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## Peptic Ulcer Disease: Mechanisms of Pathogenesis and Insights into Herbal versus Synthetic Treatments

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### ABSTRACT

Peptic ulcer disease remains a pressing health issue worldwide, most often linked to *Helicobacter pylori* infection and long-term use of non-steroidal anti-inflammatory drugs (NSAIDs). While conventional therapies such as proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), cytoprotective agents, and antibiotics have transformed patient care by reducing acid secretion and eradicating infection, they are not without drawbacks. Rising antibiotic resistance, drug-related side effects, and recurrence of ulcers continue to challenge clinicians and patients alike. In recent years, herbal medicine has gained attention as a complementary or alternative approach. Plant-derived compounds rich in flavonoids, tannins, alkaloids, and terpenoids offer anti-inflammatory, antioxidant, and antisecretory effects, while also strengthening the stomach's natural defenses. Traditional remedies such as *Anogeissus latifolia*, *Alchornea castaneaefolia*, *Decalepis salicifolia*, *Solanum nigrum*, *Ocimum tenuiflorum*, *Asparagus racemosus*, and *Curcuma longa* have shown promising results in experimental models, not only reducing ulcer formation but also accelerating healing. This review brings together evidence on both synthetic and herbal strategies, comparing their mechanisms, effectiveness, safety, and cost considerations. While PPIs and antibiotic regimens remain indispensable for *H. pylori* eradication and NSAID-induced ulcer prevention, herbal therapeutics stand out for their lower side-effect profile and potential to provide long-term mucosal protection. Looking ahead, integrated treatment approaches that combine modern pharmacology with traditional phytomedicine may offer the most balanced and sustainable path for managing peptic ulcer disease.

**Keywords:** Peptic ulcer disease, *Helicobacter pylori*, NSAIDs, Proton pump inhibitors (PPIs), Herbal medicine, Flavonoids.

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## INTRODUCTION

Peptic ulcers are not actually blisters but open sores that develop on the inner lining of the stomach, the upper part of the small intestine (duodenum), or occasionally the lower esophagus (Kuna et al., 2019). They occur when the protective mucosal layer of the digestive tract becomes weakened or eroded, allowing strong stomach acids and digestive enzymes to injure the underlying tissues. This breakdown of the protective barrier can happen for several reasons, including infection with *Helicobacter pylori* bacteria, long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) (Lanas & Chan, 2017), excessive acid production, smoking, alcohol intake, or high stress levels (Kuna et al., 2019). As the lining becomes damaged, the exposed tissue becomes inflamed and painful, leading to symptoms such as burning stomach pain, bloating, nausea, or indigestion. If left untreated, ulcers can deepen and cause complications like bleeding or perforation, making early diagnosis and management essential (Lanas et al., 2011). Peptic ulcers can be quite uncomfortable, and when they aren't treated properly, they can turn into serious health problems. In the past, these ulcers were surprisingly common almost 1 in 10 people experienced them at some point (Lanas & Chan, 2017). Over time, though, the number of cases has dropped significantly due to better hygiene, improved living conditions, and more effective medical treatments (Søreide et al., 2015). One of the biggest reasons is the reduced spread of *Helicobacter pylori* (*H. pylori*), the bacteria responsible for most ulcer cases (Datta De, 2015; Lanas & Chan, 2017). As awareness grew and antibiotics became widely available, fewer people became infected. Lifestyle changes, such as smoking less and using painkillers more carefully, have also helped lower the risk (Kuna et al., 2019). For many years, doctors believed that peptic ulcers were mainly the result of excess stomach acid, combined with stress, anxiety, or poor eating habits. While these factors can still play a role, modern research has shown that ulcers are far more complex (Lanas et al., 2011). One of the biggest discoveries was the role of *H. pylori*, a bacterium that weakens the stomach's protective lining (Lanas & Chan, 2017). Other contributors include smoking, frequent alcohol use, and long-term use of NSAIDs such as ibuprofen or aspirin, which can irritate the stomach lining (Lanas et al., 2015). In rare cases, conditions like Zollinger–Ellison syndrome cause excessive acid production, leading to severe ulcers (Kuna et al., 2019). Interestingly, not everyone who encounters the common risk factors for peptic ulcers actually develops one. This difference comes down, in part, to genetics (Søreide et al., 2015). Some individuals carry specific variations in immune-related genes that make their stomach lining more sensitive to damage or less effective at controlling inflammation (Datta De, 2015). These genetic differences can influence how strongly a person reacts to *H. pylori* infection or how well their body repairs the

mucosal barrier once it's irritated (Zhang et al., 2014). As a result, two people with the same lifestyle habits or exposures may have very different outcomes one might develop an ulcer, while the other remains completely unaffected (Søreide et al., 2015). Genetic differences can shape how our bodies respond to infections. For example, variations in the gene that regulates interleukin-1 beta, a key player in inflammation, can make someone more vulnerable to damage from *Helicobacter pylori*, the bacteria often linked to stomach ulcers (Zhang et al., 2014). This means that some people's immune systems react more aggressively, increasing the risk of ulcers (Datta De, 2015). Lifestyle choices also matter: regular use of NSAIDs such as ibuprofen or naproxen raises the chance of serious ulcer complications about fourfold, while aspirin use doubles the risk (Lanas et al., 2015). Together, genes and medicines can quietly tip the balance toward ulcer disease (Zhang et al., 2014). When medicines like NSAIDs or aspirin are taken alongside other drugs such as blood thinners, corticosteroids, or antidepressants called SSRIs the risk of harm to the stomach and intestines rises sharply (Lanas et al., 2015). These combinations can make the lining of the digestive tract more fragile, greatly increasing the chance of bleeding in the upper gut (Datta De, 2015). At the same time, many people who use NSAIDs or aspirin also carry *Helicobacter pylori*, a bacterium strongly linked to ulcer formation (Lanas & Chan, 2017). Scientists know both factors are important, but the exact way they interact remains uncertain. It is a reminder that ulcers often result from a mix of genetics, infections, and medications, rather than a single cause, making careful medical supervision essential (Datta De, 2015). Research looking at many observational studies shows that NSAIDs, aspirin, and *Helicobacter pylori* each independently raise the risk of peptic ulcers (Lanas et al., 2015). In other words, they do not have to act together to cause damage their effects alone can be enough. What is even more intriguing is that around 20% of ulcer cases occur in people who neither use NSAIDs or aspirin nor carry *H. pylori* (McColl, 2009). These are known as idiopathic ulcers. Doctors believe they may arise when the body's natural defenses, like mucus and blood flow in the stomach lining, fail to balance against harmful factors such as acid. Yet, the precise reasons remain uncertain, reminding us how complex and multifactorial ulcer disease truly is (McColl, 2009). Scientists are learning that ulcers aren't always caused by *H. pylori* or painkillers like NSAIDs. A Danish study points to psychological stress as a possible trigger, showing how the mind and body are closely linked (McColl, 2009). Other factors can also weaken the stomach's defenses. Poor blood flow, for example, reduces the lining's ability to heal, while medications such as steroids, chemotherapy drugs, or even radiation therapy can irritate the gut (Lanas et al., 2011). Viral infections, excess histamine, and unusual immune reactions like eosinophilic infiltration add further complexity. In

