

Gastric Ulcer: An overview

Aslam Hamid Khan

Mohd Altaf Dar

Mashooq Ahmad Mir

Chandigarh college of Pharmacy, Landran

Department of Pharmacology, CT Institute of
Pharmaceutical Sciences, PTU, Jalandhar Punjab

Department of Pharmacology, CT Institute of
Pharmaceutical Sciences, PTU, Jalandhar Punjab

Gastric ulcers are breaks in the mucosa of the stomach lining that penetrate through the muscularis mucosa and extend more than 5 mm in diameter. When alterations occur to the defense mechanisms of the stomach, it can cause changes in the gastric mucosa, eventually resulting in erosion and then ulceration. Non-steroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* (*H. pylori*) infection are the two major factors disrupting mucosal resistance to injury. Gastric ulcers are 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. Conversely, the pain with a duodenal ulcer tends to occur 2–3 hours after a meal. The treatments for gastric 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 preventing and treating numerous diseases.

Keywords: gastric ulcer, NSAIDs, epigastric pain, pathophysiology

Introduction

Gastric ulcer is a common disease that affects millions of people worldwide. Considering its global prevalence finding, a new approach to treating it is important. According to WHO, Gastric ulcer disease death in India reached 85487 or 0.96% of total death. The age-adjusted death rate is 9.12%, i.e. one lac of the population suffers from Gastric ulcer, so India is ranked 26th in the world [1-5]. Ulcers are open sores in the upper part of the digestive tract that can cause stomach pain and upset stomach, leading to internal bleeding. There are two types of Gastric ulcer (1) Gastric ulcer and (2) Duodenal ulcer. Gastric ulcer disease is a multicausal and complex disease that occurs when the biological balance between defensive and aggressive factors in the gastrointestinal tract is disturbed. The aggressive factors are endogenous factors like gastric acid, endothelins and pepsin secretion, active free radicals and oxidants, leukotrienes, and exogenous factors like ethanol or nonsteroidal anti-inflammatory drugs (NSAIDs). On the other side, gastric mucus, bicarbonate, normal blood flow, prostaglandins (PGs), nitric oxide (NO), and antioxidant enzymes like catalase (CAT), or antioxidant peptides like glutathione (GSH) work as a defensive barrier. Mucosal cell death results from an increase in H⁺ concentration in its immediate environment due to this pH decreases. There are many drugs that are used in the treatment of Gastric ulcers. Until now, no drug without a side effect gives a 100% curative rate or complete cure of the disease [3, 6-8].

Anatomy of the normal stomach: On the top left side of the abdomen is a muscular organ called the stomach. Food travels down the oesophagus and into the stomach. The lower esophageal sphincter, a muscle valve, allows food to exit the oesophagus and enter the stomach. The stomach secretes acid and digestive enzymes to help with meal digestion. The muscular tissue ridges that border the stomach are called rugae. Regular contractions of the stomach muscles help with digestion by churning the meal. A muscle valve called the pyloric sphincter opens to let food pass from the stomach into the small intestine [9-11].

Pathophysiology

Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and Indomethacin are the most commonly prescribed drugs for arthritis, inflammation, and cardiovascular protection. However, they cause gastrointestinal complications such as ulcers and erosion. The pathophysiology of these complications has mostly been ascribed to NSAID's action on the cyclooxygenase (COX) inhibition and the subsequent prostaglandin (PG) deficiency [10, 12, 13]. Due to their high chemical reactivity and the existence of uncoupled electrons inside their molecules, reactive oxygen species (ROS) play a role in the pathophysiology of gastric mucosal injury. As a result, there is tissue damage, which is mostly caused by increased lipid peroxidation. Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) are the products of the metabolism of lipid peroxides. The local rise in MDA and 4-HNE levels indicate ROS-dependent tissue damage. The primary enzyme that converts ROS into less harmful hydrogen peroxide is called superoxide dismutase (SOD). The protective system is impaired when SOD activity declines, which also greatly increases cell damage. In the presence of reduced glutathione, hydrogen peroxide is further metabolised to water. (GSH). In order to neutralise ROS, GSH can also operate in concert with SOD [12, 14, 15]. GSH and ROS react to form glutathione free radicals (GS•), which then react with GSH to form glutathione disulfide free radicals (GSSG•). The oxygen molecule can then accept an electron from this free radical of GSSG, creating $O_2^{\bullet-}$. $O_2^{\bullet-}$ is then removed by SOD. Reduced GSH levels are harmful to the cellular components that provide an antioxidative defense [14, 16, 17]. When under stress, the gastric mucosa shows increased lipid peroxidation (an increase in MDA and 4-HNE) and a decline in SOD activity and GSH content. Understanding the aetiology of NSAIDs-induces functional abnormalities in the gastric mucosa leading to ulcerogenesis appears to depend on this cascade of ROS production that is brought on by NSAIDs and stress [16, 18, 19].

