

UPI Journal of Pharmaceutical Medical, and Health Sciences

Content Available at www.uniquepubinternational.com

ISSN: 2581-4532

Open Access

Review Article

A review on peptic ulcer

K. Jaswanth^{*1}, C. Kiran Kumar², P. Venkatesh³

¹ B.Pharmacy final year student, Jagan's Institute of Pharmaceutical Sciences, Nellore

² Associate Professor, Dept.of Pharmacy Practice, Jagan's Institute of Pharmaceutical Science, Nellore

³ Principal Jagan's Institute of Pharmaceutical Science, Nellore

Article History	Abstract
Received: 25-11-2021 Revised: 04-12-2021 Accepted: 25-01-2022	Peptic ulcer is a chronic disease affecting up to 10% of the world's population. The formation of peptic ulcers depends on the presence of gastric juice pH and the decrease in mucosal defences. Non-steroidal anti-inflammatory drugs (NSAIDs) and Helicobacter pylori (H. pylori) infection are the two major factors disrupting the mucosal resistance to injury. Peptic ulcer disease (PUD) is characterized by discontinuation in the inner lining of the gastrointestinal (GI) tract because of gastric acid secretion or pepsin. It extends into the muscularis propria layer of the gastric epithelium. It usually occurs in the stomach and proximal duodenum. It may involve the lower esophagus, distal duodenum, or jejunum. Epigastric pain usually occurs within 15-30 minutes following a meal in patients with a gastric ulcer; on the other hand, the pain with a duodenal ulcer tends to occur 2-3 hours after a meal. The treatments of peptic ulcers, such as proton pump inhibitors (PPIs) and histamine-2 (H2) receptor antagonists, have demonstrated adverse effects, relapses, and various drug interactions. On the other hand, medicinal plants and their chemical compounds are useful in the prevention and treatment of numerous diseases. Hence, this review presents common medicinal plants that may be used for the treatment or prevention of peptic ulcers.
Keywords Peptic ulcers, proton pump inhibitors, gastrointestinal tract, Non-steroidal anti-inflammatory drugs and Helicobacter pylori.	
*Corresponding Author K. Jaswanth https://doi.org/10.37022/jpmhs.v5i1.73	

This article is licensed under a Creative Commons Attribution-Non Commercial 4.0 International License. Copyright © 2022 Author(s) retain the copyright of this article.



Introduction

An "ulcer" is an open sore. The word "peptic" means that the cause of the problem is due to acid. Most of the time when a gastroenterologist is referring to an "ulcer" the doctor means a peptic ulcer.

The two most common types of peptic ulcer are called "gastric ulcers" and "duodenal ulcers". These names refer to the location where the ulcer is found. Gastric ulcers are located in the stomach (see Figure 1). Duodenal ulcers are found at the beginning of the small intestine (also called the small bowel) known as the duodenum. A person may have both gastric and duodenal ulcers at the same time.

It is represents a serious medical problem. Approximately 500,000 new cases are reported each year, with 5 million people affected in the United States alone. Interestingly, those at the highest risk of contracting peptic ulcer disease are those generations born around the middle of the 20th century. Ulcer disease has become a disease predominantly affecting the older population, with the peak incidence occurring between 55 and 65 years of age. In men, duodenal ulcers were more common than gastric ulcers; in women, the converse was found to be true. Thirty-five percent of patients diagnosed with gastric ulcers will suffer serious complications. Although mortality rates from peptic

ulcer disease are low, the high prevalence and the resulting pain, suffering, and expense are very costly. Peptic ulcer disease (PUD) is characterized by discontinuation in the inner lining of the gastrointestinal (GI) tract because of gastric acid secretion or pepsin. It extends into the muscularis propria layer of the gastric epithelium. It usually occurs in the stomach and proximal duodenum. It may involve the lower esophagus, distal duodenum, or jejunum. Epigastric pain usually occurs within 15-30 minutes following a meal in patients with a gastric ulcer; on the other hand, the pain with a duodenal ulcer tends to occur 2-3 hours after a meal. Today, testing for *Helicobacter pylori* is recommended in all patients with peptic ulcer disease. Endoscopy may be required in some patients to confirm the diagnosis, especially in those patients with sinister symptoms. Today, most patients can be managed with a proton pump inhibitor (PPI) based triple-drug therapy.

