Bridging Gaps in Peptic Ulcer Therapy: The Role of Herbal Medicine in Healing and Prevention

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Abstract

Peptic ulcer disease (PUD) is a prevalent gastrointestinal disorder affecting nearly four million people annually, with significant morbidity arising from complications such as bleeding and perforation. It results from an imbalance between aggressive factors—Helicobacter pylori infection, non-steroidal anti-inflammatory drugs (NSAIDs), gastric acid, and pepsin—and mucosal defenses including mucus secretion, bicarbonate, prostaglandins, and blood flow. Current therapies, including proton pump inhibitors (PPIs), H_2 receptor antagonists, prostaglandin analogs, and selective COX-2 inhibitors, provide symptomatic relief but exhibit limitations such as incomplete mucosal protection, adverse effects, and high recurrence rates, particularly in NSAID-induced ulcers. Herbal medicines have gained increasing attention as potential complementary or alternative treatments due to their multi-targeted actions, affordability, and safety profiles. Plants such as Glycyrrhiza glabra, Berberis aristata, Curcuma longa, Zingiber officinale, Aloe vera, and Ocimum sanctum demonstrate antioxidant, anti-inflammatory, anti-H. pylori, and mucosal-protective properties. These herbs enhance mucus secretion, restore antioxidant enzymes (SOD, catalase, GSH), modulate prostaglandin synthesis, and promote epithelial regeneration, thereby facilitating ulcer healing and preventing recurrence. Synergistic combinations, notably Glycyrrhiza glabra with Berberis aristata, show superior gastroprotection compared to monotherapy.

This review highlights the pathophysiology of PUD, evaluates current treatment challenges, and explores the therapeutic prospects of herbal interventions. Standardized clinical trials and regulatory measures are essential to establish efficacy, safety, and integration of these plant-based therapies in peptic ulcer management.

Key words: *Peptic Ulcer Disease (PUD), Helicobacter pylori, NSAID-induced Ulcers, Herbal Medicine, Gastroprotection, Antioxidant and Anti-inflammatory Activity*

1.Introduction

The term *"peptic"* is derived from the Greek word peptikos, meaning to digest. Peptic ulcers (PUs) are lesions in the mucosal lining that extend into the muscularis mucosae, creating a hollow area surrounded by acute or chronic inflammation [1]. Peptic ulcer disease (PUD) refers to the erosion or ulceration of the lining of the digestive tract, compromising the protective mucosal barrier of the esophagus, stomach, and proximal small intestine (duodenum). It is increasingly recognized as a significant global health problem, affecting nearly 4 million people annually, with complications occurring in approximately 10–20% of cases [2]. The

highest prevalence is observed between 55 and 65 years of age, making it more common in older adults. Duodenal ulcers tend to occur more frequently in men, whereas gastric ulcers are slightly more prevalent in women [3].

PUD is typically defined as a mucosal defect greater than 3–5 mm in the stomach or duodenum, with noticeable depth, and is diagnosed endoscopically. This differs from dyspepsia, which is diagnosed based on symptoms alone. The condition arises from an imbalance between aggressive factors (such as gastric acid and pepsin) and the protective mechanisms of the gastric and duodenal mucosa [4]. Duodenal ulcers develop in the initial portion of the duodenum, while gastric ulcers occur within the stomach lining [5]. The extent of mucosal injury is influenced by individual susceptibility to non-steroidal anti-inflammatory drugs (NSAIDs) and the virulence of *Helicobacter pylori*. The mucosa has a natural capacity to resist injury caused by high acid secretion, bile reflux, and pepsin activity [6].

Additional risk factors include corticosteroid therapy, gastric malignancies or lymphoma, psychological stress, and conditions like Zollinger–Ellison syndrome, which leads to excessive acid production due to hypergastrinemia [7]. Common symptoms of PUD include recurrent heartburn, nausea, bloating, diarrhea, flatulence, and epigastric pain. These symptoms often improve with antacid use, while posterior ulcers may manifest as back pain [8]. Among the complications, bleeding is the most common and is a frequent cause of emergency admissions, with an estimated incidence of 100–170 cases per 100,000 individuals worldwide. Peptic ulcer bleeding is a potentially life-threatening condition, often presenting as hematemesis, melena (black tarry stools), or hematochezia.

