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PEPTIC ULCER: AN OVERVIEW

Gulgaz Haque[1]*, Dr. Dhiraj Kumar[2] and Jyoti Yadav[3]

[1,2,3]Department of Pharmacology, Institute of Technology and Management Gida Gorakhpur.

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***Corresponding Author**
Gulgaz Haque
Department of Pharmacology, Institute of Technology and Management Gida Gorakhpur.
gulgazhaque18298@gmail.com

ABSTRACT

A chronic condition that affects up to 10% of people worldwide is peptic ulcer disease. The presence of gastric juice pH and the lowering of mucosal defenses are prerequisites for the development of peptic ulcers. The two primary factors that are disrupting the mucosal resistance to injury are Helicobacter pylori (H. pylori) infection and non-steroidal anti-inflammatory drugs (NSAIDs). The hallmark of Peptic Ulcer Disease (PUD) is the disruption of the GI tract's inner lining due to either pepsin or gastric acid secretion. It penetrates the gastric epithelium's muscularis propria layer. Usually, it affects the proximal duodenum and stomach. The jejunum, distal duodenum, or lower esophagus could be affected. Patients with gastric ulcers typically experience epigastric pain 15–30 minutes after eating, whereas duodenal ulcer patients typically experience pain 2–3 hours later. Proton pump inhibitors (PPIs) and histamine-2 (H2) receptor antagonists, two common treatments for peptic ulcers, have been linked to side effects, relapses, and a variety of drug interactions. Conversely, medicinal plants and the chemicals they contain can be used to treat and prevent a wide range of illnesses.

KEYWORDS: Peptic ulcer, Helicobacter pylori, Non-steroidal anti-inflammatory drugs.

1. INTRODUCTION

The stomach or proximal duodenum are the typical locations of peptic ulcers, which are acid-induced lesions of the digestive tract characterized by denuded mucosa that extends into the submucosa or muscularis propria.[1] Traditionally, an acidic environment that is hypersecretory in combination with dietary factors or stress is thought to be the cause of mucosal disruption in patients suffering from acid-peptic disease. Alcohol and tobacco use,

non-steroidal antidepressants, H. pylori infection, and other risk factors Use of nonsteroidal anti-inflammatory drugs (NSAIDs) and Zollinger-Ellison syndrome.[2]

NSAID users have a four-fold increased risk of peptic ulcer complications, while aspirin users have a two-fold increased risk.[3] The risk of upper gastrointestinal bleeding increases when anticoagulants, corticosteroids, and selective serotonin reuptake inhibitors are used concurrently with NSAIDs or aspirin.[4] The role that NSAIDs and aspirin play in the pathophysiology of peptic ulcer disease is still up for debate, even though many users of these medications also have concurrent H. pylori infections. Aspirin use, NSAID use, and H. pylori infection were found to independently raise the risk of peptic ulcer disease in a meta-analysis of observational studies[5] Peptic ulcer condition can be seen in the figure.1

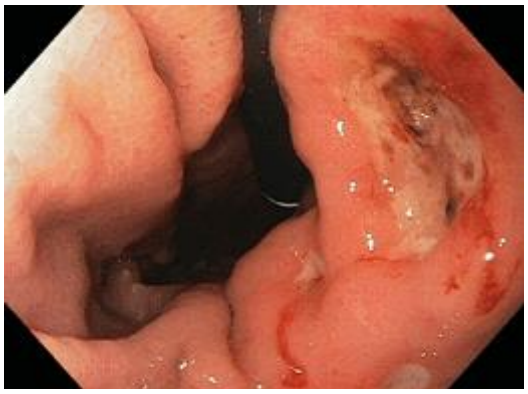


Figure 1: Photograph of a peptic ulcer taken during an upper endoscopy. This ulcer is a "gastric ulcer" because it is located in the stomach.

H. pylori-negative, NSAID-negative, and aspirin-negative peptic ulcer disease, which is classified as an idiopathic ulcer, can be diagnosed in about one-fifth of cases.[6] It is caused by the imbalance between factors that contribute to mucosal integrity and aggressive insults, but the pathogenic mechanisms behind the development of idiopathic peptic ulcers are still unknown.[2]

1.1 ETIOLOGY

Although there are many causes of PUD, the majority of the disease etiology is related to Helicobacter pylori-associated PUD and NSAID-associated PUD.[7]

Common

1. *H. pylori* infection
2. NSAIDs

3. Medications.

Rare

- Zollinger-Ellison syndrome
- Malignancy (gastric/lung cancer, lymphomas)
- Stress (Acute illness, burns, head injury)
- Viral infection
- Vascular insufficiency
- Radiation therapy
- Crohn disease
- Chemotherapy.