Signs and symptoms

Signs and symptoms of a peptic ulcer can include one or more of the following:

- abdominal pain, classically epigastric, strongly correlated with mealtimes. In case of duodenal ulcers, the pain appears about three hours after taking a meal and wakes the person from sleep;
- bloating and abdominal fullness;
- waterbrash (a rush of saliva after an episode of regurgitation to dilute the acid in esophagus, although this is more associated with gastroesophageal reflux disease);
- nausea and copious vomiting;
- loss of appetite and weight loss, in gastric ulcer;
- weight gain, in duodenal ulcer, as the pain is relieved by eating;
- hematemesis (vomiting of blood); this can occur due to bleeding directly from a gastric ulcer or from damage to the esophagus from severe/continuing vomiting.
- melena (tarry, foul-smelling feces due to presence of oxidized iron from hemoglobin);
- Rarely, an ulcer can lead to a gastric or duodenal perforation, which leads to acute peritonitis and extreme, stabbing pain, [6] requires immediate surgery.

Causes of Peptic Ulcer Disease

Peptic ulcer disease (PUD) has various causes; however, *Helicobacter pylori*-associated PUD and NSAID-associated PUD account for the majority of the disease etiology [1].

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

***Helicobacter Pylori*-Associated PUD**

H. pylorus is a gram-negative bacillus that is found within the gastric epithelial cells. This bacterium is responsible for 90% of duodenal ulcers and 70% to 90% of gastric ulcers. *H. pylori* infection is more prevalent among those with lower socioeconomic status and is commonly acquired during childhood. The organism has a wide spectrum of virulence factors allowing it to adhere to and inflame the gastric mucosa. This results in hypochlorhydria or achlorhydria, leading to gastric ulceration.

Virulence Factors of Helicobacter Pylori

1. *Urease*: The secretion of urease breaks down urea into ammonia and protects the organism by neutralizing the acidic gastric environment.
2. *Toxins*: CagA/VacA is associated with stomach mucosal inflammation and host tissue damage.
3. *Flagella*: Provides motility and allows movement toward the gastric epithelium.

NSAID-associated PUD

Nonsteroidal anti-inflammatory drugs use is the second most common cause of PUD after *H. pylori* infection [2], (2015). The secretion of prostaglandin normally protects the gastric mucosa. NSAIDs block prostaglandin synthesis by inhibiting the COX-1 enzyme, resulting in decreased gastric mucus and bicarbonate production and a decrease in mucosal blood [3].

Medications

Apart from NSAIDs, corticosteroids, bisphosphonates, potassium chloride, and fluorouracil have been implicated in the etiology of PUD. Smoking also appears to play a role in duodenal ulcers, but the correlation is not linear. Alcohol can irritate the gastric mucosa and induce acidity. Hypersecretory environment occurs in the following conditions.

- Zollinger Ellison syndrome

- Systemic mastocytosis
- Cystic fibrosis
- Hyperparathyroidism
- Antral G cell hyperplasia

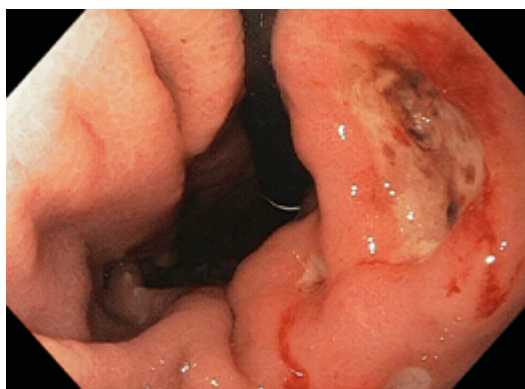


Figure 1. Photograph of a peptic ulcer taken during an upper endoscopy. This ulcer is a “gastric ulcer” because it is located in the stomach.