Bleeding peptic ulcers can cause serious side effects such anemia, hypovolemic shock, multiorgan failure, and even death if treatment is not received. Peptic ulcer bleeding is thought to cause 5–12% of deaths [9]. The normal function of the affected organs may be disrupted by the negative side effects of conventional (allopathic) therapy for ulcers. Peptic, corneal, stomach, foot, and leg ulcers are only a few of the several types and locations of ulcers that can develop both internally and externally [10].

There are many traditional and alternative therapy options available, but many of them have drawbacks like toxicity, poor efficacy, or excessive cost. Despite their widespread use, botanical products contain a range of active chemicals that can have both positive andnegative effects. As a result, the use of herbal medicine needs to be backed by suitable laws to guarantee the quality of the product and well-planned randomized trials to assess itsefficacyand safety in treating ulcers [11].
Nowadays, finding new and efficient agents is becoming more and more important. Because of their affordability, availability, and long-term appropriateness, herbal medications in particular are becoming more and more popular. The potential of some medicinal plants withanti-ulcer and ulcer-healing qualities is highlighted in this article [12].

2. Pathophysiology

The stomach and duodenum are the primary regions of the gastrointestinal tract (GIT) exposed to gastric acid and pepsin. The precise etiology of peptic ulcer disease (PUD) is multifactorial but is predominantly attributed to an imbalance between aggressive factors (acid, pepsin, bile, and *Helicobacter pylori*) and defensive mechanisms (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, enhanced mucosal blood flow, and the intrinsic resistance of mucosal cells) mentioned in fig.1

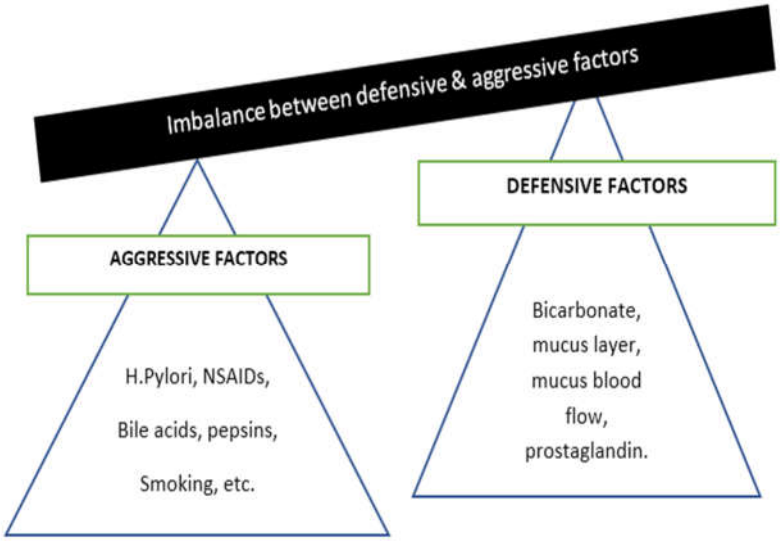

Figure 1: *Schematic representation of the pathogenesis of peptic ulcer.* The figure illustrates the imbalance between aggressive and defensive factors leading to ulcer formation. Aggressive factors such as *Helicobacter pylori* infection, NSAIDs, bile acids, pepsins, and smoking increase mucosal injury, while defensive factors including bicarbonate secretion, mucus layer, adequate mucosal blood flow, and prostaglandins protect the gastric mucosa. An imbalance tipping toward aggressive factors results in peptic ulcer development.

Peptic ulcers are acid-induced mucosal defects of the stomach and duodenum that extend into the submucosa or muscularis propria, whereas superficial mucosal damage not reaching these layers is classified as erosion. Almost half of the global population is colonized by *H. pylori*, a major causative agent of peptic ulcer disease [14]. This bacterium induces epithelial injury predominantly in the gastric antrum through an inflammatory cascade involving neutrophils, lymphocytes, plasma cells, and macrophages.

