

PEPTIC ULCER: A REVIEW ON ETIOLOGY, PATHOGENESIS AND TREATMENT

Falguni Jaiswal*, Dr. A. K. Rai, Dr. Parnay Wal , Ankita Wal and Shashi Pratap Singh

Pranveer Singh Insitute of Technology, Kanpur, Kanpur- Agra-Delhi, NH2, Bhauti, Kanpur, Uttar Pradesh 209309.

*Corresponding Author's E mail: falguni08jaiswal@gmail.com

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ABSTRACT

Peptic ulcer disease, which includes both stomach and duodenal ulcers, accounts for a significant portion of people seeking surgical advice around the world. A peptic ulcer is a lesion that develops on the stomach or duodenal lining. “Gastric ulcers” and “duodenal ulcers” are the two most prevalent peptic ulcer kinds. Peptic ulcers are caused by an imbalance between aggressive factors like hydrochloric acid (HCL), pepsin, refluxed bile, leukotrienes (LTs), reactive oxygen species (ROS), and defensive factors like the mucus-bicarbonate barrier, prostaglandins (PGs), mucosal blood flow, cell renewal and migration, nonenzymatic and enzymatic antioxidants. The most common causes of peptic ulcer disease are *H. pylori* infection and the use of nonsteroidal anti-inflammatory medications (NSAIDs). In addition, a variety of variables are implicated in the pathogenesis of gastric ulcer, including bacterial infection (*Helicobacter pylori*), certain drugs (NSAID), chemicals (Hcl/ethanol), and stomach cancer, with minor factors including stress, smoking, spicy food, and nutritional deficiencies. The goal of treating ulcers is to reduce the quantity of acid produced by your stomach, neutralize the acid produced, and protect the wounded area so it can recover. The major purpose of this review study was to summarize the ulcerogenic mechanisms of numerous mediators implicated in Peptic ulcer disease.

Keywords: Peptic Ulcer, Types, *Helicobacter pylori*, Diagnosis & Treatment.

INTRODUCTION

Peptic ulcer is a chronic disease that results from an imbalance between endogenous protective factors of gastric mucosa (mucus and bicarbonate secretion, adequate blood flow, prostaglandin E2, nitric oxide, sulfhydryl compounds and antioxidants enzymes, and others) and aggressive factors (acid and pepsin secretions). Behavioral and environmental factors such as smoking, poor diet, alcohol and non-steroidal anti-inflammatory drugs ingestion, and *Helicobacter pylori* infection, among others have also been implicated in the etiology of gastric ulcer ¹. Peptic ulcer disease is often defined as a mucosal break

greater than 3-5 mm in the stomach or duodenum with a visible depth. It is therefore an endoscopic diagnosis in contrast to dyspepsia, which is a clinical diagnosis based on symptoms alone. Peptic ulcer disease results from an imbalance between factors that protect the mucosa of the stomach and duodenum, and factors that cause damage to it. Patients with gastric and duodenal ulcers present similarly. They may report epigastric or retrosternal pain, early satiety, nausea, bloating, belching, or postprandial distress. These symptoms are non-specific and may be difficult to distinguish clinically from functional dyspepsia². Ulcers are an open sore of the skin or mucus membrane characterized by sloughing of inflamed dead tissue. Ulcers are lesions on the surface of the skin or a mucous membrane characterized by a superficial loss of tissue. Ulcers are most common on the skin of the lower extremities and in the gastrointestinal tract, although they may be encountered at almost any site. There are many types of ulcer such as mouth ulcer, esophagus ulcer, peptic ulcer, and genital ulcer³. Ulcer is one of the most common diseases affecting throughout the world population. The allopathic treatment of ulcer adversely affects the health by causing harmful side effects. It impedes the organ of which that membrane is a part from continuing its normal functions. It is of many forms which occur on both, inside and outside of the human body. Currently, different types of ulcer forms are recognized in medicine such as peptic ulcer, corneal ulcer, stomach ulcer, foot or leg ulcer etc⁴. The Gram-negative bacterium *Helicobacter pylori* remain present between the mucous layer and the gastric epithelium and are strategically designed to live within the aggressive environment of the stomach. Initially, *Helicobacter pylorus* reside in the antrum but over time migrates toward the more proximal segments of the stomach. Peptic ulcer is one of the world's major gastrointestinal disorders and affecting 10% of the world population. About 19 out of 20 peptic ulcers are duodenal. An estimated 15000 deaths occur each year as a consequence of peptic ulcer. Annual incidence estimates of peptic ulcer hemorrhage and perforation were 19.4–57 and 3.8–14 per 100,000 individuals, respectively. The average 7-day recurrence of hemorrhage was 13.9% and the average long-term recurrence of perforation was 12.2%⁵. Ulcer index Scoring of ulcer was done as follows: No ulcer=0; Superficial ulcers= 1; Deep ulcers=2; Perforation=3. Mean ulcer score for each animal will be expressed as ulcer index. The percentage of ulcer protection was determined by formula: % Protection= [(Control mean ulcer index - Test mean ulcer index)/ Control mean ulcer index 100⁶.

