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Phytochemical Gut Axis: Potential of *Cestrum nocturnum* to Modulate Gut Barrier Integrity and Inflammation

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Abstract

Background: Intestinal epithelial barrier dysfunction is a critical factor in gastrointestinal and metabolic disorders, primarily driven by disruption of tight junction (TJ) proteins such as ZO-1, occludin, and claudins. **Aim:** This review aims to evaluate the phytochemical composition of *Cestrum nocturnum* and its potential role in modulating gut barrier integrity and inflammation. **Methods:** A comprehensive literature review was conducted focusing on phytochemicals of *C. nocturnum* and mechanistic studies of structurally similar flavonoids and phenolic compounds influencing epithelial barrier function. **Results:** *C. nocturnum* contains flavonoids, phenolic acids, saponins, and terpenoids with established antioxidant and anti-inflammatory properties. Mechanistic evidence from flavonoids such as quercetin and apigenin demonstrates enhancement of TJ protein expression, inhibition of NF-κB and MAPK signalling pathways, reduction in oxidative stress, and stabilisation of cytoskeletal architecture, thereby improving epithelial barrier integrity. **Conclusion:** Although direct experimental studies on *C. nocturnum* are limited, its phytochemical profile strongly supports its potential as a gut barrier-modulating agent. Further in vitro and in vivo validation is required.

Major Findings: *C. nocturnum* contains bioactive phytochemicals capable of modulating oxidative stress and inflammatory signalling, which may stabilise tight junction proteins and improve intestinal barrier function.

Keywords: Apigenin, *Cestrum nocturnum*, Gut Barrier Integrity, Inflammation, Intestinal Permeability, Oxidative Stress

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1. Introduction

The human gastrointestinal tract is lined with a single-cell-thick layer of epithelium that acts as a crucial barrier between the lumen, which contains microorganisms, digested food, and potentially harmful antigens, and the internal environment. One important structural component of this barrier is the network of tight junctions (TJs), which is composed of transmembrane and cytoplasmic adaptor proteins such as occludin, claudins, and zonula occludens-1 (ZO-1), among others[1,2]. If inflammatory cytokines, oxidative stress, pathogenic microbes, or other things hurt this tight junction complex, the barrier becomes less stable. This makes the intestines more permeable, which can cause "leaky gut" and make it easier for antigens, toxins, or microbes to get into the lamina propria or the bloodstream[3]. Barrier disruption has been correlated with various gastrointestinal disorders, including inflammatory bowel disease (IBD), as well as metabolic conditions, where increased permeability is associated with chronic inflammation and systemic metabolic dysregulation. A lot of people are interested in natural substances that can restore or protect the function of the epithelial barrier because the tight junctions are so important for gut health and the body's overall balance[4,5]. When it comes to the molecular factors that are responsible for the disruption of the barrier, oxidative stress is a vital component. Increased reactive oxygen species (ROS),

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which are created by environmental stressors, microbial dysbiosis, or inflammation, damage proteins, lipids, and nucleic acids. They also cause cytoskeletal remodelling and TJ protein disintegration and activate pro-inflammatory pathways, including NF-κB[6]. As a result, antioxidants that neutralise ROS or stop signalling that leads to inflammation have become hopeful ways to keep the barrier intact. Actually, antioxidant treatments have been shown to improve TJ protein expression and permeability in models of colitis or toxin-induced gut injury[7,8]. More and more people are interested in phytochemicals, like flavonoids, phenolic acids, glycosides, saponins, and other secondary metabolites, because they help protect the body's barriers. Some flavonoids, like quercetin and apigenin, have been shown to increase TJ proteins (ZO-1, occludin, and claudin-1), lower cytokine production, and repair epithelial integrity in many *in vitro* and *in vivo* models[9]. It has also been shown that altering the gut microbiota through dietary or herbal substances (for example, by prebiotic or antimicrobial properties) affects TJ function and mucosal immunity, providing a "gut-axis" approach to gut-barrier health[10]. Despite this biochemical and pharmacological richness, to date, there is no systematic review exploring the potential of CN (or its phytochemicals) to influence intestinal barrier integrity or tight junction regulation. This represents an important gap given the rising recognition of gut-barrier dysfunction in chronic diseases, and the urgent need for safe, natural agents that could modulate barrier health.

