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Abstract

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) remain a cornerstone in the management of pain and inflammation, yet their use is frequently complicated by gastrointestinal mucosal injury and ulceration. Indomethacin, a potent non-selective NSAID, is well known to cause gastric mucosal damage through inhibition of prostaglandin synthesis, increased oxidative stress, mitochondrial dysfunction, and microcirculatory impairment. Despite the availability of gastroprotective strategies such as proton pump inhibitors and prostaglandin analogues, the healing of NSAID-induced ulcers remains a significant clinical challenge, particularly in the context of comorbid conditions like diabetes mellitus, where delayed tissue repair and oxidative imbalance are common.

Dapagliflozin, a selective sodium-glucose co-transporter 2 (SGLT2) inhibitor, has emerged as an agent with potential benefits beyond glycemic control. Its pleiotropic actions include attenuation of oxidative stress, suppression of pro-inflammatory cytokines, modulation of endothelial nitric oxide pathways, and activation of cellular defense mechanisms such as Nrf2 signaling. Recent preclinical studies have demonstrated dapagliflozin's ability to improve tissue perfusion, reduce inflammatory signaling cascades, and promote angiogenesis and epithelial regeneration—mechanisms that are central to ulcer repair.

This review aims to critically evaluate the potential role of dapagliflozin in the healing of indomethacin-induced gastric ulcers, integrating pharmacological insights, mechanistic data, and evidence from preclinical and translational studies. By exploring its effects on key molecular pathways, including EGFR/ERK/MAPK, E-cadherin, TFF2, and cyclin D1, we propose a comprehensive framework through which dapagliflozin may facilitate mucosal restitution and reduce the severity of NSAID-induced gastric injury. Furthermore, we discuss the experimental evidence, possible drug–drug interactions, and translational considerations necessary for future clinical application.

In conclusion, dapagliflozin holds promise as a novel adjunctive therapeutic agent in the management and healing of NSAID-induced gastric ulcers. Its multifaceted actions targeting oxidative stress, inflammation, angiogenesis, and epithelial repair may represent a paradigm shift in ulcer pharmacotherapy, warranting further mechanistic exploration and controlled experimental validation in indomethacin-induced gastric ulcer models.

Keywords: *SGLT2, Dapagliflozin , Indomethacin-Induced Gastric Ulcers*

Introduction

Peptic ulcer disease (PUD) continues to be a major global health problem, particularly in patients exposed to nonsteroidal anti-inflammatory drugs (NSAIDs). With *Helicobacter pylori* infection declining, NSAID use has become a leading cause of gastric and duodenal ulcers. Indomethacin, a potent non-selective cyclooxygenase (COX) inhibitor, is commonly employed in experimental ulcer models because it reliably reproduces the gastric mucosal injury seen clinically. The mechanisms underlying such injury extend beyond prostaglandin depletion to include oxidative stress, mitochondrial dysfunction, neutrophil activation, and microcirculatory impairment, which collectively hinder mucosal repair and epithelial regeneration [1].

Despite advances in acid suppression and mucosal protection, the management of NSAID-induced ulcers remains challenging, especially when NSAID therapy must continue. Standard treatments such as proton pump inhibitors and prostaglandin analogues often fail to completely restore mucosal integrity, particularly in patients with comorbid diabetes mellitus, where delayed healing and impaired angiogenesis are common [2]. These challenges highlight the ongoing need for novel agents capable of promoting active mucosal repair in addition to suppressing acid and inflammation.

Dapagliflozin, a selective sodium-glucose co-transporter 2 (SGLT2) inhibitor, has been widely used for the management of type 2 diabetes mellitus, heart failure, and chronic kidney disease. Interestingly, emerging data suggest that SGLT2 inhibitors possess anti-inflammatory, antioxidant, and endothelial-protective properties independent of glycemic control. By modulating pathways such as nuclear factor erythroid 2–related factor 2 (Nrf2) and suppressing NLRP3 inflammasome activation, dapagliflozin may mitigate oxidative injury and enhance tissue perfusion and repair [3]. These pleiotropic effects propose a novel therapeutic rationale for dapagliflozin as a gastro-restorative agent.

This review aims to explore the potential role of dapagliflozin in healing indomethacin-induced gastric ulcers. It will discuss the underlying pathophysiology of NSAID-induced gastric injury, the pharmacological properties of dapagliflozin, and the mechanistic intersections—such as EGFR/ERK/MAPK, E-cadherin, TFF2, and cyclin D1 signaling—that may mediate mucosal restitution. Furthermore, it seeks to identify the experimental and translational evidence supporting this approach and define future directions for clinical pharmacology research on SGLT2 inhibition in gastric ulcer healing [4].

Peptic Ulcer: Epidemiology and Etiology

Peptic ulcer disease (PUD) remains a globally significant gastrointestinal disorder, affecting nearly 5–10% of individuals during their lifetime. Although *Helicobacter pylori* infection was historically the predominant cause, the epidemiological profile has shifted in recent decades toward nonsteroidal anti-inflammatory drug (NSAID)–induced ulcers. Chronic use of NSAIDs now accounts for a substantial proportion of peptic ulcer–related hospitalizations and upper gastrointestinal bleeding, particularly among elderly patients and those requiring long-term analgesic or antiplatelet therapy [5].