TYPES OF ULCER

Peptic Ulcer

Peptic ulcer is a broad term which includes ulcers of digestive tract in the stomach or the duodenum. Earlier it was believed that one developed this type of ulcers due to stress and spicy food. However, recent research has shown that these are just the aggravating factors. The causative agent is infection caused by the bacteria *H. pylori* or reaction to certain medicines like non-steroidal anti-inflammatory

drugs. Symptoms of peptic ulcers include weight loss, poor appetite, bloating, nausea, and vomit and black stools that indicate gastrointestinal bleeding.⁷

Aphthous Ulcers

Sores that develop in the inner lining of the mouth are referred to as mouth ulcers. Mouth ulcers are common and are usually due to trauma such as from ill fitting dentures, fractured teeth, or fillings, Anemia, measles, viral infection, oral candidiasis, chronic infections, throat cancer, mouth cancer and vitamin B deficiency are some of the common causes of ulcers or sores in the mouth. Aphthous minor is amongst the most common form of oral ulcerative diseases and affects an estimated 15-20% of the population worldwide. In some populations, the prevalence has been documented as being as high as 50-66% and it is especially common in North America. The incidence of aphthous ulcers has been found to be lower in smokers than in non-smokers.⁷

ETIOLOGY AND PATHOGENESIS OF ULCER H. PYLORI

H. Pylori is the main cause of stomach ulcers, was first identified by the two Australian scientists in 1982. *H. Pylori* possess a pathogenic activity, that encodes the effector protein cytotoxin-associated gene A. After translocation into the host cell, *cagA* effects cell shape, increases cell motility, disturbs cell junctional activity and thus responsible for gastric carcinomas and gastric ulcers. *H. Pylori* causes increases expression of cytokines such as $\text{THF-}\alpha$ in gastritis. Further, $\text{IL-1}\beta$ is too overexpressed in the *H. Pylori*- induced gastritis. *H. pylori*-infected gastric mucosa showed infiltration of polymorphonuclear leukocytes, lymphocytes, monocytes and plasma cells in the lamina propria, and intraepithelial severe neutrophil infiltration. The appropriate with complete resolution of mucosal inflammation and a minimal chance for recurrence of ulcers.⁶⁻⁷

Gastric acid secretions

Gastric acid is established as one of the major ulcerogenic factor for the induction of gastric ulcer disease. It has been reported that about 50% of gastric ulcer patients are pepsin and acid hypersecretors. But on the other hand, gastric acid plays a stringent role in gastric defense. It is the first line of mucosal defense to prevent bacterial colonization and reduced their ability to entrance in the mucosal layer. Acid secretion is suggested to be stimulated by three principle secretion is suggested to be stimulated by three principle secretagogues histamine, acetylcholine and gastrin. The receptors on the surface of parietal cell include H_2 receptors responding to histamine released from specialized mast cells, receptors that are sensitive to the muscarinic gastrin. Gastrin stimulates acid secretion either by direct stimulation of parietal cells or by the release of histamine from ECL cells⁸. It has been argued consistently that pressure ulcer risk assessment scales need to be developed on the basis of multivariable analyses to identify factors which are independently associated with pressure ulcer development. An improved understanding of the relative

contribution risk factors makes to the development of pressure ulcers and an improved ability to identify patients at high risk of pressure ulcer development would enable us to better target resources in practice. Early epidemiological evidence identified that reduced activity and mobility is the key risk factor for pressure ulcer development, but the relative contribution other risk factors make cannot be reliably determined from individual studies. To inform an emerging National Institute for Health Research (NIHR) Programme Grant on pressure ulcer prevention we sought to systematically review existing research to identify factors independently associated with pressure ulcer development, that is, “a risk factor that retains its statistical association with the outcome when other established risk factors for the outcome are included in the statistical model”. The aim of this study was to identify risk factors independently predictive of pressure ulcer development in adult patient populations ⁹. Peptic ulcer disease (PUD) develops when the protective mechanisms of the gastrointestinal mucosa, such as mucus and bicarbonate secretion, are overwhelmed by the damaging effects of gastric acid and pepsin. Peptic ulcers occur mainly in the stomach [gastric ulcer (GU)] or proximal duodenum [duodenal ulcer (DU)]. *Helicobacter pylori* infection was originally identified as the main cause of PUD; however, GU has become more commonly associated with the use of nonsteroidal anti-inflammatory drugs and acetylsalicylic acid (ASA)¹⁰. Duodenal ulcers were, as expected, strongly associated with age and smoking.1920 Surprisingly, men had lower odds than women, Blacks and Hispanics had lower odds than non-Hispanic Whites, and there was little relationship between either low education or income and duodenal ulcer. Throughout this century, men have had a greater burden from duodenal ulcer than women¹¹.

USE OF FOOD FIBERS IN PEPTIC ULCER TREATMENT

The physicochemical properties of fiber fractions produce different physiological effects in the organism. Soluble fibers, found in apple, oatmeal, and pear are responsible, for instance, for an increased viscosity in the intestinal content. Insoluble fibers (whole grains, granola, flaxseed) increase stool bulk, reduce transit time in the large intestine, and make fecal elimination easier and quicker. Fibers regulate the bowel function, which make them vital for the well being of healthy people and in the dietary treatment of many pathologies ¹². Recommended daily diet preferred of pathologies as in Table 1.

TABLE 1- Recommended daily diet for peptic ulcer³⁷

Characteristics	Recommendations	
Daily energy needs (DEN)	Sufficient to maintain or recover the nutritional status 20-25 Kcal/Kg: weight loss 25-30 Kcal/Kg: maintenance 30-35 Kcal/Kg: weight gain ³¹	
	Acute phase	Recovery phase
Carbohydrate (%)²⁹	50-60	50-60
Protein (g/Kg/weight)²⁹	1.2	1.5
Lipid (%)^{18,29}	25-30	25-30
Zinc (mg)¹³	11	40
Selenium (µg)²⁰	55	400
Vitamin A (µg)¹¹³	900	3000
Vitamin C (mg)¹³	75	500
Vitamin B¹² (µg)¹³	2.4	2.4
Folic acid (µg)¹³	400	400
Iron (mg)¹³	45	45
Fibers (g)¹³	20 to 30	20 to 30
Probiotics (UFC/day)¹⁸	10 ⁹ to 10 ¹¹ lactic acid bacteria	10 ⁹ to 10 ¹¹ lactic acid bacteria

