

# Interesterified palm oil and glucose homeostasis: a systematic review of preclinical mechanistic evidence and limited human nutritional studies

## Abstract

The increasing use of interesterified palm oil as a functional replacement for partially hydrogenated fats has raised questions about its potential influence on glucose homeostasis. The present systematic review aligned the scope of inference with the available evidence by explicitly separating direct human evidence from preclinical and mechanistic evidence. A Scopus-based systematic search was conducted using predefined combinations of terms related to palm oil, interesterified or structured lipids, glucose homeostasis, insulin signalling, hepatic lipid metabolism and adipose inflammation. After relevance filtering, publication-year restriction, English-language screening and full-text accessibility assessment, 30 records were retained for qualitative synthesis. The synthesis shows that direct human evidence is limited and does not support a definitive conclusion that interesterified palm oil independently disrupts glucose homeostasis in humans. In contrast, several preclinical studies in rodent models report impaired glucose tolerance, altered insulin secretion or signalling, hepatic lipid changes, and adipose-tissue inflammatory responses after interesterified palm oil or closely related palm-oil exposures, especially under high-fat or metabolically stressful dietary conditions. Mechanistic and structured-lipid studies indicate that fatty-acid positional distribution may influence digestion, absorption and downstream lipid signalling, but these findings should not be treated as direct human clinical evidence. Unsupported pooled percentage ranges from heterogeneous animal and human studies, which were removed or qualified, and retained quantitative claims are mapped to individual studies. Overall, the evidence suggests biological plausibility for context-dependent metabolic effects, but current human evidence remains insufficient for firm population-level conclusions. Long-term, adequately powered human intervention studies using standardized dietary matrices and validated glucose-homeostasis endpoints are required.

**Keywords:** interesterified palm oil, glucose homeostasis, insulin signalling, hepatic lipogenesis, adipose inflammation

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## Introduction

The increasing global prevalence of metabolic disorders, particularly those related to impaired glucose homeostasis such as insulin resistance and type 2 diabetes, has intensified scientific attention toward dietary determinants that modulate metabolic regulation. Glucose homeostasis is a complex physiological process involving the coordinated interaction among multiple organs, including the liver, skeletal muscle, and adipose tissue, as well as tightly regulated hormonal signalling pathways primarily mediated by insulin. Disruptions in this regulatory network are often associated with alterations in lipid metabolism, inflammatory responses, and cellular signalling mechanisms, thereby highlighting the importance of dietary fat composition in shaping metabolic outcomes.<sup>1</sup>

In recent decades, the food industry has undergone significant reformulation in response to public health concerns about trans fatty acids, leading to increased utilisation of alternative lipid modification techniques. One such approach is interesterification, a process that rearranges the positional distribution of fatty acids within triacylglycerol molecules without altering their overall fatty acid composition. This modification has been widely adopted to improve the functional and physicochemical properties of fats, including melting behaviour, texture, and shelf stability, thereby enabling their application across a broad range of food products. Within this context, palm oil has emerged as a versatile and widely used lipid source due

to its balanced fatty acid profile, oxidative stability, and functional adaptability in food systems.<sup>2</sup>

Intesterified palm oil, in particular, represents a modified lipid form in which fatty acids are redistributed across the glycerol backbone, potentially influencing digestion, absorption, and metabolic processing. The positional arrangement of fatty acids, especially at the sn-2 position, has been suggested to affect lipid bioavailability and subsequent metabolic responses, including postprandial lipid handling and glucose regulation. While the physicochemical advantages of interesterified lipids are well established, their biological implications, particularly in relation to metabolic health, remain an area of ongoing investigation.<sup>3,4</sup>

Emerging evidence suggests that dietary fats may influence glucose homeostasis through multiple interconnected mechanisms, including modulation of insulin signalling pathways, regulation of hepatic lipid metabolism, and alterations in adipose tissue function.<sup>5</sup> Insulin signalling plays a central role in maintaining glucose balance by facilitating cellular glucose uptake, primarily through pathways involving insulin receptor substrate (IRS), phosphoinositide 3-kinase (PI3K), and glucose transporter type 4 (GLUT4). Variations in dietary fat composition have been associated with changes in membrane fluidity and intracellular signalling efficiency, potentially affecting insulin sensitivity.<sup>6</sup>

In parallel, the liver serves as a key metabolic organ responsible for glucose production and lipid synthesis, with processes such as *de novo* lipogenesis contributing to systemic metabolic regulation. Dietary fats have been shown to influence the expression of lipogenic transcription factors, including sterol regulatory element-binding protein-1c (SREBP-1c), which may subsequently affect hepatic lipid accumulation and glucose metabolism. The interaction between lipid intake and hepatic function is therefore considered a critical component in understanding the metabolic impact of different fat structures.<sup>7</sup>

Adipose tissue also plays a pivotal role in metabolic homeostasis, not only as an energy storage site but also as an active endocrine organ that secretes adipokines and inflammatory mediators. Chronic low-grade inflammation within adipose tissue, characterised by elevated levels of cytokines such as tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), has been linked to impaired insulin signalling and metabolic dysregulation. Dietary fat composition may influence these inflammatory pathways, thereby contributing to variations in metabolic outcomes across different dietary patterns.<sup>8</sup>

