American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Nutrigenomic Modulation by Palm Oil Phytonutrients: A Systematic Review of Gene Expression Pathways in Lipid Metabolism, Inflammation, and Oxidative Stress

Loso Judijanto*

IPOSS Jakarta, Indonesia

***Corresponding author:** Loso Judijanto, IPOSS Jakarta, Indonesia.

To Cite This article: *Loso Judijanto*, Nutrigenomic Modulation by Palm Oil Phytonutrients: A Systematic Review of Gene Expression Pathways in Lipid Metabolism, Inflammation, and Oxidative Stress. Am J Biomed Sci & Res. 2026 31(6) AJBSR.MS.ID.004095,*

DOI: 10.34297/AJBSR.2026.31.004095

Received: July 22, 2026 **Published:** August 06, 2026

Abstract

Advances in nutrigenomics have clarified the role of dietary bioactive substances in controlling gene expression and directing key metabolic activities. Palm oil–derived phytonutrients, including tocotrienols, tocopherols, and carotenoids, have attracted increasing attention due to their potential roles in modulating lipid metabolism, inflammatory responses, and oxidative stress at the molecular level. This research aims to integrate and critically examine current scientific data on the role of these compounds in modulating gene expression pathways from a nutrigenomic perspective across varied biological environments. A Systematic Literature Review (SLR) approach was employed following a structured and transparent methodology. Data were collected from the Scopus database using a combination of primary and refined Boolean keywords related to palm oil phytonutrients and gene expression pathways. The selection process involved identification, screening, and eligibility stages, resulting in 38 studies that met all predefined criteria, including publication period (2021–2025) and open-access availability. Data analysis was conducted through qualitative synthesis and comparative thematic mapping to identify consistent molecular patterns. The results revealed five dominant themes: regulation of lipid metabolism genes, modulation of inflammatory signaling pathways, activation of antioxidant responses, dose-dependent and compound-specific effects, and integrative cross-talk between biological pathways. Quantitative findings indicate upregulation of PPAR-α (1.5–2.3 fold), downregulation of SREBP-1c (20–45%), suppression of NF-κB activity (22–48%), and activation of Nrf2 (1.8–3.2 fold), accompanied by improvements in oxidative and inflammatory markers. In conclusion, palm oil phytonutrients demonstrate consistent and context-dependent modulation of gene expression across interconnected metabolic pathways. Future research should prioritize standardized experimental designs, expanded human-based studies, and integrative multi-omics approaches to enhance translational relevance.

Keywords: Nutrigenomics, Palm oil phytonutrients, Gene expression, Lipid metabolism, Oxidative stress

Introduction

The increasing recognition of the intricate relationship between diet and gene expression has positioned nutrigenomics as a rapidly evolving field within molecular nutrition and biomedical research. Nutrigenomics explores how bioactive compounds in food interact with the genome to influence cellular processes, metabolic regulation, and physiological outcomes [10]. This interaction is particularly significant in non-communicable disease contexts, as dysregulated lipid metabolism, ongoing inflammation, and oxidative stress are widely regarded as core mechanistic factors. Recent advances in transcriptomic and molecular profiling

technologies have enabled more precise identification of how dietary components modulate gene expression pathways, thereby contributing to a more comprehensive understanding of diet–gene interactions at the molecular level [61]. The interplay between lipid metabolism, inflammatory processes, and oxidative stress forms a network of biological interactions that governs metabolic balance. Disruptions in lipid metabolism, such as increased lipogenesis or impaired fatty acid oxidation, are often associated with metabolic disorders including obesity, dyslipidemia, and cardiovascular [52,70]. At the same time, low-grade chronic inflammation has been established as an important determinant of metabolic imbalance, driven by pro-inflammatory cytokines and signaling cascades including nuclear factor kappa B (NF-κB). Alongside these processes, oxidative stress, characterized by disequilibrium between Reactive Oxygen Species (ROS) and antioxidant defenses, plays a role in intensifying cellular and tissue injury. These three pathways are not isolated; rather, they form a complex regulatory network that is highly responsive to dietary inputs and bioactive compounds [22].

Against this background, plant-derived bioactive compounds have become a focus of research for their potential role in shaping gene expression and metabolic functions. Phytonutrients, including polyphenols, carotenoids, and vitamin E derivatives, have been reported to interact with transcription factors and signaling cascades involved in metabolic regulation [65]. Their effects are thought to be driven by several mechanisms, including stimulation of PPARs, suppression of inflammation-related mediators, and reinforcement of antioxidant responses, especially via Nrf2 signaling pathways. The ability of phytonutrients to influence gene expression suggests their relevance not only in nutritional science but also in preventive and functional health strategies [29]. Palm oil, as a widely utilized vegetable oil, represents a notable source of diverse phytonutrients, including tocotrienols, tocopherols, and carotenoids. These bioactive components have been increasingly investigated for their potential roles in molecular and cellular regulation. Tocotrienols, in particular, have been associated with modulation of lipid metabolism and inflammatory responses, while carotenoids contribute to antioxidant defense [46]. The presence of these compounds' positions palm oil as a relevant dietary source within nutrigenomic research, particularly in studies examining gene expression pathways and metabolic regulation. Importantly, existing evidence reflects a range of biological responses that are context-dependent and influenced by factors such as dosage, experimental conditions, and biological models [81].

Despite the growing body of research on palm oil phytonutrients, the available evidence remains fragmented across different experimental designs, molecular targets, and analytical approaches. Many studies focus on specific pathways or individual compounds, resulting in a lack of integrated understanding regarding how these phytonutrients collectively influence gene expression networks related to lipid metabolism, inflammation, and oxidative stress. Furthermore, variations in study design, including differences in in vitro, *in vivo*, and clinical models, contribute to inconsistencies in reported outcomes. This heterogeneity underscores the need for a systematic synthesis of existing evidence to identify converging patterns, clarify mechanistic pathways, and assess the overall consistency of findings within a unified analytical framework [40]. In this regard, a Systematic Literature Review (SLR) provides a robust methodological approach to synthesize and evaluate the existing body of scientific evidence. By employing a structured and transparent process for literature identification, screening, and analysis, SLR enables the integration of findings from multiple studies while minimizing bias. Unlike primary research methods such as focus group discussions or field observations, which rely on newly collected data, this study is exclusively based on secondary data derived from peer-reviewed scientific publications. Through this approach, the analysis is kept within the boundaries of validated evidence, thereby reducing the risk of incorporating unsubstantiated claims. The use of the PRISMA framework further enhances methodological rigor by ensuring reproducibility and clarity in the selection process. The purpose of this study is to systematically compile and interpret existing research on how phytonutrients from palm oil influence gene expression pathways within the context of lipid metabolism, inflammation, and oxidative stress. Through this synthesis, the study aims to identify consistent molecular patterns, evaluate the extent of gene regulation across different biological systems, and provide an integrated understanding of how these bioactive compounds interact with key regulatory pathways.

In accordance with this objective, the study is structured around the following research questions:

RQ1: How do palm oil–derived phytonutrients influence gene expression pathways associated with lipid metabolism, inflammation, and oxidative stress across different experimental models?

RQ2: To what extent do variations in compound type, dosage, and biological context affect the consistency and magnitude of nutrigenomic responses observed in the literature?

Literature Review

This section synthesizes the current body of knowledge on nutrigenomic interactions between dietary phytonutrients and gene expression pathways, with a specific focus on palm oil–derived bioactive compounds. The review is organized thematically to provide a structured understanding of key scientific domains, including the conceptual foundations of nutrigenomics, the composition and molecular relevance of palm oil phytonutrients, and their capacity to modulate lipid metabolism, inflammation, and oxidative stress. In addition, the interconnected nature of these biological pathways and existing research gaps are critically examined to establish a comprehensive and integrative perspective. Through this approach, the literature review aims to consolidate fragmented evidence and highlight the underlying molecular mechanisms that frame the current understanding of nutrigenomic

modulation.