The exact mechanism of *H. pylori*-induced gastroduodenal lesions is not fully elucidated. The infection can cause either hypochlorhydria or hyperchlorhydria, influencing the ulcer type. Cytokines released during infection suppress parietal cell function, while *H. pylori* may directly interfere with the H^+/K^+-ATPase subunit, stimulate CGRP sensory neurons linked to somatostatin, or suppress gastrin secretion [15]. Although gastric ulcers are commonly associated with low gastric acid output, about 10–15% of *H. pylori*-infected individuals exhibit hypergastrinemia and reduced antral somatostatin levels, resulting in elevated histamine release and, consequently, increased gastric acid and pepsin secretion [16]. Eradication of *H. pylori* has been shown to normalize gastrin and somatostatin mRNA expression [17].

In most cases, gastric ulcers are characterized by hypochlorhydria and mucosal atrophy [18]. Non-steroidal anti-inflammatory drugs (NSAIDs) are another major cause of PUD, accounting for over 90% of ulcers, with approximately 25% of NSAID users developing peptic ulcers [19]. NSAID-induced mucosal injury occurs through multiple mechanisms. When exposed to acidic gastric juice (pH ~2), NSAIDs become protonated and readily cross lipid membranes into epithelial cells. Inside the neutral cytoplasmic environment (pH ~7.4), they ionize, releasing H^+ ions and becoming trapped, leading to mitochondrial uncoupling, reduced ATP production, compromised cell integrity, and increased membrane permeability. This cascade promotes topical epithelial damage, superficial hemorrhage, and erosions [20].

Another key mechanism involves cyclooxygenase-1 (COX-1) inhibition, which reduces prostaglandin synthesis. Prostaglandins are essential for maintaining mucosal protection by enhancing mucus and bicarbonate secretion, increasing blood flow, and supporting epithelial repair. Aspirin irreversibly acetylates COX, whereas most NSAIDs inhibit it reversibly and dose-dependently [21]. COX has two isoforms: COX-1, involved in gastrointestinal mucosal protection, and COX-2, primarily expressed at sites of inflammation. Non-selective NSAIDs (e.g., ibuprofen, naproxen, aspirin, indomethacin) inhibit both isoforms, whereas COX-2 selective inhibitors (e.g., celecoxib, rofecoxib) preferentially inhibit COX-2, demonstrating a 3–5% lower incidence of ulceration compared to conventional NSAIDs during endoscopic evaluations [22]. **Fig.2**

