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REVIEW

Mitochondria as the Bridge between Injury and Protection: The Role of Melatonin in Non-Steroidal Anti-Inflammatory Drug-Induced Gastric Ulcers

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ABSTRACT: Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed, but their long-term use frequently results in gastric mucosal injury. Emerging evidence indicates that, beyond cyclooxygenase inhibition, mitochondrial dysfunction represents a central mechanism driving NSAID-induced gastric epithelial damage. This review aims to critically synthesize current evidence on mitochondria-centered pathways involved in NSAID-induced gastric ulceration and to evaluate the therapeutic relevance of melatonin in this context. We highlight how NSAIDs impair mitochondrial bioenergetics, promote excessive reactive oxygen species generation, disrupt membrane potential, and activate apoptotic signaling, thereby compromising mucosal integrity. Importantly, melatonin exerts multifaceted gastroprotective actions by preserving mitochondrial function, restoring redox homeostasis, modulating apoptosis, and facilitating mucosal repair. Collectively, the available data identify mitochondria as both the primary site of injury and a viable therapeutic target in NSAID-induced gastric ulcers. This mechanistic framework positions melatonin as a promising adjunct strategy for mitigating NSAID-associated gastric damage and improving mucosal defense.

KEYWORDS: Mitochondrial dysfunction; melatonin; non-steroidal anti-inflammatory drug; gastric ulcers; oxidative stress; gastroprotection

1 Introduction

Gastric ulcer disease is characterized by mucosal erosion of the stomach lining and remains a persistent global health problem with clinical consequences ranging from dyspepsia to bleeding and perforation [1]. It contributes significantly to morbidity and impaired quality of life worldwide, with ulcer-related complications accounting for considerable hospital admissions and mortality in severe cases. Among various factors, the ubiquitous use of non-steroidal anti-inflammatory drugs (NSAIDs) for acute and chronic pain, several inflammatory disorders, and cardiovascular prophylaxis are among the most common causes of gastric mucosal injury [2]. Drug-induced gastric ulceration represents a major healthcare burden, and NSAIDs are recognised as the leading pharmacological cause of peptic ulcers worldwide. The widespread, often long-term administration of NSAIDs has created a large at-risk cohort in diverse patient

populations (including older adults, individuals with musculoskeletal disease, and those taking low-dose aspirin for cardioprotection) who are regularly prescribed these NSAIDs, often for long periods [3]. The gastroduodenal complications in these patients remain clinically significant despite advances in supportive care and prophylaxis. Evidence from clinical data indicates that NSAID exposure continues to account for a significant number of hospital admissions for upper gastrointestinal bleeding and ulcer-related complications, resulting in substantial morbidity, mortality, and increasing healthcare costs [4].

NSAIDs mediate their therapeutic actions primarily through inhibition of cyclooxygenase (COX) enzymes, thereby reducing prostaglandin synthesis, resulting in the attenuation of inflammation and pain. This inhibition of prostaglandins leads to gastrointestinal toxicity since prostaglandins are essential for mucosal defence due to their ability to promote mucus and bicarbonate secretion, maintenance of the mucosal blood flow, and restitution of the epithelium [5]. Beyond prostaglandin depletion, NSAIDs can directly cause harm to the epithelial cells by disrupting the phospholipid membranes and by exerting topical irritant effects [6]. This results in an impaired mucosal barrier that has reduced capability to resist luminal acid, digestive enzymes, and microbial insults, setting the stage for erosion and ulceration. Clinical risk of gastrointestinal ulcer is modulated by drug factors (COX selectivity, dose, formulation), host factors (age, comorbidities, smoking, *Helicobacter pylori* infection, prior ulcer history), and co-medications (anticoagulants, corticosteroids) [7]. Additional systemic risk factors include chronic liver/kidney disease, critical illness, and alcohol consumption. Current clinical guidelines thus emphasize risk stratification and implication of advanced or preventive strategies, despite which, prevention remains imperfect in many settings.

Since the advent of potent acid-suppressive medications, particularly proton pump inhibitors (PPIs), the management of NSAID-induced gastric risk has focused heavily on acid suppression and eradication of *Helicobacter pylori* [8]. PPIs effectively reduce gastric acidity, promote ulcer healing, and lower the risk of rebleeding, and their administration in combination with NSAIDs has become a standard practice for high-risk patients [9]. Nevertheless, contemporary epidemiological data indicate that a substantial proportion of NSAID-associated gastric injuries still occur among patients receiving PPI co-therapy [10]. While PPIs effectively neutralize luminal acidity, they do not address NSAID-induced mitochondrial depolarization, oxidative stress, or ATP depletion, allowing intracellular injury to persist despite adequate acid control. Persistent mucosal injury leading to the development of gastroenteropathy and clinically significant complications in the setting of PPI protection reveals that acid is an important but not an exclusive mediator of NSAID-induced damage. This gap between acid suppression and complete clinical protection elicits a deeper mechanistic inquiry beyond the classical model.

Emerging mechanistic studies have revealed that, beyond acid suppression, certain underlying intracellular and subcellular processes make the gastric epithelial cells easily susceptible to injury [11]. At the centre of this reconceptualization are mitochondria—the organelles that govern cellular energy production, redox balance, and apoptotic pathways [12]. Mitochondria play a fundamental role in maintaining epithelial integrity by supporting ATP-dependent mucosal defence mechanisms, and their dysfunction is increasingly linked to gastrointestinal diseases, including peptic ulcer disorder. NSAIDs are well known for perturbing mitochondrial function through multiple pathways: stimulation of excessive reactive oxygen species (ROS) generation, uncoupling of the electron transport chain, and inhibition of oxidative phosphorylation [13]. These mitochondrial damage result in ATP depletion, oxidative damage to lipids, proteins, and DNA, loss of mitochondrial membrane potential, opening of the mitochondrial permeability transition pore (mPTP), and release of pro-apoptotic factors such as cytochrome c [13]. Consequently, activation of intrinsic apoptosis and necrotic cell death pathways compromises epithelial integrity and disrupts mucosal barrier function,

independently of acid-induced erosion [14]. This is followed by aggravated inflammatory responses by immune cells, which respond to mitochondrial danger signals and damaged epithelial surfaces, further propagating gastric tissue injury [15]. The convergence of oxidative stress, metabolic disturbance, and programmed cell death occurs in the mitochondria, which explains the persistence of NSAID-mediated gastrotoxicity despite acid suppression.

