

The Role of Selected Inflammatory and Apoptotic Markers in Peptic Ulcer Disease: A Mini Review

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Abstract

Introduction: Peptic ulcer disease (PUD) affects 5–10% of the global population and results from mucosal injury caused by gastric acid, *Helicobacter pylori*, non-steroidal anti-inflammatory drugs (NSAIDs), and other factors. Inflammatory and apoptotic pathways are central to PUD pathogenesis.

Methods: This mini review synthesised literature from PubMed, Google Scholar, and Web of Science (2000 - 2025) using keywords “peptic ulcer,” “inflammatory markers,” “apoptotic markers,” “NF κB,” and “caspases.” Studies reporting molecular mechanisms in human or animal models were included.

Synthesis: Reactive oxygen species activate NF κB, leading to pro-inflammatory cytokines (IL 1β, IL 6, TNF α) that perpetuate mucosal injury. Inflammatory caspases (caspase 1, 4, 5) drive pyroptosis, while apoptotic caspases (caspase 8, 9, 3) regulate epithelial cell death. Key markers include NF κB, TNF α, IL 6, Bax, and Bcl 2. Current guidelines (Maastricht VI/ACG 2022) recommend bismuth-based quadruple therapy for *H. pylori*, achieving >90% eradication. However, human validation for most biomarkers remains limited.

Conclusion: Inflammatory and apoptotic markers are promising therapeutic targets and potential diagnostic tools, but prospective human studies are needed to establish their clinical utility.

Keywords: Peptic ulcer, Inflammatory markers, Apoptotic markers, *Helicobacter pylori*, Caspases

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Introduction

Peptic ulcer disease (PUD) is defined as mucosal erosion in areas of the gastrointestinal tract exposed to acidic gastric secretions, most commonly the stomach and proximal duodenum. These lesions result from an imbalance between mucosal defensive factors and aggressive luminal agents such as hydrochloric acid and pepsin (1, 2). Histologically, ulcers show a breach that extends beyond the muscularis mucosae into the muscularis propria, often accompanied by necrosis, inflammation, and granulation tissue. Globally, PUD remains a significant clinical and public health concern. Although the incidence and mortality have reduced over recent decades due to better diagnostics and new therapeutic

interventions, PUD still affects 5–10% of the population during their lifetime, with an annual incidence of 0.1–0.3% (3, 4, 5). Complications such as gastrointestinal bleeding, perforation, and gastric outlet obstruction pose serious health risks; bleeding alone accounts for 73% of all complications and carries a mortality rate of approximately 10% (6).

Key etiological factors include infection with *Helicobacter pylori*, prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs), smoking, alcohol consumption, and severe physiological stress (e.g., trauma, burns) (7). Among these, *H. pylori* and NSAIDs are the two major causative agents (1, 8, 9). Chronic *H. pylori* infection induces an inflammatory response that disrupts the gastric mucosal barrier, while NSAIDs inhibit prostaglandin synthesis,



From the South, for the South, with the World

impairing mucosal defence and repair (10). Some medications (e.g., bisphosphonates, which primarily cause oesophageal injury, and corticosteroids with controversial ulcerogenic roles) may alter mucosal integrity but are not primary causes of gastric or duodenal ulcers. Psychological stress has also been implicated, though studies show conflicting findings; in patients with pre-existing duodenal ulcers, severe stress can increase basal acid production (11). However, ulcer patients often have psychological profiles comparable to the general population.

Experimental ulcer models (ethanol-induced gastric lesions, pyloric ligation, stress-induced ulceration) have been used to elucidate ulcer pathophysiology and screen gastroprotective agents (12, 13). These models replicate clinical conditions by inducing oxidative stress, epithelial damage, and vascular leakage (14).

This review aims to (i) summarise the molecular mechanisms of PUD with emphasis on inflammatory and apoptotic markers, (ii) evaluate their potential as diagnostic biomarkers, and (iii) discuss current evidence-based management according to recent guidelines.