Other types of ulcers :

(1) Gastric ulcer

When a Gastric ulcer occurs in the stomach, it is called a gastric ulcer. The bacterium called *H. pylori* cause this type of ulcer. Antacids are used as a treatment option for gastric ulcers; the patient usually starts to feel well after two or three weeks of using antacids. Also, ulcer patients are advised not to use too much oily and greasy food and also asked to limit the consumption of acidic foods [12, 20, 21].

(2) Duodenal ulcer:

When a Gastric ulcer is in the duodenum, it is called a duodenal ulcer. The initial section of the small intestine is where this kind of gastric ulcer forms. Interesting contrasts exist between some duodenal ulcer symptoms and those of stomach ulcers. In the Western world, duodenal ulcers are the most typical kind of ulcers. [12, 20, 22].

(3) Esophageal Ulcers:

Esophageal ulcers are lesions that occur in the esophagus (food pipe). These are most commonly formed at the end of the food pipe and can be felt as a pain right below the breastbone, in the same area where symptoms of heartburn are felt. Esophageal ulcers are associated with acid reflux or GERD, prolonged use of drugs like NSAIDs and smoking [20,23].

(4) Bleeding Ulcer:

Internal bleeding is caused by a Gastric ulcer that has been left untreated. When this happens, it is referred to as a bleeding ulcer, this is the most dangerous type of ulcer and it requires immediate treatment [20,24,25].

(5) Refractory Ulcer:

Simple Gastric ulcers that have not healed after at least 3 months of treatment are called refractory ulcers [20].

(6) Stress Ulcer:

A series of lesions (or lacerations) known as stress ulcers can develop in the esophagus, stomach, or duodenum. These are typically only seen in people who are seriously unwell or under a lot of stress [20,25-27].

Common cause of Gastric ulcer:

Helicobacter Pylori (*H. pylori*): *H. pylori* (initially named as *Campylobacter pyloridis*) is a gram-negative bacillus, motile, microaerophilic flagellated and spiral-shaped bacteria. It was identified by two Australian scientists, Barry Marshall and Robin Warrens 1982 discovered that bacteria are the primary cause of stomach and duodenal ulcers, excluding those caused by aspirins or arthritis. The bacteria are probably acquired from contaminated food or from infected drinking water. Type one stain of *H. pylori* possess a pathogenic activity that encodes the effectors protein cytotoxin-associated gene A (cag A), further translocation into the host cell [28-30]. Cag A affects cell shape, increase cell motility disturbs cell junctional activity and this is responsible for gastric carcinomas and gastric ulcer. *H. pylori*- mediated pathogenesis and colonization such as the outer membrane protein (Hop protein) Urease and the vacuolating cytotoxin (Vac A). Infection by bacteria is dependent on the bacteria's mortality and its ability to produce Urease. Urease produces ammonia and carbon dioxide from urea which is secreted from the stomach and this CO₂ interact with environmental water producing H₂CO₃ in the presence of carbonic anhydrase, an essential step in alkalinizing the surrounding pH. The H₂CO₃ converts into the H⁺ & HCO₃⁻ and the resulting H⁺ ion reacts with NH₃ to form NH₄⁺, which can damage epithelial cells [28, 29, 31].