Despite the growing body of literature examining the relationship between dietary fats and metabolic health, findings related to interesterified palm oil remain heterogeneous and, in some cases, inconclusive.<sup>9</sup> Differences in study design, population characteristics, duration of intervention, and overall dietary context have contributed to variability in reported outcomes. Some studies suggest modest alterations in postprandial lipid and glucose responses, while others report minimal or non-significant effects under controlled conditions. This variability underscores the need for a structured and systematic synthesis of available evidence to clarify the underlying mechanisms and contextual factors influencing these outcomes.<sup>10</sup>

Moreover, previous reviews have often addressed dietary fats in a broad context without specifically focusing on the mechanistic pathways linking interesterified lipids to glucose homeostasis. As a result, there remains a gap in the literature regarding the integration of molecular, physiological, and metabolic perspectives within a single analytical framework. A systematic literature review approach provides a robust methodological basis for addressing this gap by enabling the comprehensive identification, evaluation, and synthesis of relevant studies using transparent and reproducible criteria.<sup>11–13</sup>

Given the widespread use of palm oil and its modified forms in global food systems, it is important to assess its metabolic implications within a balanced and evidence-based framework. This is particularly relevant in the context of ongoing discussions surrounding dietary fats and health, where nuanced and context-dependent interpretations are essential to avoid oversimplification. A systematic and mechanistic understanding of how interesterified palm oil interacts with key metabolic pathways can contribute to a more informed and scientifically grounded perspective.

Therefore, this study aims to systematically review and synthesise current scientific evidence on the effects of interesterified palm oil on glucose homeostasis, with a specific focus on metabolic mechanisms involving insulin signalling, hepatic lipogenesis, and adipose tissue inflammation. By integrating findings across molecular, physiological, and clinical studies, this review seeks to provide a comprehensive and balanced evaluation of the role of interesterified lipids within the broader context of metabolic health.

In line with this objective, two research questions are formulated to guide the analysis and interpretation of findings.

RQ1: *What evidence directly or indirectly links interesterified palm oil and related structured lipid exposures with insulin signalling, hepatic lipid metabolism and adipose-tissue inflammation?*

RQ2: *How do evidence type, species or population, dietary context and study design constrain the strength of conclusions that can be drawn about human glucose homeostasis?*

These questions are addressed through a structured synthesis of the literature and form the basis for subsequent discussion and conclusions presented in this study.

## Literature review

The scientific discourse surrounding dietary fats and metabolic health has evolved considerably, particularly in response to increasing concerns over glucose dysregulation and its associated disorders. Within this context, interesterified lipids have gained attention as structurally modified fats designed to improve functional properties without altering overall fatty acid composition. This literature review synthesises current evidence on the metabolic implications of interesterified palm oil, focusing on its structural characteristics and their relationship with glucose homeostasis through insulin signalling, hepatic lipogenesis, and adipose tissue inflammation.

### Structural characteristics of interesterified lipids

Interesterification is a chemical or enzymatic process that redistributes fatty acids within the triacylglycerol (TAG) molecule, thereby altering the positional arrangement of fatty acids across the glycerol backbone. Unlike hydrogenation, which modifies the degree of saturation, interesterification maintains the original fatty acid profile while modifying its stereospecific configuration. This structural rearrangement is particularly relevant at the sn-2 position, which has been shown to influence lipid digestion, absorption, and metabolic utilisation.<sup>14</sup>

Palm oil, characterised by a balanced composition of saturated and unsaturated fatty acids, is frequently subjected to interesterification to enhance its functional properties in food systems. Studies have demonstrated that the redistribution of palmitic acid toward the sn-2 position may affect micelle formation and enzymatic hydrolysis, potentially influencing postprandial lipid responses.<sup>15</sup> However, the metabolic implications of such structural changes are not uniformly established, with some studies indicating modest effects on lipid absorption efficiency and others reporting negligible differences under controlled conditions.<sup>16</sup>

Furthermore, the physicochemical stability of interesterified palm oil contributes to its widespread application in processed foods, making it relevant to assess its metabolic impact within realistic dietary patterns. Importantly, current evidence suggests that structural modification alone does not inherently determine metabolic outcomes, as these are influenced by a combination of dietary, physiological, and environmental factors.<sup>17</sup>

### Insulin signalling and glucose regulation

Insulin signalling is a central mechanism in the maintenance of glucose homeostasis, facilitating glucose uptake and utilisation across insulin-sensitive tissues. The signalling cascade involves the activation of insulin receptors, followed by downstream pathways such as insulin receptor substrate (IRS), phosphoinositide 3-kinase (PI3K), and protein kinase B (Akt), ultimately leading to the translocation of glucose transporter type 4 (GLUT4) to the cell membrane.<sup>18</sup>

Dietary fat composition has been shown to influence insulin signalling through its effects on membrane lipid composition and intracellular signalling pathways. Saturated fatty acids, including palmitic acid, have been associated with alterations in membrane fluidity and receptor functionality, which may modulate insulin sensitivity under certain conditions.<sup>19</sup> In the context of interesterified palm oil, the repositioning of fatty acids within TAG molecules has been hypothesised to affect lipid partitioning and cellular uptake, thereby indirectly influencing insulin signalling efficiency.<sup>20</sup>