1.2 SIGN AND SYMPTOMS

A peptic ulcer may present with one or more of the following signs and symptoms:

- Traditionally, epigastric abdominal pain is closely associated with mealtimes.
  When a person has a duodenal ulcer, the pain usually wakes them up three hours after they eat.
- Bloating and fullness in the abdomen.
- Waterbrash, a surge of saliva following a regurgitation episode that lessens the acid in the esophagus, though it is more commonly linked to gastroesophageal reflux disease.
- Nausea and frequent vomiting.
- Appetite loss and weight loss in cases of gastric ulcers.
- Weight gain in cases of duodenal ulcers because eating relieves pain.
- Hematemesis, or blood vomiting, can be brought on by bleeding directly from a stomach ulcer or by prolonged, severe vomiting that damages the esophagus.
- Melena: a foul-smelling, tarry stool caused by oxidized iron from hemoglobin.
- In rare cases, an ulcer can result in a gastric or duodenal perforation, causing severe, stabbing pain and acute peritonitis[8], which calls for immediate medical attention.

1.3 PATHOGENESIS OF PEPTIC ULCER

The mechanism by which H. pylori induces the development of different types of lesions in the gastroduodenal mucosa is not fully explained. H. pylori infection can result in either hypochlorhydria or hyperchlorhydria, thus determining the type of peptic ulcer. Although cytokines that block parietal cell secretion are the primary mediators of H. pylori infection,

the bacteria can also directly impact the H+/K+ ATPase subunit, activate sensory neurons linked to somatostatin that are associated with calcitonin gene-related peptide (CGRP), or prevent the gastrin from being produced. While hyposecretion is linked to the development of gastric ulcers, 10-15% of patients infected with H. pylori have hypergastrinemia, which results in increased gastric secretion, and decreased antral somatostatin content. This causes the parietal and stomach cells to secrete more histamine, which in turn causes them to secrete more acid or pepsin.

Furthermore, somatostatin mRNA expression rises and gastrin mRNA expression decreases when H. pylori is eradicated. Hypochlorhydria is linked to gastric ulcers in the majority of patients who remain.

The systemic inhibition of constitutively expressed cyclooxygenase-1 (COX-1), which is in charge of prostaglandin synthesis and is linked to reduced mucosal blood flow, low mucus, and other adverse effects, is the primary mechanism of NSAID-associated damage to the gastroduodenal mucosa. secretion of bicarbonate and the suppression of cell division. NSAIDs reversibly and concentration-dependently inhibit the enzyme. Mucosal damage and the risk of ulcers are decreased when exogenous prostaglandins and COX-2-selective NSAIDs are used together.[10] NSAIDs cause the uncoupling of mitochondrial oxidative phosphorylation and disturb the phospholipids in mucus, which starts the damage to the mucosa. NSAIDs become protonated in acidic gastric juice (pH 2) and penetrate lipid membranes to enter epithelial cells (pH 7.4) Liberate and ionize H+. In that form, NSAIDs become trapped in epithelial cells due to their inability to cross the lipid membrane, which causes oxidative phosphorylation to uncouple and mitochondrial J. Clin. Med. 2019, 8, 179 3 of 19 cellular integrity, elevated permeability, and energy production. Individuals who take high doses or combinations of NSAIDs, are over 65, have a history of peptic ulcers or hemorrhage, and also use steroids or anticoagulants are most vulnerable to developing NSAID-induced ulcers.[1]

The main pathophysiological mechanisms and the sites of action of antiulcer treatment are shown in the Figure 1.

