Article published online: 2024-03-11

Recent Advances in Molecular Pathways and Therapeutic Implications for Peptic Ulcer Management: A Comprehensive Review

Authors
Deepak Chandra Joshi[1], Nirmal Joshi[2], Ajeet Kumar[3], Shubhrat Maheshwari[3]

Affiliations
1 Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Ajmer, India
2 Department of Pharmacology, Amrapali Institute of Pharmacy and Sciences, Haldwani, India
3 Faculty of Pharmaceutical Sciences, Rama University, Kanpur, India

Keywords
peptic ulcer, *H. pylori*, TNF-α, prostaglandins, vanoprazan

received 21.12.2023
accepted after revision 16.01.2024
published online 11.03.2024

Bibliography
Horm Metab Res 2024; 56: 615–624
DOI 10.1055/a-2256-6592
ISSN 0018-5043
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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Deepak Chandra Joshi
Central University of Rajasthan
Department of Pharmacy
School of Chemical Sciences and Pharmacy
305817 Ajmer
India
deepakjoshi024@gmail.com

ABSTRACT

Peptic ulcers, recognized for their erosive impact on the gastrointestinal mucosa, present a considerable challenge in gastroenterology. Epidemiological insights underscore the global prevalence of peptic ulcers, affecting 5–10 % of individuals, with a yearly incidence of 0.3 to 1.9 cases per thousand. Recent decades have witnessed a decline in complications, attributed to improved diagnostics and therapeutic advancements. The review deepens into *H. pylori*-associated and NSAID-induced ulcers, emphasizing their distinct prevalence in developing and industrialized nations, respectively. Despite advancements, managing peptic ulcers remains challenging, notably in *H. pylori*-infected individuals facing recurrence and the rise of antibiotic resistance. The pathophysiology unravels the delicate balance between protective and destructive factors, including the intricate molecular mechanisms involving inflammatory mediators such as TNF-α, ILs, and prostaglandins. Genetic and ethnic factors, rare contributors, and recent molecular insights further enhance our understanding of peptic ulcer development. Diagnostic approaches are pivotal, with upper gastrointestinal endoscopy standing as the gold standard. Current treatment strategies focus on *H. pylori* eradication, NSAID discontinuation, and proton pump inhibitors. Surgical options become imperative for refractory cases, emphasizing a comprehensive approach. Advances include tailored *H. pylori* regimens, the emergence of vonoprazan, and ongoing vaccine development. Challenges persist, primarily in antibiotic resistance, side effects of acid suppressants, and translating natural compounds into standardized therapies. Promising avenues include the potential *H. pylori* vaccine and the exploration of natural compounds, with monoterpenes showing therapeutic promise. This review serves as a compass, guiding healthcare professionals, researchers, and policymakers through the intricate landscape of peptic ulcer management.

Introduction

Peptic ulcers, marked by the erosion of the gastrointestinal mucosa, represent a significant clinical challenge in gastroenterology. The intricate interplay between genetic, environmental, and microbial factors underscores the complexity of peptic ulcer pathogenesis. Epidemiological studies have provided valuable insights into the prevalence and incidence of peptic ulcers, shedding light on the burden of this condition and its evolving trends over time [1]. Estimates suggest that approximately 5–10 % of individuals will experience a peptic ulcer at some time in their lives. This statistic underscores the substantial prevalence of this condition, making it a noteworthy concern in gastroenterological practice. The annual incidence of peptic ulcers varies across populations, ranging from 0.3 to 1.9 cases per thousand individuals [2]. This inci-