PEPTIC ULCER 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. ¹³. Diagnosis is usually made by endoscopic examination of the upper gastrointestinal tract (oesophago-gastro-duodenoscopy e OGD) and the majority of peptic ulcers are treated medically. Therapeutic endoscopy, interventional radiology and surgery are usually

reserved for the management of complications of peptic ulcer disease: such as bleeding, perforation and outflow obstruction. Ulcers may be single or multiple and most commonly affect the lesser curve of the stomach and the first part of the duodenum. The rapid urease test (CLO test) is widely available and the most commonly used method of detecting *H. pylori* during endoscopy. It has the advantage of being quick, cost effective, with a high sensitivity (97%) and specificity (100%) when multiple biopsies are taken. If *H. pylori* infection is present the organism will produce the enzyme urease, which catalyses the conversion of urea (within the gel in which it is placed), resulting in the production of alkaline ammonium ions that will increase the pH and result in change in the colour of the gel from yellow to red. Histological identification and microbiological culture are costly and labour intensive and are therefore used less commonly. Less invasive diagnostic tests for *H. pylori* are also available for those patients who do not proceed to endoscopy. These include a urea breath test (sensitivity 95% and specificity 100%) that relies on the ability of *H. pylori* to metabolize orally administered carbon radio-labelled urea to carbon dioxide, which is exhaled by the patient and subsequently detected on the breath. Recent studies evaluating the increasingly common *H. pylori* stool antigen test as an alternative non-invasive test have demonstrated sensitivity and specificity of approximately 95%. Serology for *H. pylori* antigen is generally not recommended as it has potential to give false positive results in those with past but no current infection¹⁴.

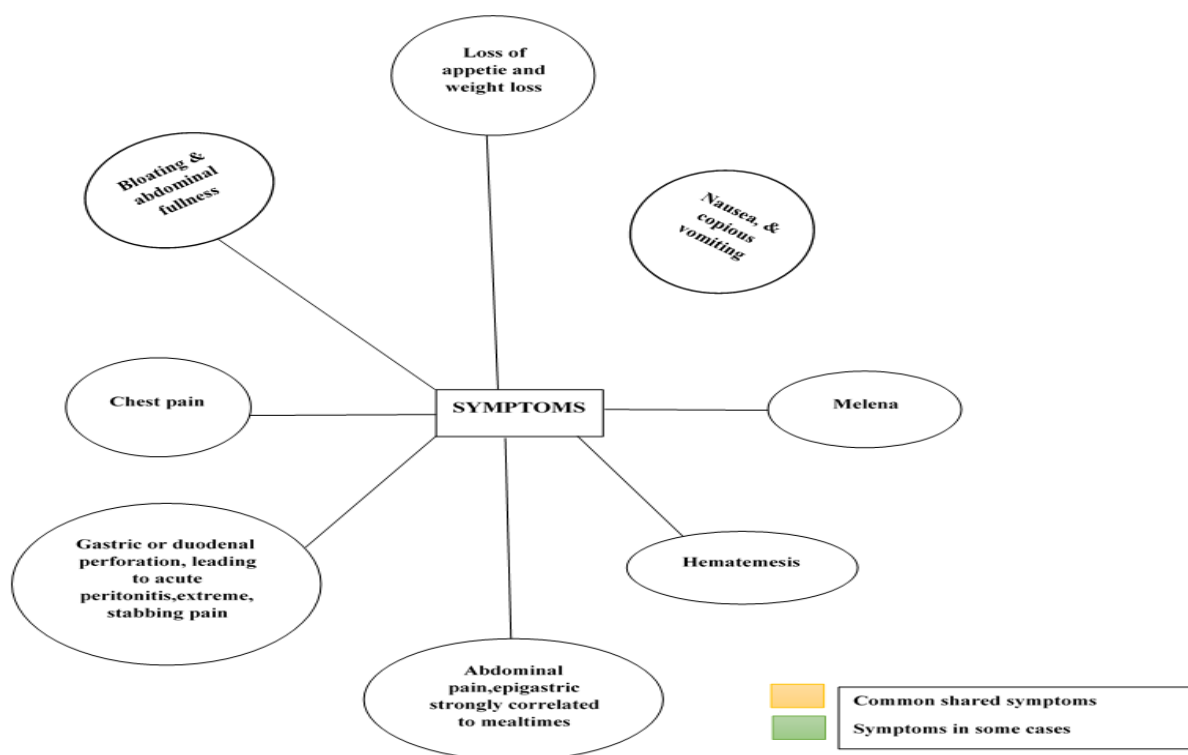


Fig. 1 - Some common symptoms of ulcer³⁸

Radiology

An erect chest X-ray is commonly performed in patients with acute upper abdominal pain suspected of perforation. CT scans can rule out other acute abdominal conditions such as acute cholecystitis, acute pancreatitis, acute appendicitis and acute mesenteric ischemia to name but a few. Some of these acute abdominal conditions may not require surgical intervention at least in the initial phase. In resource-poor healthcare facilities, an erect chest X-ray is extremely useful in detecting free air under the diaphragm confirming visceral perforation. Peptic ulcer perforation can also generate detectable sonographic signs, such as pneumoperitoneum; free intraperitoneal air tends to accumulate around the liver, duodenum, and stomach, local thickening of the gastroduodenal wall containing an echogenic focus or line, the presence of localized extraluminal gas and fluid ¹⁵.