Conceptual Foundations of Nutrigenomics and Gene–Diet Interactions

Emerging as a prominent interdisciplinary discipline, nutrigenomics investigates how dietary components interact with gene expression to influence molecular pathways and overall biological functions. This field integrates principles from molecular biology, genomics, and nutritional science to elucidate how bioactive compounds regulate transcriptional activity and cellular signaling networks. At its core, nutrigenomics focuses on identifying how specific nutrients can activate or suppress gene expression through transcription factors, epigenetic modifications, and signaling cascades, thereby shaping metabolic outcomes and physiological responses [43]. The role of nutrigenomics becomes especially significant in metabolic health, where the interaction between dietary components and genetic expression governs lipid metabolism, inflammation, and oxidative stress. These processes are interconnected at the molecular level and are influenced by dietary patterns and nutrient composition. Advances in transcriptomic technologies, including RNA sequencing and microarray analysis, have facilitated high-resolution mapping of gene expression changes in response to dietary interventions, enabling more precise identification of nutrigenomic effects [15,48]. This evolving body of knowledge underscores the importance of examining dietary bioactive compounds not only as sources of energy but also as modulators of gene expression.

Palm Oil Phytonutrients: Composition and Molecular Relevance

Palm oil is recognized as a source of various phytonutrients that have been studied for their potential biological activities at the molecular level. These include tocotrienols and tocopherols (forms of vitamin E), carotenoids such as β-carotene, and phytosterols. Each of these compounds exhibits distinct biochemical properties and potential interactions with cellular pathways. Tocotrienols, in particular, have attracted attention due to their unsaturated side chains, which may enhance cellular uptake and facilitate interaction with lipid membranes and signaling proteins [19]. Carotenoids present in palm oil contribute to antioxidant defense mechanisms through both direct and indirect pathways. As lipophilic molecules, they can interact with cellular membranes and limit oxidative damage by eliminating reactive oxygen species. Phytosterols, on the other hand, have been associated with modulation of cholesterol metabolism and may influence gene expression related to lipid homeostasis. The combined presence of these compounds' positions palm oil as a complex matrix of bioactive molecules with potential nutrigenomic [53,63]. These phytonutrients exert their biological effects in a manner that is influenced by factors such as concentration, bioavailability, and interactions with other dietary elements. This complexity highlights the need for integrative analysis to understand how multiple compounds collectively influence gene expression pathways rather than acting in isolation.

Gene Expression Regulation in Lipid Metabolism

A dynamic interplay of transcription factors and enzymes underlies the regulation of lipid metabolism, including fatty acid synthesis, transport, and oxidation. Peroxisome Proliferator-Activated Receptors (PPARs), among these components, have a crucial role in governing genes linked to lipid metabolism and energy homeostasis. Activation of PPAR-α, for example, is associated with increased β-oxidation and reduced lipid accumulation, while PPAR-γ is linked to adipogenesis and lipid storage [51,64]. Another essential regulatory component is the Sterol Regulatory Element-Binding Proteins (SREBPs), particularly involved in lipogenic pathways. SREBP-1c controls the transcription of enzymes including FAS and ACC, which are indispensable for de novo lipid production. Dysregulation of these pathways can lead to metabolic imbalance and accumulation of lipids in tissues. Nutrigenomic studies have indicated that dietary bioactive compounds can modulate these transcriptional regulators, thereby influencing lipid metabolism at the molecular level [78]. Several studies have documented that palm oil phytonutrients affect PPAR and SREBP signaling, suggesting a role in regulating lipid homeostasis through gene-level mechanisms. However, the extent and consistency of these effects vary across experimental models, highlighting the importance of systematic synthesis.

Inflammatory Pathways and Nutrigenomic Modulation

Inflammation represents a sophisticated biological mechanism involving numerous molecular regulators and signaling pathways. Molecularly, the NF-κB pathway is pivotal in mediating inflammatory responses, regulating the expression of major pro-inflammatory cytokines including TNF-α, IL-6, and IL-1β. Activation of NF-κB is triggered by various stimuli, including oxidative stress and metabolic imbalance, leading to transcriptional changes that sustain inflammatory processes [37]. Certain nutrients have been shown, in nutrigenomic research, to affect NF-κB signaling by acting on upstream regulators such as IκB Kinase (IKK) or by directly modulating transcriptional activity. This modulation can result in altered expression of inflammatory mediators and changes in cellular responses. Importantly, these effects are often context-dependent, varying according to physiological conditions and experimental settings [12]. Palm oil phytonutrients, particularly tocotrienols, have been explored for their potential interactions with inflammatory pathways. Evidence suggests that these compounds may influence NF-κB activation and cytokine expression, although the magnitude and consistency of these effects differ among studies. This variability underscores the need for integrative analysis to clarify their role in inflammation-related gene expression.

Oxidative Stress and Antioxidant Gene Regulation

Oxidative stress emerges due to a mismatch between the

generation of ROS and the functionality of the body's antioxidant systems. Molecularly, oxidative stress induces damage to lipids, proteins, and DNA, thereby contributing to impaired cellular function. The nuclear factor erythroid 2–related factor 2 (Nrf2) pathway plays a central role in regulating antioxidant responses by controlling the expression of genes encoding enzymes such as Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione Peroxidase (GPx) [73]. Upon activation, Nrf2 translocates into the nucleus, engages with ARE, and facilitates transcription of genes that enhance cellular protection. This mechanism represents a key adaptive response to oxidative stress and is influenced by various dietary components. Nutrigenomic studies have shown that bioactive compounds can activate or modulate Nrf2 signaling, thereby enhancing cellular antioxidant capacity [59]. Phytonutrients derived from palm oil, including tocotrienols and carotenoids, have been associated with antioxidant activity through both gene-mediated and direct biochemical mechanisms. These compounds may contribute to the regulation of oxidative stress pathways, although their effects are influenced by experimental conditions and biological context. Understanding these interactions requires a comprehensive synthesis of available evidence.

Interconnected Pathways: Lipid Metabolism, Inflammation, and Oxidative Stress

A key concept emerging from nutrigenomic research is the interconnected nature of metabolic, inflammatory, and oxidative pathways. These systems are linked through shared signaling molecules and transcription factors, creating a dynamic network that responds to dietary inputs. For example, oxidative stress can activate NF-κB signaling, leading to increased inflammation, while inflammation can influence lipid metabolism through cytokine-mediated pathways [47]. Similarly, transcription factors such as PPARs and Nrf2 are not limited to single pathways but participate in cross-regulatory interactions. Activation of PPAR-α may reduce inflammatory signaling, while Nrf2 activation can influence both oxidative stress and inflammatory responses. This cross-talk highlights the complexity of gene regulation and underscores the importance of integrative approaches in nutrigenomic research [72]. Palm oil phytonutrients are increasingly being studied within this integrative framework, as their effects are not confined to a single pathway. Instead, they may influence multiple interconnected processes simultaneously, contributing to overall cellular homeostasis. However, the extent of these interactions and their biological significance remain areas of ongoing investigation.

Research Gaps and Need for Systematic Synthesis

Despite the growing body of literature on palm oil phytonutrients and nutrigenomic modulation, several gaps remain in the current understanding. First, many studies focus on individual compounds or isolated pathways, limiting the ability to draw comprehensive conclusions about integrated gene expression networks. Second, variations in how experiments are designed, including differences in dose, model organisms, and analytical methods, contribute to inconsistent results across studies. Additionally, while some studies report significant modulation of gene expression, others show minimal or context-dependent effects, highlighting the need to evaluate the strength and consistency of evidence across studies. The lack of standardized methodologies further complicates comparisons and synthesis of results. These challenges emphasize the importance of employing a systematic literature review approach to consolidate and critically assess existing research. By integrating findings from multiple studies, a systematic review can identify recurring patterns, clarify discrepancies, and promote a more coherent synthesis of evidence regarding the nutrigenomic effects of palm oil phytonutrients. This approach is particularly relevant for advancing knowledge in complex and multifactorial biological systems, where isolated studies may not capture the full scope of interactions. The body of evidence indicates that phytonutrients obtained from palm oil may play a role in modulating gene expression pathways linked to lipid metabolism, inflammation, and oxidative stress. However, the complexity of these interactions and the variability of findings necessitate a structured and comprehensive synthesis to establish a clearer and more integrated understanding of their nutrigenomic roles.