Pathophysiology

Pathogenesis of Peptic Ulcer Almost half of the world’s population is colonized by *H. pylori*, which remains one of the most common causes of peptic ulcer disease [14]. The prevalence of *H. pylori* is higher in developing countries, especially in Africa, Central America, Central Asia, and Eastern Europe [5]. The organism is usually acquired in childhood in an environment of unsanitary conditions and crowding, mostly in countries with lower socioeconomic status. *H. pylori* causes epithelial cell degeneration and injury, which is usually more severe in the antrum, by the inflammatory response with neutrophils, lymphocytes, plasma cells, and macrophages. 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. The main mediators of *H. pylori* infection are cytokines that inhibit parietal cell secretion, but *H. pylori* can directly affect the H⁺/K⁺ ATPase α -subunit, activate calcitonin gene-related peptide (CGRP) sensory neurons linked to somatostatin, or inhibit the production of gastrin [7]. Although the formation of gastric ulcers is associated with hypo secretion, 10–15% of patients with *H. pylori* infection have increased gastric secretion caused by hypergastrinemia and reduced antral somatostatin content [8]. This leads to increased histamine secretion, and subsequently the increased secretion of acid or pepsin from parietal and gastric cells. Additionally, the eradication of *H. pylori*

leads to a decrease in gastrin mRNA expression and an increase in somatostatin mRNA expression [9]. In the remaining majority of patients, gastric ulcers are associated with hypochlorhydria and mucosal atrophy. The main mechanism of NSAID-associated damage of the gastroduodenal mucosa is the systemic inhibition of constitutively expressed cyclooxygenase-1 (COX-1), which is responsible for prostaglandin synthesis, and is associated with decreased mucosal blood flow, low mucus and bicarbonate secretion, and the inhibition of cell proliferation. NSAIDs inhibit the enzyme reversibly in a concentration-dependent manner. The co-administration of exogenous prostaglandins and cyclooxygenase-2 (COX-2)-selective NSAIDs use reduces mucosal damage and the risk of ulcers [10]. However, the different physicochemical properties of NSAIDs cause differences in their toxicity [11]. NSAIDs disrupt mucus phospholipids and lead to the uncoupling of mitochondrial oxidative phosphorylation, thus initiating mucosal damage. When exposed to acidic gastric juice (pH 2), NSAIDs become protonated and cross lipid membranes to enter epithelial cells (pH 7.4), where they ionize and release H⁺. In that form, NSAIDs cannot cross the lipid membrane, and are trapped in epithelial cells, leading to the uncoupling of oxidative phosphorylation, energy production, increased cellular permeability, and reduced cellular integrity. Patients who have a history of peptic ulcers or haemorrhage, are over the age of 65, also use steroids or anticoagulants, and take high doses or combinations of NSAIDs are at the highest risk for acquiring NSAID-induced ulcers.

Diagnosis

Radiologic and/or endoscopic procedures are usually required to document the presence of ulcers. Because endoscopic testing is invasive and expensive, it is only indicated in patients 60 years of age or older with new-onset dyspepsia. Patients with dyspepsia who are younger than 60 years may forego endoscopy but should be tested for *H. pylori* using noninvasive testing and treated if positive. Those who test negative for *H. pylori* should be offered a trial (4–8 weeks) of acid suppression therapy or proceed to endoscopy. Persistent dyspepsia despite a trial of acid suppressive therapy warrants upper endoscopy evaluation. Routine laboratory tests are not helpful in establishing a diagnosis of PUD. Hematocrit, hemoglobin, and stool guaiac tests are used to detect bleeding. Diagnostic tests to detect *H. pylori* presence can be either endoscopic or nonendoscopic. Endoscopic diagnosis involves extraction of gastric tissue samples that are subsequently tested for *H. pylori*.

Nonendoscopic testing methods for *H. pylori* include the urea breath test, serologic testing, and stool antigen assay. These tests are less invasive and less expensive than endoscopy.