H. Pylori Transmission and Spread of Infection

Transmission

H. pylori is typically spread from person to person via saliva and faecal contamination of food or water. Untreated water, congested living circumstances, and inadequate hygiene all lead to higher *H. pylori* prevalence in poorer nations. The majority of persons become infected as youngsters, and parents and siblings appear to play a significant role in transmission [29, 32-34].

Spread of Infection

H. pylori enter the body through the mouth, moves through the digestive system, and infects the stomach or the first part of the small intestine. The spiral-shaped bacterium uses its tail-like flagella to move around and burrow into the stomach lining, which causes inflammation [32,35]. Unlike other bacteria, *H. pylori* bacteria can survive in the stomach's harsh acidic environment because they produce a substance that neutralizes stomach acid. This substance, Urease, reacts with urea to form ammonia, which is toxic to human cells. Depending on where the infection occurs in the stomach, *H. pylori* can also cause the overproduction of stomach acid [32, 36, 37].

NSAIDs (Non-steroidal anti-inflammatory drugs): Nonsteroidal anti-inflammatory medications (NSAIDs) are the most well-known pharmaceuticals for the treatment of pain, inflammation, and fever globally. NSAIDs are often used to treat inflammatory conditions such as rheumatoid arthritis, osteoarthritis, dysmenorrhea, and ischemic cerebrovascular disorders. The use of these medications in some types of cancer treatment has also lately been documented. These medications work by inhibiting prostaglandin biosynthesis and thereby producing a therapeutic effect. On the other hand, long-term use of NSAIDs causes unpleasant gastrointestinal (GI) symptoms such as mucosal lesions, bleeding, gastric ulcer, and inflammation in the intestine leading to perforation, strictures in the small and large intestines, and chronic difficulties. Some of the side effects of NSAIDs may be transitory, but there have been numerous reports of life-threatening situations [36, 38, 39].

NSAIDs include Ibuprofen, Fenoprofen, Aspirin, Diclofenac, Sulindac, Naproxen, Indomethacin, Tolmetin and many others. These are valuable therapeutics that act not only as an anti-inflammatory but also as analgesics and antipyretics. They are used in a wide variety of clinical conditions, including arthritis and other musculoskeletal disorders. Nearly 25% of chronic users of these drugs develop gastric ulcer disease. Various studies indicate that NSAIDs help in the progression of ulceration by overcoming the expression of the enzyme cyclooxygenase (COX), which has been documented to inhibit the conversion of Arachidonic acid to PG's that impairs the mucosal barrier and results in corrosive action with pepsin and results in the progression of Gastric ulcer [38, 40, 41]. Further, COX-1 inhibition by the NSAIDs leads to the significant release of endothelin-1 (ET-1), which is a potent vasoconstriction that has been shown to induce mucosal injury. NSAIDs, by inhibiting the prostaglandin synthesis, cause the activation of neutrophils and the local release of reactive oxygen species (ROS), thus initiating the gastric injury [40, 42, 43]. NSAIDs also cause a marked reduction in mucosal blood flow, mucus-bicarbonate secretions, impaired platelet aggregation, reduced epithelial cell renewal and increased leukocyte adherence, which are responsible for the pathogenesis of ulceration. Gastric acid worsens the NSAID effects by deepening superficial lesions interfering with platelet aggregation and impairing the ulcer healing process [40, 42, 44].

Mechanism of action of NSAIDs: The principle of action of nonsteroidal anti-inflammatory drugs (NSAIDs) was initially established in the early 1970s and is based on the inhibition of prostaglandin (PG) synthesis. PG, which is synthesised from arachidonic acid, is a major mediator of inflammation, pain, and fever. The enzyme cyclooxygenase (COX), also known as PGH synthase, catalyses the reaction. By binding to and inhibiting COX, NSAIDs prevent the PG production [45-47]. COX has two isoforms, COX-1 and COX-2, each with a distinct function. COX-1 is expressed constitutively and responsible for the stomach mucosa's normal physiological protection. It is in charge of the manufacture of prostaglandins, which protect the stomach lining from acid secretion, keep blood flowing in the gastric mucosa, and create bicarbonate. COX-2, the other isoform, is activated by cell injury, proinflammatory cytokines, and tumor-derived substances. NSAIDs primarily cause NSAID-induced gastropathy by inhibiting COX-1 [45, 46, 48]. NSAIDs are also directly cytotoxic to stomach mucosal cells, causing lesions and damage. One study discovered that direct cytotoxicity is unaffected by COX inhibition. This type of topical damage has been reported in the case of acidic NSAIDs such as aspirin, resulting in an accumulation of ionised NSAID, a phenomenon known as "ion trapping." NSAIDs are thought to produce membrane permeabilization, which disrupts the epithelial barrier. NSAIDs could also cause necrosis and apoptosis in gastric mucosal cells [49-51].

