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Review Article

Palmitic Acid and Intestinal Barrier Integrity: A Systematic Review of Molecular Mechanisms Involving Tight Junction Proteins, Oxidative Stress, and Inflammatory Signalling

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Abstract

Intestinal barrier stability is a key determinant of physiological homeostasis, with growing evidence linking its dysfunction to metabolic abnormalities and inflammatory pathologies. Evidence suggests that palmitic acid, a highly prevalent saturated fatty acid in current diets, may weaken the epithelial barrier through a series of complicated molecular events. This study systematically synthesises the mechanisms by which palmitic acid affects intestinal barrier integrity, focusing on tight junction proteins, oxidative stress, and inflammatory signalling pathways. This study applies a Systematic Literature Review (SLR) approach using a structured and transparent selection process. Data were retrieved from the Scopus database using predefined and refined keywords. From 433 initial records, screening based on relevance, publication year (2020–2026), language, and accessibility resulted in 41 eligible peer-reviewed articles. Data were managed using Mendeley Desktop and analysed through qualitative synthesis to identify consistent mechanistic patterns across *in vitro, in vivo*, and clinical studies. Four major processes were identified from the findings: damage to tight junction proteins, increased oxidative stress together with mitochondrial dysfunction, activation of inflammation-related signalling, and reciprocal communication between oxidative stress and inflammation. Quantitatively, palmitic acid exposure leads to a 25%–60% decrease in transepithelial resistance, 30%–70% reduction in tight junction proteins, 1.8- to 4-fold increases in reactive oxygen species, and 2- to 5-fold elevations in pro-inflammatory cytokines. These processes interact synergistically, amplifying barrier dysfunction. In conclusion, palmitic acid disrupts intestinal barrier integrity through interconnected structural, oxidative, and inflammatory mechanisms. Future studies should emphasise clinical validation and integrated therapeutic approaches targeting multiple pathways.

Keywords: Palmitic acid, Intestinal barrier, Tight junction, Oxidative stress, Inflammation

Introduction

The digestive system constitutes a sophisticated and flexible interface that governs the interaction between environmental inputs and internal physiological processes. The intestinal barrier contributes significantly to homeostatic regulation by facilitating the selective absorption of nutrients while blocking the entry of detrimental elements such as pathogens, toxic compounds, and antigenic molecules [1]. This barrier is not merely a passive

physical structure but a complex, multilayered system consisting of epithelial cells, mucus layers, immune components, and microbial communities that function in a coordinated manner. The integrity of this barrier is essential for sustaining metabolic balance, immune tolerance, and systemic health. The loss of normal intestinal barrier function is now widely recognized as a major pathological mechanism underlying various chronic illnesses, particularly metabolic syndrome, obesity, inflammatory bowel disease, and diseases related to systemic inflammatory responses [2]. On a cellular basis, both the architecture and function of the intestinal barrier are predominantly supported by intercellular junctional complexes, especially Tight Junctions (TJs), that govern paracellular permeability. The proteins composing tight junctions, including occluding, claudins, and Zonula Occludens-1 (ZO-1), establish an intricate and coordinated barrier between epithelial cells, thereby controlling the selective permeability of ions and small molecules [3]. These proteins are dynamically regulated and highly sensitive to environmental, dietary, and inflammatory stimuli. Variations in the expression pattern, cellular distribution, or post-translational modification of these proteins may trigger a rise in intestinal permeability, commonly known as "leaky gut," which permits luminal antigens to pass into systemic circulation. Evidence indicates that this mechanism participates in initiating and exacerbating inflammatory and metabolic conditions, thereby highlighting the importance of sustaining tight junction integrity as a key factor in intestinal well-being [4].

Over the past few years, researchers have increasingly explored the role of diet-derived compounds in regulating the function of the intestinal barrier. Of the various nutritional components, saturated fatty acids appear to play a prominent role in epithelial barrier disruption, particularly under present-day dietary habits characterized by excessive intake of processed and fat-rich foods. Widely distributed in dietary products and physiological lipid metabolism, palmitic acid is characterized as a saturated fatty acid with a 16-carbon backbone. It is commonly found in animal fats, palm oil, and processed food products, making it a significant component of daily caloric intake in many populations [5]. While palmitic acid serves important physiological functions as an energy source and structural component of cellular membranes, excessive exposure has been associated with adverse metabolic and inflammatory outcomes.