Empirical evidence, however, remains heterogeneous. Some studies report modest reductions in insulin sensitivity associated with high intake of saturated fat-rich diets, including interesterified fats, particularly in populations with pre-existing metabolic risk factors. In contrast, studies conducted in healthy individuals often demonstrate minimal or non-significant changes in insulin-mediated glucose uptake, suggesting that metabolic context plays a critical role in determining outcomes.<sup>21</sup>

Moreover, short-term intervention studies indicate that fasting glucose levels are generally maintained within normal ranges following consumption of interesterified palm oil, while postprandial responses exhibit moderate variability depending on dietary composition and study design. These findings suggest that the influence of interesterified lipids on insulin signalling is likely to be subtle and modulated by broader dietary patterns rather than driven by structural modification alone.<sup>22</sup>

### Hepatic lipogenesis and lipid metabolism

The liver is a central organ in the regulation of both lipid and glucose metabolism, integrating dietary inputs with endogenous metabolic processes. Hepatic lipogenesis, particularly *de novo* lipogenesis (DNL), plays a significant role in converting excess carbohydrates into fatty acids, which are subsequently stored or exported as lipoproteins. This process is regulated by key transcription factors such as sterol regulatory element-binding protein-1c (SREBP-1c) and carbohydrate-responsive element-binding protein (ChREBP).<sup>23</sup>

Dietary fats can influence hepatic metabolism through multiple mechanisms, including modulation of gene expression, lipid oxidation, and triglyceride synthesis. In the case of interesterified palm oil, the altered structure of TAG molecules may affect hepatic lipid uptake and processing, although current evidence suggests that these effects are generally modest and context-dependent.<sup>24</sup>

Animal studies have shown that high-fat diets containing saturated fats may lead to increased hepatic lipid accumulation and changes in lipogenic enzyme activity. However, human studies present a more nuanced picture, with many reporting minimal changes in liver fat content when dietary intake is controlled and energy balance is maintained. This indicates that total caloric intake and dietary composition may exert a more significant influence on hepatic outcomes than the specific structural form of dietary fats.<sup>25</sup>

Additionally, biomarkers of liver function, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are often used to assess hepatic health in dietary intervention studies. Available evidence suggests that consumption of interesterified palm oil does not result in clinically significant alterations in these markers under typical dietary conditions, further supporting the notion of a moderate metabolic impact.<sup>26</sup>

### Adipose tissue inflammation and metabolic crosstalk

Adipose tissue is increasingly recognised as an active metabolic and endocrine organ that plays a crucial role in regulating energy balance and glucose homeostasis. Beyond its function as an energy storage site, adipose tissue secretes a range of bioactive molecules, including adipokines and cytokines, which influence systemic metabolism and inflammatory status.<sup>27</sup>

Chronic low-grade inflammation within adipose tissue has been implicated in the development of insulin resistance, primarily through the secretion of pro-inflammatory mediators such as tumour necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-6 (IL-6). These cytokines can interfere with insulin signalling pathways, thereby contributing to impaired glucose uptake and metabolic dysregulation.<sup>28</sup>

The relationship between dietary fats and adipose inflammation is complex and influenced by multiple factors, including fatty acid composition, energy balance, and individual metabolic status. While saturated fats have been associated with increased inflammatory responses in some studies, the specific role of interesterified palm oil remains less clearly defined. Available evidence suggests that inflammatory responses are generally modest and may not differ substantially from those observed with other dietary fat sources when consumed under comparable conditions.<sup>29</sup>

Furthermore, some studies indicate that balanced dietary patterns incorporating a mixture of saturated and unsaturated fats may mitigate potential inflammatory effects, highlighting the importance of overall diet quality. Adipokines such as adiponectin, which are involved in enhancing insulin sensitivity, have also been examined, with findings indicating variable responses that are not consistently linked to interesterified fat consumption.<sup>30</sup>

### Integration of mechanistic pathways

The interaction between insulin signalling, hepatic metabolism, and adipose tissue function represents a complex network of metabolic regulation that underpins glucose homeostasis. These pathways are interconnected through multiple feedback mechanisms, including hormonal regulation, substrate availability, and inflammatory signalling. As such, the impact of dietary fats, including interesterified palm oil, must be understood within this integrated framework.<sup>31</sup>

Current literature suggests that the effects of interesterified palm oil on glucose homeostasis are mediated through subtle modifications in these interconnected pathways rather than through a single dominant mechanism. Structural changes in lipid molecules may influence digestion and absorption, which in turn affect hepatic processing and systemic lipid availability. These processes may subsequently interact with insulin signalling and inflammatory pathways, contributing to variations in metabolic responses.<sup>32</sup>

Importantly, the heterogeneity of findings across studies highlights the influence of contextual factors, including study design, population characteristics, and dietary composition. This variability underscores the need for systematic approaches, such as SLR, to synthesize evidence and identify consistent patterns within the literature. By integrating findings across multiple levels of analysis, a more comprehensive understanding of the metabolic role of interesterified palm oil can be achieved.

Overall, the reviewed literature indicates that while interesterified palm oil may influence key metabolic pathways associated with

glucose regulation, the magnitude and direction of these effects are generally moderate and context-dependent. This supports the importance of evaluating dietary fats within the broader framework of dietary patterns and metabolic health rather than in isolation.