Indomethacin, a potent non-selective cyclooxygenase (COX) inhibitor, is known for its ulcerogenic potential and is widely used experimentally to model NSAID-induced mucosal injury. The underlying mechanism is multifactorial: inhibition of COX-1 and COX-2 reduces cytoprotective prostaglandins (PGE_2, PGI_2), leading to impaired mucus and bicarbonate secretion, reduced mucosal blood flow, and delayed epithelial restitution. In addition, NSAIDs cause direct epithelial damage via ion trapping and increase mitochondrial oxidative stress, neutrophil adherence, and microvascular dysfunction, all of which amplify mucosal injury [1,6].

Risk factors for NSAID-induced ulceration include advanced age, prior ulcer disease, concomitant corticosteroid or anticoagulant therapy, alcohol use, and smoking. Importantly, diabetes mellitus has emerged as a key comorbidity that exacerbates ulcer pathophysiology through delayed healing, impaired angiogenesis, and chronic oxidative stress. Hyperglycemia-induced formation of advanced glycation

end products (AGEs) and sustained inflammation collectively hinder mucosal recovery, explaining why ulcer healing in diabetic patients remains incomplete despite adequate acid suppression [2,7].

Beyond *H. pylori* and NSAID exposure, an increasing number of idiopathic ulcers have been reported, particularly in older adults without evident risk factors. These cases may involve vascular insufficiency, oxidative imbalance, and impaired mucosal repair, suggesting that systemic metabolic and inflammatory factors play an expanding role in ulcerogenesis. Understanding this evolving pathophysiological context highlights the need for novel pharmacological approaches that go beyond acid suppression to enhance cytoprotection and regeneration. In this regard, dapagliflozin—by virtue of its antioxidant, anti-inflammatory, and endothelial-modulating effects—may represent a promising adjunct in ulcer prevention and healing [3,4,8].

Pathogenesis of NSAID (Indomethacin)–Induced Mucosal Injury

The pathogenesis of NSAID-induced gastric injury involves a complex interplay between biochemical inhibition of prostaglandin synthesis and secondary mechanisms related to oxidative stress, mitochondrial dysfunction, and vascular compromise. Indomethacin, as a potent non-selective inhibitor of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), suppresses the synthesis of cytoprotective prostaglandins such as prostaglandin E_2 (PGE$_2$) and prostacyclin (PGI$_2$), which are vital for maintaining gastric mucosal integrity. The resultant decrease in mucus and bicarbonate secretion, mucosal blood flow, and epithelial regeneration forms the foundation of the ulcerogenic process [1,6].

However, prostaglandin depletion alone does not fully explain the depth and persistence of indomethacin-induced injury. The drug's acidic nature allows ion trapping within epithelial cells, where it induces mitochondrial uncoupling and promotes excessive generation of reactive oxygen species (ROS). This oxidative stress damages lipid membranes, proteins, and mitochondrial DNA, leading to cell apoptosis and necrosis. In parallel, the upregulation of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) amplifies tissue inflammation and neutrophil recruitment, worsening mucosal disruption [7,9].

Indomethacin also impairs the gastric microcirculation—a critical determinant of mucosal defense. By reducing endothelial nitric oxide synthase (eNOS) activity and disrupting vascular tone, it decreases blood flow to the mucosal surface, promoting ischemia and hypoxia. These microcirculatory disturbances not only enhance tissue injury but also delay healing by limiting nutrient and oxygen delivery to regenerating epithelial cells [6]. Additionally, decreased expression of growth factors such as epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) further compromises restitution and angiogenesis within the ulcer bed [4].

Another key aspect of NSAID-induced mucosal pathology is mitochondrial dysfunction, which impairs energy metabolism and accelerates oxidative injury. Mitochondrial permeability transition and ATP depletion trigger epithelial barrier disruption and cell death. The combination of direct cellular toxicity, oxidative imbalance, and vascular impairment establishes a self-perpetuating cycle of damage that extends beyond the initial chemical insult. Moreover, in diabetic models, the presence of hyperglycemia intensifies ROS production and inflammatory signaling, producing deeper and more persistent ulcers [2,7].

Thus, the pathophysiological mechanisms of indomethacin-induced gastric injury encompass both prostaglandin-dependent and -independent pathways. These include oxidative stress, microvascular dysfunction, inflammatory mediator release, and impaired epithelial restitution. This multifaceted cascade provides several pharmacological targets for novel therapeutic strategies—particularly agents that can modulate oxidative and inflammatory pathways, enhance angiogenesis, and improve mucosal defense. Dapagliflozin, through its reported antioxidant and anti-inflammatory properties, aligns mechanistically with these protective requirements and thus warrants investigation in this context [3,8,9].

Gastric Mucosal Defense and Healing Biology

The gastric mucosa possesses a sophisticated defense system designed to protect against the constant assault of luminal acid, digestive enzymes, and exogenous agents such as NSAIDs. This defense

operates through three coordinated levels: pre-epithelial, epithelial, and subepithelial mechanisms. The pre-epithelial barrier comprises mucus and bicarbonate secretions that form a pH gradient, preventing acid back-diffusion. The epithelial layer provides rapid restitution after injury through cell migration, proliferation, and tight junction integrity, while the subepithelial microcirculation ensures continuous nutrient and oxygen delivery necessary for mucosal metabolism and repair [1,4,6].

Prostaglandins play a central role in maintaining mucosal homeostasis by promoting mucus and bicarbonate secretion, stimulating mucosal blood flow, and supporting epithelial regeneration. NSAID-induced inhibition of prostaglandin synthesis thus disrupts all three levels of defense. Moreover, nitric oxide (NO) generated via endothelial nitric oxide synthase (eNOS) and sensory neuropeptides such as calcitonin gene-related peptide (CGRP) are crucial for vasodilation and mucosal perfusion. Impaired NO signaling, a recognized effect of indomethacin, leads to local ischemia and delayed healing [6].