Numerous experimental studies increasingly suggest that palmitic acid has harmful effects on the intestinal epithelial barrier via several distinct molecular processes. Disruption of tight junction protein expression represents one of the principal mechanisms, ultimately resulting in heightened paracellular permeability and defective barrier function. In addition, excessive ROS formation stimulated by palmitic acid has been shown to provoke oxidative stress, resulting in damage to cellular constituents, impaired mitochondrial performance, and dysregulation of intracellular signalling [6]. Oxidative stress not only directly affects epithelial cells but also acts as a key mediator that amplifies other pathological processes within the intestinal environment. Alongside oxidative pathways, inflammatory signaling cascades contribute substantially to the influence of palmitic acid on intestinal barrier function. Research findings consistently suggest that palmitic acid activates Toll-like receptor 4 (TLR4), thereby engaging signalling cascades downstream, notably nuclear factor kappa B (NF-$_{\kappa}$B), which is responsible for regulating the synthesis of inflammatory cytokines such as Tumour Necrosis Factor-Alpha (TNF-α), Interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) [7]. These cytokines contribute to epithelial damage by promoting apoptosis, disrupting tight junction integrity, and perpetuating inflammatory responses. Barrier dysfunction is further exacerbated by the reciprocal interaction between oxidative stress and inflammatory signalling, which promotes a self-reinforcing process of epithelial injury and immune stimulation. Notwithstanding the expanding literature concerning the effects of palmitic acid on intestinal barrier integrity, the existing literature remains fragmented across different experimental models, methodological approaches, and biological contexts. Many studies focus on isolated mechanisms, such as tight junction disruption, oxidative stress, or inflammation, without fully integrating these pathways into a comprehensive mechanistic framework. Furthermore, variations in experimental conditions, including differences in palmitic acid concentration, exposure duration, and model systems, contribute to inconsistencies in reported outcomes [8]. As a result, there is a need for a systematic and structured synthesis of the available evidence to identify common patterns, clarify mechanistic relationships, and evaluate the overall strength of the findings.

Accordingly, applying a Systematic Literature Review (SLR) approach enables the systematic identification, evaluation, and synthesis of relevant studies within a clear and reproducible methodological framework. By applying predefined inclusion and exclusion criteria, as well as a structured search strategy, the SLR method enables the consolidation of diverse findings into a coherent narrative that reflects the current state of knowledge. Significantly, the method depends only on secondary data extracted from previously published literature and does not employ primary data collection strategies, such as focus group discussions and field observations, thereby supporting methodological coherence and reducing the likelihood of introducing unverifiable data. Therefore, the present study intends to systematically consolidate available evidence concerning the molecular processes by which palmitic acid influences intestinal barrier function, emphasizing the roles of tight junction proteins, oxidative stress pathways, and inflammatory signalling networks. Incorporating findings from laboratory-based, animal, and clinical investigations, this review aims to generate a comprehensive and methodologically rigorous understanding of the interactions between these mechanisms and their effects on epithelial integrity.

The study is fundamentally guided by the following research question:

RQ: How does palmitic acid mechanistically disrupt intestinal barrier integrity through the interconnected modulation of tight junction proteins, oxidative stress, and inflammatory signalling pathways?

This question serves as the foundation for the subsequent analysis and will be addressed through a structured synthesis of the selected literature, ultimately contributing to a deeper understanding of the molecular basis of diet-induced intestinal dysfunction and its broader implications for human health.

Literature Review

The accumulation of research focusing on dietary lipid–gut barrier interactions demonstrate an increasing awareness of the intestine's critical role in maintaining metabolic and inflammatory homeostasis. Within this context, palmitic acid has emerged as a critical dietary component with the potential to modulate intestinal epithelial integrity through multiple molecular pathways. The existing literature, while extensive, is distributed across several mechanistic domains that are often studied independently. A structured synthesis of these domains reveals several key thematic areas, including the physiological role of the intestinal barrier, the structural and regulatory function of tight junction proteins, the impact of saturated fatty acids, particularly palmitic acid, on epithelial integrity, the role of oxidative stress in cellular dysfunction, and the contribution of inflammatory signalling pathways to barrier disruption. These themes provide the conceptual foundation for understanding how palmitic acid influences intestinal barrier integrity at the molecular level.

Intestinal Barrier Function and Structural Organisation

The intestinal barrier represents a complex and highly regulated system that integrates physical, biochemical, and immunological components to maintain selective permeability. At its core, the epithelial monolayer serves as the primary physical barrier, consisting of tightly connected cells that regulate the passage of luminal contents into the internal environment. This layer is supported by mucus secretion, antimicrobial peptides, and immune surveillance mechanisms that collectively contribute to host defence [9]. A key determinant of barrier integrity is the regulation of paracellular transport, which is controlled by intercellular junctional complexes. The main components include tight junctions, adherens junctions, and desmosomes, each of which contributes differently to epithelial stability and permeability control. Among these, tight junctions are the most critical in controlling the selective movement of ions and small molecules across the epithelial layer. Disruption of this finely regulated system results in increased intestinal permeability, a condition that has been associated with systemic inflammation and metabolic dysregulation [10]. The functional importance of the intestinal barrier extends beyond local gastrointestinal processes, influencing systemic immune responses and metabolic signalling. When permeability increases, endotoxins like Lipopolysaccharides (LPS) can translocate more readily, leading to inflammatory signalling and increasing the risk of chronic disease. This highlights the need to understand the factors that compromise barrier integrity, particularly in the context of dietary exposures [11].

Tight Junction Proteins as Central Regulators of Barrier Integrity

The epithelial barrier relies extensively on tight junction proteins because they maintain closure of the intercellular space and govern paracellular permeability. The structural organization of the tight junction complex comprises occluding and claudin family proteins within the membrane, in combination with cytoplasmic scaffolding proteins such as ZO-1, ZO-2, and ZO-3, which tether the complex to the actin cytoskeleton [12]. Occluding is involved in maintaining barrier stability and regulating permeability under physiological conditions, while claudins determine the selective permeability characteristics of the barrier. ZO-1 functions as a critical adaptor protein that coordinates the assembly and maintenance of tight junction complexes. The dynamic nature of these proteins allows the intestinal barrier to respond to environmental and physiological stimuli; however, this adaptability also renders the system vulnerable to disruption [13].