## Methodology

### Search strategy and justification for database selection

This review followed a PRISMA-guided systematic literature review approach. The search was conducted in Scopus because Scopus provides broad coverage across nutrition, food science, lipid technology, animal physiology, biomedical and agricultural journals, which is important for a topic spanning food-fat processing and metabolic outcomes. The use of Scopus alone was deliberate for reproducibility and citation-management consistency; however, this single-database design may have missed records indexed only in PubMed/MEDLINE or Web of Science and is therefore treated as a limitation rather than as evidence of comprehensive global coverage.

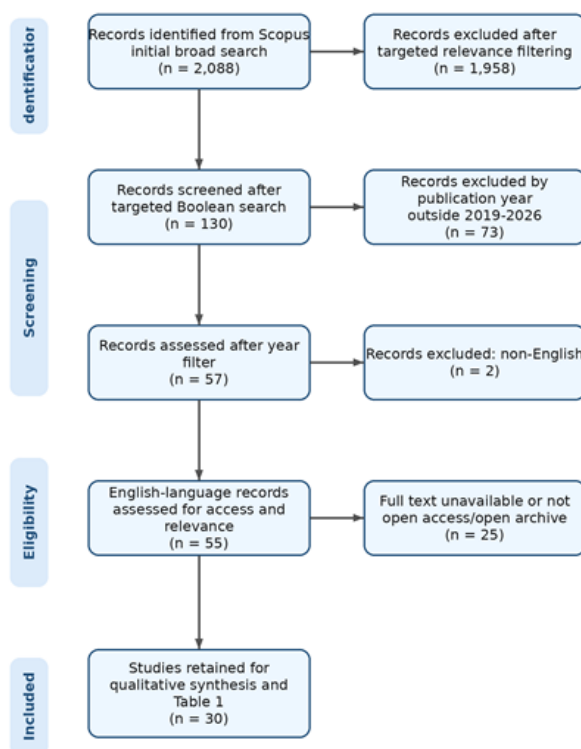
### Eligibility criteria and evidence hierarchy

Records were eligible for synthesis if they addressed at least one of the following: interesterified palm oil or interesterified palm olein; palm oil or palm-fat exposures with glucose, insulin, hepatic lipid or inflammatory outcomes; structured lipid studies directly relevant to fatty-acid positional distribution and digestion/absorption; or human dietary-fat comparator studies relevant to glucose-homeostasis mechanisms. Records were excluded from synthesis when their primary focus was oil-palm genetics, oleaginous yeast or

microalgae lipid production, crocodile fatty tissue, broiler or laying-hen performance, carcass yield, sow/goat production outcomes, or other topics without a clear metabolic link to the review question. Evidence was classified into direct human evidence, direct preclinical interesterified palm-oil evidence, palm-oil comparator evidence, structured-lipid mechanistic evidence and background synthesis evidence. Human conclusions were based only on human evidence, while animal and in vitro findings were used to discuss biological plausibility and mechanisms.

### Screening and reference-accounting procedure

The initial Scopus search using the broad phrase “Palm Oil AND Metabolism” yielded 2,088 records. A targeted Boolean strategy was then applied: (“interesterified fat” OR “interesterified oil” OR “structured lipid” OR “palm oil”) AND (“glucose metabolism” OR “glucose homeostasis” OR “glycemic” OR “blood glucose”) AND (“insulin” OR “lipogenesis” OR “liver” OR “adipose” OR “inflammation”). Relevance filtering excluded 1,958 records, leaving 130 records for screening. Restricting the publication period to 2019-2026 excluded 73 records, leaving 57. Language screening excluded 2 non-English records, leaving 55. Full-text accessibility screening excluded 25 records that were not available as open access or open archive, leaving 30 records for qualitative synthesis. These 30 records are listed in Table 1 & Figure 1 and in Supplementary File 1. The reference list was presented so that the synthesis set is clearly distinguishable from any supporting background citations. Therefore, the PRISMA count refers to the 30 synthesis records, not to every citation that may appear in an introductory or methodological context.



Note. The 30 synthesis records are listed in Table 1. Background citations are not counted as included studies.

Figure 1 PRISMA- guided screening workflow.

## Results

### Composition of the evidence base

The synthesis shows that the evidence base is heterogeneous. The 30 retained records include a small number of direct or near-direct human studies, several direct preclinical studies of interesterified palm oil, and a larger group of animal, in vitro and structured-lipid comparator studies. For this reason, the findings are presented by evidence tier rather than as a single pooled body of evidence. This prevents non-human findings from being over-interpreted as human clinical conclusions.

### Human evidence

Direct human evidence relevant to interesterified palm oil remains limited. The most directly relevant human study identified in the synthesis examined interesterified palm olein in individuals with type 2 diabetes and reported effects on postprandial glucose-dependent insulinotropic polypeptide response rather than a consistent adverse shift in fasting glucose or a definitive clinical deterioration in glucose control.<sup>33</sup> Other human records involved palm-oil comparators, palmitate/oleate manipulation, or food-matrix comparisons rather than interesterified palm oil itself.<sup>51,34–36</sup> Consequently, the article will not conclude that interesterified palm oil has a demonstrated moderate effect on human glucose homeostasis. Instead, it concludes that human data are too limited and heterogeneous for a firm conclusion.