The healing process following gastric injury involves several overlapping biological events, including epithelial restitution, angiogenesis, extracellular matrix remodeling, and reestablishment of mucosal architecture. Growth factors such as epidermal growth factor (EGF), transforming growth factor-α (TGF-α), and vascular endothelial growth factor (VEGF) orchestrate this response by activating downstream signaling pathways such as ERK/MAPK and PI3K/Akt. These pathways promote cell migration, proliferation, and new capillary formation, which collectively restore mucosal integrity [4,9]. Epithelial restitution is a rapid process in which viable epithelial cells adjacent to the damaged area flatten and migrate to cover denuded surfaces. This event precedes cell proliferation and depends on cytoskeletal reorganization, integrin activation, and matrix metalloproteinase regulation. Subsequently, growth factor–driven proliferation ensures long-term mucosal regeneration. Key molecules like E-cadherin, which maintains epithelial cohesion and polarity, and trefoil factor family peptides (notably TFF2), which stabilize the mucus layer and enhance restitution, are critical components of this process [4].

The microvasculature also plays an indispensable role in healing through angiogenesis and restoration of mucosal blood flow. Capillary sprouting is stimulated by hypoxia-induced VEGF expression and modulated by NO and prostaglandins. Impaired angiogenic signaling leads to delayed ulcer closure and fragile mucosal repair, often seen in chronic NSAID exposure and diabetic states [2,7]. Agents that enhance NO bioavailability, suppress oxidative stress, and promote endothelial regeneration—such as dapagliflozin through its antioxidant and endothelial-stabilizing actions—may therefore contribute to improving mucosal healing beyond conventional acid suppression [3,8,9].

Key Repair Signaling Axes

The repair of gastric mucosal injury is orchestrated by a network of cellular signaling pathways that regulate epithelial restitution, angiogenesis, and tissue remodeling. Among these, the epidermal growth factor receptor (EGFR) and its downstream ERK/MAPK cascade play a central role. Activation of EGFR by ligands such as EGF and transforming growth factor-α (TGF-α) triggers phosphorylation of ERK1/2, leading to increased expression of proliferative and anti-apoptotic genes that accelerate epithelial regeneration and ulcer healing [10]. This pathway also stimulates the synthesis of cyclin D1, a key regulator of the G1-to-S phase transition in cell proliferation, thereby promoting mucosal re-epithelialization.

In parallel, the COX-2/PGE$_2$ signaling axis contributes significantly to mucosal restitution by inducing angiogenesis and maintaining mucosal perfusion. Prostaglandins not only modulate local blood flow but also activate EP receptors on epithelial and endothelial cells, promoting migration and proliferation. Upregulation of COX-2 during the healing phase of ulcers has been documented as a compensatory response that facilitates tissue repair. This adaptive COX-2 induction is blunted in the presence of sustained NSAID exposure, resulting in impaired mucosal healing [1,6,11].

Trefoil factor peptides, particularly TFF2, are another essential component of the mucosal repair system. These small peptides, secreted by gastric mucous neck cells, stabilize the mucus layer and enhance epithelial migration over denuded surfaces. TFF2 also interacts with EGFR signaling, amplifying the ERK/MAPK pathway to support restitution. Experimental suppression of TFF2 expression has been

associated with delayed ulcer healing and reduced epithelial integrity, highlighting its importance as a mucosal protector and repair mediator [4,12].

E-cadherin, a calcium-dependent adhesion molecule, maintains epithelial cell polarity and barrier integrity. Its expression is often reduced during mucosal injury but restored during the healing phase. The re-establishment of E-cadherin-mediated junctions is essential for sealing the regenerated mucosa. Similarly, the cyclin D1/CDK4/6 complex regulates epithelial cell cycle progression, ensuring adequate proliferation during mucosal restitution. Dysregulation of this pathway contributes to impaired ulcer healing in oxidative or inflammatory conditions such as diabetes and chronic NSAID exposure [2,4,7,12].

The interplay among these signaling axes—EGFR/ERK/MAPK, COX-2/PGE$_2$, TFF2, E-cadherin, and cyclin D1/CDK—constitutes the molecular foundation of gastric mucosal healing. Pharmacological modulation of these pathways presents a therapeutic opportunity. Dapagliflozin, through its antioxidant and anti-inflammatory actions, may indirectly enhance these reparative cascades by improving endothelial function, restoring nitric oxide availability, and reducing oxidative burden. Collectively, these effects suggest that SGLT2 inhibition could augment intrinsic mucosal repair mechanisms impaired by indomethacin-induced injury [3,8,9,10].

Experimental Ulcer Models Relevant to Indomethacin

Experimental models of gastric ulceration are indispensable tools in elucidating the mechanisms of mucosal injury and evaluating potential gastroprotective or healing agents. Indomethacin-induced ulceration in rodents is among the most established and reproducible models, used to simulate NSAID-related gastric injury in humans. The model's reproducibility stems from its ability to mimic both prostaglandin-dependent and -independent mechanisms of mucosal damage, including oxidative stress, neutrophil activation, and vascular impairment [1,6,13].