Melatonin, the pineal hormone known for its functions in regulating circadian rhythms, has emerged as a pleiotropic cytoprotective molecule with diverse actions [16]. Melatonin is synthesized not only in the central nervous system but also locally within the gastrointestinal tract, where concentrations are considerably higher in systemic levels and exert paracrine effects on mucosal cells [17]. Melatonin also displays rhythmic secretion aligned with circadian cycles, and disruptions in circadian rhythms have been associated with impaired mucosal healing, altered gastric mobility, and increased ulcer susceptibility. Melatonin's functions include direct free-radical scavenging capability, upregulation of the activities of endogenous antioxidant enzymes, modulation of inflammatory signaling, and maintenance of mitochondrial health [18]. At the mitochondrial level, melatonin enhances the efficiency of oxidative phosphorylation, preserves membrane potential, prevents the mPTP opening, and inhibits excessive ROS production [19]. It also exerts anti-apoptotic effects by modulating the expressions of BCL-2 family proteins and inhibiting caspase activation [20]. These functions of melatonin make it an attractive candidate to counter the mitochondrial dysfunction caused by NSAIDs.

Preclinical studies have provided substantial evidence that melatonin has the ability to prevent NSAID-induced gastric lesions [21]. Various experiments have demonstrated that melatonin administration reduces mucosal erosion, preserves histological architecture, lowers the levels of oxidative markers, and prevents mitochondrial depolarization in gastric tissues exposed to NSAIDs [22]. Mechanistic data reveal that melatonin limits the accumulation of ROS, stabilizes mitochondrial respiration, prevents the opening of mPTP, and reduces apoptotic signaling within gastric mucosae [13]. Some studies also exhibit the existence of a synergy between melatonin and acid-suppressive therapies, suggesting complementary rather than redundant protective mechanisms [23]. Clinical data, although limited, seem to be promising and indicate potential symptomatic and mucosal benefits that warrant rigorous controlled trials. The synthesis of melatonin in the gut and its receptor-mediated as well as receptor-independent actions further support a physiologically relevant role in mucosal defence [24].

With an increasing clinical burden of NSAID-related gastric complications around the world, and the converging experimental evidence implicating mitochondrial dysfunction as a major mediator of mucosal injury, the integration of mitochondrial biology with melatonin's multifaceted protective actions is timely and necessary. This review will explore the evolving conceptual framework that focuses on mitochondria as the nexus of injury and protection in NSAID-mediated gastropathy, critically appraise molecular mechanisms through which NSAIDs impair mitochondrial integrity, and comprehensively evaluate how melatonin, through its antioxidant, anti-inflammatory, and protective actions, enhances mitochondrial health and interrupts the pathogenic cascade. The review will integrate preclinical mechanistic studies with available clinical data, identify lacunae in knowledge, and discuss translational opportunities for incorporating mitochondrial-targeted strategies involving melatonin into preventive and therapeutic paradigms for NSAID-induced gastric ulcers.

Given the substantial clinical burden of NSAID-induced gastric complications and the limitations of current acid-centric therapies, there is a crucial need to explore mitochondrial-targeted gastroprotective strategies. This narrative review is novel in integrating emerging mitochondrial biology with melatonin's multipotential protective actions in the context of NSAID-induced gastric injury and aims to highlight

the role of mitochondrial dysfunction as a central mechanism of NSAID-mediated gastropathy. Also, the translational perspectives and future therapeutic positioning of melatonin in preventing NSAID-induced gastric ulcers have been discussed in this review.

2 Methodology

This narrative review is based on literature retrieved from PubMed, Google Scholar and Scopus using keywords related to NSAIDs, gastric ulcers, mitochondrial dysfunction, and melatonin. Experimental and clinical studies published in English were considered and synthesized qualitatively.

3 Main Text

3.1 Risk Factors and Classical Mechanisms of NSAID-Induced Gastric Injury

The development of gastric ulcers during NSAID therapy depends on various predisposing factors related to drug exposure, host susceptibility, and comorbid conditions. Chronic NSAID administration or high-dose regimens have been the most common causes of gastric mucosal injury [2]. Advanced age further increases the vulnerability of the gastric epithelium due to diminished mucosal regenerative capacity and reduced physiological resilience [25].

Helicobacter pylori infection, along with NSAID administration, aggravates mucosal damage through additive inflammatory and oxidative actions [26]. Apart from these, lifestyle-related risk factors—such as alcohol consumption, cigarette smoking, psychological stress, and poor dietary habits further weaken the mucosal defences [27]. Varied genetic expressions of COX enzymes, prostaglandin receptors, and altered activities of drug-metabolizing enzymes also contribute to the development of NSAID-mediated gastrotoxicity [4].

Concomitant use of corticosteroids, anticoagulants, or low-dose aspirin augments the risk of gastric bleeding, while comorbid conditions such as cardiovascular disease and chronic kidney disease further increase the risks of NSAID-mediated gastric injury. Collectively, all these factors create a high-risk milieu where NSAID-induced diminution of mitochondrial health and biochemical imbalances can propagate the development of ulceration [28] (Fig. 1).

3.1.1 Classical COX-Dependent Mechanisms

Primarily, the NSAID-induced gastric injury occurs due to the inhibition of cyclooxygenase (COX) enzymes—COX-1 and COX-2—which catalyze the conversion of arachidonic acid into prostaglandins (PGs), prostacyclins, and thromboxanes [29].

Inhibition of COX-1 suppresses the production of cytoprotective prostaglandins (especially PGE_2 and PGI_2), which are involved in the regulation of mucosal blood flow, secretion of bicarbonate, and synthesis of mucus. Although the COX-2 inhibition was initially thought to be therapeutically selective, it can impair mucosal repair processes and angiogenesis during injury [29].