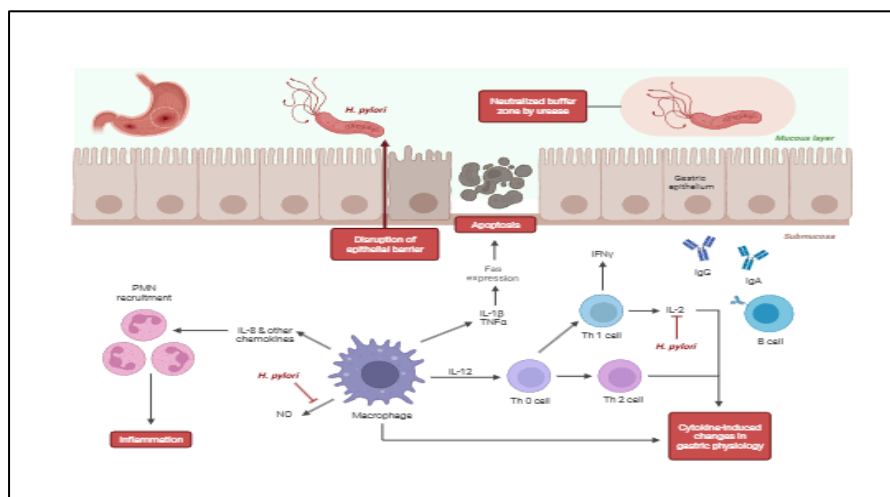
some cases, ulcers appear after gastric bypass surgery or due to metabolic disorders. These diverse causes highlight that ulcer disease is multifaceted, shaped by both physical and emotional influences (McColl, 2009). Phytochemicals, the natural compounds found in plants, have been part of traditional healing practices for centuries. Unlike many synthetic drugs, they are often considered gentler and safer, making them attractive options for long-term use (Choi et al., 2016). These plant-derived substances can help protect the body against inflammation, oxidative stress, and even chronic diseases, offering therapeutic benefits that go beyond symptom relief. What makes them especially valuable is their availability in everyday foods and herbs, meaning people can consume them not only as medicines but also as nutritional supplements. From green tea polyphenols to turmeric's curcumin, phytochemicals remind us how nature provides powerful tools to support health and well-being (Choi et al., 2016). Preclinical studies have shed light on the remarkable anti-ulcer potential of many plant-derived compounds (Kuna et al., 2019). Natural constituents such as alkaloids, tannins, flavonoids, terpenoids, glycosides, carotenoids, and saponins have each demonstrated protective effects on the stomach lining, helping to reduce inflammation, neutralize harmful free radicals, and promote healing (Doll et al., 1956; Choi et al., 2016). These findings suggest that plants long valued in traditional medicine may hold modern therapeutic promise. This manuscript highlights several medicinal plants and their active compounds that show encouraging results in managing peptic ulcers. By bridging ancient wisdom with scientific evidence, these natural agents offer safer, holistic alternatives that could complement or even reduce reliance on conventional drugs, making ulcer care more accessible and patient-friendly (Kuna et al., 2019). Omeprazole, first introduced in 1989, transformed the way doctors treat acid-related disorders. It was the pioneer of a new class of medicines called proton pump inhibitors (PPIs), which work by powerfully reducing stomach acid production (Shi & Klotz, 2008). This breakthrough quickly shifted medical practice, as PPIs proved more effective and reliable than older treatments such as histamine-2-receptor antagonists, synthetic prostaglandin analogues, and anticholinergics (Farley et al., 2000). Over time, PPIs became the gold standard for managing conditions like peptic ulcers, gastroesophageal reflux disease (GERD), and other acid-related problems. Their success not only improved patient outcomes but also simplified treatment, offering relief to millions worldwide and ushering in a new era of gastrointestinal care (Shi & Klotz, 2008). Proton pump inhibitors (PPIs) have revolutionized the management of acid-related disorders by offering stronger and longer-lasting acid suppression than older therapies. They are widely recognized for their excellent safety profile and are generally well tolerated, which has helped them gain the trust of both doctors and patients (Shi & Klotz, 2008). By 2015, six different

PPIs had been approved by the U.S. Food and Drug Administration, giving clinicians a range of options to tailor treatment. Their widespread use by primary care physicians and gastroenterologists has firmly established PPIs as the cornerstone of therapy (Farley et al., 2000). Today, they are considered the first-line treatment for multiple conditions, including esophagitis, nonerosive reflux disease, peptic ulcer disease, prevention of NSAID-induced ulcers, Zollinger–Ellison syndrome, and functional dyspepsia. Their effectiveness and reliability have made PPIs an essential tool in modern gastroenterology, improving quality of life for millions worldwide (Shi & Klotz, 2008). When paired with antibiotics, proton pump inhibitors (PPIs) become vital in clearing *Helicobacter pylori* infections. By reducing stomach acid, PPIs create a friendlier environment for antibiotics to work effectively. This combination not only heals ulcers but also tackles the root cause, offering patients lasting relief and improved digestive health (Shi & Klotz, 2008).

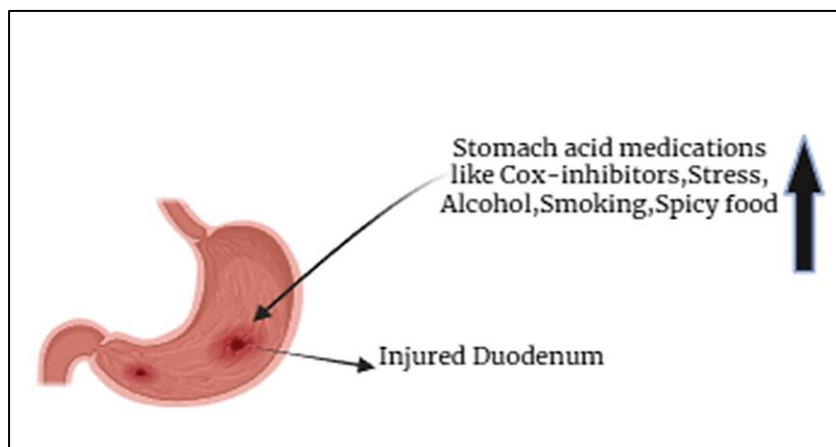
### **Pathogenesis of Peptic Ulcer:**

*Helicobacter pylori* (*H. pylori*) colonizes nearly half of the global population and remains one of the leading causes of peptic ulcer disease (Hooi et al., 2017). Its prevalence is notably higher in developing regions such as Africa, Central America, Central Asia, and Eastern Europe, where socioeconomic challenges and poor sanitation contribute to widespread transmission (Hooi et al., 2017). Most individuals acquire the infection during childhood, often in crowded living conditions with limited access to clean water and hygiene (Siddique et al., 2018). Once established in the stomach lining, *H. pylori* triggers a robust immune response involving neutrophils, lymphocytes, plasma cells, and macrophages (Siddique et al., 2018). This inflammation leads to damage and degeneration of the epithelial cells, particularly in the antral region of the stomach, setting the stage for ulcer formation (Siddique et al., 2018). The exact mechanism by which *Helicobacter pylori* causes different types of lesions in the stomach and duodenum remains incompletely understood (Zaki et al., 2013). Interestingly, *H. pylori* infection can lead to either reduced (hypochlorhydria) or increased (hyperchlorhydria) stomach acid secretion, which in turn influences the type of peptic ulcer that develops (Zaki et al., 2013). Cytokines play a central role in mediating the effects of *H. pylori* by suppressing acid secretion from parietal cells (Zaki et al., 2013). However, the bacterium also exerts direct effects such as interfering with the  $H^+/K^+$  ATPase enzyme, stimulating sensory neurons that release calcitonin gene-related peptide (CGRP) linked to somatostatin regulation, or inhibiting gastrin production (Zaki et al., 2013). While gastric ulcers are typically associated with low acid output, about 10–15% of individuals with *H. pylori* infection exhibit increased acid secretion (Zaki et al., 2013). This paradox is driven by elevated gastrin levels (hypergastrinemia) and a reduction in somatostatin within the antrum, which together

enhance histamine release and stimulate acid and pepsin production by gastric cells (Zaki et al., 2013).