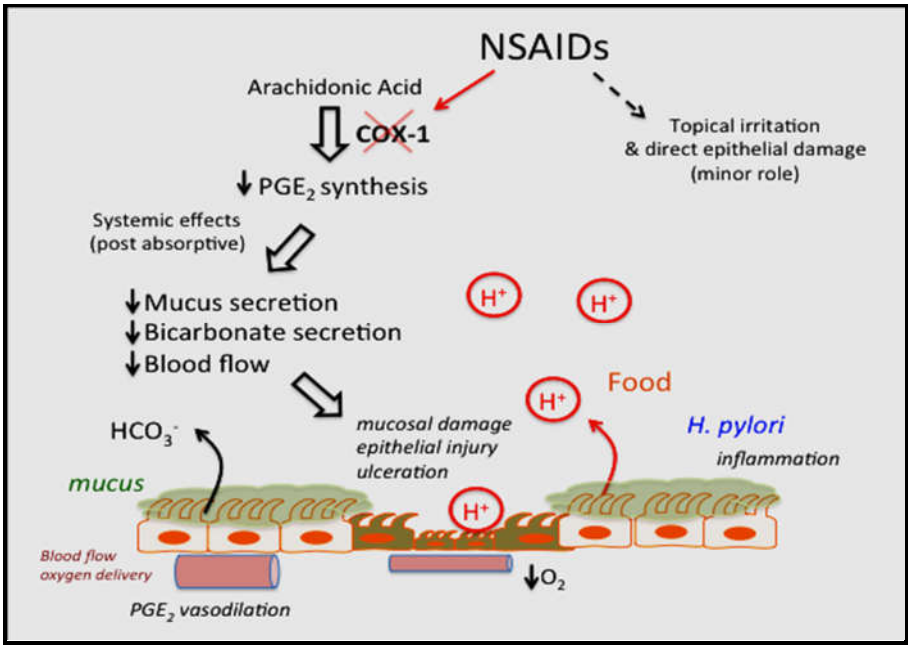

Figure 2: Pathogenesis of gastric damage by NSAIDs. Current evidence indicates that the majority of harmful effects mediated by NSAIDs result from inhibition of the synthesis of mucosal-protective prostaglandins produced by constitutive COX-1 activity. Direct drug-mediated irritant effects on epithelial cells appear to play only a minor role in GI toxicity. The presence of infections by the bacterium *H pylori* represents a separate risk factor that increases the likelihood of developing duodenal ulcers. [23]

3.Diagnosis of Peptic Ulcer

The diagnostic process for peptic ulcer disease (PUD) usually begins with clinical suspicion based on patient symptoms such as epigastric pain, burning sensation, postprandial fullness, or early satiety [24]. Duodenal ulcers often present with abdominal pain that worsens on an empty stomach and typically occurs two to three hours after meals or at night. In contrast, gastric ulcers are commonly associated with nausea, vomiting, weight loss, and postprandial abdominal discomfort [25].

Since *Helicobacter pylori* is a major cause of PUD, a "test-and-treat" strategy utilizing non-invasive tests is often recommended [26]. The primary diagnostic tests include:

3.1 Urea Breath Test

This is a preferred non-invasive method for detecting *H. pylori*. The patient ingests urea labeled with a special carbon isotope, either as a capsule, drink, or jelly. If *H. pylori* is present, it converts urea into carbon dioxide, which is then exhaled and collected in a container. Detection of the labeled carbon confirms active *H. pylori* infection [27].

3.2 Stool Monoclonal Antigen Test

Stool antigen tests using monoclonal antibodies are comparable in accuracy to urea breath tests when validated laboratory-based assays are used [28,29]. They are less expensive, require minimal equipment, and can also be employed as a test of cure. Proton pump inhibitors (PPIs) should ideally be discontinued two weeks prior to testing, although these tests are less affected by PPI use compared to urea breath tests.

3.3 Serologic Tests

Serologic testing detects *H. pylori*-specific immunoglobulin G (IgG) in the blood but cannot differentiate between active and past infection. These tests are most useful in mass screening programs or in patients unable to discontinue PPIs, such as those with gastrointestinal bleeding or continuous NSAID therapy, since they are not influenced by PPI or antibiotic use [30].

3.4 Endoscopy with Biopsy

Upper gastrointestinal (GI) endoscopy remains the gold standard for confirming a peptic ulcer diagnosis and identifying its underlying cause. During the procedure, a flexible endoscope equipped with a camera is used to visualize the esophagus, stomach, and duodenum. Tissue biopsies may be taken from the gastric mucosa for histopathological examination by a pathologist [31].

4. Treatment of Peptic ulcer drugs:

Class	Drugs	Mechanism	Adverse Effects	Refs
Proton Pump Inhibitors (PPIs)	Omeprazole, Pantoprazole, Rabeprazole, Lansoprazole, Esomeprazole	Inhibit H+/K+-ATPase (proton pump)	Headache, GI upset, Vitamin B12 deficiency, Osteoporosis	[32,33].
H2 Receptor Blockers	Cimetidine, Famotidine, Nizatidine, Ranitidine	Block H2 receptors on parietal cells	Headache, dizziness, thrombocytopenia	[34].
Antacids	Aluminium hydroxide, Magnesium hydroxide	Neutralize gastric acid, inhibit pepsin	Constipation, diarrhea, electrolyte imbalance	[35].

Potassium-Competitive Acid Blocker (P-CAB)	Vonoprazan	Inhibit H+, K+-ATPase	Diarrhea, URTI, back pain	[36,37].
Ulcer Protectives	Misoprostol, Sucralfate, Colloidal Bismuth Subcitrate (CBS)	Stimulate mucus production & enhance blood flow	Diarrhea, abdominal pain	[38].
Anti-*H. pylori* Drugs	Triple/Quadruple therapy (PPI + antibiotics ± bismuth)	Eradicate *H. pylori* via protein/DNA synthesis inhibition	GI upset, metallic taste	[39–40].