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dence rate highlights the ongoing and considerable impact of peptic ulcers on healthcare systems worldwide. In recent decades, epidemiological studies have observed a notable shift in the landscape of peptic ulcer complications, particularly in developed countries. The overall incidence of complications related to peptic ulcers has shown a decreasing trend, indicating a positive trajectory in the management and prevention of severe outcomes associated with this condition [3]. This decline in incidence is attributed to several factors, including improved diagnostic techniques, enhanced understanding of risk factors, and advancements in therapeutic interventions [4]. While much progress has occurred in understanding the etiology of peptic ulcers, their management remains a daunting task for healthcare professionals. This review aims to delve into the current landscape of peptic ulcer management, emphasizing the challenges faced in clinical practice and the imperative for exploring innovative therapeutic approaches. Peptic ulcers, comprising gastric and duodenal ulcers, have long been recognized as major contributors to gastrointestinal morbidity and healthcare expenditures [5]. These abnormalities are predominantly linked to *Helicobacter pylori* (*H. pylori*) infection, the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs), and less frequent contributors like smoking and stress [6]. The prevalence of peptic ulcers varies globally, with *H. pylori* infection being a predominant factor in developing countries and NSAID use playing a significant role in industrialized nations [7]. Consequently, the burden of peptic ulcers is substantial, affecting millions of individuals worldwide and necessitating a comprehensive understanding of their pathophysiology and effective management strategies [8]. Despite advancements in medical science, peptic ulcer management poses persistent challenges. The recurrence rates of peptic ulcers, especially in *H. pylori*-infected individuals, remain a concern. Additionally, the rise of antibiotic resistance poses a threat to the conventional treatment regimens targeting *H. pylori*. Furthermore, NSAID-induced ulcers, a common scenario in the aging population, present a management conundrum due to the limited options for pain relief in patients requiring long-term NSAID therapy [9]. The multifactorial nature of peptic ulcers demands a nuanced approach that goes beyond the conventional strategies, necessitating the exploration of novel therapeutic interventions [10]. The limitations of current treatment modalities underscore the need for novel therapeutic approaches in peptic ulcer management. Traditional regimens, including proton pump inhibitors (PPIs) and antibiotics, have been the mainstay of therapy for *H. pylori*-associated ulcers [11]. However, the emergence of antibiotic resistance and suboptimal patient compliance pose significant challenges to the effectiveness of these regimens [12]. Additionally, the management of NSAID-induced ulcers relies on discontinuing or reducing NSAID use, which may not be feasible in many clinical scenarios. Therefore, there is a compelling need for innovative strategies that address the specific challenges associated with each subtype of peptic ulcer [13].

This review seeks to offer a thorough examination of the present challenges in managing peptic ulcers and delve into the most recent advancements in therapeutic strategies. We will critically examine the existing literature on *H. pylori* eradication strategies, assess the impact of antibiotic resistance on treatment outcomes, and evaluate alternative approaches such as probiotics and phage therapy [14]. Furthermore, we will delve into the intricacies of NSAID-induced ulcers, analyzing the limitations of current management strategies and highlighting emerging interventions, including mucosal protective agents and targeted drug delivery systems [15]. The scope of this review encompasses a thorough examination of recent research findings, clinical trials, and emerging trends in peptic ulcer management. By synthesizing the existing knowledge, we aim to provide healthcare professionals, researchers, and policymakers with a comprehensive understanding of the current landscape and future directions in peptic ulcer therapeutics [16]. Our review will not only elucidate the challenges faced in clinical practice but also shed light on promising avenues for the development of novel and more effective therapeutic interventions.

Epidemiology, Causes, Types, and Pathophysiology of Peptic Ulcers

Peptic ulcers (PUs) exhibit a multifaceted epidemiological profile influenced by a combination of, environmental, genetic and lifestyle factors. Understanding the prevalence and risk factors is pivotal for effective management and prevention strategies [17]. The estimated prevalence of peptic ulcers underscores their significance in global health, affecting approximately 5–10 % of individuals during their lifetime. While this prevalence indicates a substantial burden, it is crucial to note variations across populations and regions. Epidemiological data reveal an annual incidence ranging from 0.3 to 1.9 cases per thousand individuals, emphasizing the continued impact of peptic ulcers on healthcare systems [18]. Several factors contribute to the development of peptic ulcers as shown in ▶ **Fig. 1** and identifying these risk factors is essential for targeted interventions. Notably, *H. pylori* infection stands out as a major risk factor, implicated in a significant proportion of peptic ulcer cases. Other contributors include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), smoking, advanced age, and a genetic predisposition [19].

The prevalence of *H. pylori*-associated ulcers is higher in developing countries, while NSAID-induced ulcers are more prevalent in industrialized nations. Understanding these variations is crucial for tailoring preventive measures to specific populations [20]. Recent epidemiological studies have indicated a decreasing trend in the incidence of complications related to peptic ulcers, especially in developed countries [21]. This decline can be attributed to successful *H. pylori* eradication strategies, improved diagnostics, and better management of risk factors. However, ongoing efforts are essential to address healthcare disparities and variations in risk factor prevalence globally [22].

Helicobacter Pylori-Associated PUD

Helicobacter pylorus, a gram-negative bacillus residing within gastric epithelial cells, plays a pivotal role in PUD etiology. Accountable for 90 % of duodenal ulcers and 70 % to 90 % of gastric ulcers, *H. pylori* infection is widespread among individuals with lower socioeconomic status and is frequently acquired during childhood [23].