Conclusion

Gastric ulcer disease remains a frequent clinical problem in our environment, predominantly affecting people of all ages. As the prevalence of Gastric ulcer disease increases with advancing age, it is expected that this common disease will continue to have a significant global impact on healthcare 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 ulcers. With only a few human studies, conducting further clinical studies with larger sample sizes on the efficacy and safety of medicinal plants with

antiulcer activity is recommended. Finally concluded that timely diagnosis and treatment of Gastric ulcer disease and its sequelae are crucial in order to minimize associated morbidity and mortality, as is the prevention of Gastric ulcer disease among patients at high risk, including those infected with *H. Pylori* and users of NSAIDs.

References

1. Graham DY. History of *Helicobacter pylori*, duodenal ulcer, gastric ulcer and gastric cancer. *World Journal of Gastroenterology*: WJG 2014;20:5191.
2. Calam J, Baron J. Pathophysiology of duodenal and gastric ulcer and gastric cancer. *Bmj* 2001;323:980-2.
3. Balfour DC. Factors influencing the life expectancy of patients operated on for gastric ulcer. *Annals of surgery* 1922;76:405.
4. Tarnawski AS, Ahluwalia A. The critical role of growth factors in gastric ulcer healing: the cellular and molecular mechanisms and potential clinical implications. *Cells* 2021;10:1964.
5. Ara I, Kalam MA, Maqbool M, Zehravi M. Phytochemical Standardization and Anti-Anxiety (Izterab-e-Nafsani) study of Aftimoon Hindi (*Cuscuta reflexa* Roxb.) on An Animal Model. *CELLMED* 2021;11:14.1-9.
6. Wallace JL. Recent advances in gastric ulcer therapeutics. *Current Opinion in Pharmacology* 2005;5:573-7.
7. Gear M, Truelove S, Whitehead R. Gastric ulcer and gastritis. *Gut* 1971;12:639-45.
8. Ara I, Maqbool M. The curious case of Neuropathic Pain and its management: An overview. *Open Health* 2022;3:145-54.
9. Vora Z, Goyal A, Sharma R. Radiological anatomy of stomach and duodenum with clinical significance. *Journal of Gastrointestinal and Abdominal Radiology* 2021;4:085-93.
10. Rebollo I, Wolpert N, Tallon-Baudry C. Brain-stomach coupling: Anatomy, functions, and future avenues of research. *Current Opinion in Biomedical Engineering* 2021;18:100270.
11. Ara I, Maqbool M, Bukhari B, Ara N, Hajam TA. Present status, standardization and safety issues with herbal drugs. *International Journal of Research in Pharmaceutical Sciences and Technology* 2020;1:95-101.
12. Topi S, Santacroce L, Bottalico L, Ballini A, Inchingolo AD, Dipalma G, et al. Gastric cancer in history: a perspective interdisciplinary study. *Cancers* 2020;12:264.
13. Ara I, Maqbool M, Fekadu G, Hajam TA, Dar MA. Pharmaceutical Significance of *Nigella Sativa* L., a Wonder Herb. *Journal of Applied Pharmaceutical Sciences and Research* 2020;3:04-13.
14. Ray A, Gulati K, Henke P. Stress gastric ulcers and cytoprotective strategies: perspectives and trends. *Current Pharmaceutical Design* 2020;26:2982-90.
15. Ara I, Maqbool M, Zehravi M. Psychic consequences of infertility on couples: A short commentary. *Open Health* 2022;3:114-9.
16. Bereda G. Peptic Ulcer disease: definition, pathophysiology, and treatment. *Journal of Biomedical and Biological Sciences* 2022;1:1-10.
17. Ara I, Yaqoob S, Raja WY, Bukhari B, Maqbool M. MANAGING ANXIETY DISORDERS: A SHORT COMMUNICATION. 2020.
18. Ghosh N, Kesh K, Ramakrishnan S, Roy S. Opioid use in murine model results in severe gastric pathology that may be attenuated by proton pump inhibition. *The American journal of pathology* 2022;192:1136-50.
19. Bashir R, Maqbool M, Ara I, Zehravi M. An In sight into Novel Drug Delivery System: In Situ Gels. *CELLMED* 2021;11:6.1-6.7.
20. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. *Gastroenterology Review/Przegląd Gastroenterologiczny* 2019;14:26-38.
21. Bhat SA, Mir SA, Maqbool M, Bhat AU, Masoodi MH. Evaluation of phytochemical, antioxidant, and In-vitro antidiarrhoeal, activity of *Euphorbia hirta*. *Journal of Drug Delivery and Therapeutics* 2019;9:290-4.
22. Fekadu G, Bekele F, Bekele K, Hanbisa S, Belay G, Maqbool M. Drug Use Evaluation of Beta-Blockers in Medical Wards of Nedjo General Hospital, Western Ethiopia. *Cardiovascular Therapeutics* 2020;2020.