**Figure 1: Pathophysiology of Peptic Ulcer.**



**Figure 2: Pathogenic Influences on Duodenal Health.**

Eradicating *H. pylori* has been shown to reverse these effects; gastrin mRNA levels decrease, while somatostatin mRNA expression increases (Moss et al., 1992). In most patients, however, gastric ulcers are linked to low stomach acid levels (hypochlorhydria) and thinning of the stomach lining (mucosal atrophy), highlighting the complex and variable nature of *H. pylori*-induced disease (Moss et al., 1992). When it comes to NSAID-related ulcers, the primary culprit is the systemic inhibition of cyclooxygenase-1 (COX-1), an enzyme that's normally active in the stomach and plays a key role in producing protective prostaglandins ("Vascular and upper gastrointestinal effects," 2013). These prostaglandins help maintain healthy blood flow to the mucosa, stimulate the secretion of mucus and bicarbonate, and support cell renewal ("Vascular and upper gastrointestinal effects," 2013). When COX-1 is blocked, these protective mechanisms are compromised, making the stomach lining more vulnerable to injury ("Vascular and upper

gastrointestinal effects," 2013). NSAIDs inhibit COX-1 in a reversible, concentration-dependent manner, meaning the extent of damage often correlates with the dose and duration of use ("Vascular and upper gastrointestinal effects," 2013). However, this risk can be mitigated. Using COX-2-selective NSAIDs, which spare COX-1, or supplementing with synthetic prostaglandins can significantly reduce mucosal injury and lower the risk of ulcer formation ("Vascular and upper gastrointestinal effects," 2013). Not all NSAIDs behave the same way in the body; their chemical properties influence how toxic they can be (Bjarnason et al., 2007). These drugs can damage the stomach lining by disturbing the protective mucus layer and interfering with the cell's energy production (Bjarnason et al., 2007). Here is how it happens: when NSAIDs enter the highly acidic environment of the stomach (around pH 2), they become protonated and slip through cell membranes (Bjarnason et al., 2007). Once inside the epithelial cells, which have a neutral pH (around 7.4), they release hydrogen ions (Bjarnason et al., 2007). Trapped in this form, the drugs disrupt mitochondrial function, reduce energy output, and weaken the cell's defenses (Bjarnason et al., 2007). The result is increased permeability and loss of cellular integrity, setting the stage for ulcer formation (Bjarnason et al., 2007). Certain groups of patients are especially vulnerable: those with a history of ulcers or bleeding, people over 65, individuals taking steroids or anticoagulants, and anyone on high doses or multiple NSAIDs (Narayanan et al., 2018). For them, the risk of NSAID-induced ulcers is particularly high (Narayanan et al., 2018).

## **TREATMENT:**

### **Role of *Helicobacter pylori* in Peptic Ulcer Disease:**

Getting rid of *Helicobacter pylori* is the cornerstone of healing peptic ulcers and stopping them from coming back (Siddique et al., 2018). But over time, this has become harder to achieve because the bacteria have developed resistance to many antibiotics, turning eradication into a global challenge (Siddique et al., 2018). The very first effective treatment appeared in the 1980s: a two-week course that combined bismuth, tetracycline, and metronidazole (Siddique et al., 2018). This regimen marked the beginning of targeted therapy against *H. pylori*, laying the foundation for the treatment strategies we use today (Siddique et al., 2018). The usual first-line treatment for *Helicobacter pylori* infection is a triple therapy: a proton pump inhibitor (PPI) combined with two antibiotics, typically clarithromycin plus either amoxicillin or metronidazole, taken for 7 to 14 days (Malfertheiner et al., 2017). But over the past decade, this approach has become less effective because antibiotic resistance especially to clarithromycin has risen sharply (Fallone et al., 2016). Ideally, doctors should tailor treatment based on antimicrobial susceptibility testing, which shows which antibiotics the bacteria are sensitive to (Fallone et al., 2016). Unfortunately, such testing is

not always available in routine practice. In those cases, the choice of therapy should reflect the local resistance rates; for example, if clarithromycin resistance in a region is higher than 15%, clarithromycin-based regimens should no longer be used (Fallone et al., 2016). Treatment success can be improved by prescribing a higher dose of PPI and extending the therapy to a full 14 days, rather than stopping earlier (Dore, Lu, & Graham, 2016). The preferred first-line treatment for *Helicobacter pylori* infection is usually a 14-day regimen (Sun et al., 2010). One option is a bismuth-based quadruple therapy (a proton pump inhibitor, bismuth salt, tetracycline, and metronidazole) (Sun et al., 2010). For patients who cannot take bismuth, a 14-day concomitant therapy (proton pump inhibitor, clarithromycin, amoxicillin, and metronidazole) is recommended (Sun et al., 2010). Both approaches are highly effective, with eradication rates above 90% (Sun et al., 2010). If the initial treatment fails, a second-line therapy is needed. Importantly, this should avoid using metronidazole or clarithromycin again (Chey et al., 2017). A common alternative is a levofloxacin-based triple therapy (proton pump inhibitor, amoxicillin, and levofloxacin) given for 14 days, which has shown eradication success rates of about 74–81% (Chen et al., 2016). If a patient has already tried a clarithromycin-based regimen as their first-line therapy, the next best option is usually a bismuth quadruple therapy (proton pump inhibitor, bismuth salt, tetracycline, and metronidazole), which achieves eradication rates of about 77–93% (Shiota et al., 2015). Another alternative is a high-dose dual therapy with amoxicillin and a proton pump inhibitor, since *H. pylori* rarely develops resistance to amoxicillin (Shiota et al., 2015). Even with well-established treatment guidelines, about 5–10% of patients continue to have persistent infection (Graham, Lee, & Wu, 2014). The most common reasons are poor adherence to the treatment plan or bacterial resistance to one or more antibiotics (Graham, Lee, & Wu, 2014). In such cases, susceptibility testing is strongly advised to guide the choice of further therapy. If at least three recommended regimens have failed, doctors may consider a salvage option such as rifabutin-based triple therapy (proton pump inhibitor, rifabutin, and amoxicillin) for 10 days (Graham, Lee, & Wu, 2014). This approach has eradication rates of 66–70%, but it comes with important caveats: rifabutin can cause serious side effects, including bone marrow suppression (myelotoxicity) and unusual red-colored bodily secretions (Gisbert & Calvet, 2012).

**NSAID-Induced Ulceration and the Role of Proton Pump Inhibitors:** Several approaches are available to prevent ulcers and complications caused by NSAIDs and aspirin (Khan et al., 2019). These include combining NSAIDs with a proton pump inhibitor (PPI), an H<sub>2</sub> receptor antagonist, or misoprostol; using COX-2-selective NSAIDs; or pairing these agents with other gastroprotective drugs (Khan et al., 2019). Among these options, PPIs are the most widely used

and effective (Strand, Kim, & Peura, 2017). They work by irreversibly blocking the hydrogen/potassium ATPase enzyme in gastric parietal cells, thereby significantly reducing stomach acid production (Strand, Kim, & Peura, 2017). The best protection against peptic ulcer complications is achieved by combining a COX-2-selective NSAID with a PPI (Strand, Kim, & Peura, 2017). In contrast, standard doses of H<sub>2</sub> receptor antagonists are not effective in preventing gastric ulcers (Strand, Kim, & Peura, 2017). Although misoprostol is effective in reducing ulcer risk, its use is limited due to side effects like gastrointestinal discomfort and its potential to induce abortion (daCosta DiBonaventura et al., 2012). When the offending drug is stopped, most gastric ulcers over 85% heal within six to eight weeks of PPI therapy (daCosta DiBonaventura et al., 2012). However, follow-up endoscopy is essential to confirm healing (daCosta DiBonaventura et al., 2012). If the ulcer persists, it's important to assess whether the patient has been taking their medication as prescribed (daCosta DiBonaventura et al., 2012).