### Preclinical interesterified palm oil evidence

The strongest mechanistic signal comes from rodent studies. In Swiss mice, interesterified palm oil has been associated with impaired glucose homeostasis, insulin resistance, altered insulin secretion or signalling, and deleterious liver effects.<sup>2,40</sup> Additional mouse studies report adipose-tissue inflammation, brown-adipose-tissue whitening or metabolic dysfunction under high-fat-diet conditions.<sup>41,42</sup> These studies provide evidence of biological plausibility and possible mechanisms, but they do not establish the magnitude of effect in free-living humans. Their interpretation is particularly constrained by high-fat dietary backgrounds, species differences and the metabolic stress induced by experimental diets.

### Structural lipid and absorption mechanisms

Mechanistic studies support the concept that fatty-acid positional distribution can influence lipid digestion, absorption and downstream metabolic signalling. Evidence from radiolabelled absorption work and structured-lipid digestion models suggests that palmitic acid and 2-palmitoylglycerol kinetics may be relevant to interesterified fat metabolism.<sup>6,30,16,23</sup> However, the synthesis avoids reporting a pooled numerical range for sn-2 palmitic acid redistribution because the previously stated range was not traceable to a consistent set of directly comparable interesterified palm-oil studies.

### Insulin signalling, hepatic lipid metabolism and adipose inflammation

Across the evidence tiers, insulin signalling effects are most defensible in preclinical models and least certain in humans. Rodent studies of interesterified palm oil point toward altered insulin secretion or signalling, impaired glucose tolerance and hepatic metabolic stress, but human studies are few and do not provide a pooled estimate. Similarly, hepatic lipid metabolism and adipose inflammation are supported mainly by animal and cell-model data rather than by long-term human feeding trials. Palm-oil comparator studies in rats and in vitro intestinal-immune models provide mechanistic support for

lipid metabolism, endotoxemia and inflammatory pathways, but these findings are no longer used to state a precise human metabolic effect size.<sup>12,19,44,45</sup>

## Discussion

### Evidence hierarchy and interpretation of the research questions

The synthesis addresses the two research questions by treating the evidence base as a hierarchy rather than as a single pooled body of data, because Table 1 shows that the retained records differ substantially in species, population, exposure, comparator, duration and outcome domain.<sup>2,33,40,41,43</sup> Direct human evidence is therefore interpreted separately from rodent feeding studies, in vitro intestinal-immune models and structured-lipid digestion studies, because each evidence type answers a different part of the mechanistic question and carries a different level of translational certainty.<sup>12,16,19,30,33</sup> This distinction is essential for avoiding the erroneous inference that findings from high-fat rodent models or cell systems automatically establish clinically meaningful effects in humans.<sup>2,40,45,52</sup> The most defensible overall interpretation is that interesterified palm oil has biological plausibility for influencing glucose-related pathways, while the present human evidence remains too sparse and heterogeneous to support strong population-level conclusions.<sup>33–37</sup>

This hierarchy also clarifies why the Discussion should not rely on pooled percentage estimates across all studies, because the retained records include direct interesterified palm-oil experiments, palm-oil comparator studies, palm-derived bioactive studies and non-palm structured-lipid models.<sup>6,40,47,49</sup> A numerical estimate derived by combining postprandial human observations, high-fat mouse experiments, fish feeding studies and in vitro intestinal models would imply a degree of comparability that the evidence base does not possess. For this reason, the Discussion emphasises direction of evidence, mechanistic plausibility, consistency across related pathways and limits of inference rather than a single summary effect size.

### RQ1: Evidence linking interesterified palm oil and related structured lipids with insulin signalling, hepatic lipid metabolism and adipose-tissue inflammation

With respect to RQ1, the evidence most directly links interesterified palm oil to glucose-homeostasis mechanisms through three interconnected pathways: altered insulin secretion or signalling, hepatic lipid stress and adipose-tissue inflammatory remodeling. In direct preclinical evidence, interesterified palm oil impaired glucose homeostasis and produced deleterious liver effects in Swiss mice, indicating that structural modification of palm oil can interact with hepatic and systemic metabolic regulation under experimental feeding conditions.<sup>40</sup> A later Swiss-mouse study strengthened this mechanistic signal by reporting insulin resistance together with altered insulin secretion and signalling after exposure to interesterified palm oil.<sup>2</sup> These two direct preclinical studies are especially important because they investigate interesterified palm oil itself rather than a more distant palm oil or structured lipid comparator. However, because both studies are preclinical, their findings should be read as evidence of biological plausibility and pathway disruption rather than as proof of a quantified human clinical effect.<sup>2,40</sup>

The insulin-signalling interpretation is further supported by human comparator evidence showing that fatty-acid type and dietary fat matrix can influence insulin-related outcomes, even when the exposure is not interesterified palm oil itself.<sup>33–35</sup> The most direct

human record in Table 1 examined interesterified palm olein in individuals with type 2 diabetes and found changes in postprandial glucose-dependent insulinotropic polypeptide response, which suggests endocrine responsiveness without establishing broad deterioration of fasting glucose control.<sup>33</sup> Human skeletal-muscle work comparing dietary palmitate and oleate is relevant because palmitic-acid exposure is central to palm oil biology, and the study indicates that fatty-acid composition may differentially modulate insulin sensitivity in human tissue.<sup>35</sup> A double-blind crossover study comparing an extra-virgin olive oil-enriched chocolate spread with a palm-oil-enriched spread also supports the importance of comparator fat and dietary matrix for insulin-resistance markers.<sup>34</sup> Together, these human studies support a cautious interpretation that fat structure and fat type may matter for insulin-related physiology, but they do not show that interesterified palm oil alone produces a consistent adverse human glucose-homeostasis phenotype.<sup>33–35</sup>