Table:1 Classes of antiulcer drugs with examples, mechanisms of action, common adverse effects, and references.

5. Limitations of Current Therapy in NSAID-Induced Peptic Ulcer

Despite advancements in the management of NSAID-induced peptic ulcers, several limitations persist in current therapeutic strategies. The primary treatment approach includes the use of proton pump inhibitors (PPIs), H_2-receptor antagonists, prostaglandin analogs (e.g., misoprostol), and selective COX-2 inhibitors. While these therapies offer symptomatic relief and some degree of mucosal protection, they do not fully eliminate the risk of ulcer formation or recurrence, especially in high-risk individuals.

5.1 Incomplete Mucosal Protection by PPIs

Proton pump inhibitors are the cornerstone of gastroprotection during NSAID therapy. They significantly reduce gastric acid secretion and promote ulcer healing. However, they do not directly address the underlying impairment of prostaglandin-mediated mucosal defense caused by NSAIDs. Thus, mucosal vulnerability remains, especially in the presence of other risk factors like *H. pylori*, age, or comorbidities [41]. Long-term PPI use is also associated with adverse effects such as hypomagnesemia, increased risk of enteric infections, and renal impairment [42].

5.2 Poor Tolerability and Compliance with Misoprostol

Misoprostol, a prostaglandin E1 analog, effectively counteracts NSAID-induced prostaglandin depletion and offers mucosal protection. However, its clinical utility is limited by frequent gastrointestinal side effects such as abdominal cramping, diarrhea, and nausea, which reduce patient compliance. Additionally, it is contraindicated in pregnancy due to its abortifacient properties [43].

5.3 Cost and Cardiovascular Risks of COX-2 Inhibitors

Selective COX-2 inhibitors (coxibs) were developed to minimize GI toxicity while preserving anti-inflammatory effects. While they have a lower incidence of ulcers compared to non-selective NSAIDs, concerns about increased cardiovascular risk, including myocardial infarction and stroke, have restricted their use in clinical practice [44]. Their higher cost also limits accessibility, particularly in resource-constrained settings.

5.4 Ineffectiveness in Preventing Small Intestinal Injury

current therapies like PPIs provide significant protection for the upper GI tract, they are largely ineffective in preventing NSAID-induced enteropathy (injury to the small intestine). This includes small intestinal ulcers, bleeding, and strictures, which are increasingly recognized due to advanced imaging techniques like capsule endoscopy [45].

5.5 Limited Efficacy in High-Risk Populations

Even with appropriate gastroprotective therapy, elderly patients, those with a prior history of ulcers, and individuals on concurrent anticoagulants or corticosteroids remain at high risk for ulcer recurrence and complications. Studies show that up to 25% of patients may still develop ulcers or GI bleeding despite prophylactic therapy [46].

5.6 Challenges with *H. pylori* Coinfection Management

Coinfection with *Helicobacter pylori* significantly increases the risk of NSAID-induced ulcers. While eradication therapy reduces ulcer risk, reinfection, antibiotic resistance, and treatment failure are common in many regions. Furthermore, *H. pylori* eradication alone may not prevent ulcers in chronic NSAID users if mucosal prostaglandins are continuously suppressed [47].

5.7 Lack of Patient Awareness and Adherence

Many patients, especially those using over-the-counter NSAIDs, are unaware of the gastrointestinal risks and the need for prophylactic therapy. Poor adherence to prescribed PPIs or misoprostol significantly reduces their protective efficacy, leading to preventable ulcer complications [48].

6. Prospects for Using Herbal Extracts to Treat Peptic Ulcer

(NSAID), is known to cause gastrointestinal complications, particularly peptic ulcers, through inhibition of prostaglandin synthesis, direct mucosal irritation, and impaired mucosal repair. Despite the availability of conventional therapies such as proton pump inhibitors (PPIs), H_2-receptor antagonists, and selective COX-2 inhibitors, significant limitations exist, including incomplete mucosal protection, adverse effects, and poor patient compliance. These limitations have prompted increasing interest in herbal medicine as a complementary or alternative therapeutic approach for managing aspirin-induced peptic ulcers. Herbal extracts offer a multifaceted mode of action, including anti-inflammatory, antioxidant, mucosal protective, and anti-*Helicobacter pylori* effects, with generally favorable safety profiles.