The *urea breath test* is usually first line because of its high sensitivity and specificity and short turnaround time. Concomitant acid suppressive or antibiotic therapy may give false-negative results. The urea breath test can also be used to confirm eradication of *H. pylori* infection.

Serologic testing provides a quick (within 15 minutes) office-based assessment of exposure to *H. pylori*, but it cannot differentiate active infection from previously treated infection; patients can remain seropositive for years after eradication.

Serologic testing is recommended in patients with recent or current antibiotic or acid-suppressive therapy.

Stool antigen assays can be useful for initial diagnosis or to confirm *H. pylori* eradication. They have high sensitivity and specificity and are affected less by concomitant medication use.

Treatment

The goal of therapy for peptic ulcer disease is to relieve symptoms, heal craters, prevent recurrences, and prevent complications. Medical therapy should include treatment with drugs, and attempt to accomplish the following:

- 1) Reduce gastric acidity by mechanisms that inhibit or neutralize acid secretion,
- 2) Coat ulcer craters to prevent acid and pepsin from penetrating to the ulcer base,
- 3) provide a prostaglandin analog,
- 4) Remove environmental factors such as NSAIDs and smoking, and
- 5) reduce emotional stress (in a subset of patients).

An overview of conventional antiulcer treatment options is summarized (Table No: 1)

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

Category	Medication	Mechanism action	Adverse effects
Proton Pump Inhibitors (PPIs)	Omeprazole Lansoprazole	Inhibition of the gastric H^+/K^+ -ATPase (proton pump) enzyme	Headache Abdominal pain, Diarrhea Nausea Vomiting Constipation Flatulence

	Rabeprazole Esomeprazole Pantoprazole	system	Vitamin B12 deficiency Osteoporosis
H2 Receptor Blockers	Cimetidine	Blocking the action of histamine at the	Headache , Anxiety Depression Dizziness, Cardiovascular
Antacids	Aluminum hydroxide	Increases gastric pH to	Frequency not defined: Nausea Vomiting Hypophosphatemia Chalky taste Constipation
	Magnesium hydroxide	Causes osmotic retention of fluid	Abdominal cramping Diarrhea, Electrolyte imbalance
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 Diarrhoea

Cytoprotective Agents	Misoprostol Sucralfate	Stimulate mucus production and enhance blood flow throughout the lining of the gastrointestinal tract	Abdominal pain Headache Constipation
------------------------------	---------------------------	---	--

Treatment of H. Pylori-Associated Ulcers

- Uncomplicated ulcer – In patients with uncomplicated ulcers, PPI (eg, omeprazole 20 mg twice daily) given for 14 days, along with the antibiotic regimen to treat H. pylori, is usually adequate to induce healing.
- Complicated ulcer – All patients with complicated peptic ulcers (ulcers with bleeding, perforation, penetration, or gastric outlet obstruction) should initially receive acid suppressive therapy with an intravenous PPI. Once patients are tolerating oral medications, they should be switched to an oral PPI at high-dose twice daily to enhance healing (eg, omeprazole 40 mg twice daily). Dosing should generally be reduced to once daily after four weeks. However, in patients with bleeding, the intravenous PPI can be switched to a lower oral dose (eg, 20 mg omeprazole once daily) 72 hours after endoscopy, provided there is no evidence of recurrent bleeding.

The choice of initial antibiotic regimen to treat H. pylori should be guided by the presence of risk factors for macrolide resistance and the presence of a penicillin allergy.

For initial therapy in patients without risk factors for macrolide resistance, we suggest triple therapy with a proton pump inhibitor (PPI), amoxicillin (1 g twice daily), and clarithromycin (500 mg twice daily) for 14 days (Grade 2B). We suggest substitution of amoxicillin with metronidazole only in penicillin-allergic individuals since metronidazole resistance is common and can reduce the efficacy of treatment.

We suggest bismuth quadruple therapy as initial treatment in patients with risk factors for macrolide resistance. Quadruple therapy consists of a PPI, bismuth.