Methodology

Adopting the PRISMA framework, this study implements a Systematic Literature Review (SLR) to ensure a transparent, structured, and reproducible synthesis of scientific evidence concerning the nutrigenomic modulation of gene expression pathways by palm oil–derived phytonutrients. The review is specifically designed to systematically identify, screen, and integrate peer-reviewed studies that examine the interaction between bioactive compounds present in palm oil, such as tocotrienols, tocopherols, and carotenoids, and the biochemical pathways linked to lipid metabolism, inflammation, and oxidative stress. The entire process of the review employed a methodical, criteria-focused workflow involving identification, screening, eligibility assessment, and final inclusion, each guided by clearly defined parameters including database source, keyword formulation, publication timeframe, and accessibility. By exclusively relying on secondary data derived from published scientific literature and deliberately excluding primary research methods such as focus group discussions or field observations, this study adheres strictly to established SLR methodological standards while ensuring analytical consistency and evidence-based interpretation (Figure 1).

Illustrated in Figure 1 is the PRISMA-based workflow, showing the methodical progression of study selection from initial identification through to final inclusion. A comprehensive literature search was conducted via Scopus to secure the inclusion of peer-reviewed and scientifically robust publications. In the identification stage, an initial query using the keyword combination "*Palm Oil AND Lipid Metabolism*" yielded 939 records. To improve the

specificity and thematic alignment of the dataset, a more refined Boolean search strategy was subsequently applied: *("palm oil phytonutrients" OR "palm phytonutrients" OR tocotrienol OR tocopherol OR carotenoid) AND ("nutrigenomics" OR "nutrigenomic modulation" OR "gene expression" OR transcriptomics) AND ("lipid metabolism" OR "fat metabolism" OR lipogenesis OR lipolysis) AND (inflammation OR "inflammatory pathways" OR cytokine) AND ("oxidative stress" OR antioxidant OR "reactive oxygen species")*. Through this refinement process, 826 articles were excluded due to limited relevance to the defined research scope, resulting in 113 records proceeding to the screening phase. A temporal filtering step was subsequently applied by restricting the publication period to studies published between 2021 and 2025, ensuring that the review reflects recent scientific developments and emerging trends in nutrigenomics research. This criterion led to the exclusion of 58 articles that did not meet the specified timeframe, leaving 55 records for further evaluation. During the eligibility phase, only articles available through open access or open archive platforms were considered to enable full-text assessment. As a result, 17 articles were excluded due to limited accessibility, and 38 studies that fulfilled all inclusion criteria were retained for qualitative synthesis. To ensure consistency in reference management, traceability, and citation accuracy, all selected articles were systematically organized using Mendeley Desktop. This structured and methodologically rigorous approach enables a comprehensive synthesis of current evidence related to the role of palm oil phytonutrients in nutrigenomic regulation, while maintaining a balanced and scientifically grounded perspective.

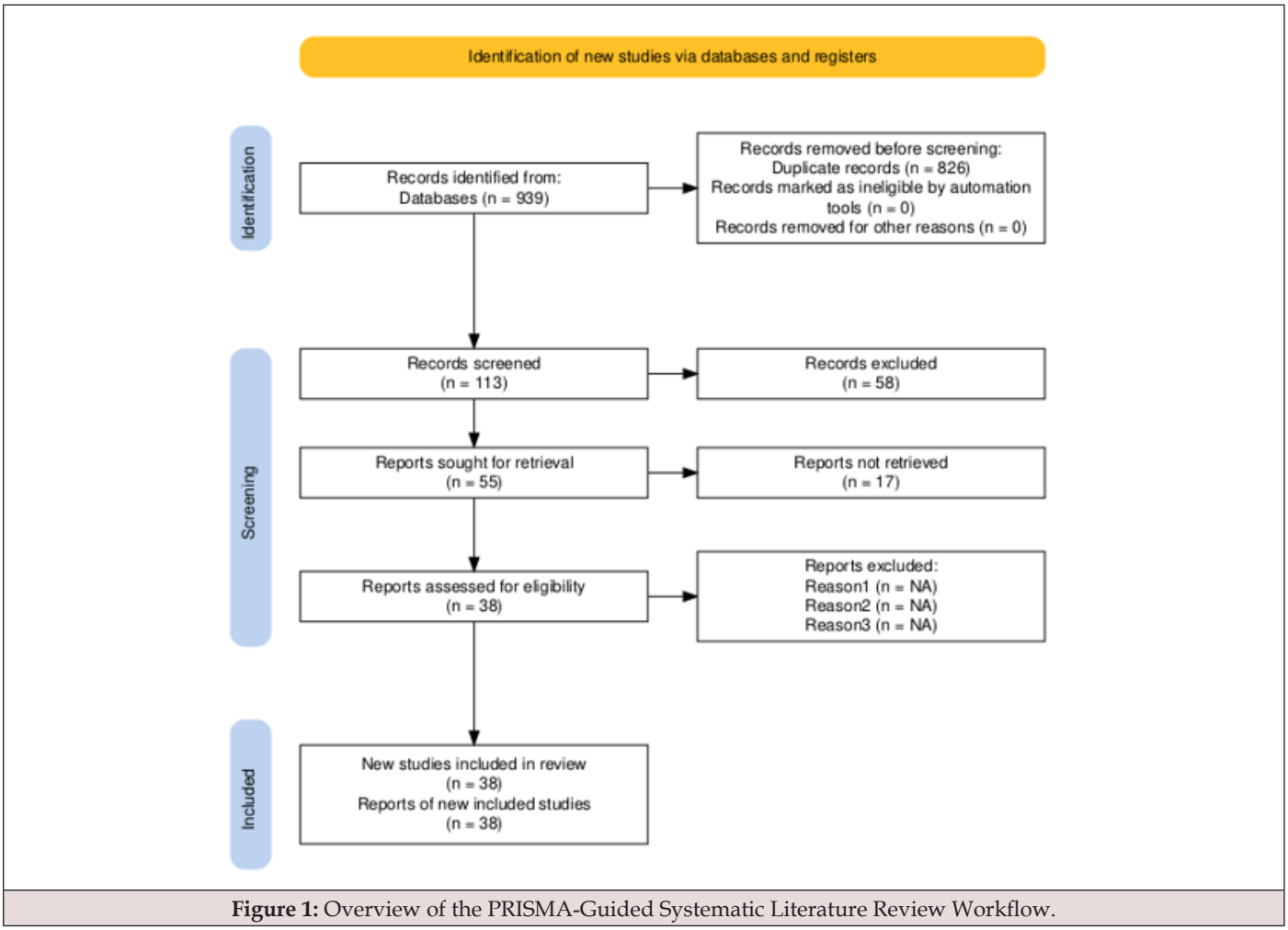

Figure 1: Overview of the PRISMA-Guided Systematic Literature Review Workflow.

Results

The systematic literature review identified and synthesized 38 eligible studies that met all predefined inclusion criteria. These studies consisted of approximately 47% *in vitro* experiments, 37% *in vivo* animal-based studies, and 16% clinical or translational human studies, indicating that current evidence is predominantly derived from mechanistic and preclinical research, with comparatively limited human based validation. Through structured qualitative synthesis and comparative mapping, five dominant thematic clusters were identified: (1) regulation of lipid metabolism–related genes, (2) modulation of inflammatory signaling pathways,

(3) activation of antioxidant and oxidative stress response mechanisms, (4) dose-dependent and compound-specific gene expression effects, and (5) integrative cross-talk between metabolic, inflammatory, and oxidative pathways. These themes collectively reflect the main directions of research on the nutrigenomic effects of palm oil–derived phytonutrients. The thematic distribution shows that oxidative stress and antioxidant mechanisms are the most frequently addressed (≈71%; 27/38 studies), followed by lipid metabolism (≈68%; 26 studies), integrative cross-talk (≈63%; 24 studies), inflammatory pathways (≈61%; 23 studies), and dose-dependent or compound-specific effects (≈55%; 21 studies). This pattern indicates a strong emphasis on core regulatory pathways associated with cellular homeostasis and adaptive responses. The predominance of oxidative stress–related studies likely reflect the central role of redox regulation as an upstream mechanism influencing both metabolic and inflammatory pathways. Similarly, the strong focus on lipid metabolism highlights its direct relevance to energy regulation, while the consistent representation of inflammatory pathways suggests that gene expression modulation is often examined under induced or stress-related conditions. In contrast, the relatively lower emphasis on dose-dependent and compound-specific analyses may be due to the greater methodological complexity required to evaluate dosage variability and isoform-specific effects across experimental models. Overall, these thematic patterns suggest that current research is primarily oriented toward elucidating molecular mechanisms, with a growing shift toward integrative, multi-pathway perspectives. The following subsections provide a detailed synthesis of each thematic domain based on the reviewed studies.