#### **PHYTO-THERAPEUTIC AGENTS FOR PEPTIC ULCER MANAGEMENT:**

Many people living with chronic ulcer conditions often explores complementary and alternative therapies to better manage their symptoms and improve their quality of life (Langmead & Rampton, 2001). In much of sub-Saharan Africa, herbal medicine remains a common choice for treating stomach ulcers (Langmead & Rampton, 2001). This widespread use is rooted in cultural traditions, accessibility, and trust in natural remedies (Langmead & Rampton, 2001). However, despite their popularity, many of these herbal treatments still lack well-defined pharmacological profiles, leaving questions about their safety and effectiveness unanswered (Langmead & Rampton, 2001).

##### ***Anogeissus latifolia* (Dhaura or Bakli):**

Rather than relying solely on the generalized effects of crude extracts, contemporary pharmacological evaluation of *Anogeissus latifolia* highlights the therapeutic potential of its isolated bioactive constituents, primarily gallic acid and ellagic acid (Govindarajan et al., 2006). These polyphenolic compounds exhibit potent gastroprotective properties mediated through specific molecular pathways, including the targeted inhibition of 5-lipoxygenase, an enzyme critical to the inflammatory cascade (Govindarajan et al., 2006). By systematically mitigating oxidative stress and enhancing mucosal defense mechanisms, these constituents offer a targeted, molecular approach to ulcer management that transcends basic symptomatic relief (Govindarajan et al., 2006).

##### ***Alchornea castaneaefolia* (Iporuru, Macochihua):**

Similarly, the gastroprotective efficacy of *Alchornea castaneaefolia* is increasingly attributed to its flavonoid-enriched fractions rather than its crude hydroethanolic extracts. Mechanistic investigations reveal that these isolated flavonoids counteract NSAID-induced mucosal damage by significantly upregulating prostaglandin E<sub>2</sub> synthesis, effectively reversing the suppression typically caused by indomethacin. Furthermore, they induce marked endocrine shifts specifically, a profound reduction in serum gastrin coupled with a substantial elevation in somatostatin levels. This suggests a sophisticated dual regulatory mechanism that fortifies mucosal defense rather than merely inhibiting acid secretion directly (Prayoga et al., 2024).

***Decalepis salicifolia* (Mahali Kand, Mahali Kizhangu):**

*Uleria salicifolia* Bedd. Ex. Hook. f. is an ethnobotanical plant found in the southwestern Ghats of India. The 50% ethanolic extract of its rhizome shows dose-dependent anti-ulcer activity (Rao et al., 2004). Mucus and bicarbonate secretion form the first line of defense against ulcer-causing agents (Rao et al., 2004). The extract significantly ( $P < 0.001$ ) increased gastric wall mucus in ethanol-induced ulcers, confirming its cytoprotective activity (Rao et al., 2004). At doses of 100 and 200 mg/kg, the rhizome extract also protected against cysteamine-induced duodenal ulcers in rats, with 68% and 90% protection, respectively (Rao et al., 2004). Lipid peroxidation serves as an indicator of reactive oxygen species (ROS) generation in tissues (Fridovich, 1986). Free radicals cause cell damage through peroxidation of membrane lipids, DNA strand breaks, and protein denaturation, ultimately leading to cellular injury (Fridovich, 1986). The extract of *Uleria salicifolia* showed strong antioxidant activity in cold-restraint stress-induced ulcers (Rao et al., 2004). It boosted the levels of superoxide dismutase (SOD), a key protective enzyme, while reducing harmful lipid peroxidation compared to untreated ulcer controls (Rao et al., 2004). Importantly, it also lowered the elevated plasma corticosterone levels that typically rise under stress (Rao et al., 2004). These findings suggest that the anti-ulcer effect of *Uleria salicifolia* is linked to strengthening the body's first line of defense through free radical scavenging (Rao et al., 2004). The close connection between its antioxidant action and the regulation of stress hormones (like corticosterone) highlights how both biochemical defense systems and endocrine responses contribute to its gastroprotective effect (Rao et al., 2004).

***Solanum nigrum* Linn (Black Nightshade, Makoi):**

*Solanum nigrum* Linn., better known as black nightshade, has a long history in Ayurveda as a remedy for gastric ulcers (Akhtar & Munir, 1989). Modern research supports this traditional use, showing that extracts from its fruits and aerial parts can protect the stomach and promote healing in several experimental ulcer models (Jainu & Devi, 2006). When given at higher doses, the fruit

extract significantly reduced ulcer formation caused by stress, indomethacin, pyloric ligation, and ethanol exposure with protection rates ranging from about 70% to 80% (Jainu & Devi, 2006). It also accelerated healing in chronic ulcers induced by acetic acid (Jainu & Devi, 2006). Mechanistically, the extract works by lowering gastric acid and pepsin secretion, while also boosting antioxidant defenses (Akhtar & Munir, 1989; Jainu & Devi, 2004). In ethanol-induced ulcers, it reduced harmful free radical activity and lipid peroxidation, both of which contribute to tissue damage (Jainu & Devi, 2004). Importantly, pretreatment with the extract suppressed gastrin the hormone that drives acid secretion, histamine release, and gastric cell proliferation and inhibited H<sup>+</sup>/K<sup>+</sup>-ATPase, the proton pump responsible for acid production (Jainu & Devi, 2006). Beyond its ulcer-protective role, *Solanum nigrum* also shows antioxidant, hepatoprotective, and antitumor activities, making it a plant of broad pharmacological interest (Son et al., 2003).

***Ocimum tenuiflorum* (Holy Basil, Sacred Basil, Hot Basil):**

*Ocimum sanctum* Linn., commonly known as Tulsi, is one of the most revered medicinal plants in Ayurveda. Beyond its spiritual significance, Tulsi has been scientifically reported to possess a wide spectrum of therapeutic properties, including anti-carcinogenic, anthelmintic, anti-rheumatic, anti-stress, antibacterial, antiseptic, antioxidant, and antifertility activities (Kiran, Rohilla, & Kalra, 2023). Among its many benefits, Tulsi demonstrates remarkable antiulcerogenic activity (Kiran, Rohilla, & Kalra, 2023). Experimental studies using ethanolic leaf extracts have shown that Tulsi provides significant protection against gastric ulcers (Prayoga et al., 2024). At a dose of 100 mg/kg, the extract reduced ulcer formation with protection indices of 65.07% (cold-restraint stress), 63.49% (aspirin-induced), 53.87% (alcohol-induced), 62.06% (pylorus ligation), and 61.76% (histamine-induced ulcers) (Prayoga et al., 2024). In the pylorus ligation model, ulcers typically arise due to excessive accumulation of gastric acid and pepsin, leading to autodigestion of the mucosa and free radical generation (Prayoga et al., 2024). Tulsi extract was found to reduce both free and total acidity, lower peptic activity, and enhance mucus secretion, thereby strengthening the gastric defense system (Prayoga et al., 2024). The incidence of ulcers across different models is often linked to increased acid secretion, weakened mucosal defenses, and oxidative stress (Kiran, Rohilla, & Kalra, 2023). Tulsi's antiulcer effect appears to work through dual mechanisms: antisecretory action (reducing acid and pepsin levels) and cytoprotective action (enhancing mucus and epithelial regeneration) (Prayoga et al., 2024). In chronic ulcer models, such as those induced by acetic acid, Tulsi accelerated healing by promoting regeneration of glandular structures and migration of epithelial cells to cover the ulcer crater (Prayoga et al., 2024). Interestingly, the fixed oil derived from Tulsi seeds also exhibited potent antiulcer activity (Kiran,

Rohilla, & Kalra, 2023). It significantly reduced ulcer indices in a dose-dependent manner across multiple models, including those induced by aspirin, indomethacin, alcohol, histamine, reserpine, serotonin, stress, and combined aspirin plus pylorus ligation (Kiran, Rohilla, & Kalra, 2023).