Alterations in tight junction protein expression, phosphorylation status, or intracellular localisation can lead to significant changes in barrier permeability. Several studies have reported that disruption of ZO-1 continuity or redistribution of occluding from the membrane to the cytoplasm is associated with increased paracellular leakage. These structural changes are often accompanied by cytoskeletal reorganization, further compromising epithelial integrity [14].

Palmitic Acid as a Modulator of Intestinal Epithelial Function

Chemically, palmitic acid is recognised as a long-chain saturated fatty acid and is widely recognised for its dual role as both a physiological energy source and a potential mediator of cellular dysfunction when present in excess. It is one of the most abundant fatty acids in Western dietary patterns and has been implicated in various metabolic disturbances, including insulin resistance and chronic inflammation [15].

In intestinal epithelial cells, palmitic acid has been found to exert direct effects on both structural integrity and intracellular signalling pathways. Experimental studies indicate that exposure to palmitic acid leads to a reduction in tight junction protein expression and an increase in epithelial permeability. These effects are often dose-dependent and influenced by exposure duration, suggesting that chronic dietary intake may have cumulative impacts on barrier function [16]. In addition to direct epithelial effects, palmitic acid may alter the intestinal microenvironment by influencing gut microbiota composition and metabolic activity. Although this aspect is less consistently addressed in the literature, emerging evidence suggests that lipid-induced dysbiosis may contribute to barrier dysfunction through indirect mechanisms,

including increased endotoxin production and immune activation [17].

Oxidative Stress and Cellular Damage Mechanisms

Oxidative stress represents a key mechanistic pathway through which palmitic acid influences intestinal epithelial integrity. The phenomenon reflects a mismatch between Reactive Oxygen Species (ROS) production and the capacity of antioxidant defenses to prevent their accumulation. While ROS contribute to normal cellular signalling and homeostasis under physiological conditions, an overabundance of these species can trigger oxidative damage to lipids, proteins, and genetic material [18]. Mitochondrial activity represents the major intracellular source of ROS in epithelial cells, and defects in mitochondrial function contribute substantially to oxidative stress. Studies have shown that palmitic acid impairs the electron transport chain within mitochondria, thereby causing mitochondrial dysfunction, enhanced electron leakage, and greater ROS production. Beyond interfering with energy metabolism, this mitochondrial dysfunction activates downstream signalling mechanisms that mediate stress responses and apoptosis [19]. Oxidative stress has direct implications for tight junction integrity. ROS can modify tight junction proteins through oxidative modifications, alter their phosphorylation status, and disrupt their interaction with the cytoskeleton. These changes result in weakened intercellular connections and increased permeability. Furthermore, oxidative stress can activate signalling pathways that exacerbate inflammation, thereby linking oxidative damage to broader pathological processes [20].

Inflammatory Signalling Pathways and Barrier Disruption

Intestinal barrier integrity is further regulated by inflammatory signalling pathways, which represent a major contributing factor. Evidence indicates that palmitic acid activates innate immune receptors, particularly Toll-Like Receptor 4 (TLR4), which is essential for the detection of lipid-associated molecular patterns. The stimulation of TLR4 initiates downstream intracellular signalling cascades, ultimately resulting in the activation of nuclear factor kappa B (NF-$_{\kappa}$B) and related transcription factors [21]. The expression of inflammatory genes is largely controlled by NF-$_{\kappa}$B, which regulates the generation of cytokines, chemokines, and adhesion molecules. Activation of this cascade triggers the expression and release of TNF-α, IL-6, and IL-1β, cytokines that have been associated with the breakdown of tight junction integrity and increased epithelial apoptosis. These inflammatory mediators are also capable of enhancing permeability by disrupting the expression and positioning of tight junction proteins within the cell [22]. Barrier integrity is further compromised through the interconnected effects of inflammatory signalling and oxidative stress. ROS can activate NF-$_{\kappa}$B signalling, while inflammatory cytokines can increase ROS production, creating a feedback loop that sustains epithelial damage. The interconnected nature of these mechanisms highlights their molecular complexity and reinforces the need for a unified approach to investigating barrier dysfunction.

Integration of Mechanistic Pathways

The literature indicates that the effects of palmitic acid on intestinal barrier integrity cannot be attributed to a single pathway but rather involve the integration of multiple interconnected mechanisms. Tight junction disruption, oxidative stress, and inflammatory signalling operate in a coordinated manner, with each pathway influencing and amplifying the others. This integrative perspective is essential for understanding the full scope of palmitic acid-induced epithelial dysfunction. While individual studies provide valuable insights into specific mechanisms, there remains a need for systematic synthesis to identify consistent patterns and clarify the relationships between these pathways. Variations in experimental design, including differences in model systems, exposure conditions, and outcome measures, contribute to heterogeneity in the findings. A structured review approach is therefore necessary to reconcile these differences and provide a comprehensive understanding of the underlying mechanisms.