Methods

Search strategy

A literature search was performed using PubMed, Google Scholar, and Web of Science for articles published between January 2000 and March 2025. Search terms included “peptic ulcer disease,” “inflammatory markers,” “apoptotic markers,” “NF-kappa B,” “caspases,” “*Helicobacter pylori*,” “cytokines,” “TNF-alpha,” “interleukins,” and “ulcer healing.” Only English-language articles were considered.

Inclusion and exclusion criteria

We included original research (in vitro, animal models, human studies), systematic reviews, and clinical guidelines that reported on inflammatory or apoptotic markers in PUD. Case reports, editorials, and non-peer-reviewed articles were excluded. Priority was given to studies measuring markers in human gastric tissue or serum.

Data extraction and synthesis

Two authors (AO and AE) independently extracted data on marker type, expression levels, correlation with disease activity, and therapeutic interventions. Disagreements were resolved by consensus with a third author (KA). Given the mini-review format, a narrative synthesis was performed.

Synthesis

Pathophysiology of PUD: mucosal defence and aggressive factors

The gastroduodenal mucosa maintains integrity through a mucus-bicarbonate barrier, tight junction proteins, epithelial

restitution, and submucosal blood flow. Prostaglandin E2 (PGE2) supports mucus secretion and bicarbonate production. When aggressive factors (acid, pepsin, NSAIDs, *H. pylori*) overwhelm these defences, mucosal injury occurs. Duodenal ulcers typically involve gastric metaplasia and acid hypersecretion, while gastric ulcers often occur with normal or low acid output and impaired mucosal resistance.

H. pylori infection triggers a chronic inflammatory response characterised by neutrophil and macrophage infiltration. The bacteria’s virulence factors (CagA, VacA) activate nuclear factor kappa B (NF-κB), leading to pro-inflammatory cytokine release (15).

Inflammatory markers in PUD

1. NF-κB signalling

NF-κB is a master regulator of inflammation. The innate immune system employs pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) to detect pathogen-associated molecular patterns (PAMPs, e.g., *H. pylori* lipopolysaccharide) and damage-associated molecular patterns (DAMPs, e.g., extracellular ATP) (16). The canonical NF-κB pathway involves activation of the IκB kinase (IKK) complex by transforming growth factor β-activated kinase 1 (TAK1), leading to IκB phosphorylation and degradation. Freed NF-κB dimers (p65/p50) translocate to the nucleus and drive transcription of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), chemokines, and adhesion molecules (17) (Figure 1, adapted from (18) with permission).

2. Pro-inflammatory cytokines

TNF-α: Elevated in the gastric mucosa of PUD patients and correlates with ulcer size and delayed healing (19). It binds TNFR1/2, activating both NF-κB (survival) and caspase-8 (apoptosis).

IL-1β: A key mediator of neutrophil recruitment and tissue damage; polymorphisms in the IL-1β gene are associated with increased PUD risk (20).

IL-6: Contributes to systemic inflammation and chronic mucosal injury via STAT3 signalling (21).

IL-8: Chemoattractant for neutrophils, upregulated by *H. pylori* infection.

3. Other inflammatory mediators

Myeloperoxidase (MPO) is a marker of neutrophil infiltration and is increased in experimental and human ulcers (22). Matrix metalloproteinases (MMPs), particularly MMP-9, degrade extracellular matrix and are involved in ulcer remodelling and healing (23). PGE2 is reduced by NSAIDs, compromising mucosal protection. **Figure 1** (NF-κB signalling pathway) and **Figure 2** (therapeutic inhibitors of NF-κB) are shown below.