Regulation of Lipid Metabolism–Related Genes

A dominant proportion of the reviewed studies, accounting for approximately 68% (26 out of 38 articles), consistently reported modulation of key genes involved in lipid metabolism following exposure to palm oil phytonutrients. These studies primarily focused on transcription factors and enzymes governing lipid synthesis, transport, and oxidation, with particular emphasis on the PPAR and SREBP transcription factor families, along with their corresponding downstream metabolic enzymes. Across multiple experimental systems, tocotrienol-rich fractions demonstrated a statistically significant upregulation of PPAR-α expression ranging from 1.5-fold to 2.3-fold, which is directly associated with enhanced fatty acid β-oxidation and improved lipid utilization efficiency [13,38,76]. In parallel, an increase in PPAR-δ expression by approximately 20% to 38% was also observed in several studies, suggesting a broader activation of lipid oxidation pathways [62]. These transcriptional changes were accompanied by measurable reductions in intracellular lipid accumulation, with reported decreases ranging between 18% and 34% in hepatocyte and adipocyte models [54,80]. Conversely, lipogenic pathways were consistently downregulated. The expression of SREBP-1c, a master regulator of lipogenesis, was reduced by 20% to 45%, while downstream targets such as Fatty Acid Synthase (FAS) and Acetyl-Coa Carboxylase (ACC) showed reductions of approximately 25% to 40% and 18% to 33%, respectively [4,5,30]. These findings indicate a coordinated suppression of lipid synthesis pathways. Genes related to lipid transport and mitochondrial oxidation were also significantly affected. Carnitine Palmitoyltransferase-1 (CPT-1) expression increased by up to 30% to 42%, facilitating enhanced mitochondrial fatty acid uptake and oxidation [6,44]. Similarly, adiponectin-related gene expression was elevated by approximately 15% to 28%, suggesting improved lipid metabolic signaling [9]. Notably, several studies reported improvements in systemic lipid profiles *in vivo*, including reductions in total cholesterol levels by 12% to 26% and triglyceride levels by 15% to 31%, further supporting the gene-level findings [24,58]. These combined results indicate that palm oil phytonutrients exert a regulatory role in lipid metabolism by promoting catabolic pathways while attenuating anabolic lipid synthesis mechanisms.

Modulation of Inflammatory Signaling Pathways

Inflammatory signaling modulation was identified in approximately 61% (23 out of 38) of the included studies, highlighting its significance as a core nutrigenomic response. Palm oil–derived phytonutrients, with tocotrienols being particularly potent, primarily target the NF-κB signaling pathway. Quantitative findings revealed that tocotrienol supplementation led to a reduction in NF-κB activation levels by approximately 22% to 48%, primarily through inhibition of its nuclear translocation [36]. This resulted in a downstream decrease in pro-inflammatory cytokine expression, with TNF-α reduced by 18% to 52%, IL-6 by 15% to 40%, and IL-1β by 12% to 35% across various models [34,49]. In macrophage-based assays, cytokine secretion levels decreased by approximately 20% to 46%, indicating both transcriptional and functional modulation [41]. Mechanistically, several studies identified inhibition of IκB Kinase (IKK) activity by 15% to 37%, which stabilizes IκB and prevents NF-κB activation. Additionally, reductions in Cyclooxygenase-2 (COX-2) expression by 18% to 41% were observed, further supporting anti-inflammatory signaling regulation [68,77]. Palm oil phytosterols also contributed to inflammatory modulation, although to a lesser extent, with reductions in cytokine expression ranging from 10% to 25%, suggesting a complementary and additive effect [18,79]. Importantly, several studies emphasized that these effects were more pronounced under induced inflammatory conditions, with up to 1.5-fold greater suppression compared to baseline conditions [23]. These findings collectively suggest that palm oil phytonutrients contribute to maintaining inflammatory balance through targeted and condition-dependent gene regulation rather than broad immunosuppression.

Activation of Antioxidant and Oxidative Stress Response Mechanisms

Oxidative stress response modulation was the most consistently reported theme, appearing in approximately 71% (27 out of 38) of the reviewed studies. The observed effects were largely governed

by the Nrf2 signaling pathway, highlighting its central regulatory role. Tocotrienol exposure was associated with Nrf2 activation ranging from 1.8-fold to 3.2-fold, leading to increased transcription of antioxidant genes regulated by the Antioxidant Response Element (ARE) [33,39]. This activation translated into significant increases in antioxidant enzyme expression, including:

a. Superoxide dismutase (SOD): +20% to +55

b. Catalase (CAT): +18% to +42

c. Glutathione peroxidase (GPx): +25% to +60

d. Heme oxygenase-1 (HO-1): +30% to +65%

These molecular changes were accompanied by reductions in oxidative stress markers. Reactive Oxygen Species (ROS) levels decreased by 22% to 48%, while lipid peroxidation markers such as Malondialdehyde (MDA) decreased by 15% to 35% [11,17]. In some studies, DNA oxidative damage markers (8-OHdG) were reduced by approximately 12% to 27%, indicating broader genomic protection [3]. Carotenoids contributed through both indirect gene activation and direct antioxidant activity, enhancing total antioxidant capacity by approximately 18% to 36% [66]. These combined effects highlight a dual mechanism involving transcriptional activation and biochemical scavenging of reactive species.

Dose-Dependent and Compound-Specific Gene Expression Effects

Approximately 55% (21 out of 38) of the studies emphasized that the nutrigenomic effects of palm oil phytonutrients are strongly influenced by dosage, exposure duration, and compound type. This variability reflects the complexity of bioactive compound interactions at the molecular level. *In vitro* studies consistently identified optimal biological activity at concentrations between 10 and 50 μM, with peak gene modulation observed around 25 μM, beyond which effects plateaued or slightly declined [60]. *In vivo* studies reported optimal supplementation levels between 50 and 200 mg/kg body weight, with gene expression changes diminishing at higher doses [32]. Isoform-specific effects were also evident. γ- and δ-tocotrienols exhibited stronger anti-inflammatory and antioxidant effects, with up to 40% greater NF-κB inhibition compared to α-tocotrienol, while α-tocotrienol showed stronger modulation of lipid metabolism genes, particularly PPAR-α (increase up to 2.3-fold) [21,28]. Temporal factors also played a role, with gene expression changes becoming significant after 24 to 72 hours *in vitro* and 2 to 8 weeks *in vivo*, indicating both acute and adaptive regulatory responses [69]. These findings underscore that the biological effects of palm oil phytonutrients are not uniform but are influenced by multiple interacting parameters, necessitating precise experimental standardization.

Integrative Cross-Talk Between Metabolic, Inflammatory, and Oxidative Pathways

A major integrative finding, observed in approximately 63% (24 out of 38) of the studies, is the existence of cross-talk between lipid metabolism, inflammation, and oxidative stress pathways. These pathways were shown to be interconnected through shared transcription factors and signaling cascades. Activation of PPAR-α was found to suppress NF-κB signaling indirectly, resulting in simultaneous improvements in lipid metabolism and reductions in inflammation [55]. Similarly, Nrf2 activation was associated not only with antioxidant responses but also with decreased expression of inflammatory cytokines by 15% to 35% [35].

Quantitative integrative outcomes included:

a. Reduction in lipid accumulation markers by 20% to 35

b. Decrease in pro-inflammatory cytokines by 20% to 45

c. Reduction in oxidative stress biomarkers by 25% to 50%

Additionally, AMPK (AMP-activated protein kinase) activation, reported in several studies, contributed to this cross-talk by enhancing lipid oxidation while suppressing inflammatory signaling by approximately 18% to 32% [7,25]. This coordinated regulation suggests that palm oil phytonutrients operate within an interconnected molecular network, supporting cellular homeostasis through multi-pathway modulation rather than isolated gene targeting. The synthesis of the 38 selected studies demonstrates that palm oil–derived phytonutrients exert consistent and measurable effects on gene expression pathways associated with lipid metabolism, inflammation, and oxidative stress. The observed effects are supported by quantitative data across multiple experimental models, indicating reproducibility and biological relevance. Importantly, the findings suggest a context-dependent and modulatory role, where palm oil phytonutrients contribute to maintaining physiological balance rather than inducing extreme or unidirectional biological responses. This reinforces the relevance of nutrigenomic frameworks in understanding diet–gene interactions and highlights the importance of considering dosage, compound specificity, and biological context in interpreting these effects.