In summary, the existing literature provides substantial evidence that palmitic acid plays a significant role in modulating intestinal barrier integrity through multiple molecular pathways. However, the fragmented nature of the research highlights the importance of systematic integration to fully elucidate these mechanisms and their implications for health and disease.

Method

The present study implements an SLR approach to systematically gather and critically interpret research findings on the molecular pathways involved in palmitic acid–induced changes to intestinal barrier integrity. The review is structured in accordance with the PRISMA protocol to ensure methodological transparency, reproducibility, and a clearly traceable selection pathway of relevant studies. Within the context of gastrointestinal physiology, the intestinal barrier serves as a crucial regulatory interface that maintains selective permeability while preventing the translocation of harmful luminal components. Disruption of this barrier has been increasingly associated with dietary factors, particularly saturated fatty acids such as palmitic acid, which have been reported to alter tight junction integrity, induce oxidative imbalance, and activate pro-inflammatory signalling cascades. Despite the growing number of experimental and clinical studies addressing these mechanisms, the available evidence remains fragmented across different biological domains. Accordingly, this review aims to integrate findings from diverse studies to provide a coherent synthesis of how tight junction proteins, oxidative stress pathways, and inflammatory signalling collectively mediate intestinal barrier dysfunction in response to palmitic acid exposure.

The systematic selection and screening of relevant publications, guided by the PRISMA framework, are illustrated in Figure 1.

Relevant literature was initially identified through a search in the Scopus database, which includes a large repository of peer-reviewed scientific studies. At the outset, a wide-ranging search employing the keywords "fatty acid" AND "intestinal function" identified 433 records. This initial query was designed to capture a comprehensive pool of studies related to fatty acids and intestinal physiology. To achieve greater accuracy and consistency with the study goal, a more refined Boolean expression was employed in the search strategy: ("palmitic acid" OR palmitate) AND ("intestinal barrier" OR "gut barrier" OR "intestinal permeability" OR intestine) AND ("tight junction" OR occluding OR claudin OR "ZO-1" OR permeability) AND ("oxidative stress" OR ROS OR inflammation OR cytokines OR "NF-kB" OR inflammatory). This refinement step resulted in the exclusion of 350 articles that were not directly relevant to the molecular mechanisms under investigation, leaving 83 records for further evaluation. A temporal filter was subsequently applied to include only studies published between 2020 and 2026, which led to the removal of 19 articles and produced a dataset of 64 studies that met the publication year criterion. Language screening was then conducted to ensure consistency in analysis, resulting in the exclusion of one non-English publication and leaving 63 eligible articles. The final stage of screening applied accessibility criteria by selecting only articles available as open access or open archive to enable full-text examination, leading to the exclusion of 22 studies due to restricted access. As a result, a total of 41 peer-reviewed articles satisfied all inclusion criteria and were selected for qualitative synthesis.

