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COMBATTING PEPTIC ULCER DISEASE IN THE ERA OF ANTIMICROBIAL RESISTANCE: INTEGRATING MODERN AND HERBAL THERAPIES FOR SUSTAINABLE MANAGEMENT

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ABSTRACT

Peptic ulcer disease (PUD), primarily driven by *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drug use, remains a global health concern. Although conventional therapies, including proton pump inhibitors (PPIs) and antibiotics, have significantly reduced the disease burden, rising antimicrobial resistance and the long-term adverse effects of PPIs pose major therapeutic challenges. This evolving landscape necessitates the development of alternative and complementary treatment strategies. In recent years, medicinal plants with antibacterial, antioxidant, acid-neutralizing, and urease-inhibitory properties have gained attention for their potential to sustainably manage peptic ulcer disease. Herbal agents such as *Glycyrrhiza glabra*, *Moringa oleifera*, *Azadirachta indica*, and *Curcuma longa* have demonstrated proven in vitro and in vivo efficacy against *H. pylori*, with additional gastroprotective benefits. Advances in extraction optimization, phytochemical standardization (via TLC, HPTLC, FTIR, and UV/Vis), and antimicrobial screening have improved the reliability and reproducibility of plant-based therapeutics. Furthermore, combining herbal remedies with existing allopathic treatments may enhance eradication rates, mitigate resistance development, and reduce the side effects. This integrative approach aligns with the World Health Organization's call for rational antimicrobial use and sustainable health care practices. However, rigorous clinical validation, safety profiling, and standardization are essential for its mainstream acceptance. This review

underscores the therapeutic promise of modern herbal integration in PUD management and advocates interdisciplinary collaboration to address the dual challenges of ulcer recurrence and antimicrobial resistance. Leveraging the synergistic strengths of both systems could offer a safe, effective, and holistic model for treating peptic ulcers in the current era.

KEYWORDS: Peptic ulcer disease, antimicrobial resistance, *Helicobacter pylori*, herbal medicine, modern methods of treating peptic ulcer disease.

1. INTRODUCTION

1.1 Peptic ulcer disease Pathophysiology of PUD: Peptic ulcer disease (PUD) is a multifactorial gastrointestinal disorder characterized by mucosal erosions in the stomach or duodenum due to the corrosive action of gastric acid and pepsin (Malfertheiner, Chan, & McColl, 2024). The disease spectrum includes gastric ulcers, duodenal ulcers, and stress-related mucosal injuries. Historically, PUD was believed to be a consequence of stress, spicy foods, and lifestyle factors. However, groundbreaking research in the late 20th century led to the discovery of *Helicobacter pylori* (*H. pylori*) as the primary etiological agent, transforming the conceptual framework and treatment paradigms of the disease (Ashraf et al., 2024).

PUD remains a significant global health concern, with a broad spectrum of clinical manifestations ranging from epigastric discomfort to gastrointestinal bleeding and perforation. Despite advancements in pharmacotherapy, PUD continues to affect millions of people worldwide, particularly in regions with limited access to healthcare and sanitation. This burden is exacerbated by the increasing resistance to standard antibiotic regimens, leading to treatment failure and recurrent infections (Graham & Fischbach, 2023).

1.2 Pathophysiology of PUD: The pathogenesis of PUD involves an imbalance between mucosal defense mechanisms and aggressive luminal factors, including hydrochloric acid, pepsin, bile salts, and reactive oxygen species. Under normal physiological conditions, the gastric mucosa is protected by mucus-bicarbonate secretion, prostaglandins, adequate mucosal blood flow, and cellular restitution (Malfertheiner et al., 2024). When these protective mechanisms are disrupted, the mucosa becomes susceptible to injury, particularly in the presence of *H. pylori* infection or NSAID consumption.

H. pylori colonizes the gastric epithelium and triggers inflammation by producing virulence factors such as CagA, VacA, and urease, which neutralize gastric acid and impair mucosal

integrity. Additionally, NSAIDs contribute to mucosal injury by inhibiting cyclooxygenase (COX) enzymes and prostaglandin synthesis, which are essential for maintaining mucosal defense (Zhang et al., 2024).