6.1 Antioxidant and Anti-inflammatory Properties

Aspirin-induced gastric injury is largely mediated through oxidative stress and inflammation. Several medicinal plants are rich in polyphenols, flavonoids, tannins, and saponins, which

neutralize reactive oxygen species (ROS) and inhibit pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β. For instance, *Glycyrrhiza glabra* (licorice) has demonstrated significant anti-inflammatory and antioxidant activity through its active constituent glycyrrhizin, which promotes mucosal healing by enhancing mucus secretion and reducing oxidative stress [49].

Similarly, Berberis aristata, known for its alkaloid berberine, exhibits gastroprotective action by reducing leukotriene and prostaglandin E2 levels and modulating oxidative enzymes such as superoxide dismutase (SOD) and catalase [50]. These properties are crucial in protecting the gastric mucosa from aspirin-induced damage.

6.2 Mucosal Defense Enhancement

Herbal extracts can strengthen the mucosal barrier by stimulating the production of mucus and bicarbonate, enhancing blood flow, and accelerating epithelial regeneration. For example, Aloe vera extract has been shown to upregulate prostaglandin E2 synthesis, promoting mucin production and angiogenesis [51]. Similarly, *Ocimum sanctum* (holy basil) and *Zingiber officinale* (ginger) have been observed to increase the expression of protective mucus and inhibit apoptosis of gastric epithelial cells [52].

6.3 Anti-*Helicobacter pylori* Activity

H. pylori infection often coexists with NSAID use and can significantly exacerbate ulcerogenesis. Certain herbal compounds, including berberine (from Berberis spp.), curcumin (from turmeric), and allicin (from garlic), have demonstrated anti-*H. pylori* activity through multiple mechanisms—such as urease inhibition, membrane disruption, and biofilm degradation [53]. These effects contribute to ulcer healing and recurrence prevention, especially in *H. pylori*-positive patients.

6.4 Synergistic and Multi-Targeted Action

Unlike synthetic drugs that typically target a single pathway, herbal extracts often contain multiple bioactive constituents that act synergistically to modulate various molecular targets involved in ulcerogenesis. For example, combining *Glycyrrhiza glabra* with *Berberis aristata* may provide superior gastroprotection compared to monotherapy by modulating COX pathways, enhancing mucin production, and neutralizing ROS simultaneously. This multi-targeted effect is particularly advantageous in managing complex conditions like aspirin-induced ulcers.[54]

7 Herbs commonly used for Peptic Ulcer Treatment:

This overview includes a summary of some of the main plants that have been mentioned in classical writings and recent studies that have demonstrated antiulcer capabilities.

7.1 Glycyrrhiza glabra (Licorice)

Glycyrrhiza glabra root extract is one of the most widely investigated natural remedies for peptic ulcer. In ethanol-, indomethacin-, and stress-induced ulcer models, doses of 50–200 mg/kg (oral) demonstrated a significant reduction in ulcer index and improved mucosal defense [1]. The extract increased mucus secretion, enhanced prostaglandin E2 levels, and decreased gastric acid secretion. Histopathological studies revealed a marked reduction in mucosal

erosion and submucosal edema at higher doses. Additionally, the antioxidant property of glycyrrhizin and flavonoids present in the plant contributed to decreased lipid peroxidation and increased superoxide dismutase (SOD) and glutathione (GSH) levels. This suggests a dual action: mucosal cytoprotection and acid suppression, making it a strong candidate for anti-ulcer therapy[55].

7.2 Berberis aristata (berberine source)

Berberine, derived from *Berberis aristata*, has shown potent anti-ulcer and anti-inflammatory effects in several ethanol- and NSAID-induced ulcer models in rats, with an effective dose range of 50–100 mg/kg [2]. The alkaloid reduced the lesion index, improved mucosal integrity, and significantly lowered TNF-α and IL-6 levels. Berberine enhanced nitric oxide (NO) bioavailability, which improved gastric mucosal blood flow. Histological evaluation demonstrated reduced epithelial cell disruption and enhanced regeneration of the gastric mucosa. Its mechanism is attributed to modulation of arachidonic acid metabolism, inhibition of reactive oxygen species (ROS), and enhancement of endogenous antioxidants. These findings indicate berberine may serve as an alternative to standard proton pump inhibitors (PPIs) in managing ulceration [56].