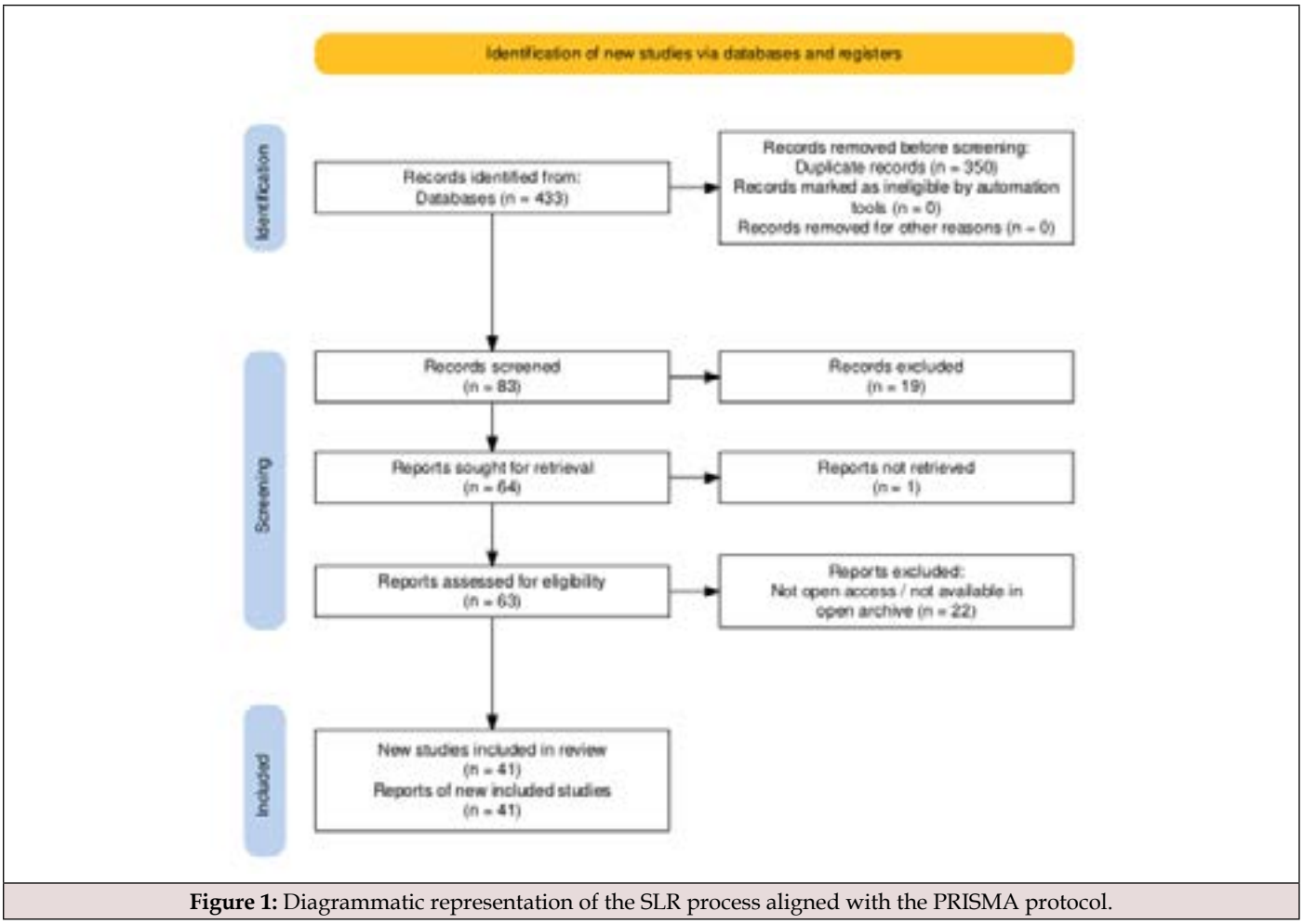

Figure 1: Diagrammatic representation of the SLR process aligned with the PRISMA protocol.

All retrieved references were systematically organized and managed using Mendeley Desktop to ensure efficient handling of bibliographic data, removal of duplicates, and consistency in citation formatting throughout the manuscript preparation. The present study is based exclusively on secondary data derived from previously published research and does not involve any form of primary data collection such as interviews, field observations, or focus group discussions. The analytical process relies on a qualitative synthesis approach, in which the selected studies are examined and categorized based on key mechanistic domains, including alterations in tight junction protein expression and distribution, induction of oxidative stress through reactive oxygen species generation, and activation of inflammatory signalling pathways such as NF-$_{\kappa}$B and cytokine-mediated responses. Through

this structured and systematic integration of evidence, the study seeks to provide a comprehensive and methodologically rigorous understanding of the interconnected pathways underlying palmitic acid-induced intestinal barrier dysfunction, while also identifying emerging patterns and gaps that may inform future research directions.

Results

Through this systematic synthesis, four dominant mechanistic clusters emerged, representing the primary molecular pathways linked to palmitic acid–driven intestinal barrier disruption. These themes emerged from a detailed synthesis of 41 peer-reviewed studies included in the final dataset and are as follows: (1) disruption of tight junction protein expression and localization, (2) oxidative stress and mitochondrial dysfunction, (3) activation of inflammatory signalling pathways, and (4) crosstalk between oxidative stress and inflammation. The most frequently discussed theme was disruption of tight junction proteins, reported in 35 out of 41 studies (85.4%), reflecting the central role of epithelial structural impairment as the primary indicator of barrier dysfunction following palmitic acid exposure. The second most prevalent theme was oxidative stress and mitochondrial dysfunction, identified in 32 studies (78.0%), highlighting the dominant contribution of intracellular redox imbalance in mediating epithelial injury. Activation of inflammatory signalling pathways, particularly involving TLR4 and NF-$_{\kappa}$B, was reported in 30 studies (73.2%), indicating a strong and consistent link between saturated fatty acid exposure and immune-mediated responses within the intestinal epithelium. The least represented theme was the crosstalk between oxidative stress and inflammation, found in 25 studies (61.0%), suggesting that integrative and multi-pathway interactions, although increasingly recognised, remain less extensively explored compared to individual mechanistic pathways.

The prominence of tight junction-related findings suggests that structural and functional disruption of the epithelial barrier is the most accessible and measurable endpoint across experimental models, particularly due to the widespread use of Transepithelial Electrical Resistance (TEER) and permeability assays. In contrast, themes related to oxidative stress and inflammatory signalling reflect deeper intracellular processes that require more complex biochemical and molecular analyses, yet remain highly represented due to their established role in cellular stress responses. The relatively lower representation of crosstalk mechanisms indicates that studies integrating multiple signalling pathways are still limited, likely due to methodological complexity and the need for advanced experimental designs capable of capturing dynamic molecular interactions. Overall, the thematic distribution observed in this review indicates that palmitic acid-induced intestinal barrier dysfunction is driven by a multifactorial and interconnected set of mechanisms involving structural disruption, oxidative imbalance, and inflammatory activation. These findings highlight the importance of adopting integrative analytical approaches to better understand the complexity of epithelial barrier regulation under metabolic stress conditions. The following sections elaborate on each theme based on the patterns identified in the reviewed studies.