PUD mortality risk factor analysis: correlation

The scatterplots in display the correlation between mortality rates and the selected covariates. As shown in, duodenal ulcers were negatively associated with mortality rates ($r=-0.19$, $p=0.07$); however, gastric ulcers were positively associated with mortality ($r=0.23$, $p=0.036$). Although both bleeding and perforated ulcers were both positively associated with mortality, the latter had a stronger association ($r=0.41$, $p<0.0001$). To test the hypothesis that survival rates are increasing in recent years, we investigated the correlation between publication year and mortality. There was a positive association between publication year and perioperative death rates ($r=0.22$, $p=0.032$); Likewise, as shown in, mortality rate increased with increasing age at surgery ($r=0.23$, $p=0.036$).¹⁵

PUD mortality risk factor analysis: meta-regression

To further investigate the sources of heterogeneity, we applied meta-regression analysis using the following covariates: study-level mean or median age at surgery, year of publication, sub-region and study quality score. Substantial heterogeneity of effect estimates on perioperative mortality rate was evident (p value for heterogeneity of <0.0001). Multivariable meta-regression model including the above-mentioned covariates indicated that per every 10-year increase in publication year, the mortality rates increased by 1%. Regions and sub-regions were not significantly associated with mortality rates. However, the association between age and mortality risk was marginally significant. With every 10-year increase in age, the mortality rate increased by 2% ($p=0.07$) ¹⁶. The treatment of acid – related diseases – peptic ulcer disease and gastroesophageal reflux disease (GERD) – has undergone several major changes in the past two decades. Although pharmacological inhibition of gastric acid secretion reliably heals duodenal and gastric ulcers, both usually recur when treatment is stopped. The discovery of the relationship between *Helicobacter pylori* and peptic disease. For the first time, it was demonstrated that

eradication of *H. pylori* infection could prevent the relapse of –i.e. cure – peptic ulcers¹⁷. Less than 3 decades ago, Robin Warren and Barry Marshall definitively identified *Helicobacter pylori* by culturing an organism from gastric biopsy specimens that had been visualized for almost a century by pathologists. In 1994, *H. pylori* was recognized as a type I carcinogen, and now it is considered the most common etiologic agent of infection-related cancers, which represent 5.5% of the global cancer burden. In 2005, Marshall and Warren were awarded the Nobel Prize of Medicine for their seminal discovery of this bacterium and its role in peptic ulcer disease. *H. pylori* is a Gram-negative bacterial pathogen that selectively colonizes the gastric epithelium. The bacterium is urease, catalase, and oxidase positive, is spiral shaped, and possesses 3 to 5 polar flagella that are used for motility. In addition, the majority of *H. pylori* strains express virulence factors that have evolved to affect host cell signaling pathways. *H. pylori* has evolved the ability to colonize the highly acidic environment found within the stomach by metabolizing urea to ammonia via urease, which generates a neutral environment enveloping the bacterium¹⁸.

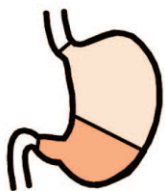
Pattern of gastritis	Gastric histology	Duodenal histology	Acid secretion	Clinical condition
 Pan-gastritis	• Chronic inflammation • Atrophy • Intestinal metaplasia	• Normal	• Reduced	• Gastric ulcer • Gastric cancer
 Antral-predominant	• Chronic inflammation • Polymorph activity	• Gastric metaplasia • Active chronic inflammation	• Increased	• Duodenal ulcer

FIG. 5- Acid secretion and the associated pattern of gastritis play an important role in disease outcome in *H. pylori* infection. The figure displays the correlations between the pattern of *H. pylori* colonization, inflammation, acid secretion, gastric and duodenal histology, and clinical outcome³⁸.

The present study also demonstrated that subjects with low education level have a higher risk of asymptomatic PUD. It has been well documented that PUD is associated with low socioeconomic status. That association may be explained by a higher risk of *Helicobacter pylori* (*H. pylori*) infection among less educated groups, probably due to poor standards of hygiene. Psychological stress, risk lifestyle behaviors, and hard physical work may be other important risk factors for PUD in low education

populations¹⁹. Several factors have been associated with the aggressiveness of *H. pylori* and hence implicated in epithelial damage, including the virulent East Asian *CagA* genotype, and environmental and dietary factors. Recently, some researchers have also proposed that certain dietary elements such as chili peppers and garlic play a protective role against *H. pylori* infection. Fox and colleagues have shown the protective role of infection of helminths and parasites against *H. pylori* infection²⁰. *Helicobacter pylori* (*H. pylori*) is a spiral shaped, gram negative, microaerophilic bacterium that persistently colonizes the gastric mucosa of humans. The estimated lifetime risk of peptic ulcer disease is 20 percent and gastric cancer is 1–2 percent with *H. pylori* infection. Epidemiological knowledge of *H. pylori* infection in early studies emphasized on *H. pylori* infection in symptomatic patients presenting for endoscopy and hence little information is known about the frequency of *H. pylori* in the general population. This study enhances the knowledge of the important role of *H. pylori* in upper gastrointestinal disease worldwide.

The specific objectives of this study were to:

1. Estimate the prevalence of *Helicobacter pylori* in asymptomatic individuals
2. Determine the association of the *Helicobacter pylori* with potential

Risk factors such as age, gender and the sociodemographic status (level of education, number of rooms and family member living in/ with, source of drinking water, sharing of a bed and animal ownership)²¹.

In the present study, we defined *H. pylori*-associated PUD as the use of any recorded *H. pylori* eradication therapy medications, such as a combination medication prescription of 7–14 days of any of the following antibiotics in the same medication order such as clarithromycin or metronidazole and amoxicillin or tetracycline, in addition to a PPIs or H₂ blockers (H₂RAs)²².