7.3 Curcuma species (Turmeric/Curcumin)

Curcuma-derived curcuminoids possess remarkable gastroprotective activity. Studies using ethanol-, indomethacin-, and pylorus ligation-induced ulcer models in rats reported significant ulcer reduction at 200–1000 mg/kg (extracts) or 100–200 mg/kg (curcumin) [3]. Curcumin enhanced mucus secretion, increased catalase and SOD activity, and inhibited myeloperoxidase (MPO) activity, reflecting decreased neutrophil infiltration. Histological analysis revealed restoration of gastric epithelial lining and reduced necrosis. Furthermore, curcumin modulates the NF-κB pathway, suppressing pro-inflammatory cytokines like TNF-α and IL-1β. Its antioxidant and anti-inflammatory dual action make it a promising herbal adjunct for chronic ulcer prevention and healing [57].

7.4 Zingiber officinale (Ginger)

Ginger and its active constituent zingerone exhibit strong anti-ulcer activity in ethanol- and indomethacin-induced ulcer models at 100–200 mg/kg (oral) [4]. The extract reduced gastric acid secretion and increased mucin content, contributing to mucosal protection. Histological observations showed decreased epithelial cell degeneration, lessened hemorrhage, and improved glandular architecture. Antioxidant enzyme levels, including SOD and catalase, were significantly restored, while malondialdehyde (MDA) levels decreased. Zingerone also inhibited gastric H+/K+-ATPase activity, showing a mechanism similar to standard anti-secretory drugs but with added antioxidant benefits [58]

7.5 Aloe vera

Aloe vera gel demonstrates effective gastroprotection in ethanol-induced gastric ulcer models at 200 mg/kg (oral) [5]. It exerts its effects through anti-inflammatory and anti-pyroptotic mechanisms, particularly via suppression of NLRP3/GSDMD signaling. The gel increased gastric mucin content, reduced ulcer area, and promoted re-epithelialization in histopathological studies. Biochemical parameters indicated elevated GSH levels and reduced

MDA and nitric oxide overproduction. Its polysaccharide-rich composition enhances mucosal barrier function, supporting both prevention and healing of ulcers [59].

7.6 Allium sativum (Garlic)

Garlic extracts, particularly aged garlic extract, have been studied in indomethacin- and ethanol-induced gastric ulcer models, with effective doses ranging from 100 to 500 mg/kg (oral) [6]. It inhibits gastric acid secretion, enhances prostaglandin synthesis, and provides strong antioxidant defense by increasing GSH and catalase levels. Histopathology revealed reduced mucosal necrosis and improved epithelial regeneration. Allicin and S-allylcysteine are key bioactives responsible for these effects. Moreover, garlic may exhibit mild antimicrobial effects against *H. pylori*, contributing to its broader anti-ulcer potential [60].

7.7 Ocimum sanctum (Holy Basil/Tulsi)

Extracts of *Ocimum sanctum* have shown significant protective effects in ethanol-, stress-, and aspirin-induced ulcer models, especially at 100–200 mg/kg [7]. The extract decreases gastric acid secretion, increases mucus and bicarbonate secretion, and exhibits strong free radical scavenging activity. Histopathological analysis showed a reduction in hemorrhagic streaks and epithelial erosion. Active constituents like eugenol and ursolic acid modulate the stress-induced hypothalamic-pituitary-adrenal (HPA) axis, lowering corticosterone levels that can aggravate ulcers [61].

