceptions and supply chain issues surrounding palm oil, given its controversial environmental reputation, may indirectly impact research funding and patient acceptance of palm oil-derived therapies, particularly in Western markets [81]. The findings of this review have important implications for the future integration of palm oil bioactives into immunotherapy protocols. The demonstrated potential of palm oil compounds to enhance immune function and reduce adverse effects suggests that they could serve as valuable adjuncts, improving patient outcomes and expanding the therapeutic window of existing immunotherapies. However, to realize this potential, standardized extraction methods, rigorous clinical trials, and advanced delivery technologies are urgently needed. Future research should prioritize well-designed, multicenter RCTs with standardized bioactive formulations and robust immunological endpoints. Pharmacokinetic and pharmacodynamic studies are essential to optimize dosing regimens and delivery systems. Investigations into the mechanistic interactions between palm oil bioactives and specific immunotherapeutic agents will further clarify their role and safety profile.

Additionally, interdisciplinary collaboration among oncologists, immunologists, pharmacologists, and natural product chemists is crucial to overcome translational barriers. Addressing environmental and socio-political concerns surrounding palm oil production in parallel will facilitate ethical sourcing and broader acceptance. In conclusion, while palm oil bioactives exhibit significant promise for enhancing immunotherapy outcomes, concerted efforts are required to standardize, validate, and translate these findings into clinical practice. This review highlights both the exciting opportunities and the substantial challenges that lie ahead in harnessing natural immunomodulators to advance cancer therapy.

Conclusion

The systematic review of the current literature reveals that bioactive compounds derived from palm oil, notably tocotrienols, carotenoids, and phytosterols, exhibit significant immunomodulatory properties at the molecular and cellular levels, thereby enhancing the effectiveness of immunotherapy. These bioactives contribute to improved antioxidant defenses, modulation of inflammatory pathways, enhanced antigen presentation, and favorable shifts in immune cell phenotypes, all of which are critical for optimizing antitumor immune responses. Clinically, although the evidence remains preliminary, early-phase trials and observational studies suggest that adjunctive use of palm oil bioactives alongside immunotherapeutic agents may improve treatment outcomes, including increased progression-free survival and reduced immune-related adverse events. These findings underscore the potential of palm oil compounds to act as supportive agents in cancer immunotherapy, improving both efficacy and safety profiles.

However, several challenges limit the clinical translation of these promising effects. Variability in bioactive content due to non-standardized extraction and formulation processes, limited large-scale randomized controlled trials, and pharmacokinetic barriers such as poor bioavailability impede consistent therapeutic application. Additionally, the lack of comprehensive safety data and the regulatory ambiguity surrounding palm oil bioactives further complicate their integration into routine immunotherapy regimens. Overcoming these obstacles requires rigorous standardization of palm oil bioactive preparations, advanced delivery technologies to enhance bioavailability, and well-designed clinical trials to validate efficacy and safety in diverse patient populations. Addressing socio-political and environmental concerns related to palm oil production is also essential to support sustainable and ethical utilization of these natural compounds. In summary, palm oil bioactives present a promising

adjunctive option for enhancing immunotherapy outcomes, yet their full clinical potential remains contingent on overcoming translational challenges through multidisciplinary research and development efforts. Continued investigation will be vital to establish standardized protocols and confirm long-term benefits and safety, thereby advancing the integration of natural immunomodulators into modern oncology practice.

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