1.3 Mortality due to PUD: Although most PUD cases are treatable with pharmacologic therapy, complications such as bleeding, perforation, and gastric outlet obstruction can lead to significant morbidity and mortality rates. Upper gastrointestinal bleeding due to peptic ulcers remains one of the most common causes of emergency hospital admissions worldwide. Mortality rates vary based on patient demographics, comorbidities, and access to healthcare. Elderly patients and those with concomitant cardiovascular or chronic kidney disease are particularly vulnerable to fatal outcomes (Malfertheiner et al., 2024).

The global burden of PUD-associated mortality has declined with the advent of *Helicobacter pylori* eradication therapy and proton pump inhibitors (PPIs). However, emerging resistance to antibiotics, especially clarithromycin and metronidazole, has compromised eradication success rates, thereby indirectly contributing to sustained morbidity and mortality from refractory ulcers and their complications (Murray et al., 2022).

1.4 *Helicobacter pylori:* *H. pylori* is a spiral-shaped, microaerophilic, gram-negative bacterium implicated in most PUD cases, especially duodenal ulcers. It infects approximately 50% of the world's population, with a higher prevalence in low- and middle-income countries due to inadequate sanitation and overcrowding (Ashraf et al., 2024). The ability of this organism to survive in the acidic environment of the stomach is attributed to its production of urease, which hydrolyzes urea into ammonia, thereby neutralizing gastric acid and enabling colonization.

The infection is usually acquired in childhood and can persist for a lifetime unless treated. Its pathogenicity stems from virulence determinants such as CagA, VacA, BabA, and outer inflammatory protein (OipA), which collectively trigger immune responses and gastric epithelial damage (Shaalan, Azrad, & Peretz, 2024). Chronic infection not only leads to ulcer formation but is also associated with gastric cancer and mucosa-associated lymphoid tissue lymphomas.

1.5 Pathogenesis of *H. pylori-induced ulcers:* The pathogenesis of *H. pylori*-induced ulcers involves a complex interplay between bacterial virulence, host immune response, and

environmental factors. Upon colonization, *H. pylori* adheres to gastric epithelial cells and injects CagA into the host cytoplasm, disrupting the tight junctions and altering the cell signaling pathways. VacA induces vacuole formation and apoptosis, whereas urease, catalase, and superoxide dismutase protect the bacteria from oxidative stress (Ashraf et al., 2024).

Although robust, the host immune response fails to clear the infection and instead results in chronic gastritis. This persistent inflammation compromises mucosal defenses, increases acid secretion, and predisposes patients to ulceration. Genetic predisposition, dietary habits, and smoking further modulate the disease severity (Hu et al., 2024). The chronicity and adaptiveness of *H. pylori* underscore the need for multifaceted therapeutic approaches that extend beyond the use of conventional antibiotics.

1.6 Modern treatment methods: Contemporary management of PUD includes a combination of antisecretory agents, antibiotics, and protective drugs. Proton pump inhibitors (PPIs) and potassium-competitive acid blockers (P-CABs) are the mainstays of acid suppression therapy (Ahmed & Clarke, 2023). PPIs, such as omeprazole, esomeprazole, and pantoprazole, are widely used because of their efficacy and safety. However, concerns regarding their long-term use, including the risk of nutrient malabsorption, kidney disease, and infections, have led to the exploration of alternative strategies (Janković, Gralnek, & Awadie, 2025).

Standard *H. pylori* eradication regimens typically include triple therapy (PPI + clarithromycin + amoxicillin/metronidazole) or quadruple therapy (PPI + bismuth + tetracycline + metronidazole). The Maastricht VI/Florence Consensus emphasizes the need for local antibiotic resistance surveillance to guide therapy (Malfertheiner et al., 2023). Despite these advancements, increasing resistance rates have necessitated the search for adjunct and alternative treatments, including probiotics, phytochemicals, and personalized medicine.