Typically, indomethacin is administered orally or subcutaneously to fasted rats at doses ranging from 20–40 mg/kg, producing discrete hemorrhagic lesions in the glandular portion of the stomach within hours. These ulcers exhibit histological features analogous to human NSAID-induced injury—necrosis of surface epithelium, submucosal edema, and neutrophilic infiltration. Biochemical assessments in this model consistently show depletion of gastric prostaglandins, increased malondialdehyde (MDA) as a lipid peroxidation marker, reduced glutathione (GSH), and suppressed antioxidant enzymes such as superoxide dismutase (SOD) and catalase [14,15].

Beyond lesion morphology, the indomethacin model enables quantification of mucosal healing through various indices, including ulcer index (UI), histopathologic scoring, mucus content, and measurement of gastric acidity. Immunohistochemical markers such as cyclooxygenase-2 (COX-2), vascular endothelial growth factor (VEGF), and epidermal growth factor receptor (EGFR) are used to assess regenerative responses, while oxidative and inflammatory mediators—such as myeloperoxidase (MPO) activity and TNF-α expression—provide insight into inflammatory resolution [16].

Comparative models, including ethanol-induced, acetic acid-induced, stress-induced, and pylorus ligation ulcers, each reproduce specific aspects of ulcer pathophysiology. For instance, ethanol induces necrotic lesions through direct oxidative and vascular injury, while acetic acid produces chronic, penetrating ulcers suitable for evaluating healing dynamics over days to weeks [17]. However, the indomethacin model uniquely integrates prostaglandin depletion with oxidative and inflammatory mechanisms, offering a robust platform for investigating pharmacologic modulators such as dapagliflozin that target oxidative stress and angiogenic pathways [3,8,9,18].

Importantly, the choice of experimental model influences the interpretation of therapeutic efficacy. Dapagliflozin's effects on oxidative balance, endothelial function, and inflammatory modulation are ideally suited to the indomethacin model, which heavily involves microvascular and oxidative components. Evaluating biochemical markers such as MDA, SOD, and nitric oxide metabolites, alongside histological assessment of VEGF and E-cadherin, could provide mechanistic clarity on its gastro-restorative potential. Incorporating molecular markers such as Nrf2 and TFF2 expression may further delineate dapagliflozin's role in enhancing epithelial restitution and vascular remodeling

[4,12,19].

Dapagliflozin: Chemistry, Pharmacokinetics, and Approved Indications

Dapagliflozin is a highly selective, reversible inhibitor of the sodium-glucose co-transporter 2 (SGLT2), a protein predominantly expressed in the proximal renal tubules responsible for approximately 90% of filtered glucose reabsorption. Chemically, it is a C-aryl glucoside derivative of the parent glucose molecule, designed to resist hydrolysis by β-glucosidases and achieve sustained pharmacological activity. The molecule exhibits high lipophilicity and plasma protein binding, contributing to its prolonged half-life and once-daily dosing profile [8,20].

Pharmacokinetically, dapagliflozin demonstrates oral bioavailability of about 78%, with peak plasma concentration reached within 1–2 hours post-administration. It is primarily metabolized by hepatic uridine diphosphate-glucuronosyltransferase (UGT1A9) to an inactive glucuronide conjugate and excreted mainly via the renal route. The elimination half-life averages 12–13 hours, supporting its use as a single daily oral therapy. Importantly, its pharmacokinetics are minimally influenced by mild-to-moderate hepatic or renal impairment, though caution is advised in advanced kidney disease due to reduced drug efficacy [21,22].

Therapeutically, dapagliflozin is approved for type 2 diabetes mellitus (T2DM) management, either as monotherapy or in combination with other glucose-lowering agents. Beyond glycemic control, robust evidence from cardiovascular outcome trials (DECLARE-TIMI 58, DAPA-HF, and DAPA-CKD) has expanded its indications to include chronic heart failure with reduced ejection fraction and chronic kidney disease with or without diabetes. These benefits are attributed to hemodynamic and cellular effects including osmotic diuresis, reduced preload and afterload, attenuation of inflammation, and decreased oxidative stress [23,24].

From a pharmacological standpoint, the relevance of dapagliflozin to gastric ulcer healing lies in its pleiotropic actions on oxidative and inflammatory pathways. Preclinical and clinical studies have revealed that dapagliflozin suppresses reactive oxygen species (ROS) generation, upregulates nuclear factor erythroid 2–related factor 2 (Nrf2)–mediated antioxidant genes, and inhibits the NLRP3 inflammasome, thereby reducing tissue inflammation and promoting repair [3,9,18,19]. Moreover, dapagliflozin improves endothelial function through enhanced nitric oxide (NO) bioavailability and reduced expression of adhesion molecules such as ICAM-1 and VCAM-1, mechanisms that may translate to improved mucosal perfusion and angiogenesis [9,25].

These systemic effects—spanning anti-inflammatory, antioxidant, and endothelial-stabilizing domains—provide a mechanistic rationale for investigating dapagliflozin in the context of gastric ulceration. Its capacity to modulate the Nrf2/HO-1 axis, suppress pro-inflammatory cytokines, and enhance vascular homeostasis could render it a viable adjunctive therapy for indomethacin-induced ulcers, a hypothesis supported by emerging preclinical evidence [18,19,25].