The inhibition of both COX enzymes weakens the gastric mucosal defence and increases susceptibility of the gastric epithelium to acid and pepsin-induced injuries. Simultaneously, the reduced levels of prostaglandins lead to diminished mucosal perfusion, compromising vital processes like oxygen delivery and nutrient exchange, while bicarbonate secretion and mucus production eventually decline [30]. This further weakens the mucosal barrier and makes way for the luminal acid to penetrate deeper into the gastric epithelial layers. Additionally, the absence of prostaglandin-mediated inhibition of parietal cells dysregulates the gastric acid secretion, which further disrupts the balance between aggressive and defensive factors [31].

While these mechanisms explain the macroscopic features of NSAID-induced ulcers, they do not fully account for the initiation of ulcer development, which occurs due to underlying early cellular events, including mitochondrial depolarization, excess generation of reactive oxygen species (ROS), and apoptosis, that precede the visible mucosal damage [32]. These findings have pointed toward the mitochondrion as a pivotal site of the damaging actions of NSAIDs, which cause gastric injury.

Collectively, NSAID-induced gastric injury follows a defined intracellular sequence beginning with mitochondrial accumulation and bioenergetic uncoupling, leading to excessive ROS generation, ATP depletion, and mitochondrial membrane destabilization. These events initiate epithelial apoptosis and release of mitochondrial danger signals that amplify inflammatory responses and compromise mucosal integrity. Melatonin intervenes at multiple nodes of this cascade by preserving mitochondrial membrane potential, suppressing ROS amplification, and inhibiting downstream inflammatory and apoptotic signaling. Thus, mitochondria serve as the convergence point for both injury initiation and cytoprotection. This mechanistic framework underpins the rationale of the present review.

3.1.2 Mitochondrial Dysfunction as a Central Event in Gastric Pathogenesis

Over the past two decades, it was understood that NSAID-induced gastric injury occurred primarily due to the inhibition of prostaglandins, but recent evidence indicates that disruption of the mitochondrial homeostasis lays the foundation for the development of gastric injuries. Mitochondria, the key regulators of cellular energy metabolism and redox homeostasis, are now identified as the primary regulators of mucosal integrity [15]. NSAIDs are known to directly target mitochondria by initiating bioenergetic failure and aggravating oxidative stress that culminate in epithelial cell death and eventual tissue breakdown [33].

NSAIDs are weak organic acids that are capable of diffusing easily across biological membranes in their non-ionized forms. On entering the cells, they accumulate within the mitochondrial matrix, where ion trapping is facilitated by the alkaline environment. Various NSAIDs (e.g., indomethacin, diclofenac, naproxen) can act as protonophores and dissipate the proton gradient across the inner mitochondrial membrane and thereby uncouple the oxidative phosphorylation [34].

This disrupts the mitochondrial membrane potential ($\Delta\Psi m$)—a critical electrochemical gradient essential for the synthesis of ATP. As oxidative phosphorylation gets impaired, cellular levels of ATP are depleted, which interferes with energy-dependent functions such as mucus secretion, ion transport, and restoration of the epithelial layer [35]. The persisting energy crisis predisposes the gastric epithelial cells towards necrosis and apoptosis, even before the initiation of ulcer formation [36].

A hallmark phenomenon of NSAID-induced mitochondrial injury is the opening of the mitochondrial permeability transition pore (mPTP), which is a nonspecific channel in the inner mitochondrial membrane [33]. It becomes permeable under conditions of calcium overload and oxidative stress [37]. NSAID exposure initiates mPTP opening, thereby leading to abrupt swelling of the matrix and ultimately rupturing the outer membrane. This causes the release of cytochrome c and pro-apoptotic factors into the cytosol, thus activating the intrinsic apoptotic pathway, which in turn, triggers the caspase-9 and caspase-3 cascades culminating in DNA fragmentation and epithelial cell death [38]. The luminal acid back-diffusion promotes loss of epithelial integrity, thereby initiating mucosal erosion and perpetual progression towards gastric ulceration [39].

Impairment of the mitochondria disrupts the electron transport chain (ETC), particularly the complexes I and III, thereby leading to electron leakage and excessive generation of ROS. Elevated levels of ROS facilitate oxidation of membrane lipids (lipid peroxidation), denaturation of mitochondrial proteins, which eventually induces mitochondrial DNA (mtDNA) damage [40]. Since mtDNA is devoid of protective histones and has

very limited repair capacity, such damage leads to permanent dysfunction of respiratory chain components, thereby triggering the cycle of ROS overproduction—a phenomenon very commonly known as the ROS amplification loop [41]. This phenomenon further aids in the declining levels of ATP, leading to metabolic insufficiency and loss of epithelial viability [36]. Experimental studies have proven that antioxidants or mitochondria-targeted agents can protect from these damaging effects, indicating the primary role of oxidative stress in NSAID-mediated toxicity [42].

Beyond biochemical disruption, NSAIDs can severely alter mitochondrial processes of fusion and fission that help to maintain mitochondrial morphology and function. In physiological conditions, mitochondrial fusion promotes the exchange of mitochondrial contents, thereby facilitating recovery from damage, while fission segregates the damaged organelles for removal through mitophagy [43]. NSAIDs disrupt the balance between fusion and fission by upregulating excessive Drp1-mediated fission and downregulating fusion proteins such as mitofusin 1 and 2 (Mfn1/2) and optic atrophy 1 (OPA1), resulting in increased numbers of fragmented and dysfunctional mitochondria [44].

This imbalance not only impairs the generation of ATP but also curbs the ability of cells to eliminate damaged mitochondria [45]. The resulting accumulation of dysfunctional organelles further mediates oxidative stress and simultaneous apoptotic signalling, thereby establishing mitochondrial dysfunction as both an initiating factor and also as a self-perpetuating amplifier of gastric mucosal injury [13].