1.7 Antimicrobial resistance: Antimicrobial resistance (AMR) is a growing global crisis that affects the management of infectious diseases, including PUD. *H. pylori* has developed resistance to commonly used antibiotics, such as clarithromycin, metronidazole, and levofloxacin, leading to treatment failure and prolonged morbidity (Murray et al., 2022). Resistance mechanisms include mutations in ribosomal RNA, efflux pump activation, and biofilm formation, all of which hinder drug efficacy.

Environmental factors, such as antibiotic overuse in agriculture, poor sanitation, and climate change, also contribute to the propagation of resistant strains (Hu et al. 2024). Surveillance data have shown alarming trends, especially in Asia and Africa, where multidrug-resistant *H. pylori* strains are increasingly prevalent. This has prompted global health organizations to prioritize research on novel antimicrobial agents and stewardship practices to preserve existing treatments.

1.8 Ways to reduce or stop antimicrobial resistance: Combating AMR requires a multifaceted strategy involving rational antibiotic use, infection prevention, surveillance, and innovation. Public health campaigns to discourage unnecessary antibiotic use and promote adherence to prescribed regimens are essential to combat this problem. Clinicians must rely on culture-based sensitivity testing or molecular diagnostics before initiating therapy to ensure targeted treatment (Graham & Fischbach, 2023).

Alternative approaches, such as bacteriophage therapy, antimicrobial peptides, and probiotics, are being explored. Herbal remedies with documented antibacterial properties provide an additional avenue for reducing the reliance on conventional antibiotics (Singh et al., 2023). Furthermore, strengthening healthcare infrastructure and ensuring access to clean water and sanitation can significantly curtail the spread of resistant organisms in the community.

1.9 Adverse effects/disadvantages of synthetic drugs: Although synthetic drugs have revolutionized the treatment of PUD, their prolonged use is not without consequences. PPIs, for instance, are linked to an increased risk of chronic kidney disease, osteoporosis-related fractures, vitamin B12 deficiency, and infections such as *Clostridioides difficile* (Janković et al., 2025). In contrast, antibiotics disrupt the gut microbiota, potentially leading to dysbiosis, allergic reactions, and increased susceptibility to opportunistic infections.

Moreover, the indiscriminate use of synthetic drugs contributes to AMR and can result in treatment-refractory infections. The high cost of newer antibiotics and adverse drug reactions impose an economic burden on healthcare systems, especially in resource-limited settings. Hence, there is a pressing need to reassess current pharmacotherapy models and explore safer and more cost-effective alternatives.

1.10 Merits of herbal drugs over synthetic drugs: Herbal medicines offer several advantages over synthetic drugs in the management of PUD. They are often cost-effective,

readily available, and associated with fewer side effects than other drugs. Phytochemicals such as flavonoids, alkaloids, tannins, and saponins, found in herbs such as *Moringa oleifera*, *Azadirachta indica*, *Glycyrrhiza glabra*, and *Curcuma longa*, exhibit anti-*H. pylori*, anti-inflammatory, and gastroprotective properties (Hu et al., 2022; Mehta et al., 2024).

These natural compounds modulate multiple molecular targets simultaneously, thereby reducing the likelihood of resistance development. Their antioxidant properties also help in scavenging free radicals, promoting mucosal healing, and improving gastrointestinal functions. Additionally, the use of herbal medicine aligns with cultural beliefs and traditional practices, enhancing patient compliance and satisfaction with treatment.

1.11 Antibacterial evaluation: Extensive research has demonstrated the antibacterial efficacy of various medicinal plants against *Helicobacter pylori* and other gastrointestinal pathogens. In vitro studies using well diffusion and broth microdilution methods have confirmed the inhibitory potential of extracts from *Moringa oleifera*, Ginger, Garlic, and Neem (Patel et al., 2024; Khan et al., 2024). These extracts often exhibit synergistic effects when combined with conventional antibiotics, enhancing their efficacy and lowering the required dosage.

Mechanistic insights have revealed that these herbal extracts disrupt bacterial membranes, inhibit urease activity, and suppress virulence gene expression (Iqbal et al., 2024; Shaalan et al., 2024). These multifaceted mechanisms underscore the potential of herbal therapeutics as adjunct or alternative treatment options for resistant *H. pylori* infections.