2. Phytochemical Composition of *C. nocturnum*

Cestrum nocturnum has a wide range of phytochemicals that are typical of the *Solanaceae* family. These include flavonoids, phenolic acids, glycosides, alkaloids, saponins, terpenoids, and fragrant volatiles[11]. Various phytochemical analyses, employing chromatographic, spectroscopic, and GC–MS techniques, have validated the existence of numerous bioactive classes, many exhibiting recognised antioxidant and anti-inflammatory properties[12].

2.1 Major Classes of Phytochemicals

2.1.1 Flavonoids

Research on alcoholic (ethanol/methanol) extracts from CN leaves has consistently detected flavonoids, such as quercetin, apigenin, and kaempferol, among others. The relative amount of flavonoids and phenolic acids in leaf extracts is quantitatively significant, highlighting their probable role in the plant's bioactivity[13]. Flavonoids are well-known for their antioxidant, anti-inflammatory, and signalling-modulating capabilities, which make them good candidates for affecting the biology of the intestinal barrier[14].

2.1.2 Phenolic Acids

Phytochemical investigations indicate the presence of phenolic acids in CN, in addition to flavonoids and other phenolic compounds[13]. These acids help get rid of free radicals, change the amount of oxidative stress, and may help protect the barrier by reducing the damage that ROS does to tight junctions[11].

2.1.3 Steroidal Glycosides and Alkaloids

Thorough reviews aggregating several phytochemical investigations of *C. nocturnum* elucidate the existence of glycosides (inclusive of steroidal glycosides) and alkaloids in diverse plant tissues[15]. These classes may have immunomodulatory and other biological effects, however their roles in intestinal barrier or TJ control are still not well understood, therefore caution should be used when it comes to toxicity[16].

2.1.4 Saponins

Phytochemical analysis of methanolic/ethanolic leaf extracts has revealed the presence of saponins as secondary metabolites in CN[12]. Saponins may exhibit mucosal-protective, surfactant, and immunoregulatory activities, which could affect mucosal integrity and microbial interactions in the gastrointestinal tract, hence influencing barrier function[17].

2.1.5 Terpenoids and Volatile Constituents

The essential oil and volatile profiles of CN, particularly from night-blooming flowers, exhibit a combination of monoterpenes, sesquiterpenes, aromatic alcohols, phenylethyl alcohol, benzyl alcohol, eugenol-like compounds, and others[18]. These unstable terpenoids and aromatics frequently have antioxidant, antibacterial, and anti-inflammatory actions. This may help make the lumen safer and lower the stress on the epithelium, which indirectly supports barrier stability[19].

2.2 Barrier-protective Mechanisms of *C. nocturnum* Flavonoids and Phenolic Acids

The flavonoids (e.g., quercetin, apigenin) and phenolic acids (e.g., caffeic, ferulic acid) found in *C. nocturnum* provide protection mainly by increasing the expression and localisation of tight junction (TJ) proteins, removing reactive oxygen species (ROS), and stopping pro-inflammatory signalling pathways[20,21]. In epithelial models, quercetin and apigenin have been demonstrated to improve transepithelial resistance, lower paracellular permeability, and promote the localisation of ZO-1, occludin, and claudins to membranes. They do this while also preventing NF-κB/MAPK activation and keeping the structure of the cytoskeleton intact[22]. Phenolic acids also help by lowering oxidative damage to TJ complexes and membranes. This gives a molecular explanation for how *C. nocturnum* phytochemicals can protect barriers[23].

3. Plant Parts and Extraction Methods

3.1 Leaves

The most researched part is the leaves. When leaves are extracted with ethanol or methanol, they make a thick mix of flavonoids, phenolic acids, saponins, and other phenolics[12,13].

3.2 Flowers

The night-blooming flowers, in particular, create essential oils that are high in volatile terpenoids and aromatic chemicals. GC–MS investigations have consistently identified several volatile compounds in essential oils produced from flowers[24]. Flower extracts may also have small levels of non-volatile phenolics and flavonoids[13].

3.3 Bark/Stem/Other Parts

Certain phytochemical investigations, particularly in extensive reviews, indicate the presence of glycosides, alkaloids, and other secondary metabolites (e.g., steroidal glycosides) in non-leaf structures like bark or stems, although full quantification is infrequent[11].

3.4 Essential Oil

Essential oils are obtained via steam or hydrodistillation of aerial parts (primarily flowers) and are rich in volatile terpenoids[25].