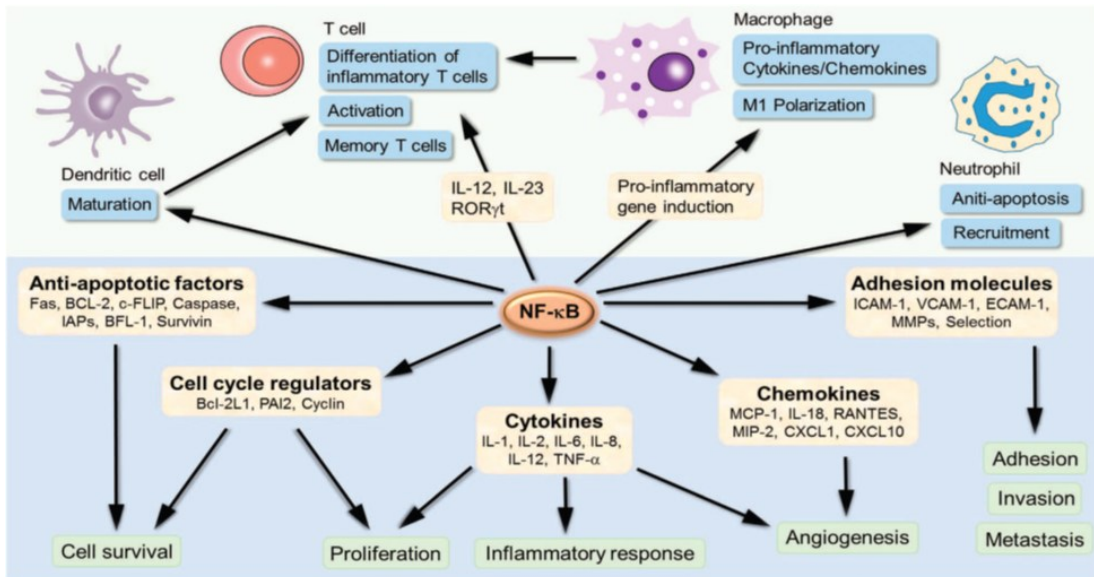


Figure 1: NF-κB Signalling and Its Role in the Regulation of Inflammation and Apoptosis
Adapted from (18) with permission

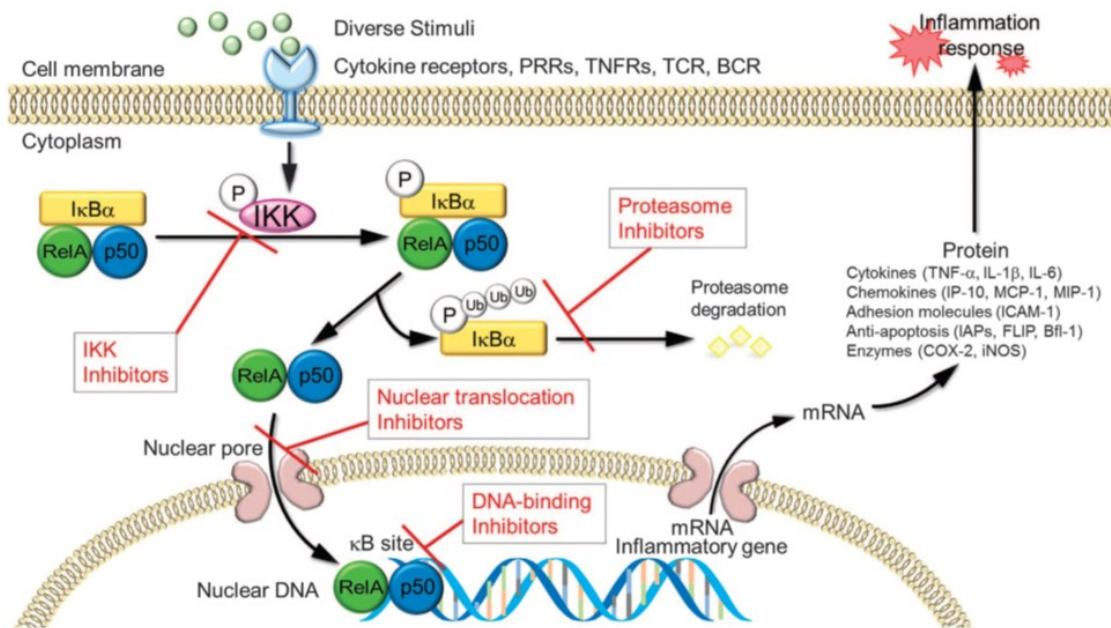


Figure 2: Treatments for inflammatory diseases that focus on NF-κB
Adapted from (18) with permission