The H⁺, K⁺-ATPase enzyme utilises ATP hydrolysis to drive electroneutral exchange of cytoplasmic protons for luminal K⁺, thus acidifying the gastric juice. Proton pump inhibitors (PPIs), such as omeprazole, are currently administered to suppress acid secretion in the treatment of acid-related diseases such as gastric ulcer or gastroesophageal reflux. This mechanism results in a relatively slow onset of acid inhibition. The short dwell-times of PPIs in the blood and their instability under acidic conditions also negatively affect their efficacy as acid-suppressing drugs. Another class of H⁺, K⁺-ATPase drugs, K⁺-competitive acid blockers (P-CABs), are under development and some are now available for clinical use. The rapid and long-lasting acid suppression by P-CABs is expected to provide more immediate and efficient therapy for acid-related disease²³. Gastric H⁺, K⁺-ATPase is responsible for gastric acid secretion. ATP-driven H⁺ uptake into the stomach is efficiently accomplished by the exchange of an equal amount of K⁺, resulting in a luminal pH close to 1. Because of the limited free energy available for ATP hydrolysis, the stoichiometry of transported cations is thought to vary from 2H⁺/2K⁺ to 1H⁺/1K⁺ per

hydrolysis of one ATP molecule as the luminal pH decreases, although direct evidence for this hypothesis has remained elusive ²⁴.

CAUSES OF NON-H. PYLORI, NON-NSAID PEPTIC ULCERS²⁵

- Gastric adenocarcinoma
- Gastric lymphoma
- Local drug irritation
- Irritation at the neck of a hiatus hernia (Cameron's ulcer)
- Idiopathic
- Anastomotic ulceration after previous gastric surgery
- After radiotherapy
- Zollinger-Ellison syndrome (gastrinoma) e particularly for duodenal ulcers
- Multiple endocrine neoplasia type-I
- Hyperparathyroidism without multiple endocrine neoplasia type-I
- Systemic mastocytosis
- Severe systemic illness stress ulcers (Cushing's ulcer)
- Idiopathic eosinophilic and lymphocytic gastritis
- Duodenal Crohn's disease
- Coeliac axis stenosis
- Hepatic artery chemotherapy²⁵.

ROLE OF H⁺-ATPASE IN MAINTAINING THE MEMBRANE POTENTIAL AND ACIDIC PH AT THE PLASMA MEMBRANE SURFACE

Plant cell growth is highly influenced by the environment, as well as by predetermined developmental programs. Plasma membrane H⁺-ATPases (H⁺-pumps) are the primary active transporters that translocate protons to the outside of each cell, providing the electrical and chemical energy that drives solute transport. In plants, this enzyme also provides an acidic environment in the cell wall that is favorable for cell expansion. In animals, a Na⁺/K⁺ ATPase provides similar function as the primary active transport system, in creating a membrane potential and a chemical gradient of sodium that drives sodium-coupled transporters and ion channels. In addition to this fundamental difference in the choice of cation used to drive transport, there is also a much higher membrane potential found in plants and this may reflect a need to drive potassium inward to very high concentrations even in soil with low potassium levels, in order to maintain turgor pressure required for plant form and function²⁶.

Assay of H⁺-K⁺ ATPase activity

Proton potassium ATPase was prepared from mucosal scrapings of goat by the method reported by Cheon, with necessary modifications. Stomach from freshly slaughtered goats was washed gently with tap water. The mucosal layer of fundus was scrapped and homogenized in ice-cold phosphate buffer, pH 7.4. The homogenate was centrifuged for 20 min at 18,000 rpm. The supernatant so obtained was recentrifuged for 60 min at 100,000 rpm. The pellet was resuspended in homogenisation buffer. Ficollsucrose discontinuous density gradient centrifugation was utilized to prepare H⁺K⁺ATPase. Protein was determined by the method of Lowry. Different concentrations of the extract 10-50 µg/ml were incubated in the reaction mixture (40 mM Tris-HCl buffer, pH 7.4, containing 2 mM MgCl₂ and 10 µg membrane protein) to make a volume of 1 ml. Then, 2 mM ATP Tris salt was utilized to start the reaction, this preparation was incubated for 20 min for 37°C. The reaction was terminated by adding 1 ml of ice-cold trichloroacetic acid (10% v/v). The H⁺-K⁺ ATPase activity was assayed in the presence and the absence of different doses of the extract and omeprazole. The amount of inorganic phosphate released from ATP was determined spectrophotometrically at 400 nm²⁷. Gastric cancer is one of the most prevalent causes of cancer deaths worldwide. Therefore, efforts are underway to eradicate this cancer type based on the elimination of *H. pylori*. Eradication of *H. pylori* before the development of significant gastric damage, can prevent cancer and the gastric cancer in such cases is known to be an inflammation-associated malignancy. It has been reported that, eradication therapy of *H. pylori* usually consists of a proton pump inhibitor or bismuth compounds in combination with different antibiotics. The conventional antibiotics most widely used for *H. pylori* therapy include amoxicillin, tetracycline, metronidazole, levofloxacin, clarithromycin and bismuth. However, the resistance of *H. pylori* to the commonly used antibiotics is still increasing worldwide, and this resistance has been considered a major reason for therapy failure in the eradication of *H. pylori* infections, with failure rates of more than 40%²⁸.

Functional Domains of Gastric HK ATPase

A binding is removed by glycopeptidase F(N-glycopeptidase). If indeed the consensus starting at asn 493 is N-glycosylated from the extracellular face, perhaps there are regions of the putative cytosolic domain of the pump protein that are membrane inserted. The membrane insertion would be between the peptide chains, rather than in the phospholipid of the bilayer, which would not allow prediction based on hydrophobicity. On the other hand, although it is unlikely that N-glycosylation occurs from the cytosolic face, it is not certain, following glycosylation, that this orientation is maintained in the mature protein, nor that all the protein is indeed glycosylated²⁹.