***Asparagus sarmentosus* Roxb (Shatavari, Wild Asparagus):**

The methanolic extract of fresh roots of *Asparagus racemosus* Willd. was evaluated for its antiulcer potential across several experimental models (Prayoga et al., 2024). The extract demonstrated significant protection against gastric ulcers induced by cold-restraint stress, pyloric ligation, aspirin plus pyloric ligation, acetic acid, and cysteamine-induced duodenal ulcers (Prayoga et al., 2024). However, it was ineffective in models involving aspirin alone and ethanol-induced ulcers. In pylorus-ligated ulcers, the extract increased mucopolysaccharide content, leading to a rise in total carbohydrates (Prayoga et al., 2024). Importantly, this protective effect was achieved without reducing gastric acid or pepsin secretion and without influencing cell proliferation (Prayoga et al., 2024). This suggests that the gastroprotection of *Asparagus racemosus* in this model is primarily cytoprotective, rather than antisecretory or acid-neutralizing (Prayoga et al., 2024). Its lack of efficacy against aspirin-induced ulcers may be explained by the extract's inability to counteract the loss of prostaglandin-mediated protection and the absence of any effect on cell proliferation both critical factors in aspirin-related mucosal damage (Prayoga et al., 2024). Interestingly, in the aspirin plus pylorus ligation model, the extract still showed activity, likely due to its cytoprotective properties in addition to supporting prostaglandin synthesis. Oxidative stress was identified as a key contributor to stress-induced ulcers. Treatment with the extract significantly reduced lipid peroxidation, correlating with its antioxidant activity (Prayoga et al., 2024). Supporting this, the polysaccharide fraction of the plant has been reported to exhibit strong in vitro antioxidant effects (Prayoga et al., 2024). Finally, *Asparagus racemosus* also promoted healing of chronic gastric ulcers induced by acetic acid, further validating its role as a natural gastroprotective agent (Prayoga et al., 2024).

***Curcuma domestica* Valetton (Turmeric, Indian Saffron)**

Medicinal plants with antioxidant and anti-inflammatory properties have demonstrated protective effects in gastroesophageal reflux disease (GERD) (Salehi et al., 2017). Among the most studied are *Curcuma longa* (turmeric), *Panax quinquefolium* (American ginseng), *Artemisia asiatica*, and *Lonicera japonica* (Salehi et al., 2017). Their beneficial actions extend beyond general antioxidant activity, involving mechanisms such as the regulation of inflammatory gene expression, enhancement of gastric mucus, suppression of gastric acid secretion, support of lower esophageal sphincter tone, and inhibition of pro-inflammatory cytokines (Salehi et al., 2017). For example,

*Panax quinquefolium* has been shown to down-regulate ICAM-1 and CINC-2 $\beta$ , proteins central to acute inflammation (Salehi et al., 2017). *Curcuma longa* and *Morus alba* improve gastric mucus function, while both plants, along with acidinol syrup, also reduce gastric acid secretion (Salehi et al., 2017). Preparations such as *Salvia miltiorrhiza* and STW 5 increase tonic contractions of the lower esophageal sphincter, thereby limiting reflux, and STW 5 additionally suppresses cytokines including IL-1 $\beta$  and TNF- $\alpha$  (Salehi et al., 2017). Experimental evidence supports these mechanisms (Oh, 2001). In rat models, pretreatment with *Artemisia asiatica* extract (DA-9601) reduced esophageal wall thickening and ulceration more effectively than ranitidine (Oh, 2001). Mahattanadul's study demonstrated that the rhizome of *Curcuma longa* protected against acute acid reflux esophagitis, though it was less effective in chronic models (Mahattanadul et al., 2006). Interestingly, when combined with dimethyl sulfoxide, an antioxidant compound, turmeric reduced ulcer severity to levels comparable with lansoprazole (Mahattanadul et al., 2006). Unlike curcumin, however, lansoprazole tended to worsen histopathological changes compared to controls, highlighting the unique role of curcumin's antioxidant and anti-inflammatory activity in GERD protection (Mahattanadul et al., 2006). Herbal medicine also shows promise in modulating *Helicobacter pylori* infection, a major contributor to gastric disease (Salehi et al., 2017). Taken together, these findings suggest that plant-derived compounds such as *Curcuma longa*, *Panax quinquefolium*, *Artemisia asiatica*, and *Lonicera japonica* hold strong potential as natural pharmaceutical candidates for the prevention and management of gastric disorders (Salehi et al., 2017).

### **Translational Challenges and Pharmacokinetic Limitations of Phytotherapeutics**

Despite the promising preclinical data surrounding plant-derived compounds, their successful translation into mainstream clinical practice is currently hindered by significant biopharmaceutical limitations (Prayoga et al., 2024). Many active constituents, particularly flavonoids, tannins, and complex polyphenols, suffer from poor aqueous solubility, extensive presystemic hepatic metabolism, and consequently, low systemic bioavailability (Kuna et al., 2019). Furthermore, the reliance on chemically induced acute ulcer models in rodents often fails to accurately replicate the chronic, multifactorial pathophysiology of human peptic ulcer disease (Prayoga et al., 2024). Additionally, the lack of rigorous chemical standardization such as validated HPLC or LC-MS/MS profiling of crude extracts introduces critical batch-to-batch variability (Langmead & Rampton, 2001). Without overcoming these pharmacokinetic hurdles and standardizing extraction protocols, the reproducibility required for rigorous clinical efficacy and regulatory approval remains out of reach (Kuna et al., 2019).

**MEDICATION THERAPIES:**

Peptic ulcers are usually treated with medicines that work in three main ways: they lower the amount of acid in the stomach, help the stomach lining protect itself, and get rid of infections like *H. pylori* (Kuna et al., 2019). The main types of medicines used include proton pump inhibitors (PPIs) and histamine-2 receptor blockers (H2RAs), which both reduce acid; antacids, which quickly neutralize acid; protective agents that coat and shield the stomach lining; prostaglandin drugs that boost natural defenses; and antibiotics that target *H. pylori* bacteria (Kuna et al., 2019). Together, these treatments aim to ease symptoms, heal the ulcer, and prevent it from coming back (Kuna et al., 2019).

**Proton Pump Blockade Agents (PPIs)**

Proton pump inhibitors (PPIs) are the main medicines used to treat peptic ulcers, whether they form in the stomach or the upper part of the intestine (duodenum) (Chan & Leung, 2002). These drugs work by blocking the acid pumps in the stomach lining, which leads to a strong and long-lasting reduction in stomach acid (Shi & Klotz, 2008). Common PPIs include omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole (Chan & Leung, 2002). Compared to older medicines like H2 blockers, PPIs provide stronger acid control, helping ulcers heal faster and easing symptoms more effectively (Shi & Klotz, 2008). Research also shows that when PPIs are combined with antibiotics to clear *H. pylori* infection, they greatly lower the chances of ulcers coming back (Malfertheiner et al., 2017).

**Histamine Type-2 Blockade Agents (H2RAs)**

Histamine-2 receptor antagonists (H2RAs), such as ranitidine, famotidine, cimetidine, and nizatidine, work by competitively blocking the action of histamine on the stomach's acid-producing parietal cells (Begg et al., 2023). This significantly reduces gastric acid secretion (Salman et al., 2025). While these drugs can heal ulcers, they are not as potent as proton pump inhibitors (PPIs) in lowering gastric acid levels (Salman et al., 2025). Another limitation is that prolonged use can lead to pharmacological tolerance (tachyphylaxis), rendering them less effective over time (Begg et al., 2023). Nevertheless, H2RAs remain a valuable alternative for patients who cannot tolerate PPIs or who require ongoing maintenance therapy to prevent ulcer recurrence (Salman et al., 2025).