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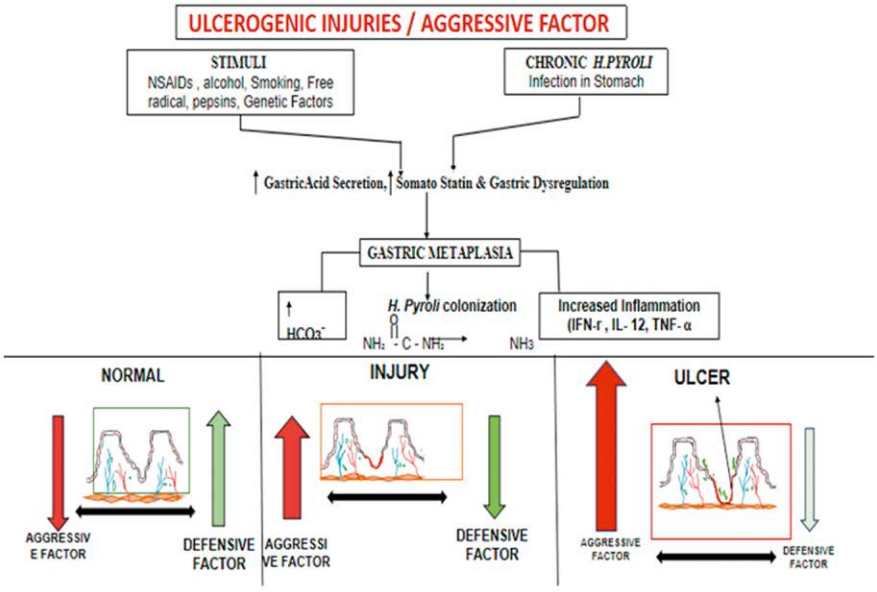

▶ **Fig. 1** Ulcerogenic/aggressive factors.

NSAID-Associated PUD

Mechanism of Action

Nonsteroidal anti-inflammatory drugs (NSAIDs) stand as the second most common cause of PUD after *H. pylori* infection. Prostaglandins, protective to the gastric mucosa, are inhibited by NSAIDs through the suppression of the COX-1 enzyme. This inhibition results in decreased production of gastric mucus and bicarbonate, alongside a reduction in mucosal blood flow, contributing to the development of peptic ulcers [24].

Mechanisms

The bacterium employs various virulence factors to adhere to and inflame the gastric mucosa, leading to hypochlorhydria or achlorhydria, ultimately resulting in gastric ulceration. Key virulence factors include:

Urease

Breaks down urea into ammonia, neutralizing the acidic gastric environment.

Toxins (CagA/VacA)

Associated with inflammation of stomach mucosa and damage to host tissue.

Flagella

Provides motility, aiding movement toward the gastric epithelium [25].

Medications

Beyond NSAIDs

Medications beyond NSAIDs, including bisphosphonates, corticosteroids, potassium chloride, and fluorouracil, have been implicated in the etiology of PUD. Smoking, though exhibiting a non-linear correlation, plays a role in duodenal ulcers, while alcohol can irritate the gastric mucosa, inducing acidity [26].

Rare Causes of PUD

Uncommon Yet Significant Contributors

Rare causes of PUD encompass various conditions, including [27]:

- Zollinger–Ellison Syndrome (ZES): marked by hypersecretion of gastric acid.
- Malignancies: Gastric, lung cancer, and lymphomas may contribute to PUD.
- Stress: Acute illness burns, and head injuries can exacerbate ulcer formation.
- Viral Infections, Vascular Insufficiency, Radiation Therapy: Uncommon factors with potential ulcerogenic effects.
- Inflammatory Conditions: Crohn's disease contributes to mucosal damage.
- Chemotherapy: An additional contributor to the multifactorial landscape of PUD.
- Systemic Conditions: Cystic fibrosis and hyperparathyroidism induce a hyper secretory environment.

Pathophysiology

A comprehensive understanding of the pathophysiology of peptic ulcers is paramount for developing targeted therapeutic approaches [28]. Peptic ulcer disease (PUD) manifests as a result of a delicate equi-

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librium disruption between the protective and destructive factors within the gastric mucosa. This intricate interplay involves various risk factors, each contributing mechanistically to the development of peptic ulcers as shown in ▶**Fig. 2 (**Pathophysiology of Peptic ulcer**)** [29].

Imbalance in Gastric Mucosal Factors

Protective Factors

The gastric mucosa is endowed with protective mechanisms that guard against ulcer formation. These include the production of mucus, bicarbonate secretion, and a robust blood flow that facilitates mucosal repair [30].