3.5 Solvent and Method Effects

The polarity of the extraction solvent has a big effect on the yield and type of chemicals that are extracted. Polar solvents like methanol and ethanol are the best for getting flavonoids, phenolics, and saponins out of plants[26]. Non-polar solvents or distillation for volatile terpenoids and essential oils[27].

The outcomes of experiments (antioxidant, anti-inflammatory, cytotoxicity) can vary significantly based on the extraction method employed. This is something to think about carefully if you want to make sure it works the same way every time. Reviews of CN say that this variability is a big problem[28].

4. Bioactivity Relevance

The phytochemical composition of *C. nocturnum* closely resembles compounds previously demonstrated in other studies to influence intestinal barrier function and tight junction integrity. Quercetin is a flavonoid that has been studied a lot and is found in CN. It helps TJ proteins (ZO-2, occludin, claudin-1, and claudin-4) come together and stay in place, which improves barrier function in human intestinal Caco-2 cell monolayers. This increases transepithelial resistance (TER) and decreases paracellular permeability[29,30]. In animal models of acute necrotising pancreatitis, which include breaking down the intestinal barrier, quercetin slowed down the breakdown of the barrier, stopped inflammatory signalling (TLR4/MyD88/p38 MAPK), and protected the epithelial cells[31,32].

Although there aren't many direct studies on *C. nocturnum* flavonoids, a larger body of research shows that phenolic compounds and saponins can improve barrier resilience, lower oxidative stress, and downregulate inflammatory mediators like NF-κB[33,34]. There aren't any specific studies on CN volatiles and the gut barrier, but terpenoids from other plants have been shown to have antimicrobial and anti-inflammatory effects, which could lower the amount of pathogens and inflammatory triggers in the gut, which could lower stress on the epithelial barrier. The fact that these terpenoids are in CN essential oil makes it more promising[35,36].

The phytochemical profile of *C. nocturnum*as is shown in Figure 1, and a strong case for how it works,

as summarised in Table 1. Its flavonoids (and related phenolics) could change how signalling cascades work (oxidative stress → NF-κB / MAPK → TJ expression), and its terpenoids and saponins could help clean the inside of the body and support the mucous membranes. This combination supports the idea that CN or standardised extracts from it might help keep the gut barrier intact or fix it, which calls for more research (*in vitro* and *in vivo*).

5. Anti-inflammatory and Antioxidant Activities of *C. nocturnum* Relevant to Gut Barrier Protection

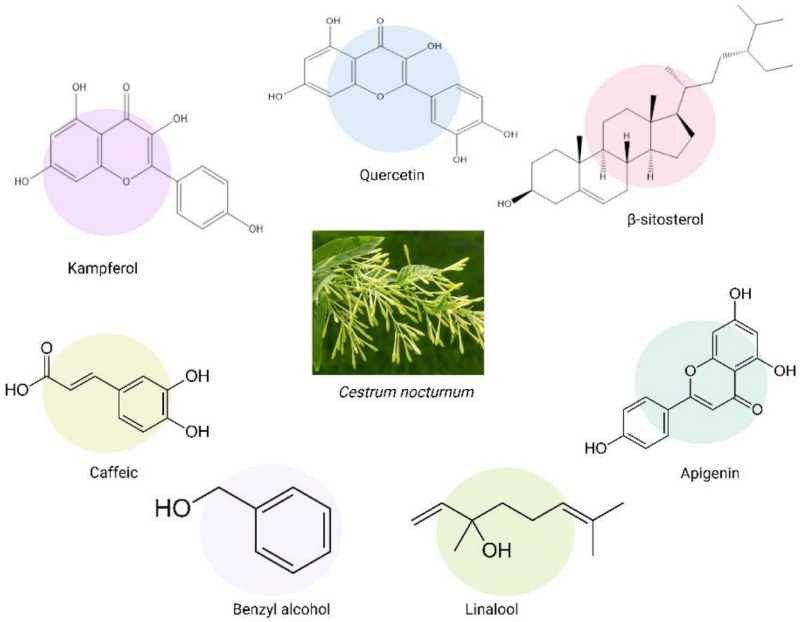
Oxidative stress and chronic inflammation are two of the main causes of problems with the intestinal epithelial barrier[40]. Too many reactive oxygen species (ROS) mess up the organisation of the cytoskeleton and the location of tight junction (TJ) proteins[41]. Pro-inflammatory cytokines like tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) speed up the breakdown of TJ proteins through the NF-κB and MAPK signalling pathways[42]. So, plant-based chemicals that have antioxidant and anti-inflammatory characteristics are thought to be good options for keeping the integrity of the epithelial cells and the balance of the gut[43]. So, plant-based chemicals that have antioxidant and anti-inflammatory characteristics are thought to be good options for keeping the integrity of the epithelial cells and the balance of the gut[15,44].