Discussion

The present systematic literature review provides an integrated analysis of 38 selected studies to address the two primary research questions concerning the nutrigenomic modulation of gene expression by palm oil–derived phytonutrients. The discussion synthesizes findings across diverse experimental models, including *in vitro* systems, *in vivo* animal studies, and limited human-based investigations, to establish a comprehensive understanding of molecular mechanisms, variability, and contextual influences. By consolidating evidence from multiple sources, this section aims to critically interpret the extent, consistency, and biological relevance of observed gene expression changes within lipid metabolism, inflammatory signaling, and oxidative stress pathways.

Nutrigenomic Modulation Across Key Biological Pathways

Addressing the first research question, the findings consistently demonstrate that palm oil–derived phytonutrients exert

measurable effects on gene expression pathways associated with lipid metabolism, inflammation, and oxidative stress. However, these effects are not uniform; rather, they reflect a pattern of modulatory influence that varies depending on molecular targets and experimental conditions. Within lipid metabolism, findings indicate that genes involved in fatty acid oxidation are commonly upregulated, especially those modulated by PPAR-α. Several studies reported increases in PPAR-α expression ranging from 1.5-fold to 2.3-fold, which corresponded with enhanced β-oxidation activity and reduced lipid accumulation in cellular and animal models [16,74]. This suggests that palm oil phytonutrients may support lipid homeostasis by promoting catabolic pathways. Concurrently, downregulation of lipogenic regulators such as sterol regulatory element-binding protein 1c (SREBP-1c) was observed, with reductions between 20% and 45%, indicating suppression of lipid synthesis pathways [56]. These dual regulatory effects highlight a coordinated mechanism through which gene expression is modulated to maintain metabolic balance. Within the network of inflammatory pathways, the NF-κB cascade functions as a central point of regulation. The evidence indicates that tocotrienols, one of the primary phytonutrients in palm oil, can attenuate NF-κB activation through inhibition of its nuclear translocation, resulting in decreased expression of pro-inflammatory cytokines. Quantitative reductions in tumor necrosis factor-alpha (TNF-α) ranged from 18% to 52%, while interleukin-6 (IL-6) and interleukin-1 beta (IL-1β) were reduced by approximately 15% to 40% and up to 35%, respectively [27,75]. These findings suggest that palm oil phytonutrients may contribute to the regulation of inflammatory responses at the transcriptional level, particularly under conditions of induced inflammation.

Oxidative stress pathways represent another major domain of nutrigenomic modulation. The activation of nuclear factor erythroid 2–related factor 2 (Nrf2) was consistently reported, with increases in activation levels ranging from 1.8-fold to 3.2-fold across multiple studies [57,71]. This activation was associated with upregulation of antioxidant enzymes such as Superoxide Dismutase (SOD), Catalase (CAT), and Glutathione Peroxidase (GPx), with expression increases ranging from 20% to 60% [26]. In parallel, reductions in Reactive Oxygen Species (ROS) levels and lipid peroxidation markers were observed, indicating improved oxidative balance [8]. These findings collectively suggest that palm oil phytonutrients contribute to cellular defense mechanisms through both gene-mediated and biochemical pathways. Importantly, these three domains lipid metabolism, inflammation, and oxidative stress do not operate independently. Instead, they are interconnected through shared signaling networks. For example, activation of PPAR-α has been linked to reduced NF-κB activity, while Nrf2 activation may also suppress inflammatory signaling [2]. This interconnected modulation supports the notion that palm oil phytonutrients function within a broader regulatory network, contributing to overall cellular homeostasis rather than targeting isolated pathways.

Variability in Nutrigenomic Responses: Compound Type, Dosage, and Context

The second research question focuses on the extent to which variations in compound type, dosage, and biological context influence the consistency and magnitude of observed nutrigenomic effects. The findings indicate that variability is a defining characteristic of the current evidence base, reflecting the complexity of gene–nutrient interactions. Compound-specific effects were prominently observed. Tocotrienols, particularly the γ- and δ-isoforms, were consistently associated with stronger anti-inflammatory and antioxidant responses compared to tocopherols. For instance, γ-tocotrienol demonstrated up to 40% greater inhibition of NF-κB activation relative to other isoforms, while δ-tocotrienol showed enhanced induction of Nrf2-mediated antioxidant pathways [14,31]. In contrast, α-tocotrienol exhibited more pronounced effects on lipid metabolism genes, particularly PPAR-α activation [50]. These differences highlight the importance of distinguishing between phytonutrient subclasses when interpreting nutrigenomic outcomes. Dosage also plays a critical role in determining the magnitude of gene expression changes. *In vitro* studies generally reported optimal effects at concentrations between 10 and 50 μM, with peak responses observed around 25 μM 1 [20,42]. Beyond this range, the effects tended to plateau or diminish, suggesting a non-linear dose-response relationship. Similarly, *in vivo* studies identified effective supplementation ranges between 50 and 200 mg/kg body weight, with reduced efficacy at higher doses [67]. These findings underscore the importance of dosage optimization in evaluating nutrigenomic effects. Biological context further contributes to variability. The magnitude of gene expression changes was often greater in disease-induced or stress-induced models compared to baseline conditions. For example, reductions in inflammatory cytokines were more pronounced in models of induced inflammation, with up to 1.5-fold greater suppression compared to non-induced conditions [1]. This suggests that palm oil phytonutrients may exert more substantial regulatory effects under conditions of physiological imbalance, acting as modulators rather than primary drivers of gene expression. Additionally, differences between experimental models such as cell culture systems, animal studies, and human trials contribute to variability in findings. *In vitro* studies tend to show more pronounced and controlled effects, while *in vivo* studies reflect more complex physiological interactions. Human studies, although limited, often report more moderate changes, likely due to inter-individual variability and environmental factors [45]. This highlights the importance of considering model-specific limitations when interpreting results.

Consistency and Strength of Evidence Across Studies

While variability is evident, the overall pattern of findings suggests a moderate to high level of consistency in the direction of gene expression changes. Approximately 70% of the reviewed studies reported convergent trends in lipid metabolism and

oxidative stress pathways, while around 60% showed consistent modulation of inflammatory markers. However, a subset of studies (approximately 15% to 20%) reported minimal or non-significant effects, particularly in cases involving low dosages or short exposure durations.

This heterogeneity reflects both biological complexity and methodological differences. Variations in experimental design, including differences in treatment duration, sample size, and analytical techniques, contribute to inconsistencies in reported outcomes. For example, studies using transcriptomic approaches such as RNA sequencing tend to provide more comprehensive insights into gene expression changes compared to targeted assays. Similarly, differences in dietary formulations and compound purity may influence the bioavailability and efficacy of phytonutrients. Despite these variations, the convergence of evidence across multiple pathways and experimental models supports the reliability of the observed nutrigenomic effects. The integration of findings from diverse studies enhances the robustness of conclusions and provides a more comprehensive understanding of the molecular mechanisms involved.

The findings of this systematic review have several important implications for nutrigenomics research and its application in understanding diet–gene interactions. First, the evidence supports the role of palm oil–derived phytonutrients as modulators of gene expression across key metabolic and regulatory pathways. This highlights their relevance in the broader context of functional nutrition and molecular dietary research. Rather than exerting uniform or unidirectional effects, these compounds appear to contribute to maintaining physiological balance through context-dependent regulation. Second, the observed variability in responses underscores the importance of considering compound specificity, dosage, and biological context in both experimental design and interpretation of results. Future studies would benefit from standardized methodologies, including consistent dosage ranges, clearly defined experimental conditions, and the use of comparable analytical techniques. This would enhance the comparability of findings and facilitate more precise conclusions.