Destructive Factors

Conversely, destructive factors, such as *H. pylori* infection, NSAID use, a family history of PUD, emigration from developed nations, and specific ethnic predispositions, can compromise the protective mechanisms, leading to the initiation and progression of peptic ulcers [31].

Defects in the Mucosa and Muscularis Mucosa

Peptic ulcers are characterized by defects in the mucosal layer that extend to the muscularis mucosa. This compromise in structural integrity exposes the inner layers to the corrosive effects of gastric acidity [32].

H. pylori Infection

Mechanism of Colonization

H. pylori, a Gram-negative bacterium, are a pivotal player in PUD. It colonizes the gastric mucosa, initiating an inflammatory response. The bacterium's unique ability to evade the host's immune system allows for persistent colonization [33].

Impact on Bicarbonate Secretion

H. pylori further disrupt the delicate balance by impairing the secretion of bicarbonate, a key component in neutralizing gastric acid. This impairment promotes increased acidity within the gastric environment, creating an ideal milieu for the development and progression of peptic ulcers [34].

Gastric Metaplasia

Prolonged *H. pylori* infection can induce gastric metaplasia, wherein the normal gastric epithelium undergoes transformation into an intestinal-like mucosa. This alteration not only contributes to mucosal damage but also enhances the vulnerability of the gastric lining to acidic insults [35].

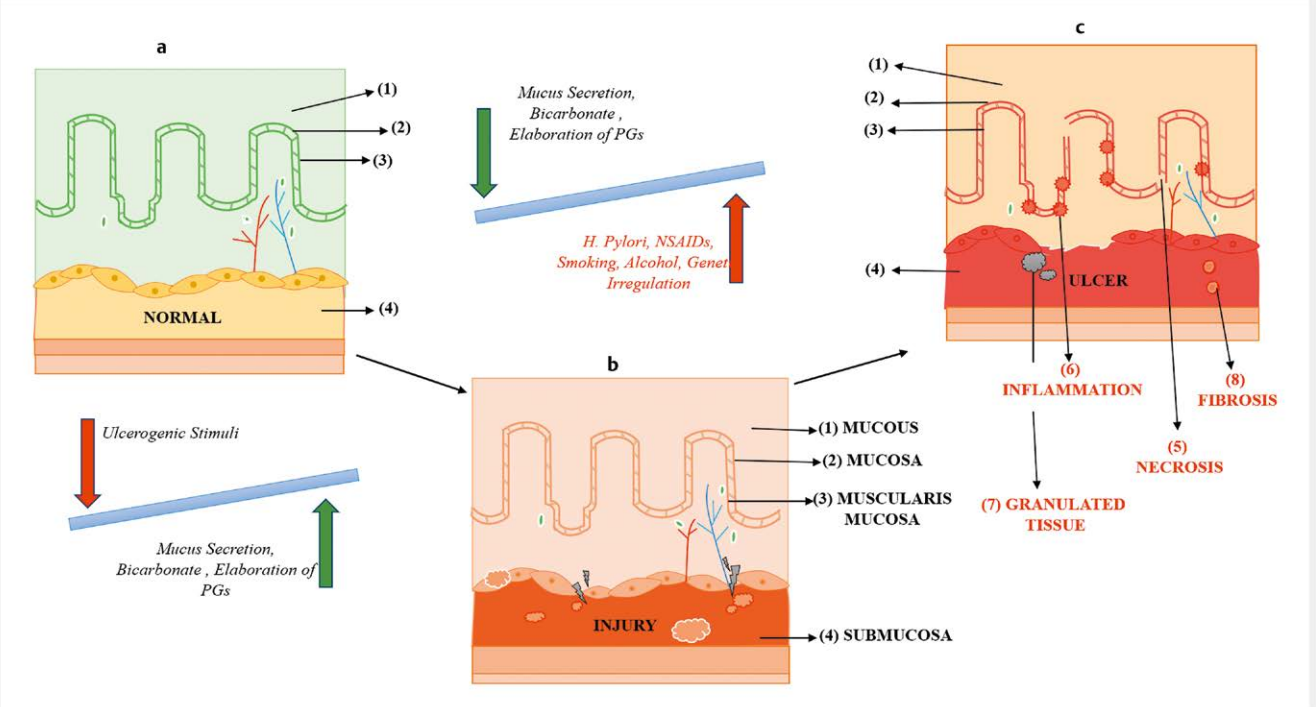
NSAID-Induced Ulcers

Prostaglandin Inhibition

Nonsteroidal anti-inflammatory drugs (NSAIDs), widely utilized for their anti-inflammatory properties, pose a significant risk for peptic ulcers. NSAIDs inhibit prostaglandin synthesis, compromising the mucosal barrier's protective effects [36].