3.1.3 Inflammatory Amplification and Mitochondrial Cross-Talk

The consequences of mitochondrial dysfunction extend way beyond energy failure, since damaged mitochondria actively contribute to amplification of inflammatory responses within the gastric mucosa. The components of mitochondria, when released during injury, act as potent signalling molecules that, in turn, activate innate immune pathways and propagate inflammation [46].

Mitochondrial injury leads to the release of damage-associated molecular patterns (DAMPs) such as mtDNA, cardiolipin, and formylated peptides into the cytoplasm or the extracellular space [47,48]. These molecules are recognized by pattern recognition receptors (PRRs), like Toll-like receptor 9 (TLR9) and the (NOD-like receptor protein-3) NLRP3 inflammasome [49].

Activation of the NLRP3 inflammasome triggers caspase-1 activation, which propagates the maturation of interleukin-1β (IL-1β) and interleukin-18 (IL-18)—potent pro-inflammatory cytokines that function in exacerbating mucosal inflammation and apoptosis of epithelial cells. These processes establish a link between mitochondrial damage and immune activation, thereby progressing tissue injury even in the absence of continued NSAID exposure [50].

NSAID-induced generation of mitochondrial ROS activates the nuclear factor kappa B (NF-κB), a key transcriptional regulator of inflammatory genes [51]. The upregulation of tumour necrosis factor-alpha (TNF-α), IL-6, and IL-8 further promotes the recruitment of neutrophils to the gastric mucosa. These activated neutrophils, in turn, release myeloperoxidase, proteolytic enzymes, and additional ROS, which, in combination, aggravate redox imbalance and epithelial damage [52].

This ROS-inflammation feedback loop provokes the inflammatory environment and delays the healing process. Persistence of inflammation compromises the protective angiogenesis and epithelial proliferation, thereby delaying mucosal recovery [53].

3.1.4 Integrative View: Mitochondria at the Core of Gastric Injury

The complex interplay between prostaglandin depletion, mitochondrial dysfunction, and aggravated inflammation contributes to the multifactorial nature of NSAID-induced gastric ulceration. While COX

inhibition impairs mucosal defence at the systemic level, mitochondrial dysfunction initiates oxidative stress, apoptosis, and inflammatory signaling, which destabilizes the cellular homeostasis [54].

The integration of these events suggests a dual mechanism of NSAID-induced gastric injury. An initial phase characterized by direct NSAID accumulation in mitochondria, ΔΨm collapse, and ROS overproduction, which is followed by mitochondrial DAMP release, cytokine upregulation, and inflammatory infiltration [54].

Ultimately, these processes seem to converge and disrupt the epithelial integrity, halt the microcirculation, and interfere with mucosal repair mechanisms. The understanding of the underlying mechanism of NSAID-mediated toxicity implies the importance of potential therapeutic targets—notably, mitochondrial antioxidants and regulators such as melatonin, which can restore the redox balance and bioenergetic stability within the gastric cells.

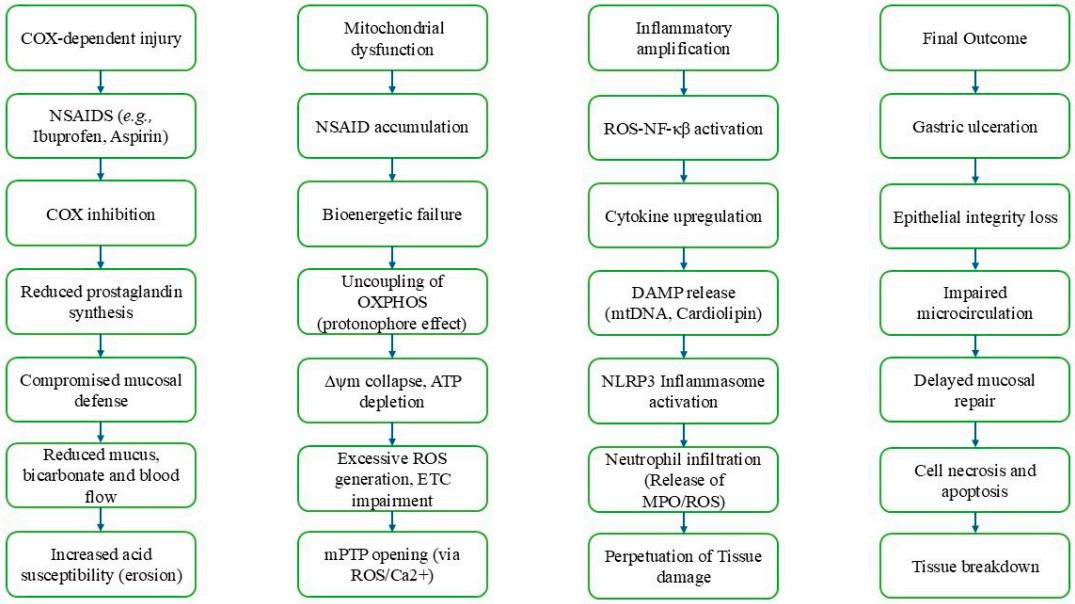

Figure 1: Systematic illustration of the intracellular mechanisms involved in the progression of gastric damage.

3.2 Melatonin: Biochemical and Mitochondrial Relevance

Melatonin (N-acetyl-5-methoxytryptamine) is a highly conserved indoleamine that has emerged as a pivotal regulator of cellular bioenergetics, intracellular redox balance, and circadian rhythm. Traditionally recognized as a neurohormone synthesized by the pineal gland, extensive investigations have unveiled its multifaceted extra-pineal functions, particularly within the gastrointestinal tract. Its potent antioxidant, anti-inflammatory, and mitochondrial-protective actions have recognized its indispensable role in counteracting oxidative tissue injury [55].