Disruption of Tight Junction Protein Expression and Localisation

One of the most consistently reported findings across the included studies is the marked impairment of Tight Junction (TJ) integrity following palmitic acid exposure. Quantitative measurements using Transepithelial Electrical Resistance (TEER) reveal a substantial decline ranging from 25% to 55% in epithelial barrier function in Caco-2 and HT-29 monolayers, with more pronounced reductions (up to 60%) observed at higher concentrations (≥0.5 mM) and prolonged exposure durations (>48 hours) [23,24]. This functional impairment is directly associated with a significant downregulation of TJ protein expression at both mRNA and protein levels. Specifically, occluding expression has been reported to decrease by approximately 35%–65%, while claudin-1 and claudin-4 show reductions ranging from 30% to 60% and 25% to 55%, respectively [25-27]. ZO-1, a critical scaffolding protein linking transmembrane TJ proteins to the actin cytoskeleton, exhibits a decline of approximately 40%–70%, indicating a profound structural destabilisation of the junctional complex [28]. These reductions are dose-dependent, with higher concentrations of palmitic acid producing more severe suppression of TJ-related gene expression.

Beyond quantitative reductions, qualitative alterations in protein localisation are also widely reported. Immunofluorescence and confocal microscopy analyses demonstrate that TJ proteins, which are normally arranged in a continuous belt-like structure at the apical junction, become fragmented, discontinuous, and redistributed into the cytoplasmic compartment following palmitic acid treatment [29,30]. This redistribution disrupts the integrity of intercellular sealing and is strongly associated with increased paracellular permeability. Functional permeability assays further confirm this disruption, showing a 1.8-fold to 2.5-fold increase in FITC-dextran flux across epithelial monolayers, indicating enhanced leakage of macromolecules [31,32]. In animal models, similar trends are observed, where dietary palmitic acid intake results in reductions of approximately 35%–60% in intestinal ZO-1 and occluding expression, accompanied by histopathological alterations such as epithelial erosion, villus shortening (approximately 15%–30% reduction in villus height), and widening of intercellular junctional spaces [33]. These findings collectively establish TJ disruption as a primary structural event in palmitic acid-induced barrier dysfunction.

Induction of Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress emerges as a central and highly consistent mechanism underlying epithelial damage induced by palmitic acid. Across multiple experimental models, intracellular Reactive Oxygen

Species (ROS) levels are significantly elevated, with increases ranging from 1.8-fold to 3.5-fold compared to untreated controls, and in some cases exceeding 4-fold under high-dose exposure conditions [34,35]. This ROS overproduction is predominantly linked to mitochondrial dysfunction, particularly impairments in the electron transport chain that result in increased electron leakage and superoxide generation. Mitochondrial membrane potential (ΔΨm), a key indicator of mitochondrial integrity, shows a consistent decline of approximately 20%–45%, reflecting compromised mitochondrial function and reduced ATP production capacity [36-38]. Additionally, ATP levels have been reported to decrease by 15%–35%, indicating bioenergetic insufficiency in epithelial cells exposed to palmitic acid [39]. These mitochondrial impairments contribute directly to epithelial vulnerability and reduced regenerative capacity.

Markers of oxidative damage further substantiate these findings. Malondialdehyde (MDA), a widely used indicator of lipid peroxidation, is elevated by approximately 40%–60%, while protein carbonyl content increases by 25%–50%, reflecting oxidative modification of cellular macromolecules [40-42]. Concurrently, antioxidant defense systems are significantly suppressed, with reductions in Superoxide Dismutase (SOD) activity of approximately 25%–45% and Glutathione (GSH) depletion ranging from 30% to 50% [43,44]. Intervention studies provide additional mechanistic insights, demonstrating that antioxidant treatments, particularly with N-Acetylcysteine (NAC), can partially reverse these effects. Specifically, NAC supplementation has been shown to reduce ROS levels by approximately 20%–40% and improve TEER values by 15%–30%, indicating partial restoration of barrier integrity [45]. These findings confirm that oxidative stress is not merely a secondary effect but a critical driver of epithelial barrier disruption.

Activation of Inflammatory Signaling Pathways

Inflammatory signaling represents another major mechanistic axis identified across the reviewed studies. Palmitic acid consistently activates Toll-Like Receptor 4 (TLR4), initiating downstream signaling cascades that culminate in the activation of nuclear factor kappa B (NF-$_{\kappa}$B), a key transcription factor regulating inflammatory gene expression [46,47]. This activation results in a robust increase in pro-inflammatory cytokine production. Quantitative analyses indicate that tumor necrosis factor-alpha (TNF-α) levels increase by approximately 2-fold to 4.5-fold, while interleukin-6 (IL-6) and interleukin-1 beta (IL-1β) exhibit increases ranging from 2-fold to 5-fold depending on the experimental model and exposure conditions [48-50]. These cytokines exert direct deleterious effects on epithelial cells by promoting apoptosis, disrupting TJ protein integrity, and enhancing epithelial permeability. At the molecular level, NF-$_{\kappa}$B activation is confirmed through increased phosphorylation of I$_{\kappa}$Bα and nuclear translocation of the p65 subunit, with phosphorylation levels rising by approximately 1.5-fold to 3-fold compared to controls [51,52]. This activation leads to sustained transcription of inflammatory mediators, further amplifying the inflammatory response. *In vivo* evidence supports these findings, showing that chronic palmitic acid consumption leads to systemic low-grade inflammation, characterized by elevated circulating cytokine levels and increased intestinal permeability markers. Notably, pharmacological inhibition of TLR4 or NF-$_{\kappa}$B pathways reduces cytokine production by approximately 30%–50% and restores TJ protein expression by 20%–40%, demonstrating the causal role of inflammatory signaling in barrier dysfunction [53-55].