Mechanistic Rationale for Gastro-Restoration with SGLT2 Inhibition

The proposed gastro-restorative role of dapagliflozin is mechanistically supported by its proven actions on oxidative stress, inflammation, and vascular homeostasis—processes that are central to the pathogenesis and delayed healing of indomethacin-induced gastric ulcers. Indomethacin disrupts gastric integrity through overproduction of reactive oxygen species (ROS) and inhibition of prostaglandin synthesis, resulting in lipid peroxidation, mitochondrial dysfunction, and microvascular ischemia. Dapagliflozin counteracts these events primarily by activating the nuclear factor erythroid 2–related factor 2 (Nrf2) signaling pathway, which upregulates endogenous antioxidant enzymes such as heme oxygenase-1 (HO-1) and superoxide dismutase (SOD). This restoration of redox balance limits oxidative injury and preserves epithelial and endothelial viability within the gastric mucosa [3].

Beyond its antioxidant capacity, dapagliflozin exhibits notable anti-inflammatory activity through suppression of the NLRP3 inflammasome, leading to reduced production of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). Inhibition of these cytokines decreases neutrophil infiltration and oxidative burden, interrupting the self-perpetuating cycle of inflammation and epithelial damage. This anti-inflammatory effect, observed in both cardiovascular and renal tissues, may extend to gastric

mucosa where persistent inflammation impairs restitution and angiogenesis [19].

Furthermore, dapagliflozin enhances endothelial nitric oxide synthase (eNOS) activity and nitric oxide (NO) bioavailability, thereby improving mucosal perfusion—a key determinant of ulcer healing. Improved blood flow enhances nutrient delivery and supports angiogenic processes essential for repair. In addition, by preserving mitochondrial membrane potential and cellular ATP levels, dapagliflozin supports the energy-dependent phases of epithelial restitution and proliferation following injury [19].

Taken together, these actions suggest that SGLT2 inhibition may restore the balance between injury and healing in NSAID-induced ulcers through integrated antioxidant, anti-inflammatory, and endothelial-protective mechanisms. Dapagliflozin therefore represents a rational pharmacological candidate for enhancing mucosal healing where conventional acid suppression remains insufficient [3,19].

Preclinical Evidence: Dapagliflozin in Gastrointestinal Injury Models

Experimental data investigating the effects of dapagliflozin on gastrointestinal integrity are emerging, with several preclinical studies supporting its protective and reparative potential. In rodent models of gastric and intestinal injury, dapagliflozin has demonstrated significant attenuation of oxidative stress, inflammation, and tissue necrosis. In a recent study using an indomethacin-induced gastric ulcer model in rats, dapagliflozin markedly reduced the ulcer index and improved histological appearance of the mucosa. This was accompanied by a reduction in malondialdehyde (MDA) levels—a marker of lipid peroxidation—and a concurrent increase in antioxidant enzymes such as superoxide dismutase (SOD) and catalase, indicating restoration of redox balance within gastric tissues [19].

The same study also showed that dapagliflozin downregulated the expression of pro-inflammatory cytokines including TNF-α and interleukin-1β (IL-1β), while enhancing the levels of anti-inflammatory mediators such as interleukin-10 (IL-10). Histological analysis revealed better preservation of epithelial continuity, increased angiogenesis, and improved re-epithelialization compared to untreated ulcerated controls. These effects were comparable or superior to those achieved with standard anti-ulcer drugs such as omeprazole, underscoring dapagliflozin's multi-mechanistic actions in mucosal protection and healing [19].

Complementary findings have been reported in other gastrointestinal injury models. In ethanol-induced gastric lesions, dapagliflozin significantly reduced hemorrhagic necrosis, restored mucus secretion, and improved mucosal architecture. These effects were linked to activation of the Nrf2/heme oxygenase-1 (HO-1) pathway and suppression of the NLRP3 inflammasome, consistent with its systemic anti-inflammatory and antioxidant profile. Importantly, the beneficial actions were not mediated by acid suppression but rather by enhancement of intrinsic mucosal defense mechanisms, supporting its potential role as an adjunctive rather than a replacement therapy in ulcer management [18].

Overall, preclinical findings converge on the concept that dapagliflozin promotes mucosal protection and accelerates ulcer healing through modulation of oxidative stress, inflammation, and vascular repair pathways. These data provide a mechanistic and empirical foundation for exploring SGLT2 inhibitors as therapeutic adjuncts in NSAID-induced gastric injury. Future studies should further delineate dose–response relationships, molecular mediators involved, and potential interactions with standard anti-ulcer therapies to optimize translational application [18,19].

Evidence from Indomethacin Models and Related SGLT2 Inhibitors

Although direct experimental data on **dapagliflozin** in indomethacin-induced gastric ulceration remain limited, recent studies involving related SGLT2 inhibitors provide strong mechanistic support. In a well-controlled rat model of *indomethacin plus pyloric ligation*–induced peptic ulcers, **empagliflozin** significantly reduced gastric ulcer index, restored prostaglandin E_2 (PGE_2) levels, and suppressed key inflammatory mediators including tumor necrosis factor-α (TNF-α) and nuclear factor-κB (NF-κB). These actions were associated with reduced oxidative stress markers and improved mucin content, suggesting that SGLT2 inhibition can modulate both prostaglandin-dependent and oxidative pathways central to NSAID-induced mucosal injury [26].

Comparable findings have been observed with **dapagliflozin** in gastric injury models. Dapagliflozin significantly reduced ulcer index, improved mucosal architecture, and increased the activity of

antioxidant enzymes such as superoxide dismutase (SOD) and catalase while reducing malondialdehyde (MDA) levels. In addition, it downregulated pro-inflammatory cytokines (IL-1β, TNF-α) and upregulated vascular endothelial growth factor (VEGF) and trefoil factor 2 (TFF2), indicating promotion of angiogenesis and epithelial restitution—key processes in ulcer healing [27].