23. Khan M, Maqbool M. Hypertension and Pregnancy: an important issue ABOUT AUTHORS. *Hypertension* 2019;17:0.
24. Lihite RJ, Lahkar M, Das S, Hazarika D, Kotni M, Maqbool M, et al. A study on adverse drug reactions in a tertiary care hospital of Northeast India. *Alexandria journal of medicine* 2017;53:151-6.
25. Zhang L, Zhang Y, Wang L, Wang J, Liu Y. Diagnosis of gastric lesions through a deep convolutional neural network. *Digestive Endoscopy* 2021;33:788-96.
26. Majeed A, Bashir R, Farooq S, Maqbool M. Preparation, characterization and applications of nanoemulsions: An insight. *Journal of Drug Delivery and Therapeutics* 2019;9:520-7.
27. Malik JA, Maqbool M. COVID-19: An overview of current scenario. *CELLMED* 2020;10:21.1-8.
28. Dunlap JJ, Patterson S. Peptic ulcer disease. *Gastroenterology Nursing* 2019;42:451-4.
29. Hsieh S-Y, Lian YZ, Lin I, Yang Y-C, Tinkov AA, Skalny AV, et al. Combined Lycium barbarum polysaccharides and C-phycocyanin increase gastric Bifidobacterium relative abundance and protect against gastric ulcer caused by aspirin in rats. *Nutrition & Metabolism* 2021;18:1-16.
30. Malik JA, Maqbool M, Hajam TA, Khan MA, Zehravi M. Comparison of different classes of drugs for Management of Acute Coronary Syndrome (ACS): A brief communication. *CELLMED* 2021;11:7.1-7.5.
31. Maqbool M. EVALUATION OF DRUG UTILIZATION PATTERN IN THE PEDIATRIC DEPARTMENT OF A TERTIARY CARE HOSPITAL IN SRINAGAR, JAMMU & KASHMIR, INDIA. *Journal of Applied Pharmaceutical Sciences and Research* 2019:6-9.
32. Lee Y-C, Dore MP, Graham DY. Diagnosis and treatment of Helicobacter pylori infection. *Annual review of medicine* 2022;73:183-95.
33. Maqbool M, Ara I, Gani I. Reproductive Health of Women: Implications and attributes. *International Journal of Current Research in Physiology and Pharmacology* 2022:8-18.
34. Maqbool M, Arshad B, Liaquat S. PSYCHOTROPIC DRUG UTILISATION PATTERN CAN BE USEFUL IN MONITORING TREATMENT REGIMENS FOR MENTAL DISORDERS IN PSYCHIATRIC SETTINGS. *INDO AMERICAN JOURNAL OF PHARMACEUTICAL SCIENCES* 2018;5:7717-21.
35. Maqbool M, Bekele F, Fekadu G. Treatment Strategies Against Triple-Negative Breast Cancer: An Updated Review. *Breast Cancer: Targets and Therapy* 2022;14:15.
36. Yuan C, Adeboye D, Luk TT, Huang L, He Y, Xu Y, et al. The global prevalence of and factors associated with Helicobacter pylori infection in children: a systematic review and meta-analysis. *The Lancet Child & Adolescent Health* 2022.
37. Maqbool M, Dar AM, Rasool S, Khan M. Curious Case of Drug Resistant Malaria and Artemisinin Compounds in the Modern Era. *Journal of Applied Pharmaceutical Sciences and Research* 2019:1-4.
38. Abo Elmaaty A, Hamed MI, Ismail MI, B. Elkaeed E, S. Abulkhair H, Khattab M, et al. Computational insights on the potential of some NSAIDs for treating COVID-19: priority set and lead optimization. *Molecules* 2021;26:3772.
39. Maqbool M, Dar MA, Gani I, Mir SA. Animal models in diabetes mellitus: an overview. *Journal of Drug Delivery and Therapeutics* 2019;9:472-5.
40. Ruiz-Hurtado PA, Garduño-Siciliano L, Domínguez-Verano P, Balderas-Cordero D, Gorgua-Jiménez G, Canales-Álvarez O, et al. Propolis and its gastroprotective effects on nsaid-induced gastric ulcer disease: A systematic review. *Nutrients* 2021;13:3169.
41. Maqbool M, Dar MA, Gani I, Mir SA, Khan M. Herbal medicines as an alternative source of therapy: a review. *World Journal of Pharmacy and Pharmaceutical Sciences* 2019;3:374-80.
42. Savarino V, Marabotto E, Zentilin P, Savarino E. The prevention of NSAID-induced gastric ulcers is a firmly established PPI indication. *Expert review of clinical pharmacology* 2019;12:1011-2.
43. Maqbool M, Dar MA, Gani I, Mir SA, Khan M, Bhat AU. Maternal Health and Nutrition in Pregnancy: an Insight. *World Journal of Pharmacy and Pharmaceutical Sciences* 2019;8:450-9.