A central mechanistic explanation for possible insulin-signalling effects is that interesterification changes the positional distribution of fatty acids within triacylglycerols, which may affect digestion, absorption and delivery of lipid-derived signalling molecules.<sup>6,30,16</sup> The radiolabelled absorption and bioavailability work on palmitic acid and 2-palmitoylglycerol is particularly relevant because 2-palmitoylglycerol is a metabolite linked to the digestion of interesterified fat and may influence the timing and form in which palmitate enters metabolic pathways.<sup>6</sup> Structured-lipid digestion models further support the concept that sn-position and triacylglycerol structure can regulate lipid absorption through physicochemical events during digestion.<sup>6,30</sup> These mechanistic studies do not directly prove adverse human glucose effects, but they provide a plausible bridge between altered fat structure and downstream metabolic responses observed in animal studies.<sup>6,16,30</sup>

The hepatic component of RQ1 is supported primarily by preclinical interesterified palm-oil studies and palm-oil comparator studies rather than by long-term human liver-outcome trials.<sup>31,40,44</sup> It has been directly reported that deleterious liver effects accompany impaired glucose homeostasis in Swiss mice fed interesterified palm oil, which links the exposure to hepatic stress within the same experimental model.<sup>40</sup> Palm-oil comparator work in rats showed that high dietary intake of palm oils compromised glucose tolerance, while a high olive-oil intake affected liver lipid metabolism and integrity, indicating that both fat type and organ-specific lipid handling shape metabolic outcomes.<sup>44</sup> Comparative work in healthy rats fed palm oil, soybean oil or insect fat further demonstrates that dietary lipid source can modify hepatic lipid metabolism and the plasma metabolome, which is relevant for interpreting hepatic mechanisms even though it is not a direct interesterified palm-oil study.<sup>31</sup> These findings support the interpretation that hepatic lipid metabolism is a key pathway through which palm-oil-derived fats may influence systemic glucose regulation under certain experimental conditions.<sup>31,40,44</sup>

The adipose-tissue component of RQ1 is most strongly represented by direct preclinical studies showing inflammatory or functional changes in white and brown adipose depots after interesterified palm-oil exposure.<sup>41,43</sup> Consumption of interesterified palm oil in a high-fat-diet mouse model was associated with white-adipose-tissue inflammation and broader metabolic disturbances, suggesting that adipose immune activation may participate in the link between modified fat intake and glucose regulation.<sup>41</sup> A subsequent high-fat-diet mouse study reported brown adipose tissue whitening and functional impairment after interesterified palm-oil consumption, which is relevant because brown adipose tissue contributes to energy

expenditure and substrate handling.<sup>42</sup> Peixoto et al.<sup>43</sup> similarly reported that palm and interesterified palm oil enhanced brown-fat whitening and contributed to metabolic dysfunction in C57BL/6J mice, reinforcing the view that adipose tissue is not merely a passive lipid-storage depot in this literature.<sup>43</sup> The adipose findings therefore extend the mechanistic interpretation beyond insulin receptors and liver metabolism to include tissue-level inflammatory and thermogenic remodelling.<sup>41–43</sup>

Additional palm-oil comparator and in vitro evidence help explain how adipose and inflammatory responses may connect with systemic insulin sensitivity.<sup>12,19,45</sup> Rat studies of palm oils or lard during high-fat intake reported peripancreatic adipose-tissue remodelling and inflammation, which is relevant because inflammatory changes near pancreatic tissue may influence endocrine and metabolic regulation in high-fat contexts.<sup>19</sup> A bicameral Caco-2 model demonstrated dietary-fat-induced chylomicron-mediated lipopolysaccharide translocation, suggesting a mechanism by which fat digestion could contribute to metabolic endotoxemia and inflammatory signalling.<sup>12</sup> An in vitro human intestinal-immune cell model further showed that palm oil can induce metabolic endotoxemia pathways that are modifiable by blueberries, supporting the plausibility of gut-immune-lipid crosstalk in palm-oil-related metabolic effects.<sup>19</sup> These studies are not direct human feeding evidence for interesterified palm oil, but they are useful for interpreting how gut-derived inflammatory signals could amplify or modify adipose and insulin-signalling responses.<sup>12,19,45</sup>

The integration of insulin, hepatic and adipose mechanisms suggests that interesterified palm oil should be discussed as a potential modulator of a network rather than as a single-pathway exposure.<sup>2,30,41,43</sup> Altered lipid digestion and metabolite availability may affect insulin secretion and signalling, hepatic lipid burden and inflammatory responses in adipose tissue, and these pathways may reinforce each other under high-fat or metabolically stressful dietary conditions.<sup>2,33,41</sup> The strongest direct evidence for this network currently comes from rodent models rather than from human trials, which means the mechanistic signal is credible but translationally incomplete. The answer to RQ1 is therefore that interesterified palm oil and related structured-lipid exposures are linked to glucose-homeostasis mechanisms through converging evidence on lipid absorption, insulin signalling, liver metabolism and adipose inflammation, but the directness of this evidence differs substantially across studies.<sup>2,41,6,33</sup>

## **RQ2: How evidence type, species or population, dietary context and study design constrain conclusions about human glucose homeostasis**