NSAID-related peptic ulcer

- Any Patients with PUD should eliminate or reduce use of NSAIDs (including aspirin). If possible, alternative agents such as acetaminophen or a nonacetylated salicylate (eg, salsalate) should be used for pain relief.
- Patients with NSAID-associated ulcers should be treated with a PPI (eg, omeprazole 20 to 40 mg daily) for four to eight to weeks based on the size of the ulcer. In patients with peptic ulcers who need to remain on NSAIDs or aspirin, maintenance antisecretory therapy with a PPI (eg, omeprazole 20 mg daily) can reduce the risk of ulcer complications or recurrence.

Prophylactic regimens against PUD are often required in patients receiving long-term NSAID or aspirin therapy for osteoarthritis, rheumatoid arthritis, or cardio protection. Misoprostol, H2RAs, PPIs, and COX-2 selective inhibitors have been evaluated in controlled trials to reduce the risk of NSAID-induced PUD (Table No:2).

Misoprostol: Synthetic PG E1 analog that exogenously replaces PG stores. Limited use, because of high frequency of bothersome GI effects such as abdominal pain, flatulence, and diarrhea. Not Use in pregnancy; Abortifacient effects. Table No: 2 Oral drug regimens to heal peptic ulcers or maintain ulcer healing in the absence of antibiotic therapy

Category	Drug	DU or GU healing (mg/day)	Maintenance of DU or GU healing (mg/day)
Mucosal protectant	Sucralfate	1gr 4times a day 2gr two times a day	1gr 4times a day 1-2gr two times a day
H2-receptor antagonists	Cimetidine	300mg 4times a day 400mg two times a	400-800mg daily

		day 800mg at bet times	
	Famotidine	20mg two times a day 40mg at bet times	20-40mg daily
	Nizatidine	150mg two times a day 300mg at bet times	150-300mg daily
	Ranitidine	150mg two times a day 300mg at bet times	150-300mg daily
Proton pump inhibitor	dexlansoprazole	30-60mg daily	30-60mg daily
	Esomeprazole	20-40mg daily	20-40mg daily
	lansoprazole	15-30mg a dialy	15-30mg a dialy
	Omeprazole	20-40mg daily	20-40mg daily
	Pantoprazole	40mg daily	40mg daily
	Rabeprazole	20 mg daily	20 mg daily

H2-Receptor Antagonists: Standard doses of H2RAs (e.g., famotidine 40 mg/day) are effective in preventing NSAID-related duodenal ulceration but not gastric ulceration (the most frequent type of ulcer-associated with NSAIDs).

Proton Pump Inhibitors: is more effective than H2RAs in reducing the risk of nonselective NSAID-related gastric and duodenal ulceration. PPIs are also as effective as misoprostol but better tolerated. All PPIs are effective when used in standard doses.

COX-2 Selective Inhibitors: Selective COX-2 inhibitors are no more effective than the combination of a PPI and a nonselective NSAID in reducing the incidence of ulcers and are associated with a greater incidence of CV events (e.g., ischemic stroke).

Celecoxib is the only agent in this class that remains on the market; its postulated improved GI safety when compared to nonselective NSAIDs.

Longer-term studies evaluating the CV risks associated with the use of COX-2 inhibitors have found a higher incidence of CV mortality with these agents compared to traditional NSAIDs

Sucralfate

Is a negative charged, non absorbable agent that forms a complex by binding with positively-charged proteins in exudates, forming a viscous, paste-like, adhesive substance.

Limited use, need for multiple daily dosing, large tablet size, and interaction with a number of other medications (e.g., digoxin and fluoroquinolones).

Side effects: constipation, nausea, metallic taste, and the possibility for aluminum toxicity in patients with renal failure.

Subsalicylate, and two antibiotics (metronidazole and tetracycline) given four times daily for 14 days.

Stress-Related Mucosal Damage

Stress ulceration is defined as ulceration of the upper gastrointestinal (GI) tract (esophagus, stomach, and duodenum) that occurs due to hospitalization.

Stress ulceration is common in critically ill patients. Prevention of stress ulcers involves maintaining hemodynamic stability. Stress ulcer prophylaxis (SUP) is only indicated in intensive care unit (ICU) patients with certain risk factors.