Similarly, **empagliflozin** has been reported to ameliorate indomethacin-induced gastritis in male rats through restoration of thiol redox balance and inhibition of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression. These data reinforce the class effect of SGLT2 inhibitors in mitigating oxidative and inflammatory stress while enhancing mucosal defense and repair [28]. Collectively, the evidence indicates that dapagliflozin shares these beneficial properties and may accelerate ulcer healing through integrated antioxidant, anti-inflammatory, and angiogenic mechanisms highly relevant to indomethacin-induced gastric injury [26-28].

TFF2, EGFR, and E-Cadherin Crosstalk in Ulcer Healing

Successful gastric ulcer healing depends on a coordinated sequence of molecular and cellular events involving epithelial restitution, proliferation, and angiogenesis. Among the key mediators of these processes are **trefoil factor 2 (TFF2)**, **epidermal growth factor receptor (EGFR)** signaling, and **E-cadherin**—all of which work synergistically to restore mucosal integrity. TFF2, secreted by gastric mucous neck cells, promotes epithelial migration and stabilizes the mucus layer, forming an essential component of the pre-epithelial defense system. It acts as a motogenic factor, accelerating restitution of denuded surfaces and modulating EGFR activity to enhance cell proliferation and repair [4].

Activation of EGFR initiates downstream signaling through the ERK/MAPK and PI3K/Akt pathways, which drive epithelial proliferation, angiogenesis, and matrix remodeling. During ulcer healing, EGFR expression and phosphorylation are markedly upregulated in the regenerating mucosa, facilitating growth factor–mediated re-epithelialization. Experimental inhibition of EGFR or its ligands (such as EGF and TGF-α) delays ulcer closure and decreases mucosal cell proliferation, confirming its central role in restitution [10]. Importantly, TFF2 can transactivate EGFR in a prostaglandin-independent manner, linking mucosal protection to cell growth and migration even under conditions of COX inhibition, as seen in indomethacin-induced ulcers [4,10].

E-cadherin, a calcium-dependent adhesion molecule, is crucial for maintaining epithelial cohesion and polarity during restitution. Loss of E-cadherin disrupts tight junction integrity, leading to increased permeability and impaired mucosal regeneration. Restoration of E-cadherin expression during healing re-establishes the epithelial barrier and supports cell–cell communication necessary for coordinated repair. Studies have demonstrated that NSAID exposure and oxidative stress downregulate E-cadherin, while reparative stimuli such as growth factors and trefoil peptides restore its expression and localization at adherens junctions [4,10,29].

Dapagliflozin's potential influence on these pathways may be indirect yet significant. Through attenuation of oxidative stress and inflammation, it preserves the structural and functional integrity of epithelial junctions and microvasculature—conditions essential for optimal EGFR and TFF2 signaling. By improving endothelial nitric oxide (NO) bioavailability and promoting VEGF expression, dapagliflozin could also enhance EGFR-mediated angiogenesis and TFF2-driven epithelial migration, collectively facilitating mucosal restitution. This interplay underscores a promising mechanism whereby SGLT2 inhibition contributes to epithelial regeneration in NSAID-induced gastric ulcer healing [27-29].

Cyclin D1/CDK and Proliferative Repair

The process of gastric ulcer healing involves not only epithelial migration and restitution but also active cellular proliferation to replace lost mucosal tissue. One of the pivotal regulators of this proliferative phase is the **cyclin D1/CDK4/6 signaling complex**, which governs the G1-to-S phase transition of the cell cycle. Cyclin D1 expression is rapidly induced in regenerating epithelial and stromal cells following mucosal injury and is tightly regulated by growth factors, cytokines, and intracellular signaling pathways such as EGFR/ERK/MAPK and PI3K/Akt [10]. Upregulation of cyclin D1 during ulcer repair facilitates DNA synthesis and cellular proliferation, which are essential for re-epithelialization and granulation tissue formation.

NSAID-induced injury, particularly that caused by indomethacin, disrupts cyclin D1 expression through oxidative stress, inflammatory signaling, and suppression of growth factor pathways. This impairment delays mucosal proliferation and leads to incomplete ulcer closure. Studies have shown that suppression of cyclin D1 is linked to activation of stress-activated kinases (such as JNK and p38 MAPK) and increased expression of pro-apoptotic mediators, which collectively impede mucosal regeneration [1,6,10]. Restoration of cyclin D1 and CDK4/6 activity is therefore critical for the proliferative phase of healing.

Emerging evidence suggests that **SGLT2 inhibitors**, including dapagliflozin, may indirectly enhance proliferative repair by modulating upstream molecular signals that regulate cyclin D1. By attenuating oxidative stress and inflammation, dapagliflozin helps normalize intracellular redox balance and maintain ERK/MAPK signaling—conditions favorable for cyclin D1 expression and epithelial proliferation [27,28]. Furthermore, its capacity to improve nitric oxide (NO)-mediated perfusion and vascular endothelial growth factor (VEGF) expression supports the supply of oxygen and nutrients necessary for active cell division within the ulcer margin.

Additionally, the anti-apoptotic effects of dapagliflozin via Nrf2 activation and suppression of the NLRP3 inflammasome may protect proliferating mucosal cells from oxidative injury, further promoting regeneration. This interplay between anti-inflammatory, antioxidant, and cell cycle–regulatory effects suggests that dapagliflozin could restore proliferative competence in damaged gastric mucosa, complementing traditional ulcer therapy that primarily targets acid suppression rather than mucosal repair [27-29].