Peptic ulcer treatment and helicobacter pylori eradication

Recent studies found that liver cirrhosis increased the risk of peptic ulcers. The prevalence of peptic ulcers is higher in decompensated cirrhosis than in compensated cirrhosis. Currently, PPIs are the mainstay treatment option of peptic ulcers in the general population. Cirrhotic patients also have a high proportion of helicobacter pylori infection. Helicobacter pylori promotes the conversion of urea into ammonia, which enters into the systemic circulation. Helicobacter pylori infection contributes to the development of hyperammonemia and subsequent episodes of HE in cirrhosis. Helicobacter pylori eradication has been improved by PPIs-based triple therapy. Notably, blood ammonia concentration is significantly reduced after PPIs-based triple treatment in cirrhotic patients. As well known, the application of PPIs triple therapy can effectively treat helicobacter pylori infection which can increase the risk of HE. Therefore, it might be true that PPIs reduce the risk of HE in patients with helicobacter pylori infection³⁰.

Risk factors for the presence of symptoms in patients with PUD

Subjects with symptomatic PUD had higher alcohol consumption than those with asymptomatic PUD ($p=0.025$). Furthermore, the presence of active-stage ulcers was more common in subjects with symptomatic PUD than in subjects with asymptomatic PUD ($p=0.003$). Between the symptomatic and asymptomatic PUD groups, there were no significant differences in age, sex, BMI, smoking, *H. pylori* infection, use of NSAIDs, ulcer location, or ulcer number. Multivariate analysis revealed that heavy drinking (OR, 2.515; 95% CI, 1.315–4.812; $p=0.005$) and active-stage ulcer (OR, 2.143; 95% CI, 1.323–3.472; $p=0.002$) were independent risk factors for the presence of symptoms in PUD³¹.

PATHOGENESIS

The intestinal mucosa is composed of 3 layers: epithelium, lamina propria, and muscularis mucosa. Gastritis is described as the presence of inflammatory cells. Gastropathy occurs when there is gastric mucosal damage with no inflammatory cells. Peptic ulcers occur when gastric or duodenal inflammation leads to defects of the muscularis mucosa. The acidic gastric contents, which normally aid in digestion, become corrosive when there is an increase in acid production or a disruption of protective factors. Parietal cells of the stomach produce gastric acid via proton pumps (H^+/K^+ ATPase) in response to acetylcholine from vagal efferents, histamine from enterochromaffin cells, and gastrin from G cells. There are several mechanisms to protect the gastric mucosa, including a mucus layer, a pH-neutral buffer zone, an epithelial layer, and a rich gastric blood supply. The mucus layer is composed of mucin secreted by surface foveolar cells. This mucus layer acts as a diffusion barrier and overlies a pH-neutral buffer zone composed of bicarbonate secreted by epithelial cells. Prostaglandin release mediates mucin secretion from surface foveolar cells and bicarbonate release from epithelial cells. Epithelial cells have

tight junctions that act as an additional barrier of protection. A rich gastric blood supply redistributes excess protons that reach the lamina propria. Ultimately, peptic ulcers are formed when the damaging factors overcome the protective mechanisms³². Hypothermic stress ulcer was involved with significant reduction of GSH ($p < 0.01$), but not SOD and catalase in combination with decrease in mucin and protein ($p < 0.01$ - 0.001 respectively). Hesperidin treated animals showed significantly increased level of GSH, protein (0.05) and mucin (0.001) only at highest dose 450 mg/kg, other doses were ineffective. Gastric wall mucosa plays a main role in the protection of the gastric walls from aggressive factors that are responsible for gastric damage. The mucous layer forms a barrier between gastric wall and acid. Normal animal gastric mucosa showed clear and proper arrangement of cells in photographic representations. Indomethacin induced redness, spot and hemorrhagic ulcers.³³

Diabetes mellitus is 1 of the most well-known chronic diseases in almost all countries. With the development of society and technology, people have changed their lifestyle, as characterized by decreased physical exercise and increased obesity, which are responsible for the increase in the number of people with diabetes mellitus. It was estimated that 415 million people all over the world had diabetes in 2013, and the number is expected to rise to 592 million by 2035. In addition, the complication of diabetes mellitus is also an issue urgent to be solved. Diabetic foot ulcer (DFU) is 1 of the most common complications of diabetes and leads to high hospital costs. It was reported that the total additional medical cost associated with diabetes for treating diabetic

foot diseases in America ranges from \$9 to \$13 billion. These chronic, nonhealing foot ulcers occur in approximately 15% of all people with diabetes and are responsible for patients' decreased quality of life. Unfortunately, if a DFU has developed, there is a high risk of wound progression, which may result in amputation. It was reported that >85% of foot amputations in patients are caused by DFU. Therefore, the International Diabetes Foundation is paying more attention to DFUs, taking into consideration the substantial social, medical, and economic burdens³⁴.

ULCER PREVENTION

The realization in recent years that selective cyclooxygenase (COX)-2 inhibitors were not as 'GI safe' as their promotional materials suggested led to several evaluations of alternative methods for preventing gastric ulceration induced by non-steroidal anti-inflammatory drugs (NSAIDs). Proton pump inhibitors (PPIs) have long been suggested to reduce the incidence of serious gastrointestinal complications during NSAID use. further support to this notion by reporting that the use of PPIs was associated with a significant reduction in the risk of ulcer in both acute and chronic users of NSAIDs. Moreover, the 'number needed to treat' to avoid one peptic ulcer in the elderly was low: three for both acute and chronic

NSAID users. Chan et al. examined the utility of PPIs for prevention of recurrent ulcer bleeding in patients taking aspirin to prevent vascular diseases. Patients who presented with ulcer bleeding were randomized, after their ulcers had healed, to receive aspirin plus a PPI (esomeprazole), or another antiplatelet drug (clopidogrel). Clopidogrel is an ADP receptor antagonist that inhibits platelet aggregation and is recommended for patients who have major gastrointestinal intolerance of aspirin³⁵.