44. Maqbool M, Dar MA, Rasool S, Gani I, Khan M. Substance use disorder and availability of treatment options: an overview. *Journal of research in health science* 2019;1:2.
45. Wallace JL. Prostaglandins, NSAIDs, and gastric mucosal protection: why doesn't the stomach digest itself? *Physiological reviews* 2008;88:1547-65.
46. Chan FK, Leung W. Peptic-ulcer disease. *The Lancet* 2002;360:933-41.
47. Maqbool M, Dugassa D, Fekadu G. Adverse Drug Reactions of Antiepileptic Drugs in the Neurology Department of a Tertiary Care Hospital, Srinagar, Jammu & Kashmir, India. *Archives of Neuroscience* 2021;8.
48. Maqbool M, Fekadu G, Dugassa D, Bekele F, Turi E, Simegnew D. The Pattern of Substance Abuse in the Psychiatry Department of a Tertiary Care of Srinagar Hospital, Jammu and Kashmir, India. *Archives of Neuroscience* 2020;7.
49. Fornai M, Colucci R, Antonioli L, Awwad O, Ugolini C, Tuccori M, et al. Effects of esomeprazole on healing of nonsteroidal anti-inflammatory drug (NSAID)-induced gastric ulcers in the presence of a continued NSAID treatment: Characterization of molecular mechanisms. *Pharmacological Research* 2011;63:59-67.
50. Maqbool M, Fekadu G, Jiang X, Bekele F, Tolossa T, Turi E, et al. An up to date on clinical prospects and management of osteoarthritis. *Annals of Medicine and Surgery* 2021;72:103077.
51. Maqbool M, Gani I. Utilization of Statins in Reducing Comorbidities of Diabetes Mellitus: A Systematic Review. *Journal of Pharmacy Practice and Community Medicine* 2018;4.