5.1 Antioxidant Activity of *C. nocturnum*

Several *in vitro* studies report significant antioxidant potential of CN leaf and flower extracts. Ahmad *et al.*, demonstrated that methanolic leaf extracts of *C. nocturnum* exhibited strong free-radical scavenging activity using DPPH and ABTS assays, along with high total phenolic and flavonoid content, indicating a direct correlation between phytochemical richness and antioxidant capacity[37].

Table 1. Key phytochemicals identified in *C. nocturnum*, their source, extraction method and bioactivity relevance

Phytochemical/ Class	Plant Part	Extraction Method	Evidence in *C. nocturnum*	Known Biological Activity Relevant to Gut Barrier	Key Reference
Flavonoids (quercetin derivatives)	Leaves	Methanol/ Ethanol	Identified via phytochemical screening and chromatography	Enhances TJ protein assembly (ZO-1, occludin, claudins), improves epithelial barrier integrity	13,29
Flavonoids (apigenin derivatives)	Leaves	Methanol/ Ethanol	Reported in phytochemical surveys	Restores TJ proteins, suppresses inflammatory cytokines in colitis models	37,38
Kaempferol derivatives	Leaves/ flowers	Alcoholic extracts	Detected in phytochemical screening	Antioxidant, anti-inflammatory, barrier-supportive potential	13
Phenolic acids (caffeic, ferulic acid)	Leaves	Methanol/ aqueous extract	Detected in phenolic profiling	Reduces oxidative stress, protects epithelial integrity	37
Saponins	Leaves/ stem	Alcoholic extract	Confirmed via phytochemical screening	Anti-inflammatory, immunomodulatory, and mucosal support potential	37
Steroidal glycosides	Leaves/ stem	Polar solvent extracts	Reported in genus-level phytochemical analyses	Immunomodulatory activity; safety/ toxicity relevance	37
Terpenoids (linalool, benzyl alcohol, phenylethyl alcohol)	Flowers	Essential oil (steam distillation, GC-MS)	Identified in essential oil composition	Antioxidant, antimicrobial; may reduce luminal inflammatory burden	36
Volatile aromatic compounds	Flowers	Essential oil extraction	Confirmed via GC-MS profiling	Antioxidant and antimicrobial activity	39



Representative bioactive compounds identified in *C. nocturnum* include flavonoids (kaempferol, quercetin, apigenin), phenolic acid (caffeic acid), phytosterol (β-sitosterol), and volatile compounds (benzyl alcohol and linalool).

Figure 1. Major phytochemical constituents of *C. nocturnum*.

Similarly, Haggag reported elevated antioxidant indices in ethanolic extracts of CN leaves, attributing these effects primarily to flavonoids and phenolic acids detected via chromatographic profiling[13]. Essential oil fractions derived from CN flowers also exhibit antioxidant activity. Al-Reza et al. (2010) identified multiple terpenoid and aromatic constituents in CN essential oil and demonstrated dose-dependent radical scavenging effects[39]. From a gut-barrier standpoint, antioxidant activity is significantly essential as reactive oxygen species (ROS) directly hinder tight junction protein expression and enhance epithelial permeability[45]. Studies using independent epithelial models have demonstrated that oxidative stress diminishes the expression of ZO-1 and occludin, whereas antioxidant therapies reinstate barrier integrity and decrease paracellular permeability[6]. Thus, the antioxidant capacity of CN extracts provides mechanistic support for potential epithelial protection via reduction of oxidative damage.

5.2 Anti-Inflammatory Effects of *C.nocturnum*

Anti-inflammatory activity is one of the most consistently reported pharmacological properties of *C. nocturnum*[46]. Anti-inflammatory activity of *Solanaceae cestrum* species has been demonstrated; for example, methanol extracts of *C. diurnum* significantly reduced carrageenan-induced paw oedema and downregulated NF-κB p65 expression in a TNF-α-activated macrophage model, suggesting inhibition of pro-inflammatory signalling pathways[47]. Although this evidence originates from *C. diurnum* rather than *C. nocturnum*, both species share similar phytochemical profiles, including flavonoids, phenolics, and glycosides, as documented in comparative pharmacognosy reviews[48]. Similarly, Farooqi *et al.*, demonstrated that alcoholic extracts of *C. nocturnum* significantly reduced experimentally induced inflammation and nociceptive responses in animal models, further confirming its anti-inflammatory and analgesic activity[49]. Since the activation of NF-κB is a key factor in breaking down the intestinal epithelial barrier by making tight junctions internalise and the cytoskeleton shrink, stopping this pathway is thought to be an important strategy to protect the gut barrier[29].