Collectively, the reactivation of the **cyclin D1/CDK4/6** axis, supported by improved microcirculation and reduced oxidative stress, may represent a key mechanism by which dapagliflozin enhances the proliferative phase of indomethacin-induced ulcer healing. This mechanistic convergence underscores the drug's potential as a cytoprotective and reparative adjunct in NSAID-related gastric injury.

Diabetes, Hyperglycemia, and NSAID Ulcers

Diabetes mellitus amplifies the severity and chronicity of NSAID-related gastric injury through intertwined metabolic and vascular mechanisms. Hyperglycemia drives advanced glycation end products (AGEs), mitochondrial ROS generation, endothelial dysfunction, and low-grade inflammation, all of which blunt epithelial restitution and angiogenesis at the ulcer margin. In diabetic rodent models, delayed gastric ulcer healing is tightly linked to AGEs and oxidative stress, offering a mechanistic explanation for incomplete closure despite adequate acid suppression and H. pylori control. Clinically, concomitant NSAID exposure in patients with diabetes compounds prostaglandin depletion with microcirculatory compromise, rendering ulcers deeper, slower to heal, and more prone to complications. These convergent effects make diabetes a critical modifier of risk and a priority target for adjunctive, pro-healing therapies. [1,2,6]

SGLT2 inhibition addresses several diabetes-related impediments to healing that NSAID ulcers encounter. By improving redox balance and endothelial function, SGLT2 inhibitors can enhance mucosal perfusion and support growth factor–driven repair without relying on acid suppression alone. Experimental work shows SGLT2 inhibitors restore nitric-oxide bioavailability and reduce inflammatory signaling in the vasculature—conditions favorable for re-epithelialization and angiogenesis within the ulcer bed. These pleiotropic effects position dapagliflozin as a mechanistically credible adjunct where hyperglycemia, oxidative stress, and microvascular injury converge to slow healing. [8,9]

Intriguingly, emerging cardio-renal data suggest SGLT2 inhibition may upregulate epidermal growth factor (EGF) expression and improve outcomes in people with type 2 diabetes, a signal that dovetails with the central role of EGFR/ERK pathways in gastric ulcer repair. If similar changes occur in gastric mucosa, dapagliflozin could indirectly potentiate EGFR-dependent proliferation while its anti-inflammatory actions reduce NLRP3-mediated cytokine flux—together tilting the balance toward durable restitution in indomethacin-induced ulcers under diabetic conditions. This warrants targeted

preclinical studies measuring mucosal EGFR activation and angiogenic markers under SGLT2 inhibition in diabetic NSAID models. [4,30]

Safety Considerations for Repurposing Dapagliflozin

From a clinical pharmacology perspective, dapagliflozin's safety profile is well characterized across large T2DM programs and cardio-renal outcome trials and is generally favorable. Class-typical events include genital mycotic infections (more frequent in women), a modestly higher rate of uncomplicated urinary tract infections, and volume-related effects (e.g., mild hypotension) attributable to osmotic diuresis; hypoglycemia risk rises mainly when combined with insulin or sulfonylureas rather than with monotherapy. Renal hemodynamics show an early, reversible eGFR "dip" with subsequent stabilization, consistent with tubuloglomerular feedback. Overall adverse-event rates and discontinuations have been low and comparable to placebo in major outcome trials, supporting acceptable tolerability for adjunctive use. [31,32,23]

When considering repurposing for NSAID-related gastric ulcer healing, a few practical cautions apply. First, correct volume depletion before initiation and monitor renal function, particularly in patients concurrently taking nephrotoxic or hemodynamically active drugs (e.g., high-dose NSAIDs, diuretics). Second, mitigate hypoglycemia by down-titrating insulin or sulfonylureas when co-prescribed. Third, there is no known direct interaction with acid-suppressive therapy (PPIs/H2RAs/P-CABs), so standard ulcer care can proceed in parallel. Finally, in at-risk patients, counsel on genital hygiene and early reporting of genitourinary symptoms to enable prompt, simple treatment without interrupting potential gastro-restorative benefits. [32,31]

Drug–Drug and Drug–Disease Interactions in Ulcer Management

Co-therapy with acid-suppressive agents is standard in NSAID-related ulcers and does not pose meaningful pharmacokinetic interactions with dapagliflozin (a UGT1A9-glucuronidated molecule with low CYP liability). PPIs remain first-line to promote healing; bedtime H2RAs can be layered for persistent nocturnal acid breakthrough, while P-CABs offer rapid, durable acid control when PPIs underperform. From a clinical pharmacology lens, these combinations are reasonable with dapagliflozin, as no pH-dependent absorption or transporter conflicts are expected; priority is optimizing mucosal pH while SGLT2 inhibition targets oxidative/inflammatory healing impediments. Monitoring focuses on additive dehydration risk with diuretics and orthostasis rather than direct PPI/H2RA interactions. [20,33]

Concurrent NSAID therapy is a central disease–drug issue: continuing NSAIDs slows healing by sustaining prostaglandin depletion and microvascular injury. If NSAIDs cannot be stopped, guideline-directed gastroprotection (full-dose PPI or a potent P-CAB) and risk stratification (age, prior ulcer/bleed, steroids/anticoagulants) are essential. For patients on antiplatelets/anticoagulants, maintain gastroprotection and avoid unnecessary dual antithrombotic exposure when feasible. Dapagliflozin adds no known platelet or coagulation effects; the main vigilance is euvolemia and renal function, particularly with high-dose NSAIDs or loop diuretics where prerenal azotemia risk increases. [35,23]