3.2.1 Circadian Regulation and Gastrointestinal Significance

The secretion of melatonin regulates the circadian rhythm accordingly, with peak plasma concentrations occurring during the night. Nocturnal surges in melatonin levels coincide with decreased gastric acid secretion and an associated enhanced mucosal blood flow, suggesting its physiological role in promoting mucosal defence during fasting periods [56]. Moreover, secretion of gastric melatonin responds dynamically to both mechanical and chemical stimuli, implying its active role in the maintenance of mucosal integrity in both basal and stress conditions [57]. The high luminal concentration of melatonin post food ingestion serves as

a first-line antioxidant barrier against certain dietary and inflammatory oxidants, thereby establishing its physiological relevance in gastric cytoprotection [58,59].

3.2.2 Nuclear and Mitochondrial Binding Sites

In addition to melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2) receptors, melatonin also interacts with non-receptor binding sites, such as MT3, also known as quinone reductase 2 (NQO2). This enzyme participates in detoxification processes and thus protects against oxidative stress [60]. Mitochondria have high-affinity binding sites for melatonin, which suggests its intrinsic regulatory role within the organelle. These binding sites allow melatonin to directly regulate the respiratory chain components, reduce the excess electron leakage, and maintain the integrity of mitochondrial membranes, functions which are crucial for the prevention of NSAID-induced mitochondrial injury [61].

3.2.3 Regulation of Mitochondrial Bioenergetics

By optimizing electron transfer within the respiratory chain, melatonin facilitates the efficiency of oxidative phosphorylation, which thereby reduces electron leakage and minimizes the formation of ROS. It has been reported that melatonin-treated mitochondria are capable of exhibiting higher respiratory control ratios with improved ATP generation, and lower proton leaks, thus reflecting an enhanced coupling efficiency [62]. This bioenergetic optimization is an essential factor in gastric epithelial cells exposed to NSAIDs, which have a disrupted oxidative phosphorylation and depleted levels of ATP, a key event in early mucosal injury [13].

3.2.4 Stabilization of Mitochondrial Membrane Potential and Prevention of mPTP Opening

The collapse of the mitochondrial membrane potential ($\Delta\Psi m$) and the subsequent opening of the mitochondrial permeability transition pore (mPTP) mark the initiation of mitochondrial dysfunction. Melatonin has the ability to stabilize $\Delta\Psi m$, which prevents the loss of ionic homeostasis and the release of pro-apoptotic factors such as cytochrome c [63]. Melatonin maintains membrane integrity and inhibits the onset of apoptosis through its interaction with cardiolipin and regulation of the mitochondrial calcium influx. These functions directly counteract the toxic effects of NSAIDs on gastric mitochondria, which promote mPTP opening and cell death in gastric epithelial tissues [64].

3.2.5 Regulation of Mitochondrial Dynamics and Biogenesis

The morphology and functions of mitochondria are governed by the balance between fission and fusion processes, along with the selective removal of damaged mitochondria by means of mitophagy. Melatonin actively contributes to the maintenance of this dynamic equilibrium. It inhibits the excessive mitochondrial fission by downregulating the expression of dynamin-related protein 1 (Drp1) and promotes fusion through the upregulation of mitofusins (Mfn1/2) and optic atrophy protein 1 (Opa1). Additionally, melatonin initiates mitochondrial biogenesis by activating the Sirtuin 1 (SIRT1)–peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) signalling axis [65]. This particular pathway enhances the transcription of nuclear and mitochondrial genes involved in redox metabolism and antioxidant defence, thus replenishing the functionality of mitochondria and sustaining the cellular viability under stress conditions.

3.2.6 Promotion of Mitophagy and Quality Control

Under conditions of oxidative stress or drug-induced oxidative injury, damaged mitochondria can induce cellular dysfunction if not efficiently eliminated. Melatonin primarily regulates the PTEN-induced

kinase 1 (PINK1)/Parkin pathway, which facilitates the clearance of defective mitochondria by promoting mitophagy [66,67]. The selective autophagic removal of compromised organelles prevents the accumulation of dysfunctional mitochondria and the consequent release of pro-inflammatory mitochondrial damage-associated molecular patterns (mtDAMPs). Thus, melatonin not only preserves mitochondrial integrity but also prevents the secondary inflammatory amplification induced by NSAID-induced gastric injury [68].

3.3 Gastroprotective Mechanisms of Melatonin in NSAID-Induced Ulceration

The pathogenesis of NSAID-induced gastric ulceration is multifaceted, including inflammation, oxidative stress, mitochondrial dysfunction, and impaired tissue repair mechanisms. In this complex scenario, melatonin actively functions as a potent gastroprotective molecule by regulating multiple pathways that mediate cellular survival and mucosal defence. Melatonin counteracts the deleterious consequences of NSAID exposure through its antioxidant, anti-inflammatory, and regenerative effects, and restores gastric homeostasis by maintaining mitochondrial stability [58,69]. The following subsections outline the principal mechanisms involved in the gastroprotective functions of melatonin.

Melatonin exerts gastroprotection by intervening at four critical mechanistic levels: (i) preservation of mitochondrial membrane potential, (ii) suppression of ROS amplification, (iii) inhibition of mitochondrial-driven apoptosis, and (iv) attenuation of inflammation secondary to mitochondrial DAMP release.

3.3.1 Mitochondrial Protection and Bioenergetic Restoration

Experimental studies have demonstrated that melatonin prevents NSAID-induced depolarization of the mitochondrial membrane, which perturbs the disruption of the $\Delta\Psi m$ and ionic homeostasis. The stabilization of the inner mitochondrial membrane by melatonin ensures the inhibition of the opening of mPTP. Consequently, the leakage of pro-apoptotic factors such as cytochrome *c* and apoptosis-inducing factor (AIF) into the cytoplasm is also prevented. This inhibition cascade further curtails the downstream activation of caspase-9 and caspase-3, thereby halting apoptotic cell death in the gastric epithelium [70].

Additionally, melatonin preserves the synthesis of ATP by facilitating the efficiency of the electron transport chain and hence, reducing the electron leakage. The eventual restoration of bioenergetic functions of the mitochondria ensures adequate energy availability for cellular repair and defence processes. Maintaining the ATP levels is particularly important in the gastric mucosa, since energy demand is high due to the ongoing secretion and regeneration processes [62].