USE OF ANTIOXIDANTS TO ERADICATE *HELICOBACTER PYLORI*

Some authors show that the best treatment is the eradication of the bacteria¹⁸. Accordingly, some studies in humans⁴⁰ used antioxidants to eradicate *H. Pylori* and observed that vitamin C has important effects in the bacteria eradication in patients with peptic ulcer. But these studies

showed that smaller doses of vitamin C for a longer period of time had a better response when compared with higher doses. Thus, it is observed that patients with peptic ulcer by *H. pylori* can take up to 500 mg/day of vitamin C for a period of three months, which does not exceed the recommended UL of 2000 mg, according to DRIs¹³. Another antioxidant used to eradicate *H. pylori* is the capsaicin present in pepper and chilies. Studies on animals showed that capsaicin has effect in healing gastrointestinal lesions. Likewise, some researchers³⁹ studied the effect

of capsaicinoids in individuals with peptic ulcer by *H.pylori* or aspirin and showed that these substances are gastroprotective only in individuals with aspirin-induced lesions. It is worth noting that peppers may be associated with irritations in the gastric mucosa, and may not have a gastroprotective effect in some individuals with peptic ulcer³⁶.

Depression, a type of mood disorder, is characterized by emotional dysregulation and depressive cognition, which induces distress in patients. In patients with depression, stress not only plays a major role in pathogenesis but also is associated with the disturbance of the hypothalamus-pituitary-adrenal (HPA) axis. Additionally, patients with depression have been reported to experience somatic consequences associated with HPA axis dysregulation. Regarding the gastrointestinal (GI) system, evidences have shown that depression is associated with irritable bowel syndrome, ulcerative colitis, dyspepsia, and gastroesophageal reflux disease. However, few studies have reported evidence regarding the relationship between peptic ulcer disease (PUD) and depression. PUD, including gastric and peptic ulcers, is a prevalent GI disease with a high mortality. Evidence has shown that both physical stress and psychological stress are closely related to PUD. Notably, PUD risk among schizophrenia or anxiety disorder patients has been documented, but not for depression patients. To make the diagnosis of unipolar depression, patient should not have mania or hypomania, or their diagnosis should be bipolar disorders (BD) instead. However, evidence had shown that some patients with BD have unipolar depression as their initial presentation, before mania or hypomania. Eventhough the differential diagnosis between BD

and unipolar depression was challenging, they shared the common manifestation of having depressive episode. Particularly, we have previously demonstrated a positive association between BD and PUD. However, we could not identify whether the depression, mania, or hypomania predisposed the patients having subsequent PUD. Therefore, we investigated the association between depression and PUD. We hypothesized that if depression was associated with subsequent PUD, more concern would be raised among patients with unipolar depression or depressive episode of BD ³⁹.

CONCLUSION

Peptic ulcer illness is still a common clinical concern in our society, affecting people of all ages. Peptic ulcer disease is predicted to continue to have a large global influence on health-care delivery, health economics, and patient quality of life as the prevalence of the illness rises with age.

Peptic ulcer illness continues to be a problem in medical visits. The majority of people who present with dyspepsia should be examined for peptic ulcer disease. Gastric acid secretion must be understood in order to determine which portion of the stomach is most impacted by the etiologic agent of peptic ulcer disease. *H. pylori* has remained a risk factor for the development of peptic ulcer disease until now. This bacteria's predilection location determines its clinical prognosis. Understanding the pathophysiology of peptic ulcers can help doctors be more aware of potential complications, such as stomach cancer.

REFERENCES

1. Lemos LMS, Martins T, Tanajura GH. Evaluation of antiulcer activity of chromanone fraction from *Calophyllum brasiliense* Camb, *Journal of Ethnopharmacology*. 2012; 432– 439.
2. Sverdén E, Agréus L, Jason M Dunn gastroenterologist . *Practice*. 2019; 2:1-8.
3. Shoba FG, A Review on Antiulcer Activity of Few Indian Medicinal Plants, *International Journal of Microbiology*. 2014; 1-14.
4. Singh AK, Singh SK, Singh PP, Biotechnological aspects of plants metabolites in the treatment of ulcer: A new prospective, *Biotechnology Reports*. 2018; 2215-017.
5. Shoba FG, A Review on Antiulcer Activity of Few Indian Medicinal Plants, *International Journal of Microbiology*. 2014; 1-14.
6. Umre R, Ganeshpurkar A, Ganeshpurkar A, In vitro, in vivo and in silico antiulcer activity of ferulic acid, *Future Journal of Pharmaceutical sciences*. 2018; 2314-7245.
7. Kaur A, Singh R, Sharma R, Kumar S, Peptic Ulcer: A review on Etiology and Pathogenesis, *International Research Journal of Pharmacy*. 2012; 2230- 8407.
8. Coleman S, Gorecki C, Nelson E.A, Patient risk factors for pressure ulcer development: Systematic review, *International Journal of Nursing Studies*. 2013; 974-1003.