Consequently, although direct molecular investigations into NF-κB signalling in *C. nocturnum* are presently absent, the persistent *in vivo* anti-inflammatory effects demonstrated by CN extracts, alongside mechanistic data from analogous *Cestrum* species and flavonoid-rich plant extracts, endorse the

biological feasibility that *C. nocturnum* may confer protective benefits against inflammation-induced epithelial barrier impairment.

5.3 Synergistic Antioxidant–Anti-inflammatory Interactions

CN's anti-inflammatory and antioxidant qualities are mechanistically related rather than separate occurrences. Oxidative stress stimulates inflammatory pathways, whereas inflammation further amplifies ROS generation, creating a feedback loop that exacerbates barrier degradation. Polyphenols and flavonoids found in CN interrupt this cycle by simultaneously scavenging free radicals and inhibiting pro-inflammatory transcription factors[50]. Ahmad *et al.,* demonstrated that CN extracts not only reduced oxidative stress markers but also inhibited enzymatic targets related to metabolic inflammation, such as α-amylase, suggesting broader systemic anti-inflammatory potential[37]. This dual activity is highly relevant to gut physiology, where epithelial cells are constantly exposed to inflammatory and oxidative insults from luminal contents. Similar polyphenol-rich plant extracts have been shown to enhance epithelial resilience by maintaining cytoskeletal stability and TJ localisation under inflammatory stress conditions[9,51].

5.4 Implications for Gut Barrier Integrity

Although direct experimental investigations have not yet investigated the impact of *C. nocturnum* on intestinal permeability or tight junction protein expression, the cumulative antioxidant and anti-inflammatory evidence robustly endorses its biological feasibility as a gut-barrier modulator. Independent mechanistic investigations have demonstrated that flavonoids, including quercetin and apigenin, both identified components of CN, reestablish epithelial barrier function by promoting tight junction protein assembly and decreasing cytokine-induced leakage in Caco-2 monolayers and colitis models[29,38]. Since CN has these flavonoids as well as phenolic and terpenoid chemicals that help, it makes sense to think that standardised CN extracts could have the same protective effects on the structure of the intestinal epithelium.

6. Mechanistic Evidence Linking Flavonoids to Tight Junction Regulation and Intestinal Barrier Protection

Tight junction (TJ) proteins, such as zonula occludens-1 (ZO-1), occludin, and claudins, constitute the principal molecular barrier that controls paracellular permeability in intestinal epithelial cells[52]. Inflammatory cytokines, oxidative stress, or microbial agents can break up these junctional complexes, which causes the cytoskeleton to shrink, junctional proteins to move into the cell, and the epithelial layer to become more permeable[53,54]. As a result, restoring or stabilising TJ architecture has become a significant goal of treatment for inflammatory disorders and problems with the intestinal barrier[1,55]. Researchers have looked into flavonoids, especially quercetin and apigenin, which are both found in *C. nocturnum*, a lot to see if they can help keep epithelial integrity through direct and indirect molecular processes[20,56].

6.1 Quercetin-mediated Tight Junction Stabilisation

Quercetin is one of the dietary flavonoids that has been studied the most in terms of how it affects the intestinal barrier. Suzuki and Hara demonstrated that quercetin significantly enhanced the functionality of the epithelial barrier in human Caco-2 intestinal monolayers by facilitating the aggregation and translocation of tight junction (TJ) proteins, including ZO-2, occludin, claudin-1, and claudin-4, to the membrane. Quercetin treatment resulted in increased transepithelial electrical resistance (TEER) and reduced paracellular permeability, indicating improved functionality of the epithelial barrier[29]. The same study found that quercetin stopped the activation of protein kinase C-delta (PKCδ), which kept the actin cytoskeleton stable and stopped TJ disarray. The cytoskeleton must be intact for tight-junction anchoring to work because TJ proteins are always changing how they connect to actin filaments[29]. Additional *in vitro* studies have confirmed these barrier-enhancing effects. Gamero-Estevez *et al.*, demonstrated that quercetin induced the reorganisation of tight junction complexes in epithelial cell monolayers over time. As a result, the barrier stayed

stronger for a long time and was less permeable when there was inflammation[57]. Quercetin's ability to protect epithelial cells is supported by *in vivo* studies. Zhang *et al.*, found that giving quercetin to mice reduced damage to the intestines caused by lipopolysaccharide (LPS) by restoring the expression of ZO-1 and occludin and stopping the production of inflammatory cytokines at the same time[58]. These results demonstrate that quercetin is a powerful modulator of tight junction integrity in both cellular and animal models.