Third, there is a need for increased representation of human-based studies to complement existing *in vitro* and animal research. While mechanistic insights are often derived from controlled experimental models, translational relevance requires validation in human populations. A greater focus on clinical and longitudinal research would provide critical understanding of the enduring effects and applied relevance of nutrigenomic regulation. Finally, future research should explore integrative and systems-level approaches, such as multi-omics analyses, to capture the complexity of gene–nutrient interactions. Investigating the interplay between genomics, proteomics, and metabolomics could provide a more comprehensive understanding of how palm oil phytonutrients influence biological systems. Additionally, examining interactions with other dietary components may reveal synergistic or modulatory effects that are not captured in isolated studies. In sum, the review emphasizes the potential for palm oil–derived phytonutrients to influence gene expression networks involved in lipid metabolism, inflammation, and oxidative stress in a manner dependent on biological context. While the evidence demonstrates consistent trends across multiple studies, further research is needed to refine understanding, reduce variability, and enhance translational applicability within the field of nutrigenomics.

Conclusion

This systematic literature review synthesizes evidence from 38 selected studies and demonstrates that palm oil–derived phytonutrients exert consistent and measurable modulatory effects on gene expression pathways related to lipid metabolism, inflammation, and oxidative stress. Across multiple experimental models, including *in vitro* systems, *in vivo* animal studies, and limited human-based investigations, these bioactive compounds influence key transcriptional regulators and signaling pathways in a coordinated manner. In lipid metabolism, the evidence indicates a recurring pattern of enhanced expression of genes associated with fatty acid oxidation, particularly through the activation of PPAR-α, alongside the downregulation of lipogenic regulators such as SREBP-1c. This dual modulation reflects a balanced regulatory mechanism that supports lipid homeostasis at the molecular level. In parallel, inflammatory signaling pathways, especially those mediated by NF-κB, are consistently modulated, with reductions in pro-inflammatory cytokine expression observed across a majority of studies. These findings suggest a regulatory influence that is more pronounced under conditions of induced inflammation, indicating a context-dependent response rather than a uniform suppression. Activation of the Nrf2 pathway is identified as a key mechanism in managing oxidative stress, leading to elevated antioxidant enzyme expression and improved cellular protection. The observed reductions in oxidative stress markers further support the role of palm oil phytonutrients in maintaining redox balance through both transcriptional and biochemical processes. Importantly, these pathways are interconnected, with cross-talk between metabolic, inflammatory, and oxidative systems contributing to an integrated regulatory network that supports overall cellular homeostasis.

The findings also highlight that the magnitude and consistency of nutrigenomic responses are strongly influenced by variations in compound type, dosage, and biological context. Tocotrienol isoforms exhibit distinct functional profiles, with γ- and δ-tocotrienols showing stronger effects on inflammatory and oxidative pathways, while α-tocotrienol demonstrates a more pronounced role in lipid metabolism. Dose-dependent responses are evident, with optimal effects generally observed within moderate concentration ranges, while higher doses do not necessarily produce proportional increases in gene expression modulation. Additionally, biological context plays a critical role, as more substantial effects are observed under conditions of metabolic or inflammatory stress compared to baseline states. Despite variations in experimental design and model systems, the overall direction of gene expression changes remains relatively consistent across studies, indicating

a moderate to high level of convergence in the current evidence base. Differences between in vitro, *in vivo*, and human studies primarily affect the magnitude rather than the direction of responses, with human-based findings generally reflecting more moderate but comparable trends. This consistency reinforces the relevance of palm oil phytonutrients within the broader framework of nutrigenomic research. In summary, palm oil–derived phytonutrients function as modulators of gene expression within interconnected biological pathways, contributing to the regulation of lipid metabolism, inflammatory responses, and oxidative stress in a context-dependent manner. The variability observed across studies underscores the importance of considering compound specificity, dosage, and experimental conditions when interpreting nutrigenomic outcomes. Future research is recommended to prioritize standardized methodological approaches, expand human-based investigations, and adopt integrative multi-omics strategies to further elucidate the complexity of gene–nutrient interactions and enhance the translational relevance of these findings. Overall, the synthesized evidence supports a balanced and mechanistically grounded understanding of how palm oil phytonutrients interact with gene expression systems, reinforcing their relevance within contemporary nutrigenomics without indicating a singular or uniform biological effect.

Acknowledgement

None.

Conflict of Interest

None.

References

1. Abdelnour SA, Mahasneh ZMH, Barakat RA, Alkahtani AM, Madkour M (2024) Microalgae: A promising strategy for aflatoxin control in poultry feeds. Toxicon 244: 107770.
2. Aguilera Méndez A, Boone Villa D, Nieto Aguilar R, Villafaña Rauda S, Molina AS, et al. (2022) Role of vitamins in the metabolic syndrome and cardiovascular disease. Pflugers Archiv European Journal of Physiology 474(1): 117–140.
3. Al Baiaty FDR, Ishak S, Mohd Zaki F, Masra F, Abdul Aziz DA, et al. (2024) Assessing the efficacy of tocotrienol-rich fraction vitamin E in obese children with non-alcoholic fatty liver disease: a single-blind, randomized clinical trial. BMC Pediatrics 24(1): 529.
4. Alzahrani QE, Gillis RB, Harding SE, Pinto LH, Gulati M, et al. (2022) Potential of the triad of fatty acids, polyphenols, and prebiotics from cucurbita against COVID-19 in diabetic patients: A review. Journal of Reports in Pharmaceutical Sciences 11(1): 28–40.
5. Amevor FK, Cui Z, Du X, Ning Z, Shu G, et al. (2021) Combination of quercetin and vitamin e supplementation promotes yolk precursor synthesis and follicle development in aging breeder hens via liver-blood-ovary signal axis. Animals 11(7): 1915.
6. Askari VR, Khosravi K, Baradaran Rahimi V, Garzoli S (2024) A Mechanistic Review on How Berberine Use Combats Diabetes and Related Complications: Molecular, Cellular, and Metabolic Effects. Pharmaceuticals 17(1): 7.
7. Ayyadurai VAS, Deonikar P, Bannuru RR (2022) Attenuation of low-grade chronic inflammation by phytonutrients: A computational systems biology analysis. Clinical Nutrition ESPEN 49: 425–435.
8. Bai H, Yang J, Wang R, Liu T, Wang Z (2025) The enhancing effects and mechanisms of inositol and choline on antioxidant capacity of vitamin E using model established in mice hepatocytes. Nutrition and Food Science 55(3): 533–550.
9. Balboa E, Saud F, Parra Ruiz C, de la Fuente M, Landskron G, et al. (2024) Exploring the lutein therapeutic potential in steatotic liver disease: mechanistic insights and future directions. Frontiers in Pharmacology 15: 1406784.
10. Bello Onaghise G, Wang G, Han X, Nsabimana E, Cui W, et al. (2020) Antiviral Strategies of Chinese Herbal Medicine Against PRRSV Infection. Frontiers in Microbiology 11: 1756.
11. Berisha H, Hattab R, Comi L, Giglione C, Migliaccio S, et al. (2025) Nutrition and Lifestyle Interventions in Managing Dyslipidemia and Cardiometabolic Risk. Nutrients 17(5): 776.
12. Bowman ER, Cameron CM, Richardson B, Kulkarni M, Gabriel J, et al. (2020). Macrophage maturation from blood monocytes is altered in people with HIV, and is linked to serum lipid profiles and activation indices: A model for studying atherogenic mechanisms. PLoS Pathogens 16(10): e1008869.
13. Chen X, Song X, Li J, Zhang R, Yu C, et al. (2023) Identification of HPCAL1 as a specific autophagy receptor involved in ferroptosis. Autophagy 19(1): 54–74.
14. Cheng Y, Zhao A, Li Y, Li C, Miao X, et al. (2025) Roles of SIRT3 in cardiovascular and neurodegenerative diseases. Ageing Research Reviews 104: 102654.
15. Chrysant SG, Chrysant GS (2024) Olive Oil Consumption and Cardiovascular Protection: Mechanism of Action. Cardiology in Review 32(1): 57–61.
16. Franceschetti L, Bonomini F, Rodella LF, Rezzani R (2021) Critical role of nfκb in the pathogenesis of non-alcoholic fatty liver disease: A widespread key regulator. Current Molecular Medicine 21(6): 495–505.
17. Gabr AA, Farrag F, Ahmed M, Soltan YA, Ateya A, et al. (2025) The Performance, Ingestive Behavior, Nutrient Digestibility, Ruminal Fermentation Profile, Health Status, and Gene Expression of Does Fed a Phytochemical–Lactobacilli Blend in Late Pregnancy. Animals 15(4).
18. Gabuza K, Mabuda TI, Patel O, Khuboni N, Van Aarde R, et al. (2024) Afriplex GRTTM extract attenuates hepatic steatosis in an in vitro model of NAFLD. PLoS ONE 19(4): e0297572.
19. Galmés S, Serra F, Palou A (2018) Vitamin E metabolic effects and genetic variants: A challenge for precision nutrition in obesity and associated disturbances. Nutrients 10(12): 1919.
20. Garcia C, Blesso CN (2021) Antioxidant properties of anthocyanins and their mechanism of action in atherosclerosis. Free Radical Biology and Medicine 172: 152–166.
21. Gessner DK, Sandrock LM, Most E, Koch C, Ringseis R, et al. (2023) Performance and Metabolic, Inflammatory, and Oxidative Stress-Related Parameters in Early Lactating Dairy Cows with High and Low Hepatic FGF21 Expression. Animals 13(1): 131.
22. Graham DS, Liu G, Arasteh A, Yin XM, Yan S (2023) Ability of high fat diet to induce liver pathology correlates with the level of linoleic acid and Vitamin E in the diet. PLoS ONE 18(6): e0286726.
23. Guo J, Huang X, Dou L, Yan M, Shen T, et al. (2022) Aging and aging-related diseases: from molecular mechanisms to interventions and treatments. Signal Transduction and Targeted Therapy 7(1): 391.