Melatonin also mitigates the NSAID-induced damage in mitochondrial morphology and dynamics. It balances the mitochondrial fission and fusion processes, and promotes the retention of normal elongated mitochondrial networks that mediate oxidative metabolism and resist the apoptotic stimuli. The restoration of structural integrity reinforces mitochondrial resilience and prevents the progression of cellular injury. The integrated actions of melatonin preserve the mitochondrial energy supply and inhibit bioenergetic collapse, in turn, sustaining the integrity of gastric epithelial integrity during NSAID-mediated oxidative stress [71].

3.3.2 Anti-Inflammatory and Cytoprotective Pathways

Although inflammation is a secondary process, it has a crucial role in amplifying the NSAID-induced gastric mucosal injury. The generation of ROS in the mitochondria by NSAIDs activates the redox-sensitive transcription factors, such as nuclear factor kappa B (NF-κB), which in turn, upregulate the expression of pro-inflammatory cytokines and enzymes, including tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, and cyclooxygenase-2 (COX-2). This inflammatory milieu further compromises the mucosal defence system and perpetuates tissue damage [72].

The exceptional capability of melatonin as a strong anti-inflammatory agent helps to modulate the key signalling pathways. It suppresses the activation and nuclear translocation of NF-κB, which in turn, downregulates the transcription of cytokines and other inflammatory enzymes. Among them, the inhibition of COX-2 expression attenuates the prostaglandin-dependent inflammation, thereby reducing oedema and infiltration of neutrophils in the gastric mucosa [73].

Further, melatonin modulates the metabolism of nitric oxide (NO) by influencing the various isoforms of nitric oxide synthase (NOS). It can selectively downregulate iNOS, which produces excessive NO and significantly contributes to nitrosative stress, while simultaneously upregulating the endothelial NOS (eNOS), which generates physiological levels of NO that support mucosal blood flow and repair. This dual regulation of NO production preserves microcirculatory function and thus reduces oxidative burden [74,75].

A hallmark of NSAID-induced gastric injury is neutrophil infiltration, which causes enhanced myeloperoxidase (MPO) activity and further aggravates ROS production. Melatonin reduces the accumulation of neutrophils and subsequently inhibits the increase in MPO activity, thereby effectively limiting the oxidative and enzymatic injuries inflicted on the mucosal tissues [76,77]. Interruption of this endless cycle of inflammation and oxidative stress orchestrated by melatonin seemingly establishes a cytoprotective environment conducive to mucosal recovery.

3.3.3 Pro-Survival Signaling and Tissue Regeneration

One of the primary mechanisms of gastric mucosal healing involves the stimulation of phosphatidylinositol 3-kinase (PI3K)/Akt and extracellular signal-regulated kinase (ERK1/2) pathways [78]. These kinases critically regulate the processes of cell survival, proliferation, and differentiation. Melatonin activates the PI3K/Akt axis, which enhances the expression of anti-apoptotic proteins such as Bcl-2 and simultaneously suppresses the pro-apoptotic mediators like Bax, thereby shifting the cellular balance towards survival [79]. Concurrently, ERK1/2 signalling promotes the proliferation of gastric epithelial cells, which facilitates the replacement of damaged mucosal layers [80].

Melatonin also upregulates the expression of growth factors essential for mucosal healing, which include vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) [81,82]. VEGF-mediated angiogenesis is an essential process because it restores microvascular perfusion and oxygen delivery to the injured mucosa, while EGF propagates epithelial migration and restitution [83]. Both these processes accelerate tissue regeneration and re-epithelialization of ulcerated areas. Moreover, melatonin influences the expression of matrix metalloproteinases (MMPs) and subsequently their tissue inhibitors, thereby maintaining a balance in extracellular matrix remodelling during healing [69]. The combined effects of melatonin on cell survival, proliferation, angiogenesis, and matrix reorganization seemingly create an optimal environment for functional tissue regeneration and facilitate mucosal protection.

3.4 Therapeutic Implications

The growing understanding of melatonin's role in gastric mucosal defence unfurls promising avenues for its translation from experimental pharmacology into clinical therapeutics. Thus, melatonin emerges as a compelling candidate for adjunct therapy in patients requiring long-term NSAID administration because of its pleiotropic actions and extensive safe profile.

3.4.1 Melatonin as an Adjunct Therapy in Chronic NSAID Users

Chronic use of NSAIDs is one of the primary causes of gastric and duodenal ulceration, especially in elderly or comorbid populations [84]. In spite of prophylactic PPI therapy, residual mucosal injury

persists due to uncontrolled aggravation of oxidative stress. Incorporation of melatonin as an adjunct gastroprotective agent could bridge this therapeutic gap. Its multifaceted role in maintaining mitochondrial health, restoration of the intracellular redox equilibrium, and suppression of inflammatory cascades complements the actions of conventional acid-suppressive medications. Clinical studies have already demonstrated that melatonin is extremely efficacious in enhancing the healing process of ulcers [85]. It also reduces the levels of oxidative stress biomarkers when administered alongside standard anti-ulcer medications [86,87]. This synergistic approach may not only lessen the ulcer recurrence rates but also reduce the required doses of PPIs or prostaglandin analogues, which can minimize their adverse effects.

3.4.2 Formulation and Delivery Strategies

Although orally administered melatonin exhibits excellent bioavailability and mucosal absorption, its short half-life and first-pass metabolism could limit the sustenance of its therapeutic efficacy [88]. To overcome these challenges, various advancements in formulation strategies have been explored. Enteric-coated and sustained-release formulations ensure prolonged plasma levels of melatonin, leading to steady delivery into the gastric mucosa throughout NSAID dosing intervals [89]. Additionally, nanocarrier-based delivery systems—including liposomes, solid lipid nanoparticles, and polymeric nanospheres—can enable targeted delivery to mitochondria-rich gastric epithelial cells. These nanoformulations can further enhance the intracellular retention, protect melatonin from premature degradation, and optimize its antioxidant potential at the site of injury [90]. In the future, the development of mitochondria-targeted melatonin analogs, designed with lipophilic cations such as triphenylphosphonium (TPP^+), could further improve their accumulation and efficacy. Such precision delivery systems could essentially transform melatonin from a general antioxidant into a next-generation mitochondrial pharmacotherapeutic molecule [61].