6.2 Apigenin and Flavone-driven Barrier Protection

Apigenin, another flavonoid found in *C. nocturnum* leaf extracts, has also been shown to have strong effects that protect the intestines' barrier[59]. Fu *et al.*, examined apigenin in a dextran sulfate sodium (DSS)-induced colitis model and noted a substantial restoration of tight junction (TJ) protein expression, specifically ZO-1, occludin, and claudin-1. Apigenin therapy reduced epithelial damage, inhibited inflammatory cytokines, and enhanced the histological structure of the intestinal mucosa[38]. Apigenin also changed the gut microbiota, which is important because it made more good bacteria that are linked to the health of the mucosa. Flavonoids are hard to control when it comes to the gut barrier because they affect both epithelial cells and bacteria[60]. In models of DSS-induced colitis, apigenin and its glycosylated derivatives exhibit protective effects. Apigenin restores the expression of tight-junction proteins, inhibits inflammatory cytokines, and alters the gut microbiota. Studies show that apigenin-7-O-glucoside strengthens the intestinal barrier and changes how inflammatory signalling works. This supports the idea that flavone glycosides can help keep the barrier strong[38].

6.3 Regulation of Inflammatory Signalling Pathways

Experimental studies show that quercetin stops NF-κB from moving into the nucleus and stops inflammatory mediators from working in models of intestinal injury[31,61]. In the same way, apigenin has been shown to stop the activation of MAPK and NF-κB in models of intestinal inflammation, which lowers the disruption of TJ by cytokines[62,63]. Flavonoids protect the organisation of the cytoskeleton and the stability of TJ proteins under inflammatory stress by weakening these signalling pathways.

6.4 Implications for *C. nocturnum*

Phytochemical profiling studies have validated the existence of flavonoids, such as quercetin and apigenin, in *C. nocturnum* leaf extracts[13]. While direct investigations assessing CN extracts on intestinal tight junction regulation are presently absent, the substantial mechanistic data indicating barrier protection by these flavonoids offer a scientifically sound foundation for hypothesising analogous benefits from standardised CN extracts. Because CN extracts also have antioxidant and anti-inflammatory properties, it's possible that their combined phytochemical makeup could have a synergistic effect on keeping the epithelial barrier intact through several different pathways, such as stabilising TJ proteins, stopping inflammatory signalling, and lowering oxidative stress.

6.5 Mechanistic Link Between Phytochemicals and Gut Barrier Protection

The protective effects of *C. nocturnum* phytochemicals on intestinal barrier integrity can be explained through interconnected molecular mechanisms. Flavonoids such as quercetin and apigenin enhance the expression and localisation of tight junction proteins, including ZO-1, occludin, and claudins, thereby improving epithelial barrier function and reducing paracellular permeability[29,38]. These compounds also inhibit key inflammatory signalling pathways, particularly NF-κB and MAPK, which are responsible for cytokine-induced disruption of tight junctions and epithelial damage[31,62,64]. In addition, phenolic compounds reduce oxidative stress by scavenging reactive oxygen species (ROS), thereby preventing cytoskeletal disruption and tight junction disassembly[45,65]. Activation of antioxidant defence pathways such as Nrf2 further enhances epithelial resilience and supports tight junction integrity under inflammatory conditions[66]. Furthermore, phytochemicals may indirectly support barrier integrity by modulating gut microbiota composition and promoting short-chain fatty acid production, which enhances mucosal immunity and epithelial stability[67,68]. Collectively, these mechanisms provide a strong biological basis for the gut

barrier-protective potential of *C. nocturnum*, despite the current lack of direct experimental validation.