Compromised Bicarbonate Secretion

Similar to *H. pylori*, NSAIDs compromise the ability of mucosal cells to secrete bicarbonate. This dual impact exacerbates the susceptibility of the mucosa to gastric acidity [37].



▶**Fig. 2** Pathophysiology of peptic ulcer.

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Genetic and Ethnic Factors

Hereditary Predisposition

A family history of PUD, especially in first-degree relatives, indicates a genetic predisposition. Specific genetic variations influence an individual's susceptibility to peptic ulcers [38].

Ethnic Disparities

Certain ethnic groups, including African American and Hispanic populations, exhibit an increased vulnerability to PUD. The mechanistic underpinnings of these disparities warrant further exploration [39].

Peptic ulcer disease (PUD) is a complex gastroenterological condition, and recent advances in molecular research have provided unprecedented insights into the intricate pathways that govern its development [39]. Peptic ulcer disease (PUD) unfolds through intricate molecular mechanisms involving altered levels of specific prostaglandins, cytokines, and interleukins, each playing a distinctive role in the erosion of the gastric layer and the subsequent development of ulcers [40].

Inflammatory Mediators in Ulcer Formation

Inflammation plays a central role in the initiation and progression of peptic ulcers. Recent studies have highlighted the involvement of various inflammatory mediators in orchestrating the cascade of events leading to mucosal damage [41].

Tumor Necrosis Factor-alpha (TNF-α)

TNF-α, a key proinflammatory cytokine, has emerged as a pivotal player in ulcer development. It induces mucosal damage by promoting the secretion of other inflammatory mediators, disrupting the balance between protective and aggressive factors in the gastric mucosa [42].

Interleukins (ILs)

Specific interleukins, such as IL-1 and IL-6, have been implicated in the modulation of mucosal inflammation. These cytokines contribute to the breakdown of the mucosal barrier, creating an environment conducive to ulcer formation [43].

Leukotrienes and Prostaglandins

The interplay between leukotrienes and prostaglandins is crucial in regulating gastric mucosal integrity. Imbalances in their production, influenced by inflammatory stimuli, contribute to the erosive effects on the mucosa, paving the way for ulceration [44]. In the context of PUD, a key player is the dysregulation of prostaglandins, particularly the decrease in prostaglandin E2 (PGE2). Prostaglandins are critical for maintaining the integrity of the gastric mucosa by promoting mucus and bicarbonate secretion, which act as protective barriers against the corrosive effects of gastric acid [45]. Nonsteroidal anti-inflammatory drugs (NSAIDs), commonly implicated in peptic ulcer development, inhibit the synthesis of prostaglandins by blocking the cyclooxygenase (COX) enzyme, particularly COX-1 [46]. This inhibition results in decreased PGE2 production, leading to compromised mucosal defense mechanisms and an increased susceptibility to mucosal injury [47].

Cytokines and Their Role in Ulcerogenesis

TGF-β (Transforming Growth Factor-beta)

TGF-β, traditionally recognized for its role in tissue repair, exhibits a dual role in ulcerogenesis. While it participates in mucosal healing, dysregulation of TGF-β signaling can lead to fibrosis and scarring, perpetuating the ulcerative process [48].

IL-10 (Interleukin-10)

IL-10, known for its anti-inflammatory properties, serves as a crucial counterbalance to proinflammatory cytokines. Dysregulation of IL-10 expression can disrupt this balance, fostering an inflammatory microenvironment that facilitates ulcer development [49].

Signaling Pathways

NF-κB (Nuclear Factor-kappa B)

NF-κB, a central player in inflammatory responses, is implicated in the pathogenesis of peptic ulcers. Activation of NF-κB signaling pathways contributes to the transcription of proinflammatory genes, perpetuating the inflammatory milieu in the gastric mucosa [50].

MAPK (Mitogen-Activated Protein Kinase) Pathway

The MAPK pathway, comprising extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases (JNK), and p38, is intricately involved in cellular responses to stress and inflammation. Dysregulation of the MAPK pathway has been linked to the erosion of the mucosal barrier, fostering conditions conducive to ulcer formation [51].