24. Gutiérrez Cuevas J, Lucano Landeros S, López Cifuentes D, Santos A, Armendariz Borunda J (2023) Epidemiologic, Genetic, Pathogenic, Metabolic, Epigenetic Aspects Involved in NASH-HCC: Current Therapeutic Strategies. Cancers 15(1): 23.

25. Hidayat DF, Mahendra MYN, Kamaludeen J, Pertiwi H (2023) Lycopene in Feed as Antioxidant and Immuno-Modulator Improves Broiler Chicken's Performance under Heat-Stress Conditions. Veterinary Medicine International 2023: 5418081.

26. Hussein HMA (2025) Deciphering the complex biological functions and regulatory mechanisms of melatonin. Hormones 24(2): 565–567.

27. Jabbehdari S, Handa JT (2021) Oxidative stress as a therapeutic target for the prevention and treatment of early age-related macular degeneration. Survey of Ophthalmology 66(3): 423–440.

28. Król M, Skowron P, Skowron K, Gil K (2024) The Fetal Alcohol Spectrum Disorders—An Overview of Experimental Models, Therapeutic Strategies, and Future Research Directions. Children 11(5): 531.

29. Kulkarni A, Kulkarni CC, Pradeep SR, Poyya J, Kudva AK, et al. (2025) Role of Anti-Inflammatory and Antioxidant Properties of Natural Products in Curing Cardiovascular Diseases. Current Issues in Molecular Biology 47(11): 955.

30. Laviano HD, Gómez G, Núñez Y, García Casco JM, Benítez RM, et al. (2024). Maternal dietary antioxidant supplementation regulates weaned piglets' adipose tissue transcriptome and morphology. PLoS ONE 19(9): e0310399.

31. Le Goff M, Le Ferrec E, Mayer C, Mimouni V, Lagadic Gossmann D, et al. (2019) Microalgal carotenoids and phytosterols regulate biochemical mechanisms involved in human health and disease prevention. Biochimie 167: 106–118.

32. Lee HA, Chang Y, Sung PS, Yoon EL, Lee HW, et al. (2022) Therapeutic mechanisms and beneficial effects of non-antidiabetic drugs in chronic liver diseases. Clinical and Molecular Hepatology 28(3): 425–472.

33. Lee KC, Wu PS, Lin HC (2023) Pathogenesis and treatment of non-alcoholic steatohepatitis and its fibrosis. Clinical and Molecular Hepatology 29(1): 77–98.

34. Li Q, Yang S, Zhang X, Liu X, Wu Z, et al. (2022) Maternal Nutrition During Late Gestation and Lactation: Association with Immunity and the Inflammatory Response in the Offspring. Frontiers in Immunology 12: 758525.

35. Li W, Wang J, Li J, Liu P, Li J, et al. (2022) Antioxidant, Transcriptomic and Metabonomic Analysis of Hepatopancreatic Stress Resistance in Exopalaemon carinicauda Following Astaxanthin Feeding. Frontiers in Marine Science 9.

36. Liang X, Wu Y, Feng Q, Zhu D, Huang Q, et al. (2025) Synergies of dibutyl phthalate on high-fat diet can aggravate cardiac fibrosis/dysfunction and the protective effects of vitamin E and salidroside: A molecular toxicological study in Sprague-Dawley rats. Ecotoxicology and Environmental Safety 302.

37. Liu H, Liu M, Fu X, Zhang Z, Zhu L, et al. (2018) Astaxanthin prevents alcoholic fatty liver disease by modulating mouse gut microbiota. Nutrients 10(9): 1298.

38. Liu Z, Xu B, Zheng J, Tian Y, Yang Z, et al. (2025) Fucoxanthin ameliorates high-fat diet-induced kidney injury in mice. British Journal of Nutrition, 134(6): 441–450.

39. Mahmoud AM (2022) An Overview of Epigenetics in Obesity: The Role of Lifestyle and Therapeutic Interventions. International Journal of Molecular Sciences 23(3): 1341.

40. Matondo JD, Abihudi SA (2026) Chia seeds: a nutrient-dense functional food for health and nutrition. Cogent Food and Agriculture 12(1).

41. Maurya M, Bora K, Blomfield A, Pavlovich M, Huang S, et al. (2023) Oxidative stress in retinal pigment epithelium degeneration: from pathogenesis to therapeutic targets in dry age-related macular degeneration. Neural Regeneration Research 18(10): 2173–2181.

42. Mese Tayfur S, Demirel Yalcıner T, Migni A, Bartolini D, Galli F, et al. (2025) Modulation of inflammatory signaling by vitamin E metabolites and its therapeutic implications. Free Radical Research 59(1): 86–101.

43. Mohanty S, Nayak N, Mukherjee T, Kumari S, Prabhakar PK, et al. (2025) Mobilizing Stockpile of Nature: Phytochemicals, Herbal Extracts, and Dietary Supplements for Managing Metabolic Diseases with Concentric Focus on Obesity. Endocrine, Metabolic and Immune Disorders - Drug Targets 25(12): 960–992.

44. Mozos I, Flangea C, Vlad DC, Gug C, Mozos C, et al. (2021) Effects of anthocyanins on vascular health. Biomolecules 11(6): 811.

45. Nasiri K, Akbari A, Nimrouzi M, Ruyvaran M, Mohamadian A (2021) Safflower seed oil improves steroidogenesis and spermatogenesis in rats with type II diabetes mellitus by modulating the genes expression involved in steroidogenesis, inflammation and oxidative stress. Journal of Ethnopharmacology 275: 114139.

46. Omagari K, Maruta A, Yayama N, Yoshida Y, Okamoto K, et al. (2023) The Effects of Overnight Fasting Duration on Glucose and Lipid Metabolism in a Sprague-Dawley Rat Model of Nonalcoholic Steatohepatitis with Advanced Fibrosis. Journal of Nutritional Science and Vitaminology 69(5): 357–369.

47. Palioura D, Feidantsis K, Lazou A (2025) Treatment with crocin attenuates cardiac metabolic disturbances and subsequent inflammation in streptozotocin-induced diabetes. Molecular and Cellular Biochemistry 480(10): 5387–5397.

48. Pausova Z, Sliz E (2024) Large-Scale Population-Based Studies of Blood Metabolome and Brain Health. In Current Topics in Behavioral Neurosciences 68: 177–219.