**Acid-Neutralizing Agents (Antacids)**

Antacids are simple medicines made from bases like aluminum hydroxide, magnesium hydroxide, and calcium carbonate (Kuna et al., 2019). They work by directly neutralizing stomach acid, which gives quick relief from pain or discomfort caused by ulcers (Kuna et al., 2019). However, while

they ease symptoms, they do not actually speed up ulcer healing (Kuna et al., 2019). Antacids act fast, making them a good option when someone needs immediate relief, but the effect wears off quickly, so they have to be taken often (Kuna et al., 2019). Nowadays, stronger medicines like proton pump inhibitors (PPIs) and H<sub>2</sub> blockers are preferred for long-term acid control, which means antacids are mostly used for short-term, quick fixes rather than as the main treatment (Begg et al., 2023).

### **Gastric Mucosa Protectants**

Mucosal protective medicines, like sucralfate and bismuth compounds, play an important role in shielding the stomach lining (Kuna et al., 2019). Sucralfate works by forming a protective coating over the ulcer, binding to the damaged tissue so that it's less exposed to stomach acid and digestive enzymes like pepsin (McCarthy, 1991). Bismuth-based drugs, such as bismuth subsalicylate, not only help protect the stomach lining but also act against *H. pylori* bacteria (Dore, Lu, & Graham, 2016). Because of this, they are often used alongside antibiotics in treatment plans aimed at clearing *H. pylori* infection and supporting ulcer healing (Dore, Lu, & Graham, 2016).

### **Prostaglandin Derivatives**

Misoprostol is a synthetic analog of a naturally occurring substance in the body called prostaglandin E<sub>1</sub> (Rostom, 2009). It helps protect the stomach lining by boosting the production of mucus and bicarbonate, while also lowering stomach acid levels (Rostom, 2009). This makes it especially helpful in preventing ulcers caused by long-term use of painkillers like NSAIDs (Rostom, 2009). However, misoprostol is not without limitations; it can cause gastrointestinal side effects such as diarrhea and stomach cramps (Rostom, 2009). Importantly, it should never be used during pregnancy because it can trigger uterine contractions (Rostom, 2009).

### **Helicobacter pylori Eradication Therapy**

*Helicobacter pylori* is a common cause of peptic ulcer disease (Malfertheiner et al., 2017). To treat this infection, doctors typically use a treatment known as triple therapy, which combines two antibiotics such as clarithromycin, amoxicillin, or metronidazole with a proton pump inhibitor (PPI) to decrease stomach acid production (Malfertheiner et al., 2017). If the bacteria are resistant to the antibiotics in triple therapy, a more powerful treatment called quadruple therapy is used (Sun et al., 2010). This adds bismuth subsalicylate to the mix along with metronidazole, tetracycline, and a PPI (Sun et al., 2010). Successfully eliminating *H. pylori* not only aids in the healing of ulcers but also helps prevent their recurrence, reducing the need for long-term use of acid-suppressing medications (Malfertheiner et al., 2017). The treatment of peptic ulcers has changed dramatically over the years (Kuna et al., 2019). Today, proton pump inhibitors (PPIs) are the

cornerstone of therapy because they strongly suppress stomach acid and promote healing (Kuna et al., 2019). Other medicines, like H<sub>2</sub> receptor blockers and mucosal protective agents, can be used as alternatives or in combination to support treatment (Kuna et al., 2019). The biggest breakthrough, however, came with the use of antibiotics to eliminate *Helicobacter pylori*, the bacteria responsible for many ulcers (Kuna et al., 2019). By tailoring treatment to the specific cause of the ulcer and the individual needs of each patient, doctors can achieve the best outcomes and greatly reduce the chances of the ulcer coming back (Kuna et al., 2019).

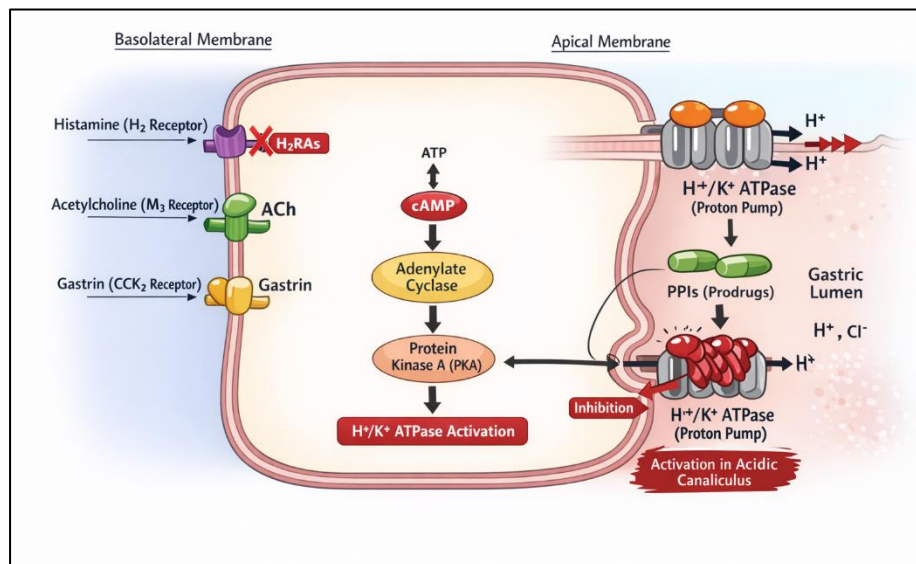
### **PHARMACOLOGICAL MECHANISMS AND THERAPEUTIC APPLICATIONS:**

Peptic ulcers are usually treated with medicines that either lower stomach acid, neutralize the acid that is already there, or strengthen the stomach's natural defenses (Kuna et al., 2019). The main groups of drugs include proton pump inhibitors (PPIs), H<sub>2</sub>-receptor blockers (H<sub>2</sub>RAs), antacids, protective agents like sucralfate or bismuth, and antibiotics to eliminate *Helicobacter pylori* (*H. pylori*), the bacteria often responsible for ulcers (Kuna et al., 2019). Each of these medicines works in its own way and has different levels of effectiveness (Kuna et al., 2019). Doctors choose the right combination based on the cause of the ulcer and the patient's individual needs, which helps ensure the best healing and reduces the chance of the ulcer coming back (Kuna et al., 2019).

#### **Proton Pump Inhibitors (PPIs):**

Proton pump inhibitors (PPIs) function as prodrugs that require activation in a highly acidic environment to exert their pharmacological effects (Shi & Klotz, 2008). Upon systemic absorption, these weak bases diffuse into the parietal cell and accumulate in the highly acidic secretory canaliculi, where they undergo an acid-catalyzed molecular rearrangement to form a reactive thiophilic sulfenamide intermediate (Shi & Klotz, 2008). This active species forms irreversible covalent disulfide bonds with specific cysteine residues on the luminal surface of the H<sup>+</sup>/K<sup>+</sup> ATPase enzyme, effectively halting terminal gastric acid secretion (Strand, Kim, & Peura, 2017). Pharmacokinetically, PPIs such as omeprazole, pantoprazole, and esomeprazole are extensively metabolized by the hepatic cytochrome P450 system, predominantly via the CYP2C19 and CYP3A4 isoenzymes (Shi & Klotz, 2008). This extensive hepatic metabolism necessitates careful consideration of potential drug-drug interactions; for instance, competitive inhibition of CYP2C19 by omeprazole can attenuate the bioactivation of clopidogrel (Shi & Klotz, 2008). While PPIs are significantly superior to H<sub>2</sub>RAs in maintaining the sustained intragastric pH elevation required for mucosal healing and *H. pylori* eradication, long-term PPI therapy induces profound hypochlorhydria (Strand, Kim, & Peura, 2017). This altered gastric milieu can lead to the

malabsorption of pH-dependent micronutrients (e.g., Vitamin B12) and has been associated with an increased risk of osteoporotic fractures and enteric infections (Strand, Kim, & Peura, 2017).