1.12 Acid neutralizing capacity: The acid-neutralizing capacity (ANC) of herbal formulations is a crucial parameter for evaluating their gastroprotective potential. Polyherbal preparations containing *Phyllanthus emblica* and *Glycyrrhiza glabra* have demonstrated significant ANC, comparable to that of standard antacids (Mankar et al., 2024). Similarly, extracts of *Desmodium triflorum* and *Pogostemon heyneanus* have shown notable in vitro antacid effects (Jayasuriya et al., 2023). These botanical agents not only buffer gastric acid but also form mucosal protective layers, offering dual therapeutic effects. Given the adverse effects of long-term proton pump inhibitor use (Janković et al., 2025), herbal alternatives with proven ANC provide safer gastroprotective options.

1.13 Urease inhibitory assay: *Helicobacter pylori* relies on urease to survive in the acidic gastric environment, making urease inhibition a key therapeutic strategy. *Glycyrrhiza glabra* bioactives have shown strong urease inhibition in both in vitro and in silico models (Iqbal et al., 2024). Additionally, flavonoid compounds and *Moringa oleifera* seed extracts have demonstrated promising antiurease activity (Hu et al., 2022; PubMed, 2023). Urease inhibition not only impairs bacterial colonization but also reduces inflammation and mucosal damage (Shaalan et al. 2024). These findings support the integration of plant-based urease inhibitors in the management of *H. pylori* infections, especially amid growing antimicrobial resistance (Murray et al., 2022).

1.14 Standardization/characterization of herbal drugs: Standardization and characterization are essential to ensure the identity, purity, efficacy, and reproducibility of herbal drugs. Thin-layer chromatography (TLC) and high-performance thin-layer chromatography (HPTLC) are widely used for the qualitative and quantitative analysis of phytoconstituents. For example, HPTLC has been successfully used to estimate curcuminoids in *Curcuma longa* and gallic acid in *Terminalia chebula* (Kumar et al., 2024; Das et al., 2022). TLC fingerprinting also helps distinguish between closely related plant species and validates their botanical identity (López et al., 2023). Spectroscopic methods, such as UV/Vis and FTIR spectroscopy, further enhance characterization by identifying functional groups and assessing the presence of specific phytocompounds. FTIR has proven useful for authenticating *Withania somnifera* root extracts and profiling bioactive compounds in *Moringa oleifera* and metal oxide nanoparticles derived from it (El Ouardy et al., 2023; Kumar et al., 2023). UV/Vis spectroscopy is particularly effective for quantifying the total phenolic and flavonoid content in herbal formulations (Sharma et al., 2022).

The combination of chromatographic and spectroscopic techniques offers a comprehensive approach to quality control, which is especially important in the development of herbal therapeutics to ensure safety, consistency, and regulatory compliance across different batches and geographical sources (Rahman et al., 2024).

2. CONCLUSION

Peptic ulcer disease (PUD), primarily driven by *Helicobacter pylori* infection and NSAID use, remains a global health burden despite advances in modern pharmacotherapy. However, the increasing prevalence of antimicrobial resistance and adverse effects associated with the long-term use of proton pump inhibitors underscore the urgent need for alternative or

complementary therapeutic strategies. Integrating standardized, scientifically validated herbal remedies with conventional treatments offers a promising and sustainable approach to managing chronic diseases. Herbal agents such as *Moringa oleifera*, *Glycyrrhiza glabra*, and *Azadirachta indica* demonstrate potent anti-*H. pylori* activity, urease inhibition, and acid-neutralizing capacity, supporting their role in gastroprotection and infection control. Analytical tools such as HPTLC, FTIR, and UV/Vis spectroscopy ensure the consistency and efficacy of herbal formulations. A holistic strategy combining modern evidence-based therapy with phytomedicine can enhance treatment outcomes, reduce drug resistance, and promote gastrointestinal health in a safe and sustainable manner.

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