9. Sung JJY, Kuipers EJ, El-Serag HB, Systematic review: the global incidence and prevalence of peptic ulcer disease *Alimentary Pharmacology & Therapeutics*. 2009; 938-946.
10. Sonnenberg A, Everharti JE, The Prevalence of Self-Reported Peptic Ulcer in the United States, *American Journal of Public Health*. 1996; 201-205.
11. Vomero ND, Colpo E, Nutritional care in peptic ulcer, *ABCD Arq Bras Cir Dig*. 2014; 298-302.
12. Rosenstock S, Jørgensen T, Bonnevie O, Risk factors for peptic ulcer disease: a population based prospective cohort study comprising 2416 Danish adults, *Stomach*. 2003; 186–193.
13. Proctor MJ, Complications of peptic ulcers, *Oesophagus and Stomach*. 2014; 599- 606.
14. Pansa A, Kurihara H, Memon AM, Updates in laparoscopic surgery for perforated peptic ulcer disease: state of the art and future perspectives, *Annals of Laparoscopic and Endoscopic Surgery*. 2020; 1-7.
15. Peiffer S, Pelton M, Keeney L, Kwon EG, Risk factors of perioperative mortality from complicated peptic ulcer disease in Africa: systematic review and meta-analysis, *BMJ Open Gastroenterology*. 2019;1-12.
16. Williams MP, & Pounder RE, Review article: the pharmacology of rabeprazole, *Aliment Pharmacol Ther* . 1999; 3-10.
17. Wroblewski LE, Peek RM, Wilson KT, *Helicobacter pylori* and Gastric Cancer: Factors That Modulate Disease Risk, *Clinical Microbiology* . 2010; 714-730.
18. Wang FW, Tu MS, Mar GY, Prevalence and risk factors of asymptomatic peptic ulcer disease in Taiwan, *World J Gastroenterol*. 2011; 1199-1203.
19. Mhaska RS, Ricardo I, Azizan A, Assessment of Risk Factors of *Helicobacter Pylori* Infection and Peptic Ulcer Disease, *Journal of Global Infectious Diseases*. 2013; 60-67.
20. Mungazi SG, Chihaka OB, Muguti GI, Prevalence of *Helicobacter pylori* in asymptomatic patients at surgical outpatient department: Harare hospitals, *Annals of Medicine and Surgery* .2018; 153–157.
21. Liang CM, Yang SC, Wu CK, Risk of Recurrent Peptic Ulcer Disease in Patients Receiving Cumulative Defined Daily Dose of Nonsteroidal Anti-Inflammatory Drugs, *Journal of Clinical Medicine*. 2019; 1-11.
22. Abe k, Shimokawa J, Naito M. The cryo-EM structure of gastric H⁺, K⁺-ATPase with bound BYK99, a high-affinity member of K⁺- competitive, imidazo [1,2-*a*] pyridine inhibitors, *Scientific Reports* .2017; 1-9.
23. Majumdar M, Bebb J, Atherton J, *Helicobacter pylori* infection and peptic ulcers, *Stomach* .2010; 154-160.

24. Abe K, Tania K, Friedrich T, Cryo-EM structure of gastric H⁺, K⁺-ATPase with a single occupied cation-binding site, *Pans.* 2012; 18401–18406.
25. Haruta M, Gray WM, Sussman MR, Regulation of the plasma membrane proton pump (H⁺-ATPase) by phosphorylation, *ScienceDirect.* 2015; 68–75.
26. Yadav P, Ganeshpurkar A, Rai G, *In vitro* H⁺ -K⁺ ATPase inhibitory potential of methanolic extract of *Cissus quadrangularis* Linn, *Pharmacognosy Research.* 2012; 123-126.
27. El-Shouny WA, Ali SA, Hegazy HM, Abd Elnabi MK, *Syzygium aromaticum* L, Traditional herbal medicine against cagA and vacA toxin genes-producing drug resistant *Helicobacter pylori*, *Journal of Traditional and Complementary Medicine.* 2019; 1-12.
28. Sachs G, Munson K, Balaji VN, Functional Domains of the Gastric HK ATPase, *Journal of Bioenergetics and Biomembranes.* 1989; 573-588.
29. Zhu J, Yu H, Mancuso A, Proton pump inhibitors in liver cirrhosis: a review of benefits and harms, *AME Medical Journal.* 2017; 1-9.
30. Lee SP, Sung IK, Kim JH, Lee SY, Risk Factors for the Presence of Symptoms in Peptic Ulcer Disease, *Clinical Endoscopy.* 2017; 578-584.
31. Sierra D, Wood M, Kolli S, Pediatric Gastritis, Gastropathy, and Peptic Ulcer Disease, *Pediatrics in Review.* 2019; 542-549.
32. Bigoniya P, Singh K, Ulcer protective potential of standardized hesperidin, a citrus flavonoid isolated from *Citrus sinensis*, *Revista Brasileira de Farmacognosia.* 2014; 330-340.
33. Zha M-L, Cai J-Y, Chen H-L, A Bibliometric Analysis of Global Research Production Pertaining to Diabetic Foot Ulcers in the Past Ten Years, *The Journal of Foot & Ankle Surgery.* 2018; 1–7.
34. Wallace J.L, Recent advances in gastric ulcer therapeutics, *Current Opinion in Pharmacology.* 2005; 5:573–577.
35. Singh AK, Singh SK, Singh PP, Biotechnological aspects of plants metabolites in the treatment of ulcer: A new prospective, *Biotechnology Reports.* 2018; 2215-017.
36. Kusters JG, Vliet AHMV, and Kuipers EJ, Pathogenesis of *Helicobacter pylori* Infection, *Clinical Microbiology Reviews.* 2006; 449–490.
37. Kuna L, Jakab J, Smolic R, Raguz-Lucic N, Vcev A, and Martina Smolic M, Peptic Ulcer Disease: A Brief Review of Conventional Therapy and Herbal Treatment Options, *Journal of Clinical Medicine.* 2019; 1-19.
38. Kamboj AK, Hoversten P, and Leggett CL, Upper Gastrointestinal Bleeding: Etiologies and Management, *Concise Review for Clinicians.* 2019; 697-703.

39. Hsu C-C, Hsu Y-C, Chang K-H, Lee C-Y, Chong L-W, Lin C-L, Depression and the Risk of Peptic Ulcer Disease, Medicine Observational Study. 2015; 1-8