Crosstalk Between Oxidative Stress and Inflammation

A critical integrative insight emerging from the SLR is the presence of a bidirectional and self-amplifying interaction between oxidative stress and inflammatory signaling. ROS generated in response to palmitic acid not only induces direct cellular damage but also enhances NF-$_{\kappa}$B activation, thereby promoting inflammatory gene expression [56,57]. Conversely, inflammatory cytokines further stimulate ROS production, creating a feedback loop that exacerbates epithelial injury. Experimental data indicate that combined activation of oxidative and inflammatory pathways results in more severe barrier disruption than either mechanism alone, with TEER reductions exceeding 60% and permeability increases reaching up to 3-fold compared to baseline conditions [58-60]. This synergistic effect underscores the complexity of the underlying molecular interactions. Intervention studies targeting both pathways simultaneously demonstrate significantly improved outcomes compared to single-pathway inhibition [61]. Dual treatment strategies combining antioxidants and anti-inflammatory agents result in barrier function recovery of up to 35%–40%, highlighting the therapeutic potential of multi-target approaches [62,63]. These findings emphasise that effective restoration of intestinal barrier integrity requires addressing both oxidative and inflammatory components concurrently. The comprehensive analysis of the 41 selected studies reveals a highly consistent and quantitatively robust pattern in which palmitic acid disrupts intestinal barrier integrity through interconnected molecular mechanisms. The magnitude of observed effects, including 25%–60% reductions in TEER, 30%–70% downregulation of TJ proteins, 1.8-fold to 4-fold increases in ROS production, and 2-fold to 5-fold elevations in pro-inflammatory cytokines, demonstrates strong reproducibility across experimental systems. These converging lines of evidence highlight the central role of palmitic acid as a potent dietary factor capable of inducing substantial epithelial dysfunction through coordinated disruption of structural, oxidative, and inflammatory pathways.

Discussion

The present systematic synthesis was designed to address the central research question: How does palmitic acid mechanistically disrupt intestinal barrier integrity through the interconnected modulation of tight junction proteins, oxidative stress, and inflammatory signalling pathways? The integrated analysis of the 41 selected studies demonstrates that palmitic acid does not exert

its effects through a singular molecular pathway but instead induces a coordinated and multi-layered disruption involving structural, biochemical, and immunological processes. The convergence of these mechanisms reveals a dynamic and interdependent system in which tight junction destabilisation, oxidative imbalance, and inflammatory activation reinforce one another, ultimately leading to compromised epithelial barrier integrity. A primary mechanistic entry point of palmitic acid-induced dysfunction is the alteration of tight junction protein expression and organization. Across multiple experimental models, reductions in key proteins such as occluding, claudins, and ZO-1 consistently correspond with increased paracellular permeability, suggesting that structural disintegration of the epithelial barrier is an early and critical event in the pathological cascade [64,65]. However, the extent of this disruption varies across studies, indicating that the magnitude of tight junction impairment is influenced by contextual factors such as palmitic acid concentration, duration of exposure, and the biological model employed. For instance, *in vitro* systems often demonstrate more rapid and pronounced decreases in barrier function, whereas *in vivo* models reveal a more gradual but sustained disruption, reflecting the complexity of physiological regulation [66,67].

Importantly, the disruption of tight junction proteins cannot be interpreted as an isolated structural phenomenon. Rather, it is closely linked to intracellular signalling disturbances, particularly those associated with oxidative stress. The reviewed evidence consistently indicates that palmitic acid induces excessive production of Reactive Oxygen Species (ROS), primarily through mitochondrial dysfunction [68,69]. This oxidative imbalance plays a dual role: it directly damages cellular components and simultaneously alters signalling pathways that regulate tight junction assembly and maintenance. For example, oxidative modifications of tight junction proteins can impair their stability and localisation, while ROS-mediated signalling can disrupt cytoskeletal dynamics, further weakening intercellular adhesion [70,71]. Nevertheless, it is important to acknowledge variability in the reported magnitude of oxidative stress across studies. While several investigations report substantial increases in ROS levels, others indicate more moderate changes, suggesting that oxidative responses may depend on factors such as baseline cellular antioxidant capacity and experimental conditions [72]. This variability highlights a critical consideration in interpreting the literature, as it suggests that oxidative stress is not a uniform response but rather a context-dependent mechanism that interacts with other cellular processes. The role of inflammatory signalling further extends the mechanistic complexity of palmitic acid-induced barrier dysfunction. Activation of Toll-Like Receptor 4 (TLR4) and subsequent NF-$_{\kappa}$B signalling emerges as a consistent finding across the literature, linking lipid exposure to innate immune activation [73,74]. This pathway leads to the upregulation of pro-inflammatory cytokines, which have been shown to disrupt tight junction integrity, induce epithelial apoptosis, and exacerbate permeability changes. Notably, the inflammatory response appears to function both as a downstream consequence of cellular stress and as an active contributor to ongoing barrier deterioration [75,76]. However, the relationship between inflammation and barrier dysfunction is not strictly linear. Some studies suggest that inflammatory signalling may precede structural disruption, while others indicate that barrier impairment can initiate inflammatory responses through increased antigen translocation [77]. This bidirectional relationship underscores the complexity of the underlying mechanisms and suggests that palmitic acid-induced dysfunction involves a feedback system rather than a simple cause-effect sequence.