7.8 Phyllanthus niruri

Methanolic extract of *Phyllanthus niruri* effectively prevents ethanol-acid-induced gastric mucosal injury at 200–400 mg/kg [8]. It significantly reduced gastric lesion scores, improved antioxidant enzyme activity (SOD, catalase), and inhibited lipid peroxidation. Histology showed restored mucosal folds and reduced inflammatory infiltrates. Lignans and polyphenols present in the plant contribute to its anti-inflammatory and anti-secretory action [62]

7.9 Psidium guajava (Guava)

Psidium guajava leaf and seed extracts exert protective effects in ethanol- and aspirin-induced ulcer models at 200–400 mg/kg (oral) [9]. The extract reduced gastric acidity, increased mucin production, and significantly decreased the ulcer index. Histopathological findings demonstrated reduced congestion and epithelial erosion with near-normal mucosal structure. Its flavonoid content, particularly quercetin, is responsible for free radical scavenging and cytoprotection [63].

7.10 Nigella sativa (Black Seed)

Nigella sativa oil and thymoquinone provide gastroprotection in ethanol- and NSAID-induced ulcers, with thymoquinone at 10–20 mg/kg and oil at 50 mg/kg (oral) showing significant reduction in ulcer index [10]. It enhances SOD, catalase, and GSH while reducing pro-inflammatory cytokines such as IL-6 and TNF-α. Histopathological studies revealed reduced mucosal necrosis and accelerated healing. Its mechanism involves both antioxidant and anti-secretory activity, making it an effective complementary therapy [64].

Future Direction

Future research on herbal interventions for peptic ulcer disease (PUD) should focus on several critical areas to overcome current therapeutic limitations. Firstly, standardization of herbal extracts is essential to ensure consistent phytochemical composition, potency, and bioavailability. Well-designed randomized controlled clinical trials are needed to validate the preclinical evidence supporting herbs such as *Glycyrrhiza glabra*, *Berberis aristata*, *Curcuma longa*, and their combinations in managing NSAID- and *Helicobacter pylori*-induced ulcers. Advanced techniques like molecular docking, network pharmacology, and metabolomics may help elucidate the multi-targeted mechanisms underlying their gastroprotective effects.

Secondly, the development of novel herbal formulations, including nanoparticle-based drug delivery systems, gastro-retentive tablets, and synergistic polyherbal combinations, could improve therapeutic efficacy, patient compliance, and mucosal retention. Furthermore, long-term safety evaluations are necessary to assess potential herb–drug interactions, reproductive toxicity, and chronic use implications.

Finally, integration of herbal therapies into evidence-based clinical guidelines and the establishment of stringent regulatory frameworks will enhance their acceptance as complementary or alternative strategies in ulcer management. Collaborative research between pharmacologists, clinicians, and traditional medicine experts will be pivotal in translating these plant-based therapies from bench to bedside.

Conclusion

Peptic ulcer disease (PUD) remains a major gastrointestinal health burden globally, with significant morbidity, mortality, and socioeconomic impact. Despite the availability of conventional therapies—such as proton pump inhibitors, H_2 receptor antagonists, prostaglandin analogs, and selective COX-2 inhibitors—therapeutic limitations persist, including incomplete mucosal protection, adverse drug reactions, high recurrence rates, and poor efficacy in NSAID-induced enteropathy. The multifactorial etiology of PUD, involving *Helicobacter pylori* infection, NSAID use, oxidative stress, and impaired mucosal defense, necessitates a more holistic and multi-targeted therapeutic approach.

Herbal medicines have emerged as promising candidates due to their antioxidant, anti-inflammatory, mucosal protective, and anti-*H. pylori* properties, along with their affordability and safety. Plants such as *Glycyrrhiza glabra*, *Berberis aristata*, *Curcuma longa*, *Zingiber officinale*, and *Ocimum sanctum* demonstrate significant gastroprotective potential by modulating reactive oxygen species, enhancing prostaglandin E_2 synthesis, restoring endogenous antioxidants (SOD, catalase, GSH), and promoting epithelial regeneration. Furthermore, polyherbal combinations, particularly *Glycyrrhiza glabra* with *Berberis aristata*, show synergistic effects superior to monotherapy. The integration of these herbal approaches, supported by standardized formulations and clinical validation, holds the potential to revolutionize ulcer management by reducing recurrence, improving safety, and minimizing adverse drug interactions. However, their clinical translation requires rigorous scientific validation, standardized dosing, quality control, and inclusion in therapeutic guidelines to bridge the gap between traditional wisdom and modern evidence-based medicine.

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