With respect to RQ2, the strength of conclusions about human glucose homeostasis is constrained first by the small number of direct human studies and by the fact that several human records are comparator or mechanistic studies rather than direct interesterified palm-oil interventions.<sup>33,36</sup> Direct human evidence in individuals with type 2 diabetes has been provided, but its main reported relevance in Table 1 concerns postprandial glucose-dependent insulinotropic polypeptide response rather than long-term glycaemic control, insulin sensitivity by clamp methods or incident diabetes outcomes.<sup>33</sup> It has been examined palm or soybean oils within starch-based meals and found that meal microstructure altered in vitro digestibility with limited major glycaemic effects, indicating that the food matrix can attenuate or reshape the effect of fat type on acute responses.<sup>36</sup> There have been informative studies for fatty-acid and palm-oil comparator mechanisms, but neither study should be treated as direct evidence that interesterified palm oil itself causes a specific human glucose-homeostasis effect.<sup>34,35</sup>

Population characteristics further constrain inference because the available human studies involve different metabolic backgrounds and different endpoint priorities.<sup>33,37–39</sup> Findings in individuals with type 2 diabetes may not generalise to healthy adults because incretin responses, beta-cell function and insulin sensitivity are already altered in diabetes.<sup>33</sup> Findings from healthy young adults in a palm-oil-enriched spread comparison may not generalise to individuals with obesity, non-alcoholic fatty liver disease or type 2 diabetes because baseline metabolic risk can modify dietary-fat responses.<sup>34,38</sup> A sequential feeding trial of coconut oil and palm olein oil focused on serum lipids and provides only indirect glucose-homeostasis information, reinforcing that not every palm-oil human study is equally informative for the review question.<sup>37</sup> The broader palm-oil biomarker systematic review is useful for context, but it cannot substitute for direct, contemporary intervention evidence on interesterified palm oil.<sup>39</sup>

Species and model differences are a second major constraint because several of the strongest mechanistic signals come from mice or rats maintained under high-fat dietary conditions. Rodent models allow controlled feeding, tissue sampling and pathway interrogation, but their dietary exposures, metabolic rates and adipose-depot responses may differ substantially from those of humans consuming mixed diets. High-fat-diet models can reveal susceptibility pathways, but they may also magnify effects that would be smaller or absent under isocaloric human dietary patterns. Fish feeding evidence shows that palm oil can affect glucose metabolism responses in large yellow croaker, but the non-mammalian model makes human nutritional translation especially limited.<sup>8</sup> Therefore, animal evidence should be used to identify mechanisms and hypotheses rather than to quantify expected human glucose responses.<sup>46</sup>

Dietary context is a third constraint because interesterified palm oil rarely acts in isolation from total fat intake, energy balance, carbohydrate load, comparator fat and food matrix. Starch-based meal studies indicate that the physical microstructure of a meal containing palm or soybean oils can influence digestibility and acute glycaemic outcomes, which means the same fat may behave differently depending on the surrounding food matrix.<sup>36</sup> The chocolate-spread comparison indicates that replacing a palm-oil-enriched matrix with an extra-virgin-olive-oil-enriched matrix can alter insulin-resistance markers, showing that comparator selection changes interpretation.<sup>34</sup> Rat studies of blended oils show that the balance among monounsaturated, polyunsaturated and saturated fatty acids can influence health-related outcomes, which cautions against attributing effects solely to interesterification when fatty-acid ratios and total diet quality also vary.<sup>23</sup> High dietary intake studies comparing palm oils and olive oil demonstrate that different lipid sources can produce different glucose and hepatic outcomes under high-intake conditions, which further supports diet-context-sensitive interpretation.<sup>44</sup>

The directness of the exposure is a fourth constraint because Table 1 includes interesterified palm oil, native palm oil, palm olein, palm mid fraction, palm-oil-derived tocotrienols, structured lipids and human milk fat substitutes. Palm-oil-derived tocotrienol studies in diabetic rats are relevant to inflammation and palm bioactives, but they do not evaluate interesterified palm oil as a dietary fat matrix. Palm mid fraction research is relevant to food-fat replacement and palm-fat application, but it provides limited direct evidence for glucose-homeostasis effects of interesterified palm oil.<sup>50</sup> Structured-lipid studies in human milk fat substitutes and triacylglycerol digestion models support the importance of fatty-acid positional distribution, but their exposures are not palm-specific and cannot be treated as direct interesterified palm-oil feeding evidence. This

exposure gradient explains why the synthesis distinguishes direct evidence from contextual and mechanistic evidence.

Outcome heterogeneity is a fifth constraint because the studies assess different biological endpoints, including postprandial incretin response, insulin-resistance markers, glucose tolerance, hepatic lipid metabolism, adipose inflammation, endotoxin translocation and lipid absorption kinetics. Postprandial incretin responses are not equivalent to fasting glucose, glycated haemoglobin, euglycaemic-clamp insulin sensitivity or long-term diabetes risk, so they should not be collapsed into a single glucose-homeostasis endpoint. Hepatic lipid metabolism endpoints are relevant because liver fat and hepatic insulin resistance can influence systemic glucose control, but liver outcomes from rodents require cautious translation to humans. Adipose-tissue endpoints are relevant because inflammation and brown-fat dysfunction can affect insulin sensitivity and energy balance, but these outcomes are also highly model-dependent. In vitro endotoxin-translocation endpoints provide mechanistic insight but do not capture whole-body hormonal regulation, energy expenditure or compensatory glucose handling.