Mechanisms of Erosion

The mechanisms by which these inflammatory mediators contribute to the erosion of the gastric layer involve a complex interplay of events as shown in ▶ **Fig. 3** (Intricated mechanisms involved in peptic ulcer erosion) [52]. The decreased prostaglandin levels, especially PGE2, compromise the protective mucosal barrier, allowing gastric acid to exert its corrosive effects on the underlying tissue. TNF-α, IL-1, and IL-6 contribute to inflammation and disrupt the finely tuned equilibrium between protective and aggressive factors in the gastric mucosa [53]. TNF-α, in particular, is known to induce apoptosis of gastric epithelial cells, further compromising the mucosal barrier. In addition to their direct effects on the gastric mucosa, these mediators also influence other crucial pathways. For instance, the activation of NF-κB, a downstream target of TNF-α, promotes the transcription of pro-inflammatory genes, sustaining the inflammatory environment [54]. The MAPK pathway, including ERK, JNK, and p38, when dysregulated, contributes to the erosion of the mucosal barrier, creating an environment conducive to ulcer formation [55].

Diagnostic Approaches

Accurate diagnosis of peptic ulcer disease (PUD) is essential for guiding appropriate therapeutic interventions and preventing complications [56]. The diagnostic landscape has evolved significantly, incorporating a range of tools and techniques to identify and classify peptic ulcers. This comprehensive overview details the latest diagnostic approaches, emphasizing the importance of a thorough

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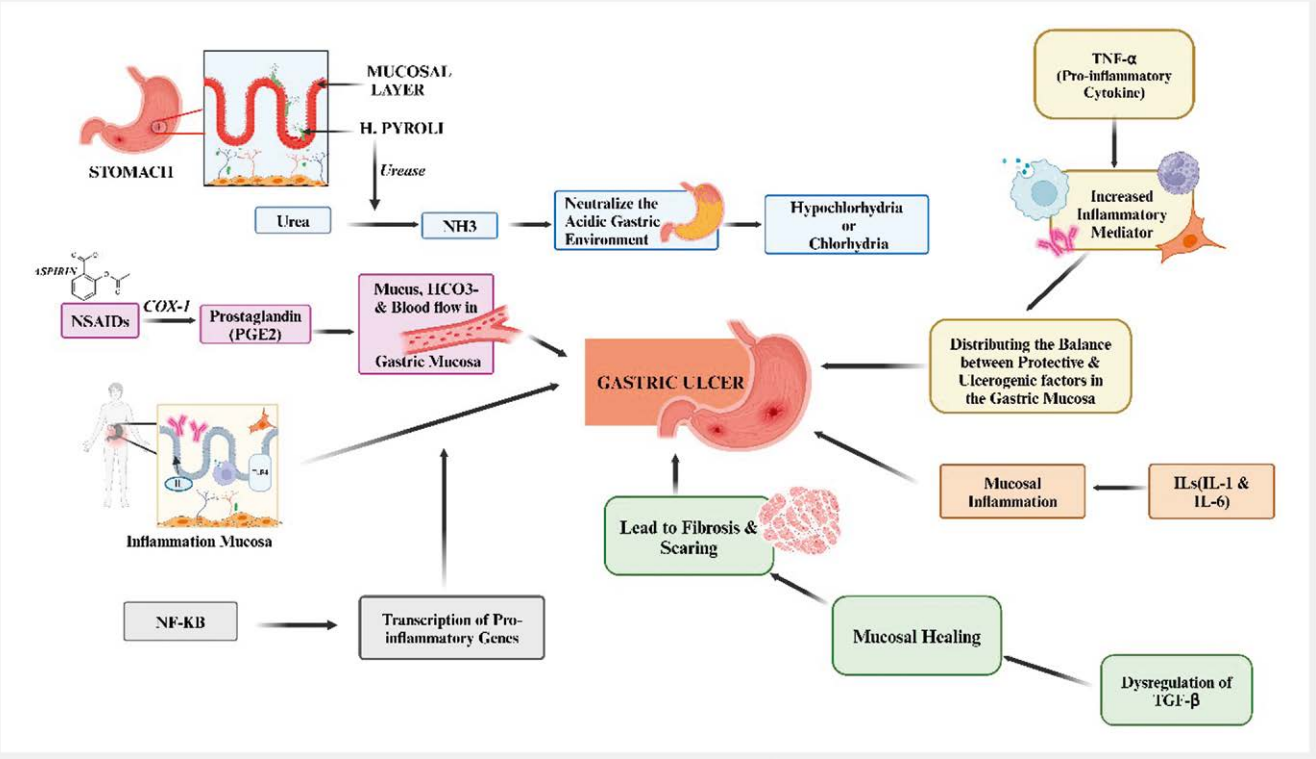

▶ **Fig. 3** Intricated mechanisms involved in peptic ulcer erosion.

initial assessment and subsequently delving into specific investigations [57].