Zollinger-Ellison Syndrome (ZES)

Is caused by a gastrin produced tumor called a gastrinoma. This results in a state of gastric acid hypersecretion in which patients develop diarrhea and malabsorption. High-dose oral PPI therapy is the treatment of choice for ZES and may be used long term in patients when the tumor cannot be identified or fully resected.

Conclusion

Peptic ulcer disease remains a frequent clinical problem in our environment predominantly affecting all age of people. As the prevalence of peptic ulcer disease increases with advancing age it is expected that this common disease will continue to have a significant global impact on health-care delivery, health economics and the quality of life of patients.

Peptic ulcer disease remains a frequent clinical problem in our environment predominantly affecting all age of people. As the prevalence of peptic ulcer

disease increases with advancing age it is expected that this common disease will continue to have a significant global impact on health-care delivery, health economics and the quality of life of patients.

Peptic ulcer disease remains a frequent clinical problem in our environment predominantly affecting all age of people. As the prevalence of peptic ulcer disease increases with advancing age it is expected that this common disease will continue to have a significant global impact on health-care delivery, health economics and the quality of life of patients.

Peptic ulcer disease remains a frequent clinical problem in our environment predominantly affecting all age of people. As the prevalence of peptic ulcer disease increases with advancing age it is expected that this common disease will continue to have a significant global impact on health-care delivery, health economics and the quality of life of patients.

Peptic ulcer disease remains a frequent clinical problem in our environment predominantly affecting all age of people. As the prevalence of peptic ulcer disease increases with advancing age it is expected that this common disease will continue to have a significant global impact on health-care delivery, health economics and the quality of life of patients.

Peptic ulcer disease remains a frequent clinical problem in our environment predominantly affecting all age of people. As the prevalence of peptic ulcer disease increases with advancing age it is expected that this common disease will continue to have a significant global impact on health-care, Delivery, health economics and the quality of life of patients.

Peptic ulcer disease remains a frequent clinical problem in our environment predominantly affecting all age of people. As the prevalence of peptic ulcer disease increases with advancing age it is expected that this common disease will continue to have a significant global impact on health-care. Delivery, health economics and the quality of life of patients.

Peptic ulcer disease remains a frequent clinical problem in our environment predominantly affecting all age of people. As the prevalence of peptic ulcer disease increases with advancing age it is expected that this common disease will continue to have a significant global impact on health-care

Delivery, health economics and the quality of life of patients. Peptic ulcer disease remains a frequent clinical problem in our environment predominantly affecting all age of people. As the prevalence of peptic ulcer disease increases with advancing age it

is expected that this common disease will continue to have a significant global impact on health-care delivery, health economics and the quality of life of patients. Peptic ulcer disease remains a common clinical problem in our environment predominantly affecting all age of people. As the prevalence of peptic ulcer disease increases with advancing age it is expected that this common disease will continue to have a significant global impact on health-care delivery, health economics and the quality of life of patients. The standard anti-gastric ulcer drugs might present a synergistic effect against *H. pylori* and gastric ulcer disease and improve the outcome for patients with gastric ulcer. With only a few human studies, it is recommended to conduct further clinical studies with larger sample sizes on the efficacy and safety of medicinal plants with antiulcer activity. Finally concluded that timely diagnosis and treatment of peptic ulcer disease and its sequelae are crucial in order to minimize associated morbidity and mortality, as is prevention of peptic ulcer disease among patients at high risk, including those infected with *H. pylori* and users of NSAIDs.