3.4.3 Drug–Drug Interactions and Dosing Considerations

The safety profile of melatonin is well established; however, its co-administration with other medications warrants careful consideration. While a number of studies indicate a minimal interaction potential, melatonin can modulate the activities of cytochrome P450 1A2 (CYP1A2) and cytochrome P450 1A2 (CYP2C19), possibly affecting the pharmacokinetics of certain NSAIDs or PPIs [91].

The optimization of the dose of melatonin persists as an essential translational challenge. The experimental models often use supraphysiological concentrations, while human studies employ doses ranging from 3 to 10 mg/day for gastroprotective outcomes [92]. Establishing a standardized therapeutic regime through dose–response and pharmacodynamic studies will prove to be critical for clinical adoption. Furthermore, entraining dosing schedules to circadian rhythms could maximize therapeutic benefit while maintaining physiological alignment.

3.5 Translational Outlook: From Bench to Bedside

The translational trajectory of the therapeutic potential of melatonin in NSAID-induced gastric injury mirrors the broader evolution of mitochondria-focused medicine. A detailed overview of the different gastroprotective agents have been highlighted in Table 1. Preclinical findings have consistently demonstrated its essential role in preventing oxidative injury, along with preservation of mitochondrial function, and acceleration of the mucosal repair [42,93]. The next step involves a rigorous clinical validation through randomized controlled trials that assess the prevention of ulcers, their healing rates, and quality-of-life outcomes in chronic NSAID users. Integration of melatonin into clinical protocols could represent a cost-effective and physiologically compatible intervention, particularly in populations at high risk for

gastrointestinal complications. Moreover, its broad-spectrum antioxidant and anti-inflammatory effects may extend its therapeutic potential to certain pathologies like stress ulcers, ischemia-reperfusion injury, and H. pylori-associated gastritis [94,95].

Table 1: Comparative evaluation of melatonin vs. conventional gastroprotective agents.

Characteristic	Melatonin	Proton Pump Inhibitors (PPIS)	H2 Blockers	Antacids	Sucralfate
Efficacy	*Melatonin:* Modest efficacy. Some small trials suggest melatonin can improve GERD symptoms (heartburn, epigastric pain) and may aid ulcer healing [96,97].	*PPIs:* Very high efficacy. These are the most potent acid-suppressors available, first-line for GERD/ulcer healing. PPIs achieve superior ulcer healing and symptom relief compared to H2Ras [98,99].	*H2 Blockers:* Moderate efficacy. Effective for GERD and duodenal ulcers, but weaker acid suppression than PPIs. (e.g., cimetidine's effect on duodenal ulcers is similar to sucralfate.) Generally used for milder symptoms [100].	*Antacids:* Low/modest efficacy. They neutralize acid quickly for short-term relief of heartburn, but do not promote healing. Historically first-line for PUD relief, now restricted to mild intermittent GERD symptom relief [101,102].	*Sucralfate:* Moderate efficacy. Acts by coating/protecting the mucosa, not by acid suppression. Effective in ulcer healing (duodenal ulcers) comparably to H2 blockers, but does not reduce acid production [103, 104].
Side Effects	Generally, very well tolerated. Common mild effects include headache, dizziness, nausea and daytime drowsiness. No serious systemic effects at typical doses [105].	Common: gastrointestinal upset (nausea, constipation or diarrhea), headache, dizziness. Long-term PPI use has been linked to vitamin B12, magnesium and calcium malabsorption (osteoporosis risk). Rarely, rebound acid hypersecretion on withdrawal [106].	Generally mild. Rare side effects include headache or diarrhea. Cimetidine (an older H2RA) can rarely cause confusion or hormonal effects; famotidine has fewer CNS effects. Tolerance (tachyphylaxis) can develop with prolonged use [107].	Common GI side effects: constipation (with aluminum-containing), diarrhea (with magnesium-containing), flatulence. Heavy use can cause acid rebound (stomach produces more acid) and electrolyte imbalances (e.g., altered calcium/phosphate). Generally low systemic toxicity [108].	Very few systemic effects. The main side effect is constipation. Sucralfate is minimally absorbed, so systemic toxicity is rare. (Aluminum load can accumulate in renal failure) [109].
Patient Tolerance	**High.** Most patients tolerate it well. The mild sedative effect can be beneficial (especially if taken at bedtime) and is not usually problematic. No tolerance or dependency issues [110].	**High (short-term).** Generally well tolerated for acute therapy; easy once-daily dosing. However, some patients are concerned about long-term risks (rebound acidity, nutrient absorption, fracture), which may affect adherence [111].	**High.** Well tolerated; H2 blockers have been used long-term in many patients. Not habit-forming. However, their efficacy may wane over time (tachyphylaxis) [112].	**Good (for occasional use).** Safe and easy to take as needed, but requires frequent dosing for persistent symptoms. The chalky taste/texture and necessity of taking with every symptom can reduce adherence if overused [108].	**Moderate.** Very safe, but multiple-daily dosing (typically 4 times/day on an empty stomach) is inconvenient. Some patients find the regimen burdensome, which can limit long-term adherence [109].

3.6 Future Prospects for Mitochondrial-Targeted Melatonin Analogues

The emerging field of mitochondrial-targeted pharmacology has led to the development of synthetic melatonin analogues with enhanced lipophilicity, receptor affinity, and accumulation in the mitochondria. The structural modification of melatonin's indole moiety and its side chains may yield derivatives with superior stability and organelle specificity, offering improved gastroprotective potency. Combining melatonin's antioxidant scaffold with mitochondria-targeting moieties (e.g., TPP^+ conjugation or peptide-based carriers) could yield newer and developed compounds capable of precise subcellular localization. These innovations can be immensely potent to redefine gastroprotective therapy by directly addressing the subcellular nexus of NSAID-induced injuries [90,113].