Initial Investigations

Upper Gastrointestinal Endoscopy

Regarded as the primary and highly accurate diagnostic test for peptic ulcer disease (PUD), upper gastrointestinal endoscopy demonstrates sensitivity and specificity of up to 90 %. Specifically advised for individuals aged 50 and above experiencing new-onset dyspeptic symptoms, this procedure enables the direct observation of gastric and duodenal ulcers [58]. The American Society of Gastrointestinal Endoscopy advocates for its application in patients who exhibit upper abdominal pain or dyspeptic symptoms indicative of PUD, particularly in the presence of alarm symptoms [59].

Helicobacter pylori Carbon-13 Urea Breath Test or Stool Antigen Test

Rapid and reliable, these non-invasive tests assess the presence of *H. pylori* infection, a significant contributor to PUD. The carbon-13 urea breath test detects the radiolabeled carbon dioxide exhaled by the lungs in the presence of urease produced by *H. pylori.* Stool antigen tests and serologic testing are alternative methods to identify *H. pylori* infection [60].

Full Blood Count (FBC)

A complete blood workup, including FBC, aids in identifying anaemia, a potential consequence of bleeding associated with peptic ulcers. Additionally, liver function tests, and levels of amylase and lipase contribute to a comprehensive assessment [61].

Investigations to Consider

Fasting Serum Gastrin Level

When Zollinger-Ellison syndrome is suspected, measuring fasting serum gastrin levels becomes crucial. Increased levels may indicate the presence of gastrin-secreting tumors [62].

Urine NSAID Screen

Given the role of NSAIDs in peptic ulcer development, a urine screen for nonsteroidal anti-inflammatory drugs (NSAIDs) can be considered, especially in patients with a history of NSAID use [63].

Helicobacter pylori Testing

Serologic Testing, Urea Breath Test, and Stool Antigen Test

These tests aid in detecting *H. pylori* infection. These tests not only diagnose the infection but also play a crucial role in confirming eradication post-treatment [64].

Endoscopic Biopsy

Endoscopic biopsy, while not routinely recommended, becomes essential if eradication treatment fails or if antibiotic resistance is

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suspected. Biopsies from multiple sites increase sensitivity, with gastric ulcers commonly found on the lesser curvature and duodenal ulcers in the first part of the duodenum [65].

Imaging Studies

Barium Swallow and Abdominal CT Scan

In situations where upper gastrointestinal endoscopy is contraindicated, a barium swallow may be indicated. Additionally, a contrast-enhanced abdominal CT scan can provide insights into complications such as perforation and gastric outlet obstruction [66].

Current Treatment Options

Initial Management

Eradication of Helicobacter pylori (*H. pylori*)

Central to PUD management is the identification and eradication of *H. pylori* infection. Successful eradication is associated with higher healing rates, as demonstrated in a meta-analysis revealing significantly elevated ulcer remission rates in patients free of *H. pylori* compared to those with persistent infection. Treatment regimens for *H. pylori* involve a multi-faceted approach, and the choice of therapy is paramount in achieving lasting eradication [67].

Discontinuation of NSAIDs

NSAIDs and peptic ulcer development, discontinuation or avoidance of NSAIDs is a crucial step in managing PUD. NSAIDs, including aspirin, elevate the risk of peptic ulcer disease and are linked to increased complications, making their cessation an integral component of initial management [68].

Addressing Rare or Unclear Causes

Unraveling the etiology of peptic ulcers is essential. Rare causes, such as infections, Crohn's disease, or ischemia, require specific and targeted interventions. Gastrointestinal bleeding, often linked to severe coronavirus infections, emphasizes the need for a comprehensive evaluation to exclude rare causes of PUD. The prevalence of PUD in this context underscores the importance of addressing potential complications promptly [69].

Initial Antisecretory Therapy

Choice of Therapy – Proton Pump Inhibitors (PPIs)

Antisecretory therapy takes center stage in promoting ulcer healing. Proton pump inhibitors (PPIs), exemplified by omeprazole, have emerged as the preferred choice due to their superior efficacy compared to H_2-receptor antagonists (H_2RAs). PPIs provide robust acid suppression, resulting in easy controlling of symptoms and more rates of ulcer healing. Notably, PPIs outperform H_2RAs in healing NSAID-related ulcers, further solidifying their role in the therapeutic arsenal [70].

Medical Treatment

Antisecretory Drugs and Other Interventions

Antisecretory drugs, primarily PPIs, stand as the cornerstone of medical treatment for PUD. These drugs block acid production, offering symptomatic relief and fostering the healing process. Management may incorporate calcium supplements to mitigate the potential risk of bone fractures linked with long-term PPI use. NSAID-induced PUD necessitates the discontinuation or dose reduction of NSAIDs, and prostaglandin analogues like misoprostol may be employed as prophylaxis [71].