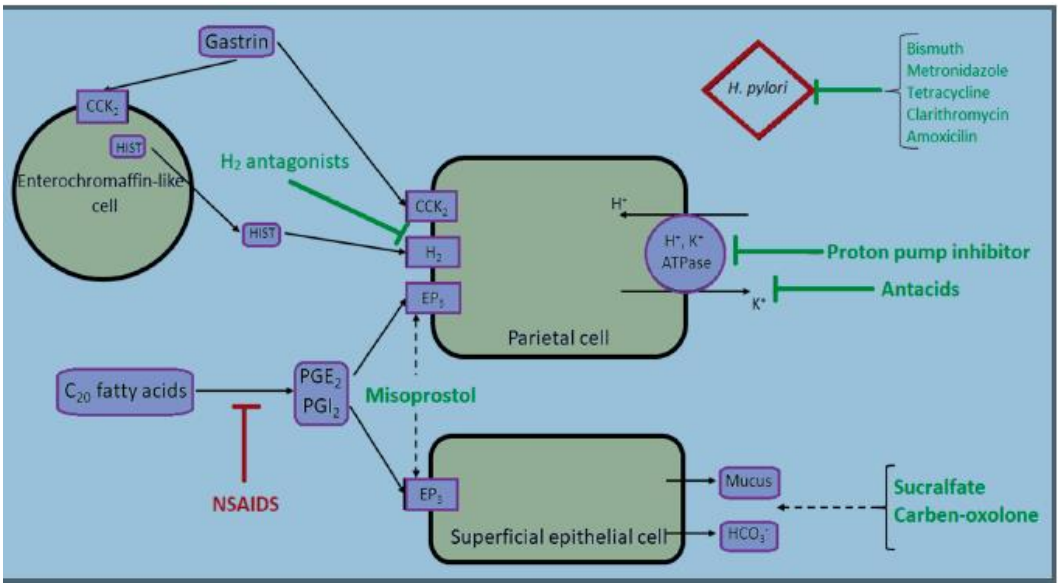
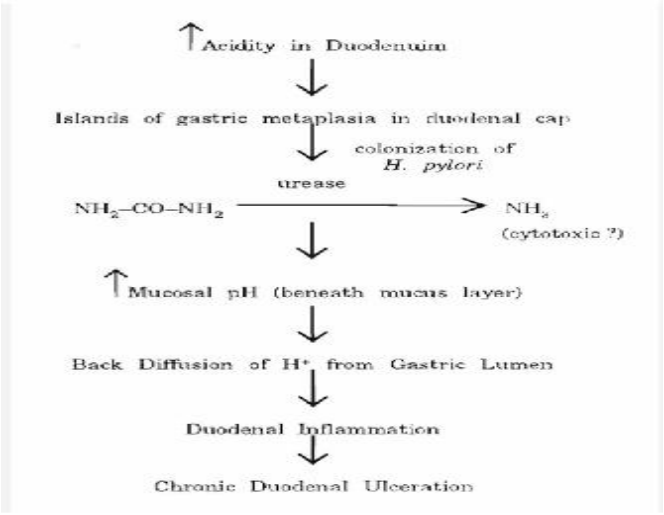


Figure 1: Schematic presentation of main pathophysiological mechanisms involved in the development of peptic ulcer disease, and the sites of action of the most commonly used pharmacological options in the treatment of peptic ulcer disease.

CCK2 = Cholecystokinin Receptor; PGE2 = Prostaglandin E2.

PGI2 = Prostaglandin I2; EP3 = Prostaglandin E receptor 3; HIST = Histamine.



peptide (CGRP) sensory neurons linked to somatostatin, or inhibit the production of gastrin.[9]

1.4 DIAGNOSIS

All participants were asked if they had been diagnosed with a peptic ulcer within the 11-year observation period. Participants with a first-time diagnosed ulcer reported how and when the diagnosis was made. To ensure that all first-time diagnosed ulcers were recorded, information

was also obtained from the National Danish Hospital Discharge Registry (NDHDR) in which all cases of hospital admissions in Denmark are registered with a discharge diagnosis. The search included the following PUD diagnoses (WHO ICD-8 codes: 531. X (gastric ulcer), 532. X (duodenal ulcer), and 533. X (gastro-duodenal ulcer)). Medical records from those who reported an ulcer or who were registered with a PUD diagnosis in the NDHDR were retrieved and reviewed. Only ulcers verified by upper endoscopy, barium meal examination, or surgery were regarded as true incident ulcers.[19]

Most peptic ulcers are treated medically after diagnosis is typically made by upper gastrointestinal tract endoscopic examination (esophagus-gastro-duodenoscopy, or OGD). Typically, surgery, interventional radiology, and therapeutic endoscopy Jaiswal along with others.designed to treat peptic ulcer disease complications like bleeding, perforation, and obstruction of the outflow. Single or multiple ulcers most often affect the lower curve of the stomach and the upper portion of the duodenum. The most popular technique for identifying H. pylori during endoscopy is the rapid urease test (CLO test), which is easily accessible. Its advantages include high sensitivity, speed, and affordability.