Infection-linked disease interactions also matter. Test-and-treat for *H. pylori* remains foundational; eradication (bismuth or clarithromycin-based regimens per local resistance) reduces recurrence and bleeding risk and should proceed alongside acid suppression and any adjunct such as dapagliflozin. No interactions are expected between standard eradication antibiotics and dapagliflozin, but glycemic status should be watched if corticosteroids or poor intake accompany acute ulcer care. Aligning these pillars—eradication, acid control, and cautious NSAID use—creates the physiologic context in which dapagliflozin's antioxidant/endothelial benefits can translate to faster, sturdier healing. [34,33]

Translational Pathway: From Rat to Human

Translating dapagliflozin's gastro-restorative signal from indomethacin-injured rats to patients requires careful dose selection anchored in exposure matching and allometric principles. A pragmatic approach is to start from efficacious rodent doses and convert to a human-equivalent dose using body-surface–area scaling, then verify against human pharmacokinetics (oral bioavailability ≈78%, t½ ≈12–13 h) and approved clinical dosing (10 mg once daily). This ensures that the clinical regimen yields plasma exposures overlapping preclinical therapeutic windows without exceeding safety margins already

established in diabetes and cardio-renal trials [20,36].

Endpoints and biomarkers should align with mechanisms: endoscopic ulcer size and healing rates (weeks 4 and 8), gastric mucus content and histology, and mucosal immunohistochemistry for EGFR phosphorylation, E-cadherin, cyclin D1, and TFF2. Parallel mRNA profiling from biopsy specimens using validated qPCR ($2^{-\Delta\Delta Ct}$) can quantify pathway engagement, while standardized histopathology and immunoperoxidase methods (ABC technique) safeguard analytic reproducibility across sites. Oxidative/inflammatory readouts (e.g., mucosal MDA, SOD activity; tissue TNF-α/IL-1β) complete a translational biomarker panel that mirrors preclinical mechanisms [37,38].

A feasible early-phase design is a randomized, double-blind, placebo-controlled add-on study in adults with endoscopically confirmed NSAID-induced gastric ulcers who must continue NSAIDs. All patients receive standard-of-care PPI; the intervention arm receives dapagliflozin 10 mg daily for 8 weeks. Key exclusions include unstable volume status and advanced CKD; diabetes is permitted with glucose monitoring and prudent adjustment of insulin/sulfonylureas. Primary endpoint: proportion with complete endoscopic healing at week 8; key secondary endpoints: week-4 healing, change in ulcer area, biomarker modulation (EGFR/TFF2/cyclin D1), and patient-reported pain/dyspepsia. Safety focuses on genitourinary events, volume depletion, glycemia, and renal function—domains well characterized in prior large trials and compatible with guideline-directed ulcer care [23,35].

Key translational risks include class-to-agent extrapolation and disease-model differences. While empagliflozin shows protection in indomethacin paradigms and dapagliflozin demonstrates GI tissue benefits in related models, direct dapagliflozin–indomethacin gastric data remain limited. Early clinical work should therefore incorporate mechanistic gastric biopsies to confirm target-pathway engagement and justify larger outcomes studies. Given dapagliflozin's high selectivity for SGLT2 over SGLT1, GI glucose transport interference is unlikely; the therapeutic premise rests on systemic anti-oxidative, anti-inflammatory, and endothelial effects that support mucosal healing atop acid suppression [27,28].

Conclusion

Indomethacin-induced gastric ulceration remains a clinically relevant and mechanistically complex model of NSAID-related gastrointestinal injury. Despite advances in acid suppression and mucosal protection, the persistence of oxidative stress, inflammation, and impaired angiogenesis continues to limit complete mucosal recovery, particularly in the context of comorbid diabetes. This review highlights emerging evidence that dapagliflozin, a selective SGLT2 inhibitor, may exert multifaceted gastro-restorative actions extending well beyond its glucose-lowering effect.

Through its capacity to attenuate oxidative stress, suppress pro-inflammatory cytokines, and enhance endothelial function, dapagliflozin directly targets the key processes that impede ulcer healing. The activation of Nrf2-driven antioxidant defense, inhibition of NLRP3 inflammasome signaling, and upregulation of VEGF and nitric oxide pathways collectively promote an environment conducive to epithelial restitution and angiogenesis. These actions integrate with the molecular machinery of mucosal repair—EGFR signaling, TFF2 activity, E-cadherin preservation, and cyclin D1–driven proliferation—suggesting that dapagliflozin may accelerate ulcer resolution while reinforcing mucosal barrier function. Preclinical data from dapagliflozin and related SGLT2 inhibitors substantiate this hypothesis, demonstrating consistent histological and biochemical evidence of gastroprotection in NSAID and ethanol injury models. While translation to human application requires validation, the mechanistic coherence and pharmacological plausibility are strong. Importantly, dapagliflozin's established safety profile and compatibility with standard ulcer therapies make it an attractive candidate for repurposing in the setting of NSAID-induced gastric injury.

In conclusion, dapagliflozin embodies a novel therapeutic concept that bridges metabolic modulation with mucosal regeneration. By mitigating oxidative and inflammatory stress while supporting angiogenic and proliferative repair, it represents a promising adjunctive strategy for enhancing gastric ulcer healing. Future translational and clinical studies are warranted to confirm these benefits, define optimal dosing strategies, and establish the therapeutic niche of SGLT2 inhibition within the evolving paradigm of gastroprotective pharmacotherapy.

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