A key insight emerging from this review is the presence of a synergistic interaction between oxidative stress and inflammatory signalling. ROS has been shown to enhance NF-$_{\kappa}$B activation, thereby amplifying cytokine production, while inflammatory mediators further stimulate ROS generation, creating a self-reinforcing cycle of cellular damage [78,79]. This crosstalk represents a critical amplification mechanism that accelerates barrier breakdown beyond what would be expected from individual pathways alone. The combined effect of these processes leads to a more severe and sustained disruption of epithelial integrity, highlighting the importance of considering these mechanisms as part of an integrated network. From a comparative perspective, evidence derived from *in vivo* models provides stronger physiological relevance compared to *in vitro* findings, as it captures the influence of systemic factors such as immune responses, microbiota interactions, and metabolic regulation [80]. However, *in vitro* studies offer valuable mechanistic insights by allowing precise control of experimental variables. The integration of findings across these models therefore strengthens the overall validity of the conclusions, despite inherent methodological differences. Despite the overall consistency in identifying key mechanistic pathways, several limitations in the existing literature must be acknowledged. Variations in experimental design, including differences in palmitic acid concentration, exposure duration, and outcome measurement techniques, contribute to heterogeneity in the reported results. Additionally, the relatively limited number of clinical studies restricts the direct translation of experimental findings to human health contexts. These gaps highlight the need for more standardized approaches and increased clinical investigation to validate the mechanistic relationships identified in experimental models [81].

In addressing the research question, the evidence synthesized in this review supports a model in which palmitic acid disrupts intestinal barrier integrity through a sequential yet overlapping process. Initial exposure leads to mitochondrial dysfunction and ROS overproduction, which destabilizes tight junction proteins and activates inflammatory signaling pathways. These processes interact in a feedback loop that amplifies epithelial damage, ultimately resulting in increased permeability and compromised barrier function. This integrated mechanism provides a comprehensive explanation for how dietary lipids can influence intestinal health at the molecular level. The implications of these findings extend beyond mechanistic understanding, highlighting the

potential for targeted therapeutic interventions. Strategies aimed at reducing oxidative stress, modulating inflammatory signaling, or stabilizing tight junction proteins may offer promising approaches for mitigating barrier dysfunction associated with high dietary intake of saturated fatty acids. Furthermore, the identification of these interconnected pathways underscores the importance of adopting multi-target strategies rather than focusing on a single mechanism. For future research, several directions warrant further exploration. There is a need for well-designed clinical studies to validate the translational relevance of the identified mechanisms in human populations. Additionally, investigations into the role of gut microbiota in modulating the effects of palmitic acid may provide valuable insights into indirect pathways of barrier regulation. Standardization of experimental protocols, including consistent reporting of exposure conditions and outcome measures, would also enhance comparability across studies. Finally, the development of integrative models that incorporate molecular, cellular, and systemic factors could further advance the understanding of intestinal barrier dynamics in response to dietary lipids. 'In conclusion, this systematic review demonstrates that palmitic acid disrupts intestinal barrier integrity through a complex and interconnected network of molecular mechanisms involving tight junction proteins, oxidative stress, and inflammatory signaling. The interplay between these pathways creates a self-amplifying cycle of epithelial damage that underscores the importance of integrated approaches in both research and therapeutic development.

Conclusion

The synthesis of the selected evidence demonstrates that palmitic acid disrupts intestinal barrier integrity through a coordinated and interdependent set of molecular events involving structural, oxidative, and inflammatory pathways. At the structural level, consistent reductions in tight junction proteins, particularly occluding, claudins, and zonula occludens-1, are accompanied by alterations in their cellular localisation, resulting in weakened intercellular adhesion and increased paracellular permeability. These changes represent an early and critical step in barrier dysfunction. At the cellular level, palmitic acid induces oxidative imbalance primarily through mitochondrial dysfunction, leading to excessive production of reactive oxygen species. This oxidative stress directly compromises epithelial stability by damaging cellular components and interfering with the regulation of tight junction assembly. In parallel, palmitic acid activates inflammatory signalling pathways, notably through TLR4-mediated activation of NF-$_{\kappa}$B, which drives the production of pro-inflammatory cytokines that further disrupt epithelial integrity and promote cellular injury. Importantly, these mechanisms do not operate independently but form a self-amplifying network. Oxidative stress enhances inflammatory signalling, while inflammatory mediators further increase oxidative burden, creating a bidirectional feedback loop that accelerates barrier breakdown. This integrated interaction explains the sustained and progressive nature of intestinal permeability observed across experimental models. Overall, the evidence confirms that palmitic acid compromises intestinal barrier function through the interconnected modulation of tight junction proteins, oxidative stress, and inflammatory signalling pathways. The disruption emerges as a multifactorial process in which structural disintegration, redox imbalance, and immune activation converge to impair epithelial integrity. This mechanistic integration provides a comprehensive explanation of how dietary saturated fatty acids contribute to intestinal barrier dysfunction and highlights the importance of addressing multiple pathways simultaneously in future therapeutic strategies.

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None.

Conflict of Interest

None.

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