For individuals who choose not to have an endoscopy, there are also less invasive diagnostic tests available for H. pylori. One of these is a urea breath test (specificity 100%, sensitivity 95%), which depends on H. pylori's capacity to convert carbon radiolabelled urea taken orally into carbon dioxide, which the patient exhales and leaves behind, and which can be found on their breath. The sensitivity and specificity of the increasingly popular H. pylori stool antigen test, which is a non-invasive alternative, have been shown in recent studies to be around 95%. It is generally not advised to perform H. pylori antigen serology because it may result in false positive results in people who have previously had an infection but are not currently infected.[20]

1.4 TREATMENT

The objectives of peptic ulcer disease treatment are to reduce symptoms, close craters, stop complications, and avoid recurrences. Drug therapy should be a part of medical therapy, and the following goals should be pursued:

1) Diminish the acidity of the stomach through methods that prevent or balance acid *production*,

2) Apply coating to ulcer craters to stop acid and pepsin from reaching the base of the ulcer, offer a prostaglandin analog,

4) eliminate environmental contaminants like smoking and NSAIDs, and

5) lessen psychological stress (in certain patients).

Table No. 1: Provides a summary of the traditional antiulcer treatment options.

Table 1: Mechanisms of action and adverse effects of the most commonly used antiulcer treatment options.

MEDICINE	MECHANISM OF ACTION	ADVERSE REACTION	REFRENSES
PROTON PUMP INHIBITOR Omeprazole Lansoprazole Rabeprazole Esomeprazole Pantoprazole	Inhibition of the gastric H+/K+-ATPase (proton pump)	Headache Abdominal pain Diarrhea Nausea Vomiting Constipation Flatulence Vitamin B12 deficiency Osteoporosis	[11,12]
H2 ANTAGONIST Cimetidine Famotidine Nizatidine Ranitidine	Blocking the action of histamine at the histamine H2 receptors of parietal cells	Headache Anxiety Depression Dizziness Cardiovascular events Thrombocytopenia	[13]
ANTACID Aluminum hydroxide Magnesium hydroxide	Increases gastric pH to greater than four, and inhibits the proteolytic activity of pepsin Frequency not defined:	Vomiting Hypophosphatemia Chalky taste Constipation Abdominal cramping Diarrhea Electrolyte imbalance	[14]
Potassium-Competitive Acid Blocker Vonoprazan	Inhibits H+, K+-ATPase in gastric parietal cells at the final stage of the acid secretory pathway	Nasopharyngitis Fall Contusion Diarrhea Upper respiratory tract inflammation Eczema Constipation Back pain	[15,16]
Cytoprotective Agents Misoprostol Sucralfate	Stimulate mucus production and enhance blood flow throughout the lining of the gastrointestinal tract	Diarrhea Abdominal pain Headache Constipation	[17,18]

1.5 MEDICINAL PLANT IN PEPTIC ULCER TREATMENT

Phytotherapy, or the use of medicinal plants to treat a variety of illnesses, is as old as humanity. Additionally, there has been an increase in interest in complementary therapies and the use of herbal products in recent years, particularly those made from herbal remedies.[21,22] Additionally, medicinal plants are thought to be the main source of potentially novel drugs due to the emergence of different side effects from the use of conventional drugs for a wide range of diseases. Crude plant extracts are the primary source of novel pharmaceuticals, and have demostrated encouraging outcomes when used to treat stomach ulcers.[23] It is well known that many medications, including sucralfate, bismuth, anticholinergics, antimicrobial agents, proton pump inhibitors, and antacids, are not entirely effective and can have a variety of negative side effects, including gynecomastia, hypersensitivity, impotence, and hematopoietic changes.[24,25] The ability of medicinal plants to generate diverse and renewable secondary metabolites, also referred to as phytochemical constituents, is what gives them their medicinal qualities. As a result, many plants have employed these phytochemicals as a defense mechanism against infections.[26] However, the emergence of resistant pathogens has forced pharmaceutical companies to rethink how they develop traditional antibiotics and instead create novel antimicrobial medications made from medicinal plants.[27] However, as antimicrobial medications, synthetic antibiostics continue to rule the market.

It is crucial to stress that herbal products could include a variety of bioactive ingredients with both harmful and advantageous effects. Therefore, laws to regulate the quality of herbal products as well as increased education for physicians and patients regarding herbal therapy are required.particularly for additional randomized studies to ascertain the efficacy and safety of numerous products in the treatment of gastrointestinal and other disorders.[28]

Ultimately, the knowledge gained from Ayurveda combined with modern medicine may produce better antiulcer medications made from medicinal plants that have fewer adverse effects.[29]

Table 3 lists many medicinal plants that are beneficial for treating gastric ulcer disease and have strong antibacterial activity against H. pylori.

Table 2: Overview of herbal antiulcer treatment and H. pylori eradication.