7. Integrative Mechanistic Model: Linking *C. nocturnum* Phytochemistry to Intestinal Barrier Protection

The biological effects of *C. nocturnum* on intestinal health cannot be attributed to a single compound or pathway, as shown in Figure 2. Instead, they arise from a complex interaction of phytochemical, cellular, and microbial processes. Based on what we know about phytochemistry and how flavonoids and polyphenols work, we can suggest an integrative model in which CN extracts affect the integrity of the gut barrier through three main interconnected axes:

i. direct signalling modulation of epithelial cells,
ii. regulation of antioxidant and inflammatory pathways, and
iii. barrier support through microbiota.

Cestrum nocturnum extract, which is high in flavonoids, phenolics, and terpenoids, improves the function of the intestinal barrier by acting as an antioxidant, anti-inflammatory, and microbiota-modulating agent. These actions stabilise tight junction proteins (ZO-1, occludin, claudin), lower inflammation and permeability in the intestines, and protect the epithelium.

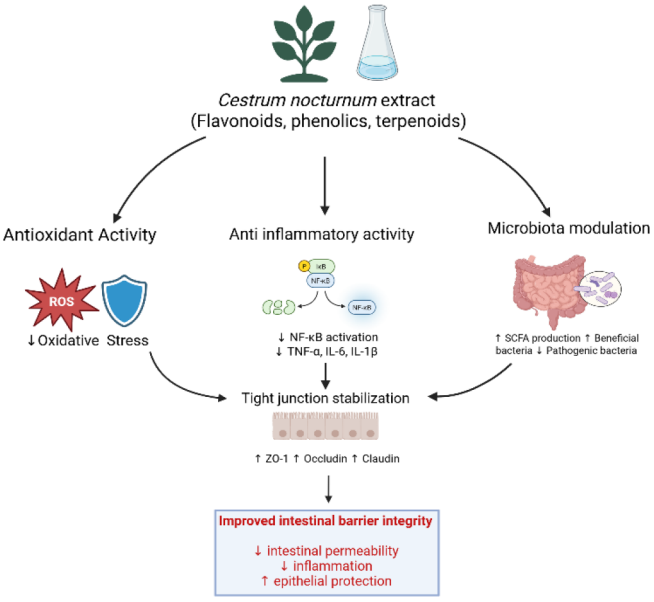


Figure 2. Mechanism of action of *C. nocturnum* extract in improving intestinal barrier integrity.

7.1 Direct Epithelial Signalling Pathways

One significant mechanism by which CN phytochemicals may affect barrier integrity is through the direct control of epithelial tight-junction (TJ) assembly. Flavonoids like quercetin and apigenin, which are found in CN leaf extracts, have been shown to help TJ proteins like ZO-1, occludin, claudin-1, and claudin-4 stay in the right place and stabilise them. This makes the cell membranes less permeable and increases the electrical resistance between cells[29]. Quercetin stops the activity of protein kinase C-delta (PKCδ), which keeps TJ complexes anchored to the cytoskeleton and stops actin from breaking down junctions[64]. Apigenin similarly restores TJ protein expression and epithelial architecture in inflammatory models[62]. Because CN extracts have these flavonoids in them[13], it's possible that standardised CN preparations could have similar TJ-stabilising effects via changing how cytoskeletal signalling and membrane junctional assembly work.

7.2 Antioxidant and Redox-sensitive Signalling Integration

Oxidative stress is a key factor in breaking down the epithelial barrier. Too many reactive oxygen species make tight-junction complexes less stable and turn on redox-sensitive inflammatory pathways like NF-κB and MAPK activation[6]. CN extracts exhibit strong antioxidant activity due to high flavonoid and phenolic content[37]. This antioxidant capability may help protect barriers by lowering oxidative damage to epithelial membranes, keeping actin cytoskeleton organisation intact, and stopping redox-mediated TJ internalisation. Furthermore, the activation of the NRF2 antioxidant system by plant polyphenols has demonstrated enhancement of epithelial resilience and tight junction protein expression[69]. Thus, CN-derived polyphenols may act not only as radical scavengers but also as regulators of endogenous cellular defence mechanisms relevant to gut-barrier stability.

7.3 Inflammatory Pathway Modulation

It is known that inflammatory cytokines like TNF-α and IL-1β can make epithelial cells more permeable by causing the cytoskeleton to shrink and TJ proteins to be taken up by cells[29,70]. *In vivo* pharmacological investigations show that extracts from *C. nocturnum* greatly reduce inflammatory oedema and nociceptive

responses, showing that they have functional anti-inflammatory effects[15,46]. Additionally, mechanistic studies in the closely related species *C. diurnum* demonstrate direct inhibition of NF-κB p65 signalling[47]. There isn't any molecular signalling evidence for CN right now, but the fact that all *Cestrum* species have the same phytochemical structure supports the idea that CN may stop inflammatory transcriptional cascades, which would protect the integrity of the epithelial barrier.