The structured-lipid evidence is valuable for explaining why interesterification could matter biologically even when human outcome evidence remains limited (Menta et al., 2026; He et al., 2025; Ni et al., 2026). Interesterification changes the stereospecific arrangement of fatty acids rather than simply changing the amount of saturated fat, and digestion models support the principle that triacylglycerol structure can influence absorption pathways (Menta et al., 2026; He et al., 2025; Ni et al., 2026). If the absorbed lipid species, timing of lipid appearance or intestinal signalling environment differ after interesterification, downstream effects on incretin biology, hepatic substrate handling or inflammatory tone are plausible. Nevertheless, plausibility is not equivalent to clinical demonstration, and the current evidence cannot define a general human effect size or risk threshold.

A balanced answer to RQ2 is therefore that evidence type, species, dietary context and design features collectively narrow the strength of conclusions that can be drawn about human glucose homeostasis. Direct human evidence supports caution rather than certainty, while direct rodent evidence supports mechanistic concern under high-fat or metabolically stressful conditions. Comparator and structured-lipid studies strengthen biological plausibility but also demonstrate that findings depend on exposure definition, comparator selection and matrix composition. The most appropriate conclusion is not that interesterified palm oil has a proven moderate effect in humans, but that it is a mechanistically plausible exposure whose human relevance remains unresolved.

## Implications for interpretation and future research

The most important implication for interpretation is that human nutritional claims should be limited to what human data can support, while animal and cell evidence should be used to specify mechanisms requiring confirmation. Future trials should compare interesterified palm oil directly with native palm oil, palm olein, unsaturated-fat comparators and realistic food matrices under isocaloric conditions, because comparator choice and matrix composition strongly affect interpretation. These trials should include participants with different metabolic phenotypes, including healthy adults, individuals with obesity and individuals with type 2 diabetes, because baseline metabolic status may alter postprandial, insulin-signalling and inflammatory responses. Future studies should also use standardized endpoints such as fasting glucose, oral-glucose-tolerance responses, insulin sensitivity indices, incretin hormones, hepatic fat markers and inflammatory biomarkers so that results can be compared across trials.

Future mechanistic work should explicitly connect lipid structure to biological outcomes by measuring triacylglycerol positional distribution, digestive lipid products, absorption kinetics and downstream tissue responses within the same study design. Studies should examine whether 2-palmitoylglycerol kinetics, chylomicron formation or endotoxin-translocation pathways mediate effects on insulin signalling or inflammation, because these pathways offer a plausible link between structured-fat digestion and metabolic regulation. Preclinical studies should align dose, fat matrix and comparator selection more closely with human dietary exposures so that mechanistic findings are more translatable. Human trials should be sufficiently long to detect changes in insulin sensitivity, liver fat and inflammatory tone, because acute postprandial studies alone may miss slower hepatic and adipose adaptations.

In summary, the expanded Discussion answers RQ1 by identifying plausible links between interesterified palm oil and glucose-homeostasis mechanisms through insulin signalling, hepatic lipid metabolism, adipose inflammation and lipid-absorption pathways. It answers RQ2 by showing that the strength of human conclusions is limited by sparse direct human evidence, reliance on preclinical high-fat models, exposure heterogeneity, dietary-matrix effects and endpoint diversity. The interpretation is therefore more comprehensive but also more cautious: interesterified palm oil is biologically plausible as a context-dependent modulator of metabolic pathways, but a definitive claim about human glucose homeostasis requires direct, standardised and long-term human intervention evidence.

## Limitations

It has to be acknowledged that there are some limitations in this review:

First, the search was limited to Scopus. Although this database was chosen for broad interdisciplinary coverage, omission of PubMed/MEDLINE, Web of Science, and other databases may have introduced selection bias.

Second, the synthesis set contains heterogeneous evidence tiers. Human, rodent, fish, in vitro, and structured-lipid comparator studies cannot be treated as equivalent evidence for human nutrition.

Third, open-access and open-archive restrictions may have excluded relevant full-text studies.

Fourth, the available evidence did not support a meta-analysis or reliable pooled percentage estimates; the review therefore uses a qualitative synthesis and study-level traceability tables.

Fifth, several previously cited tangential references were removed from the analytic argument. This improves relevance but may reduce the breadth of contextual coverage.

## Conclusion

This systematic review indicates that the relationship between interesterified palm oil and glucose homeostasis should be interpreted through an evidence hierarchy. Direct human evidence is limited and currently insufficient to conclude that interesterified palm oil independently causes clinically meaningful disruption of human glucose homeostasis. Preclinical studies provide biologically plausible signals involving insulin signalling, hepatic lipid metabolism and adipose-tissue inflammation, especially under high-fat or metabolically stressful dietary conditions. Structured lipid and absorption studies further suggest that fatty-acid positional distribution may influence lipid handling, but these mechanistic findings do not

substitute for human feeding evidence. Accordingly, the conclusion is that interesterified palm oil warrants further investigation, particularly in long-term, controlled human trials with clearly defined comparators and standardized metabolic endpoints. Until such evidence is available, conclusions should remain cautious, context-specific and clearly separated by evidence type.

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## Conflicts of interest

The author declares there is no conflict of interest.

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