H. pylori-Induced PUD Treatment

The first-line treatment for *H. pylori*-induced ulcer involves a triple regimen composed of two antibiotics and a PPI. The selection of antibiotics considers the presence of antibiotic resistance. If initial therapy fails, then quadruple therapy with bismuth and alternative antibiotics is instituted [72].

Refractory Disease and Surgical Treatment

Surgical treatment becomes imperative in cases of refractory disease, where patients remain unresponsive to medical interventions or are at high risk of complications. Refractory peptic ulcers, those persisting despite 8–12 weeks of PPI therapy, may be indicative of persistent *H. pylori* infection, ongoing NSAID use, or significant comorbidities hindering ulcer healing. Surgical options, such as vagotomy or partial gastrectomy, are considered for such cases, ensuring a comprehensive approach to address the underlying causes [73].

Advances and Challenges in Peptic Ulcer Treatment and Management

In the realm of treating Peptic Ulcer Disease (PUD), recent advances reflect a shift towards more nuanced and personalized strategies. Traditional approaches to *Helicobacter pylori (H. pylori)* eradication have evolved, with tailored regimens acknowledging the variable landscape of antibiotic resistance [74]. This move optimizes treatment outcomes and seeks to mitigate the diminishing efficacy of conventional therapies. A noteworthy breakthrough comes in the form of vonoprazan, a novel acid suppressant. By competitively inhibiting gastric H^+/K^+-ATPase, vonoprazan exhibits promise in eradicating clarithromycin-resistant *H. pylori* strains. However, the prolonged use of acid suppressants, whether traditional or novel, introduces potential side-effects, including hypergastrinemia, pneumonia, bacterial overgrowth, and C. difficile infection, necessitating careful consideration in treatment planning [75].

In the preventive arena, ongoing research into a vaccine against H. pylori offers hope for a ground-breaking development. While still in its developmental phase, this vaccine holds potential as a primary prevention measure, aiming to reduce the incidence of *H. pylori* infection and its associated complications [76]. Moreover, the quest for novel therapeutic avenues has led to the exploration of natural products, particularly monoterpenes derived from medicinal plants. These compounds, with diverse chemical structures, exhibit anti-ulcer, healing, and antimicrobial activities, positioning them as promising alternatives for PUD management [77].

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However, persistent challenges underscore the complexity of effectively managing PUD. Antibiotic resistance in *H. pylori*, though showing a declining trend, remains a significant hurdle. Resistance rates, particularly to clarithromycin, impact the success rates of conventional antibiotic-based therapies. Moreover, the side-effects associated with prolonged acid suppressant use, including vonoprazan, necessitate vigilant monitoring and careful dosage considerations [78]. As efforts are directed towards developing new anti-*H. pylori* drugs and exploring natural compounds, bridging gaps in translating these findings to clinical applications remains a challenge. Further research is needed to understand the mechanisms of action, optimal dosages, and potential interactions of monoterpenes, positioning them as potential but yet-to-be-standardized therapeutic agents. The landscape of PUD treatment is marked by a dichotomy of promising advances and persistent challenges. Tailored eradication strategies, novel acid suppressants, vaccine development, and the exploration of natural compounds represent positive strides. However, the intricate web of challenges, including antibiotic resistance, side-effects of acid suppressants, and the need for innovative *H. pylori* management, necessitates ongoing research and a comprehensive approach to enhance the precision and efficacy of PUD treatment modalities [79].

Conclusion

In summarizing our dive into peptic ulcer management, some crucial points emerge. Strategies targeting *Helicobacter pylori*, along with new acid suppressants and the prospect of an *H. pylori* vaccine, mark significant progress. Natural compounds like monoterpenes also show promise. Challenges, such as *H. pylori* resistance and how to best use acid suppressants, remain. The conclusion here is a call for ongoing research. Understanding new therapies, figuring out the right doses, and decoding potential interactions are the tasks ahead. In essence, this review points to the importance of ongoing research in peptic ulcer management. The journey forward involves a steady pursuit of knowledge, delving deeper into the details of treating peptic ulcers. As we stand at the brink of scientific progress, the focus remains on the ongoing evolution of peptic ulcer management through dedicated research.

Acknowledgement

The authors express their gratitude towards Head and Faculty members of Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, India; Faculty of Pharmaceutical Sciences, Rama University, Kanpur, India and Amrapali Institute of Pharmacy and Sciences, Haldwani, India for providing research environment and all necessary facility for conducting research.

Conflict of Interest

The authors declare that they have no conflict of interest.

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