NSAIDs also change the gut microbiome, including decreasing the gut microbiome-derived short-chain fatty acid, butyrate [114]. As a histone deacetylase inhibitor (HDACi), butyrate significantly regulates many systemic processes, including regulating mitochondrial function [115], with implications for the wider systemic changes associated with NSAIDs' induction of gastric ulcers [4]. Butyrate also increases the mitochondrial melatonergic pathway in intestinal epithelial cells, indicating that the NSAIDs' suppression of butyrate will impact on local melatonin production. Both melatonin and butyrate increase mitochondrial sirtuin-3 [116], thereby decreasing oxidant production by the electron transport chain and increasing mitochondrial ATP production by disinhibiting the pyruvate dehydrogenase complex. Melatonin and butyrate may therefore optimize mitochondrial function via sirtuin-3, which is inhibited by NSAIDs [117]. The regulation of local melatonin, butyrate and sirtuin-3, especially in intestinal epithelial cells, provides significant clinical treatment targets in NSAID-induced gastric ulcers and requires future investigation.

However, this review is narrative in nature and does not employ a systematic search or quantitative synthesis, which may introduce selection bias. Much of the mechanistic evidence discussed is derived from preclinical studies, limiting direct clinical extrapolation. Additionally, human data on melatonin as an adjunct therapy for NSAID-induced gastric injury remain limited and heterogeneous.

4 Comprehensive Mechanistic Summary

NSAID-induced gastric ulceration represents a multifactorial and mitochondria-centered disease process in which prostaglandin depletion, mitochondrial dysfunction, oxidative stress, inflammation, and impaired tissue repair operate in a tightly interconnected manner. Following systemic or luminal exposure, NSAIDs—owing to their weak acidic nature—accumulate preferentially within gastric epithelial mitochondria through ion trapping, where they function as protonophores and uncouplers of oxidative phosphorylation. This leads to dissipation of the mitochondrial membrane potential ($\Delta\Psi m$), impaired electron transport chain efficiency, and profound depletion of ATP, thereby compromising energy-dependent mucosal defense mechanisms such as mucus secretion, epithelial restitution, ion transport, and maintenance of tight junction integrity. Simultaneously, electron leakage from dysfunctional respiratory complexes I and III results in excessive generation of reactive oxygen species, initiating lipid peroxidation, protein oxidation, and mitochondrial DNA damage, which further amplifies mitochondrial dysfunction through a self-perpetuating ROS amplification loop.

The sustained oxidative and metabolic stress promotes opening of the mitochondrial permeability transition pore, mitochondrial swelling, and rupture of the outer mitochondrial membrane, facilitating cytosolic release of cytochrome c and other pro-apoptotic factors that activate the intrinsic caspase-dependent apoptotic cascade. In parallel, NSAIDs disrupt mitochondrial dynamics by favoring excessive fission over fusion and impair mitophagy, leading to accumulation of fragmented, dysfunctional mitochondria that exacerbate bioenergetic failure and apoptotic susceptibility. Beyond epithelial cell death, injured mitochondria act as active

inflammatory signaling hubs by releasing mitochondrial damage-associated molecular patterns, including mtDNA and cardiolipin, which activate pattern-recognition receptors, inflammasomes, and redox-sensitive transcription factors such as NF-κB. This signaling culminates in the upregulation of pro-inflammatory cytokines, enhanced neutrophil infiltration, myeloperoxidase-mediated oxidative injury, microcirculatory dysfunction, and delayed mucosal repair, thereby sustaining ulcer progression even in the presence of adequate acid suppression [54].

Melatonin intervenes in this pathogenic cascade at multiple hierarchical levels and restores gastric homeostasis by directly targeting mitochondrial dysfunction. By localizing within mitochondria, melatonin stabilizes ΔΨm, preserves oxidative phosphorylation efficiency, suppresses ROS overproduction, and prevents mPTP opening, thereby maintaining ATP availability and inhibiting apoptosis. Concurrently, melatonin regulates mitochondrial dynamics and quality control by suppressing excessive fission, promoting fusion and biogenesis, and activating mitophagy pathways that eliminate damaged organelles. Its potent antioxidant and anti-inflammatory actions further attenuate NF-κB activation, cytokine release, neutrophil recruitment, and nitrosative stress, while its pro-survival signaling enhances angiogenesis, epithelial proliferation, and extracellular matrix remodeling. Collectively, these integrated actions establish mitochondria as the central nexus linking NSAID-induced injury to melatonin-mediated cytoprotection, redefining NSAID-associated gastric ulceration as a mitochondria-driven disorder and providing a strong mechanistic rationale for mitochondrial-targeted melatonin-based gastroprotective strategies [58,69].

5 Conclusion

Mitochondria occupy a central seat in the pathophysiology of NSAID-induced gastric injury, acting as both the site of origin and amplification of oxidative stress, apoptotic signaling, and eventual bioenergetic dysfunction. Thus, melatonin emerges as a dual-action cytoprotective molecule, capable of safeguarding mitochondrial integrity while simultaneously exerting potent antioxidant and anti-inflammatory effects. The intrinsic safety, circadian alignment, and multimodal mechanism of the molecule collectively reinforce the therapeutic paradigm of targeting mitochondrial homeostasis for a durable gastric mucosal defence system. The transition of melatonin from an experimental molecule into a clinically viable gastroprotective agent appears to be increasingly attainable. Although melatonin shows promise as a gastroprotective agent, its role should be interpreted with caution, and claims of universal efficacy should be avoided. Hence, future clinical trials are essential to establish its efficacy as both a prophylactic adjunct and a therapeutic agent in NSAID-induced ulceration. Melatonin further serves as a model compound in the burgeoning field of mitochondrial pharmacology, implying that preservation of mitochondrial health is a cornerstone of modern cytoprotection. This mechanistic synthesis shifts NSAID-induced gastropathy from an acid-centric disorder to a mitochondria-driven disease process with direct therapeutic implications.

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