**Figure 3: Molecular Targets of Antisecretory Agents within the Gastric Parietal Cell.**

#### **H<sub>2</sub>-Receptor Antagonists (H<sub>2</sub>RAs):**

Proton pump inhibitors (PPIs) function as prodrugs that require activation in a highly acidic environment to exert their pharmacological effects (Shi & Klotz, 2008). Upon systemic absorption, these weak bases diffuse into the parietal cell and accumulate in the highly acidic secretory canaliculi, where they undergo an acid-catalyzed molecular rearrangement to form a reactive thiophilic sulfenamide intermediate (Shi & Klotz, 2008). This active species forms irreversible covalent disulfide bonds with specific cysteine residues on the luminal surface of the H<sup>+</sup>/K<sup>+</sup> ATPase enzyme, effectively halting terminal gastric acid secretion (Strand, Kim, & Peura, 2017). Pharmacokinetically, PPIs such as omeprazole, pantoprazole, and esomeprazole are extensively metabolized by the hepatic cytochrome P450 system, predominantly via the CYP2C19 and CYP3A4 isoenzymes (Shi & Klotz, 2008). This extensive hepatic metabolism necessitates careful consideration of potential drug-drug interactions; for instance, competitive inhibition of CYP2C19 by omeprazole can attenuate the bioactivation of clopidogrel (Shi & Klotz, 2008). While PPIs are significantly superior to H<sub>2</sub>RAs in maintaining the sustained intragastric pH elevation required for mucosal healing and *H. pylori* eradication, long-term PPI therapy induces profound hypochlorhydria (Strand, Kim, & Peura, 2017). This altered gastric milieu can lead to the malabsorption of pH-dependent micronutrients (e.g., Vitamin B12) and has been associated with an increased risk of osteoporotic fractures and enteric infections (Strand, Kim, & Peura, 2017).

#### **Antacids:**

Antacids, composed of weakly basic inorganic salts of aluminum, magnesium, and calcium, operate independent of receptor-mediated pathways (Kuna et al., 2019). They directly neutralize existing gastric hydrochloric acid to form water and neutral salts, providing rapid, acute symptomatic relief (Kiran, Rohilla, & Kalra, 2023). This chemical neutralization acutely elevates intragastric pH, which subsequently inactivates pepsinogen and bolsters the mucosal protective gel (Kuna et al., 2019). However, from a biopharmaceutical perspective, the primary clinical concern with antacids is their propensity to alter the gastrointestinal absorption of concurrently administered therapeutics (Kiran, Rohilla, & Kalra, 2023). This occurs through the premature dissolution of enteric coatings in the higher-pH gastric environment, alterations in gastric emptying rates, or direct chemical chelation (e.g., forming insoluble complexes with fluoroquinolones and tetracyclines) (Kuna et al., 2019). Furthermore, while systemic absorption is generally minimal, overconsumption can precipitate clinically significant toxicities, such as milk-alkali syndrome (metabolic alkalosis and hypercalcemia) with excessive calcium carbonate ingestion, or systemic heavy metal accumulation in patients with compromised renal function (Kiran, Rohilla, & Kalra, 2023).

### **Cytoprotective Agents:**

Cytoprotective agents are medicines that help strengthen the stomach's natural defenses against acid (Kuna et al., 2019). Examples include sucralfate, misoprostol, and bismuth compounds (Kuna et al., 2019). Sucralfate works by binding to proteins at the site of an ulcer, creating a protective barrier that shields the damaged tissue from further acid injury (McCarthy, 1991). It is especially useful for preventing stress ulcers in critically ill patients (McCarthy, 1991). Misoprostol, a prostaglandin E1 analog, boosts the stomach's protective mucus and bicarbonate while also reducing acid secretion (Rostom, 2009). Its main role is in preventing ulcers caused by NSAIDs, though its use is limited because it can cause diarrhea and, importantly, uterine contractions making it unsafe during pregnancy (Rostom, 2009). Bismuth compounds not only coat the stomach lining for protection but also have mild antibacterial activity against *H. pylori* (Dore, Lu, & Graham, 2016). For this reason, they are often included in quadruple therapy regimens aimed at eradicating *H. pylori* infection (Dore, Lu, & Graham, 2016).

### **Antibiotics for *H. pylori* Eradication**

*Helicobacter pylori* infection is one of the main causes of peptic ulcer disease (Malfertheiner et al., 2017). To get rid of the bacteria, doctors use antibiotics such as clarithromycin, amoxicillin, metronidazole, and tetracycline (Malfertheiner et al., 2017). The usual treatment combines two antibiotics with a proton pump inhibitor (PPI), known as triple therapy (Malfertheiner et al., 2017).

In some cases, a bismuth compound is added, creating quadruple therapy (Sun et al., 2010). Successfully clearing *H. pylori* not only heals the ulcer but also greatly lowers the chance of it coming back (Malfertheiner et al., 2017). The challenge today is that resistance to certain antibiotics especially clarithromycin and metronidazole has become more common (Malfertheiner et al., 2017). Because of this, newer approaches like sequential therapy (using different drugs in stages) and concomitant therapy (using multiple drugs at the same time) are being adopted to improve success rates (Malfertheiner et al., 2017).

### **Comparison of Botanical Extracts and Synthetic Drugs for Gastric Ulcer Healing:**

Researchers have been exploring the potential of AL (*Anogeissus latifolia*) bark as a treatment for stomach ulcers (Govindarajan et al., 2006). Early studies show that the hydroalcoholic extract of this bark may help protect the stomach lining (Govindarajan et al., 2006). It seems to work by reducing harmful processes like lipid peroxidation (LPO) and lowering superoxide dismutase (SOD) activity, both of which can damage cells (Govindarajan et al., 2006). At the same time, it boosts catalase activity, an enzyme that helps neutralize oxidative stress (Govindarajan et al., 2006). Put simply, AL bark may strengthen the stomach's natural defenses against ulcer formation (Govindarajan et al., 2006). Because the leaves contain gallic acid, ellagic acid, and their derivatives in significant amounts, both the leaf extracts and the volatile oil showed moderate antibacterial and antifungal effects (Prayoga et al., 2024). The hydroethanolic extract of the leaves and bark of *Alchornea castaneaefolia* A. Juss. has demonstrated significant antiulcer activity in experimental models (Prayoga et al., 2024). At an oral dose of 1000 mg/kg, both leaf and bark extracts markedly inhibited ulcer formation, achieving 88% and 86% protection, respectively, in HCl/ethanol-induced gastric lesions in mice (Prayoga et al., 2024). Similarly, they provided 62% and 60% inhibition in indomethacin/bethanechol-induced ulcer models (Prayoga et al., 2024). Pre-treatment with the leaf extract offered notable mucosal protection, reducing ulcer incidence by 55% in hypothermic restraint stress-induced ulcers and by 34% in pylorus-ligated mice (Prayoga et al., 2024). Interestingly, the extract did not exhibit antisecretory effects in the Shay model, suggesting its mechanism of action is not linked to direct suppression of gastric acid secretion (Prayoga et al., 2024). Beyond acute models, the leaf extract also reduced the mean ulcer area and promoted healing in chronic gastric ulcers induced by acetic acid in rats, highlighting its potential role in both prevention and recovery (Prayoga et al., 2024). A flavonoid-enriched fraction isolated from the hydroethanolic leaf extract further confirmed these findings. At 100 mg/kg, this fraction provided 52% protection against HCl/ethanol-induced lesions and 79% protection against NSAID-induced gastric damage (Prayoga et al., 2024). However, it did not significantly enhance

mucoprotection in pylorus-ligated animals (Prayoga et al., 2024). Mechanistic studies revealed that pretreatment with the flavonoid fraction led to a substantial increase in prostaglandin E2 levels, which are typically suppressed by indomethacin (Prayoga et al., 2024). Additionally, it caused a marked reduction in serum gastrin levels and nearly tripled serum somatostatin concentrations compared to controls (Prayoga et al., 2024). Since gastrin stimulates gastric acid secretion, while somatostatin inhibits it, these hormonal changes suggest that the gastroprotective effects of *Alchornea castaneaefolia* are mediated through modulation of mucosal defense factors rather than direct acid inhibition (Prayoga et al., 2024). *Decalepis salicifolia* (also known as *Uleria salicifolia*) has shown encouraging results in protecting against ulcers (Rao et al., 2004). In studies with rats, its rhizome extract helped reduce damage in several types of ulcer models including those caused by excess acid (pylorus ligation), aspirin use, cysteamine-induced duodenal ulcers, and alcohol-related loss of stomach mucus (Rao et al., 2004).