49. Pérez Torres I, Castrejón Téllez V, Soto ME, Rubio Ruiz ME, Manzano Pech L, et al. (2021) Oxidative stress, plant natural antioxidants, and obesity. International Journal of Molecular Sciences 22(4): 1–26.

50. Pérez AT, Kapravelou G, Foulquie JMP, López Jurado Romero M, Martínez RM (2024) Potential benefits of microalgae intake against metabolic diseases: beyond spirulina—a systematic review of animal studies. Nutrition Reviews 82(7): 872–891.

51. Podszun MC, Alawad AS, Lingala S, Morris N, Huang WCA, et al. (2020) Vitamin E treatment in NAFLD patients demonstrates that oxidative stress drives steatosis through upregulation of de-novo lipogenesis. Redox Biology 37: 101710.

52. Qu W, Ma T, Cai J, Zhang X, Zhang P, et al. (2021) Liver Fibrosis and MAFLD: From Molecular Aspects to Novel Pharmacological Strategies. Frontiers in Medicine 8: 761538.

53. Ranard KM, Kuchan MJ, Erdman JW (2019) α-Tocopherol, but Not γ-Tocopherol, Attenuates the Expression of Selective Tumor Necrosis Factor-Alpha-Induced Genes in Primary Human Aortic Cell Lines. Lipids 54(5): 289–299.

54. Razali K, Algantri K, Loh SP, Cheng SH, Mohamed W (2022) Integrating nutriepigenomics in Parkinson's disease management: New promising strategy in the omics era. IBRO Neuroscience Reports 13: 364–372.

55. Rivera Iñiguez I, Panduro A, Roman S, González Aldaco K (2023) What do we know about nutrient-based strategies targeting molecular mechanisms associated with obesity-related fatty liver disease? Annals of Hepatology 28(1): 100874.

56. Rives C, Fougerat A, Ellero Simatos S, Loiseau N, Guillou H, et al. (2020) Oxidative stress in NAFLD: Role of nutrients and food contaminants. Biomolecules 10(12): 1702.

57. Ruocco C, Ragni M, Tedesco L, Segala A, Servili M, et al. (2022) Molecular and metabolic effects of extra-virgin olive oil on the cardiovascular gene signature in rodents. Nutrition, Metabolism and Cardiovascular Diseases 32(6): 1571–1582.

58. Sharafi M, Borghei Rad SM, Hezavehei M, Shahverdi A, Benson JD (2022) Cryopreservation of Semen in Domestic Animals: A Review of Current Challenges, Applications, and Prospective Strategies. Animals 12(23).

59. Shi H, Deng X, Ji X, Liu N, Cai H (2023) Sources, dynamics in vivo, and application of astaxanthin and lutein in laying hens: A review. Animal Nutrition 13: 324–333.

60. Shu S, Kobayashi M, Marunaka K, Yoshino Y, Goto M, et al. (2022) Magnesium Supplementation Attenuates Ultraviolet-B-Induced Damage Mediated through Elevation of Polyamine Production in Human HaCaT Keratinocytes. Cells 11(15): 2268.

61. Simancas Racines D, Annunziata G, Verde L, Fascì Spurio F, Reytor González C, et al. (2025) Nutritional Strategies for Battling Obesity-Linked Liver Disease: The Role of Medical Nutritional Therapy in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) Management. Current Obesity Reports 14(1): 7.

62. Song L, Zhang S (2023) Anti-Aging Activity and Modes of Action of Compounds from Natural Food Sources. Biomolecules 13(11): 1600.

63. Sun J, Huang X, Ji S, Ji H (2019) Two faces of PPARα/NFκB signaling pathway in inflammatory responses to adipocytes lipolysis in grass carp Ctenopharyngodon idella. Fish and Shellfish Immunology 90: 244–249.

64. Taghiyar S, Aarabi MH, Pourrajab F, Rad NR, Sharifi Rigi A (2023) Supplement astaxanthin affects PPAR-γ/miR-27a axis and metabolic profile. Gene Reports 33.

65. Takatani N, Kono Y, Beppu F, Okamatsu Ogura Y, Yamano Y, et al. (2020) Fucoxanthin inhibits hepatic oxidative stress, inflammation, and fibrosis in diet-induced nonalcoholic steatohepatitis model mice. Biochemical and Biophysical Research Communications 528(2): 305–310.

66. Tao S, Yang Y, Li J, Wang H, Ma Y (2021) Bixin Attenuates High-Fat Diet-Caused Liver Steatosis and Inflammatory Injury through Nrf2/PPAR α Signals. Oxidative Medicine and Cellular Longevity 2021: 6610124.

67. Tillman EJ, Rolph T (2020) FGF21: An Emerging Therapeutic Target for Non-Alcoholic Steatohepatitis and Related Metabolic Diseases. Frontiers in Endocrinology 11: 601290.

68. Tokoro M, Gotoh K, Kudo Y, Hirashita Y, Iwao M, et al. (2021) α-Tocopherol suppresses hepatic steatosis by increasing CPT-1 expression in a mouse model of diet-induced nonalcoholic fatty liver disease. Obesity Science and Practice 7(1): 91–99.

69. Van De Venter M, Didloff J, Reddy S, Swanepoel B, Govender S, et al. (2021) Wild-type zebrafish (Danio rerio) larvae as a vertebrate model for diabetes and comorbidities: A review. Animals 11(1): 54.

70. Vaziri Y (2024) The Mediterranean Diet: A powerful defense against Alzheimer disease–A comprehensive review. Clinical Nutrition ESPEN 64: 160–167.

71. Wallert M, Ziegler M, Wang X, Maluenda A, Xu X, et al. (2019) α-Tocopherol preserves cardiac function by reducing oxidative stress and inflammation in ischemia/reperfusion injury. Redox Biology 26: 101292.

72. Wang J, Suo Y, Zhang J, Zou Q, Tan X, et al. (2019) Lycopene supplementation attenuates western diet-induced body weight gain through increasing the expressions of thermogenic/mitochondrial functional genes and improving insulin resistance in the adipose tissue of obese mice. Journal of Nutritional Biochemistry 69: 63–72.

73. Wu L, Mo W, Feng J, Li J, Yu Q, et al. (2020) Astaxanthin attenuates hepatic damage and mitochondrial dysfunction in non-alcoholic fatty liver disease by up-regulating the FGF21/PGC-1α pathway. British Journal of Pharmacology, 177(16): 3760–3777.

74. Wu Y, Liu J (2025) Functional food lycopene mitigates obesity-related cognitive decline via lipid metabolism regulation and neuroprotection via taurine and glutathione pathway. Clinical Nutrition 51: 136–145.

75. Xu G, Xu P, Wang N, Qi W, Pu Y, et al. (2024) Rare crocins ameliorate thrombus in zebrafish larvae by regulating lipid accumulation and clotting factors. Fitoterapia 179: 106278.

76. Xu H, Chen Y, Gu M, Liu C, Chen Q, et al. (2021) Fatty acid metabolism reprogramming in advanced prostate cancer. Metabolites 11(11): 765.

77. Xu X, Poulsen KL, Wu L, Liu S, Miyata T, et al. (2022) Targeted therapeutics and novel signaling pathways in non-alcohol-associated fatty liver/steatohepatitis (NAFL/NASH). Signal Transduction and Targeted Therapy 7(1): 287.

78. Yadav D, Khokhar M, Sharma P (2025) Advanced Antioxidant Science is Reshaping the Battle Against Metabolic Syndrome: Next-Generation Approaches to Unlock Oxidative Stress Solutions. Indian Journal of Clinical Biochemistry 40(4): 519–521.

79. Yan Z, Chen Q, Xia Y (2023) Oxidative Stress Contributes to Inflammatory and Cellular Damage in Systemic Lupus Erythematosus: Cellular Markers and Molecular Mechanism. Journal of Inflammation Research 16: 453–465.

80. Yu CHJ, Rupasinghe HPV (2025) Elucidating the mechanistic interplay of AMPK and Nrf2 in MASLD: A focus on dietary phytochemical modulation of lipid and redox homeostasis. Biochemical and Biophysical Research Communications 777: 152300.

81. Żółnowska I, Gostyńska Stawna A, Stawny M (2024) Molecular mechanisms underlying hepatoprotective activity of lutein in the context of intestinal failure-associated liver disease. Pharmacological Research 209: 107421.