References

1. Narayanan M, Reddy KM, Marsicano E. Peptic Ulcer Disease and Helicobacter pylori infection. *Mo Med*. 2018 May-Jun;115(3):219-224.
2. Lanas Á, Carrera-Lasfuentes P, Arguedas Y, García S, Bujanda L, Calvet X, Ponce J, Perez-Aísa Á, Castro M, Muñoz M, Sostres C, García-Rodríguez LA. Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-inflammatory drugs, antiplatelet agents, or anticoagulants. *Clin Gastroenterol Hepatol*. 2015 May;13(5):906-12.e2.
3. Huang JQ, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. *Lancet*. 2002 Jan 05;359(9300):14-22.
4. Siddique, O.; Ovalle, A.; Siddique, A.S.; Moss, S.F. Helicobacter pylori infection: An update for the internist in the age of increasing global antibiotic resistance. *Am. J. Med*. 2018, 131, 473–479.
5. Hooi, J.K.Y.; Lai, W.Y.; Ng, W.K.; Suen, M.M.Y.; Underwood, F.E.; Tanyingoh, D.;

- Malfertheiner, P.; Graham, D.Y.; Wong, V.W.S.; Wu, J.C.Y.; et al. Global prevalence of *Helicobacter pylori* infection: Systematic review and meta-analysis. *Gastroenterology* 2017, 153, 420–429.
6. Bhat S. SRB's Manual of Surgery. 2013: 364.
7. Zaki, M.; Coudron, P.E.; McCuen, R.W.; Harrington, L.; Chu, S.; Schubert, M.L. H. *Pylori* acutely inhibits gastric secretion by activating CGRP sensory neurons coupled to stimulation of somatostatin and inhibition of histamine secretion. *Am. J. Physiol. Gastrointest. Liver Physiol.* 2013, 304, G715–G722.
8. El-Omar, E.M.; Oien, K.; El-Nujumi, A.; Gillen, D.; Wirz, A.; Dahill, S.; Williams, C.; Ardill, J.E.; McColl, K.E. *Helicobacter pylori* infection and chronic gastric acid hyposecretion. *Gastroenterology* 1997, 113, 15–24. [CrossRef]
9. Moss, S.F.; Legon, S.; Bishop, A.E.; Polak, J.M.; Calam, J. Effect of *helicobacter pylori* on gastric somatostatin in duodenal ulcer disease. *Lancet* 1992, 340, 930–932.
10. Bhala, N.; Emberson, J.; Merhi, A.; Abramson, S.; Arber, N.; Baron, J.A.; Bombardier, C.; Cannon, C.; Farkouh, M.E.; FitzGerald, G.A.; et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: Meta-analyses of individual participant data from randomised trials. *Lancet* 2013, 382, 769–779.
11. Bjarnason, I.; Scarpignato, C.; Takeuchi, K.; Rainsford, K.D. Determinants of the short-term gastric damage caused by NSAIDs in man. *Aliment. Pharmacol. Ther.* 2007, 26, 95–106.
12. Aihara T, Nakamura E, Amagase K, Tomita K, Fujishita T, Furutani K et al. Pharmacological control of gastric acid secretion for the treatment of acid-related peptic disease: past, present, and future. *Pharmacol Ther* 2003;98:109-127.
13. Tasman-Jones C. Pathogenesis of peptic ulcer disease and gastritis: Importance of aggressive and cytoprotective factors. *Scand J Gastroenterol.* 1986; 21: 1-5.
14. Lindstrom E, Chen D, Norlen P, Andersson K, and Hakanson R. Control of gastric acid secretion: the gastrin-ECL cell-parietal cell axis. *Comp Biochem Physiol A Mol Integr Physiol* 2001;128: 505–514.
15. Terence C, Enrique R. CCK2 receptor mediates rapid protein kinase D activation through a protein kinase C-dependent pathway. *FEBS Lett* 2001;489:101-106.
16. Waldum HL, Kleveland PM, Sandvik AK, Brenna E, Syversen U, Bakke I, and Tommeras K. The cellular localization of the cholecystokinin 2 receptor in the stomach. *Pharmacol Toxi col* 2002;91:359–362.
17. Hunyady BL, Lyomi ARZ, Hoffman BJ, Mezey EV. Gastrin-Producing Endocrine Cells: A Novel Source of Histamine in the Rat Stomach. *Endocrinology* 1998;139:4404-4415.
18. Sandvik AK, Kleveland PM, Waldum HL. Muscarinic M2 stimulation releases histamine in the totally isolated, vascularly perfused rat stomach. *Scand J Gastroenterol* 1988;23: 1049-56.