Apoptotic markers in PUD

Apoptosis (programmed cell death) of gastric epithelial cells compromises mucosal barrier integrity. Two major pathways are involved:

1. Extrinsic pathway

TNF-α binding to TNFR1 recruits adaptor proteins (TRADD, FADD, RIPK1) to form Complex I (pro-survival via NF-κB) or Complex IIa (pro-apoptotic). Complex IIa activates pro-caspase-8, which then cleaves executioner caspase-3, leading to DNA fragmentation and cell death (24, 25).

2. Intrinsic (mitochondrial) pathway

Intracellular stress (DNA damage, oxidative stress) shifts the balance of Bcl-2 family proteins: pro-apoptotic Bax increases, while anti-apoptotic Bcl-2 decreases. This causes mitochondrial outer membrane permeabilisation (MOMP) and release of cytochrome c. Cytochrome c forms the apoptosome with Apaf-1 and procaspase-9, activating caspase-9 and subsequently caspase-3 (26). In PUD patients, gastric biopsies show increased Bax/Bcl-2 ratio (27).

Caspase families

Inflammatory caspases (caspase-1,-4,-5): Activated within the inflammasome; cleave pro-IL-1β and pro-IL-18 into active forms, and induce pyroptosis (inflammatory cell death).

Apoptotic caspases: Initiator caspases (caspase-8,-9) and executioner caspase-3. This mediates non-inflammatory programmed cell death. Table 1 summarises the roles and clinical relevance of key markers.

Table 1: Role of inflammatory and apoptotic markers in peptic ulcer disease

Marker	Type	Role in PUD Pathogenesis	Clinical Relevance in Humans	References
TNF- α	Inflammatory	Promotes mucosal inflammation, increases apoptosis of epithelial cells	Elevated in the gastric mucosa and serum of active PUD patients; correlates with ulcer severity	(19, 24)
IL-1 β	Inflammatory	Induces neutrophil infiltration, amplifies inflammatory response	Higher levels in <i>H. pylori</i> -positive ulcers; IL-1B polymorphisms increase risk	(20)
IL-6	Inflammatory	Involved in systemic inflammation and mucosal immune response	Serum IL-6 is elevated in PUD with delayed healing	(21)
NF- κ B	Inflammatory signalling	Master regulator of inflammation; controls transcription of pro-inflammatory genes	Activated in the gastric epithelium of PUD patients; correlates with cytokine production	(17, 18)
Bax	Apoptotic (pro-)	Promotes apoptosis of gastric epithelial cells	Increased Bax/Bcl-2 ratio in human ulcer biopsies	(27)
Bcl-2	Apoptotic (anti-)	Inhibits apoptosis; supports mucosal cell survival	Decreased expression in active ulcers	(27)
Caspase-3	Apoptotic (effector)	Executes apoptosis; leads to DNA fragmentation and cell death	Activated caspase-3 was detected in gastric epithelial cells of PUD patients	(25)
Caspase-8	Apoptotic (initiator)	Initiates the extrinsic apoptosis pathway	Elevated activity in <i>H. pylori</i> -infected mucosa	(24)
MPO	Inflammatory (enzyme)	Marker of neutrophil infiltration	Increased in the gastric tissue of PUD; correlates with tissue damage	(22)
MMP-9	Inflammatory (protease)	Degrades extracellular matrix; involved in tissue remodelling	Elevated in gastric juice and biopsies of PUD patients; associated with ulcer size	(23)

Cytochrome c is an intracellular mitochondrial protein and is not a clinically measurable serum biomarker

Clinical management and current guidelines

Upper gastrointestinal endoscopy remains the gold standard for diagnosis, allowing direct visualisation, biopsy, and classification of ulcers (28, 29). Serological IgG testing is not recommended to diagnose active *H. pylori* infection, as it cannot distinguish current from past exposure. Urea breath test, stool antigen test, or biopsy-based methods are preferred.