7.4 Microbiota-driven Barrier Support

Phytochemicals also have indirect barrier-protective effects via changing the gut microbiome. Flavonoids and phenolic acids help good bacteria grow, make more short-chain fatty acids (SCFAs), especially butyrate, which strengthens epithelial tight junctions and boosts mucosal immunity[65,71]. Apigenin treatment has been shown to change the makeup of gut microbiota while also restoring tight junction protein expression and lowering inflammation in the intestines[38]. Also, CN extracts have antimicrobial properties against harmful bacteria[72], which may lower the amount of inflammation in the lumen and the stress on epithelial cells caused by pathogens, which helps keep the barrier stable.

7.5 Knowledge Gaps and Translational Considerations

Even though the mechanisms seem very likely, there are still some important experimental gaps. At present, there are no direct studies examining CN extracts on intestinal epithelial monolayers (such as Caco-2 permeability assays), DSS/LPS-induced colitis models, or microbiome sequencing analysis. Before the CN extract can be used in real life, its composition needs to be standardised, its dose needs to be optimised, and its safety needs to be checked.

However, the convergence of phytochemical composition, anti-inflammatory activity, antioxidant capacity, and microbiota-modulating potential positions *C. nocturnum* as a promising candidate for future gut-barrier research and phytotherapeutic development.

8. Limitations and Safety Considerations

Cestrum nocturnum shows promise as a drug, but some problems need to be fixed.

8.1 Lack of Direct Gut-barrier Studies

At present, there are no published studies on the effects of CN extract on intestinal permeability, tight junction protein regulation and Gut epithelial signalling pathways. This review is based on mechanistic inference from the literature on flavonoids and polyphenols, which, although biologically plausible, necessitates experimental validation.

8.2 Phytochemical Variability

Phytochemical composition of CN varies depending on geographic location, plant part used, harvest time, extraction solvent and environmental conditions. Such variability complicates reproducibility and standardisation[11].

8.3 Toxicity and Safety Profile

Cestrum nocturnum has been reported to possess mild to moderate toxicity in livestock and experimental models when consumed in uncontrolled quantities. Toxicological reports suggest the presence of steroidal glycosides and alkaloids that may contribute to adverse effects at high doses[15,73].

9. Conclusion

This review emphasises C. *nocturnum* as a phytochemically abundant yet inadequately researched medicinal plant with significant biological potential for intestinal barrier modulation. Evidence is mounting that CN has flavonoids (like quercetin and apigenin), phenolic acids, saponins, steroidal glycosides, and terpenoid-derived volatiles. These are all types of compounds that have antioxidant, anti-inflammatory, antimicrobial, and epithelial-protective effects. Although direct experimental studies assessing CN-mediated tight-junction regulation and intestinal permeability are presently absent, a substantial body of mechanistic literature on structurally analogous flavonoids offers a robust basis for hypothesising barrier-protective effects.

Putting together all the available information supports a multi-pathway model in which CN phytochemicals may affect the integrity of the gut barrier by stabilising tight junction protein complexes, blocking oxidative and inflammatory signalling cascades, and improving mucosal homeostasis through the microbiota. These converging mechanisms are critically important to intestinal disorders

characterised by epithelial dysfunction, including inflammatory bowel disease, metabolic endotoxemia, obesity-related gut permeability, and chronic low-grade inflammation. There are still big holes in our knowledge, even with this promising framework. By filling in these gaps, we will be able to better understand CN's potential as a treatment and make it easier to develop it as a candidate for functional food formulations or phytotherapeutics aimed at gut health.

In summary, *C. nocturnum* is a biologically plausible and scientifically promising candidate for future research on gut barriers. This review establishes a conceptual framework and experimental guide for transitioning CN from conventional medicinal applications to evidence-based applications for gut health by integrating phytochemistry with epithelial biology and microbiota interactions.

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Author Contribution

Ansh Tripathi: Literature review, data curation, manuscript drafting, writing-original draft; Avijit Mazumdar: Supervision, critical revision of the manuscript, validation, final approval of the version to be published; Priyanka Bansal: Conceptualisation, validation. All authors have read and agreed to the published version of the manuscript.