**Table 1: Comprehensive Pharmacological Summary of Investigated Phytotherapeutics in Peptic Ulcer Models**

| Botanical Source (Plant Name)   | Key Phytochemical(s)/ Fraction                     | Primary Mechanism(s) of Action                                                                                       | Experimental Model(s)                                                              | Ulcer | Effective Dose                                     | References (APA)            |
|---------------------------------|----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------|----------------------------------------------------|-----------------------------|
| <i>Anogeissus latifolia</i>     | Gallic acid, Ellagic acid                          | Inhibits 5-lipoxygenase; increases catalase; reduces lipid peroxidation (LPO) and superoxide dismutase (SOD)         | Aspirin, ethanol, cold stress, pylorus ligation                                    |       | 200 mg/kg                                          | (Govindarajan et al., 2006) |
| <i>Alchornea castaneaefolia</i> | Flavonoid glycosides (Flavonoid-enriched fraction) | Increases PGE <sub>2</sub> synthesis; elevates serum somatostatin; suppresses serum gastrin                          | HCl/ethanol, indomethacin/bethanechol, hypothermic restraint stress, acetic acid   |       | 100 mg/kg (flavonoid fraction); 1000 mg/kg (crude) | (Prayoga et al., 2024)      |
| <i>Decalepis salicifolia</i>    | Polysaccharides / Antioxidant fractions            | Increases gastric wall mucus and SOD; reduces lipid peroxidation and plasma corticosterone                           | Pylorus ligation, aspirin, ethanol, cold-restraint stress, acetic acid, cysteamine |       | 100 and 200 mg/kg                                  | (Rao et al., 2004)          |
| <i>Solanum nigrum</i>           | Fruit and aerial part extracts                     | Lowers gastric acid/pepsin; suppresses gastrin; inhibits H <sup>+</sup> /K <sup>+</sup> -ATPase; boosts antioxidants | Stress, indomethacin, pyloric ligation, ethanol, acetic acid                       |       | Higher doses (dose-dependent)                      | (Jainu & Devi, 2006)        |
| <i>Ocimum tenuiflorum</i>       | Ethanolic leaf extract, fixed seed oil             | Reduces free/total acidity and peptic activity; enhances mucus secretion and epithelial regeneration                 | Cold-restraint stress, aspirin, alcohol, pylorus ligation, histamine               |       | 100 mg/kg                                          | (Kuna et al., 2019)         |
| <i>Asparagus racemosus</i>      | Polysaccharide fraction                            | Purely cytoprotective (increases mucopolysaccharides/carbohydrates); reduces lipid peroxidation                      | Cold-restraint stress, pyloric ligation, acetic acid, cysteamine                   |       | Dose-dependent                                     | (Prayoga et al., 2024)      |
| <i>Curcuma longa</i>            | Curcumin                                           | Improves gastric mucus function; regulates inflammatory gene expression; reduces gastric acid                        | Acute acid reflux esophagitis                                                      |       | Not specified (comparable to lansoprazole)         | (Mahattanadul et al., 2006) |

**Table 2: Comparative Safety and Biopharmaceutical Profiles of Synthetic Anti-Ulcer Agents versus Phytochemicals**

| Therapeutic Agent / Class                                       | Biopharmaceutical & Pharmacokinetic Profile                                                                                   | Key Adverse Effects & Clinical Limitations                                                                      | References (APA)                                |
|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| <b>Proton Pump Inhibitors (PPIs)</b> (e.g., <i>Omeprazole</i> ) | Requires acidic environment for activation; strongly reduces acid production; acts on H <sup>+</sup> /K <sup>+</sup> -ATPase. | Vitamin B12 and magnesium malabsorption; increased risk of enteric infections, kidney disease, and osteoporotic | (Shi & Klotz, 2008; Strand, Kim, & Peura, 2017) |

|                                                                                                         |                                                                                                                                                               |                                                                                                                                                  |                                           |
|---------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
|                                                                                                         |                                                                                                                                                               | bone fractures with long-term use.                                                                                                               |                                           |
| <b>Histamine-2 Receptor Antagonists (H2RAs)</b> ( <i>e.g.</i> , <i>Cimetidine</i> , <i>Ranitidine</i> ) | Competitively blocks H2 receptors on parietal cells, decreasing cAMP and protein kinase activation.                                                           | Pharmacological tolerance limits long-term efficacy; cimetidine interacts with liver enzymes (CYP450) and can induce gynecomastia.               | (Salman et al., 2025)                     |
| <b>Antacids</b> ( <i>Al</i> , <i>Mg</i> , <i>Ca</i> salts)                                              | Chemically neutralizes gastric HCl; rapid onset but short duration; alters gastric pH.                                                                        | Magnesium causes diarrhea; Aluminum causes constipation; Calcium carbonate can cause metabolic alkalosis (milk-alkali syndrome).                 | (Begg et al., 2023)                       |
| <b>Synthetic Prostaglandins</b> ( <i>Misoprostol</i> )                                                  | Prostaglandin E1 analog; boosts mucus and bicarbonate production.                                                                                             | Gastrointestinal discomfort (diarrhea, stomach cramps); strictly contraindicated in pregnancy due to uterine contractions.                       | (Rostom, 2009)                            |
| <b>Isolated Phytochemicals / Botanical Extracts</b>                                                     | Slower onset of action with effects accumulating over time; primarily enhance mucosal defense and antioxidant pathways rather than directly suppressing acid. | Generally well-tolerated with mild GI upset or allergic reactions; clinical utility limited by poor standardization and unknown bioavailability. | (Kuna et al., 2019; Prayoga et al., 2024) |

## CONCLUSION AND FUTURE PERSPECTIVES

The therapeutic landscape of peptic ulcer disease is at a critical inflection point. While the profound acid-suppressing capabilities of proton pump inhibitors and targeted *H. pylori* eradication regimens remain the clinical gold standard, their long-term pharmacokinetic liabilities and the escalating threat of antibiotic resistance necessitate a paradigm shift. Phytotherapeutics offer a mechanistically distinct approach, pivoting away from absolute acid suppression toward the restoration of mucosal integrity via antioxidant pathways, prostaglandin E2 upregulation, and precise endocrine modulation. However, for botanical agents to transition from ethnomedical curiosities to rigorously validated clinical therapeutics, the scientific community must move beyond evaluating crude extracts in acute animal models. Future research must prioritize the isolation of active phytoconstituents and the application of novel drug delivery systems (NDDS), such as nanocarriers, phytosomes, or liposomes, to circumvent their inherent biopharmaceutical limitations particularly poor systemic bioavailability and rapid presystemic metabolism. Furthermore, as the concurrent use of synthetic antisecretory drugs and herbal supplements rises, robust pharmacokinetic profiling to identify potential CYP450-mediated herb-drug interactions is clinically imperative. Ultimately, a synergistic, evidence-based integration of standardized, isolated phytoconstituents with conventional pharmacotherapy governed by strict regulatory and biopharmaceutical frameworks holds the most promise for the sustainable, long-term management of peptic ulcer disease.

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