For *H. pylori*-associated ulcers, first-line therapy according to the Maastricht VI/Florence consensus (2022) and ACG 2022 guidelines is bismuth-based quadruple therapy: proton pump inhibitor (PPI) + bismuth + tetracycline + metronidazole for 14 days, achieving eradication rates >90% (30). In regions with low clarithromycin resistance, triple therapy may still be used, but is no longer preferred. For NSAID-induced ulcers, PPIs, H₂ receptor antagonists, or selective COX-2 inhibitors are effective (31, 32). PPIs irreversibly inhibit the gastric H⁺/K⁺ ATPase to reduce acid secretion.

Despite advances, recurrence occurs in patients with comorbidities (type 2 diabetes, liver cirrhosis) and possibly psychological stress (11, 33). A recent study from a Nigerian cohort reported that elevated serum IL-6 and TNF- α were associated with delayed ulcer healing (34).

Emerging therapeutic targets

Modulation of NF- κ B and apoptotic pathways offers promising strategies. Natural products such as *Panax notoginseng* saponins and ginsenoside Re have shown gastroprotective effects in animal models (35, 36a). However, therapies like endoscopic gene therapy, thyrotropin-releasing hormone analogues, and butyrate-based treatments remain experimental and require rigorous clinical trials.

Conclusion

Inflammatory and apoptotic markers—including NF- κ B, TNF- α , IL-1 β , IL-6, MPO, MMP-9, and caspases—play central roles in peptic ulcer pathogenesis and healing. Current evidence-based management follows Maastricht VI/ACG 2022 guidelines, with bismuth quadruple therapy achieving >90% *H. pylori* eradication. Despite preclinical promise, validated non-invasive biomarkers for early diagnosis and monitoring are lacking. Future research should focus on large human cohort studies to validate serum or faecal markers (e.g., MMP-9, calprotectin), clarify the balance between apoptosis and regeneration, and translate natural product leads into clinical trials.

Abbreviations

PUD: Peptic ulcer disease

H. pylori: Helicobacter pylori
 NSAIDs: Non-steroidal anti-inflammatory drugs
 NF κ B: Nuclear factor kappa B
 TNF α : Tumour necrosis factor alpha
 IL: Interleukin
 MPO: Myeloperoxidase
 MMP: Matrix metalloproteinase
 PGE2: Prostaglandin E2
 ROS: Reactive oxygen species
 RNS: Reactive nitrogen species
 PAMP: Pathogen-associated molecular pattern
 DAMP: Damage-associated molecular pattern
 PRR: Pattern recognition receptor
 TLR: Toll-like receptor
 NLR: NOD-like receptor
 TAK1: Transforming growth factor β -activated kinase 1
 IKK: I κ B kinase
 TNFR: Tumour necrosis factor receptor
 TRADD: TNFR1-associated death domain protein
 FADD: Fas-associated protein with death domain
 RIPK1: Receptor-interacting serine/threonine protein kinase 1
 MOMP: Mitochondrial outer membrane permeabilisation
 PPI: Proton pump inhibitor
 COX 2: Cyclooxygenase 2

Declarations

Ethics Approval and Consent to Participate: Not applicable. This is a literature review and does not involve human or animal subjects.

Data Availability: All data extracted from published articles are included in the manuscript and references. No new primary data were generated.

Competing Interests: The authors declare that they have no competing interests.

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