MEDICINAL PLANT	POSSIBLE MECHANISM	EFFECTS	ADVERSE EFFECT	REFRENCES
Korean red ginseng	Inhibition of H. pylori-induced 5-lipoxygenase (5-LOX) activity; preventing pro-inflammatory interleukin (IL)-8 or 5-LOX mRNA	Anti-inflammatory effect; increase eradication rates of H. pylori; reduction of gastric inflammation and oxidative DNA damage	Interaction with conventional drugs	[29,30]
Zingiber zerumbet	Gastroprotective mechanism of zerumbone (significant increased in the endogenous antioxidant GSH, reduction of lipid peroxidation level); other mechanism need to be investigated	Antioxidant, antiproliferative, anti-inflammatory, antisecretory effect; reduction of ulcer area formation	Nausea and vomiting in pregnant women; restless, heartburn; interaction with conventional drugs (anticoagulants, analgesics)	[35,36]
Allium sativum	Inhibition of lipoprotein oxidation and lower serum glucose induction of antioxidant enzymes; mechanisms need to be more investigated	Antioxidant; suppressive effect of H. pylori-induced gastric inflammation in vivo and in vitro	Interaction with conventional drugs	[31]
Camellia sinensis (Green tea polyphenols)	Suppression of tumor necrosis factor-alpha (TNF-_) gene expression; inhibition of urease	Antioxidant; improvement in the function of intestinal bacterial flora	Interaction with conventional drugs; dizziness, diarrhea, headaches, insomnia, heartbeat, may cause deficiency of iron	[37,38]
Zingiber officinalis	Inhibition of PGE2 and parietal cell H+, K+-ATPase	Anti-inflammatory effect; antioxidant	Nausea and vomiting in pregnant women; restless, heartburn; interaction with conventional drugs (anticoagulants, analgesics)	[33-35]
Curcuma loga	Inhibition of H. pylori-induced 5-LOX activity	Anti-inflammatory; antioxidant	Not determined	[32]

1.6 HERB-DRUG INTERACTION

Worldwide usage of herbal supplements is growing, and this is also leading to an increase in side effects and medication interactions. Pharmacokinetic or pharmacodynamic interactions can occur when a medication and a herbal supplement interact. The outcome of pharmacokinetic interaction is utilizing the same mechanism of absorption, distribution, metabolism, or excretion to alter the drug's pharmacologic action and blood concentration when given in combination with a herbal supplement. Pharmacodynamic interactions occur when a co-administered drug's mechanism of action is directly impacted, without affecting the drug's concentration; instead, the drug's clinical effects are exacerbated or neutralized.[37]

Drugs like digoxin, doxorubicin, rosuvastatin, and verapamil that are transported by P-gp have their concentrations reduced by allium sativum extract.[39] The most researched interaction between Allium sativum and warfarin has not yet been validated by randomized clinical trials. Furthermore, it restricts platelet aggregation, thus individuals receiving anticoagulant medication or those with clotting disorders should use it cautiously.[40] Zingiber officinalis inhibits thromboxane synthetase, which lengthens bleeding times; however, a clinical trial has not supported this.[41] Because ginkgo biloba inhibits platelet aggregation, it may raise the risk of bleeding, particularly when taken with anticoagulant medications. Although ginkgo biloba contains flavonoids that have antiplatelet activity, these compounds have no effect on human blood coagulation or platelet function.[40]

CONCLUSION

In our setting, peptic ulcer disease is still a common clinical issue that primarily affects individuals of all ages. It is anticipated that peptic ulcer disease will continue to have a major global impact on patient quality of life, health economics, and the delivery of healthcare as its prevalence rises with age. In our setting, peptic ulcer disease is still a common clinical issue that primarily affects individuals of all ages. Given how common peptic ulcers are UPI Journal of Pharmacy and Medical Science, 5(1), 2022: 19–26 Jaswanth et al.

The prevalence of this common disease rises with age, and it is anticipated that it will continue to have a major global influence on patient quality of life, health economics, and the delivery of healthcare.

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Herbal remedies and conventional anti-gastric ulcer medications may work in concert to combat H. pylori and gastric ulcer illness, as well as to help patients with the condition's prognosis. Considering the paucity of human research, more clinical trials involving increased sample sizes regarding the safety and effectiveness of therapeutic herbs having antiulcer properties. Designing studies to look into and clarify the mechanisms of action of medicinal plants used to treat or prevent peptic ulcers would also be beneficial.

Lastly, licensing is necessary for herbal products used for medicinal purposes in order to improve their quality and safety and guarantee that claims of potential efficacy are validated by randomized controlled trials.

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