Peptic Ulcer Disease: Retrospection on History, Pathophysiology its Mainstream and Herbal Drug Therapy

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Abstract
Peptic ulcer, a persistent condition affecting approximately 10% of the global population, arises due to factors such as gastric juice pH and a decline in mucosal defenses. The primary causes of mucosal resistance disruption leading to peptic ulcers are attributed to the use of NSAIDs and Helicobacter pylori (H. pylori) infection. Despite traditional treatments such as proton pump inhibitors (PPIs) and histamine-2 (H2) receptor antagonists, limitations like adverse effects, relapses, and potential drug interactions have been observed. The main objective of antiulcer therapy is to either prevent acid secretion from gastric parietal cells or neutralize the acid before it reaches ulcerated areas in the gastrointestinal tract. Conventional approaches for duodenal ulcers, including diet, antacids, and anticholinergics, have been in practice for an extended period. However, only antacids have been definitively proven effective for healing, albeit requiring administration in large and frequent doses. Addressing the pathophysiology and optimal treatment strategies for non-NSAID, non-H. pylori associated peptic ulcers remains challenging. The review underscores the H. pylori infection and NSAID use as the most prevalent risk factors for ulcer development. Additionally, genetic predisposition, stress, and comorbidities elevate the risk of ulcer occurrence. Successful eradication and prevention of these risk factors are crucial to averting the presence of ulcers and their complications. Conversely, medicinal plants and their chemical compounds emerge as valuable in preventing and treating various diseases. Consequently, the review provides insights into the etiology, pathogenesis, chemotherapy, and common medicinal plants that may be employed in the treatment or prevention of peptic ulcers.
Keywords: duodenal ulcer, gastric ulcer, Helicobacter pylori, NSAIDs, peptic ulcer disease.

Introduction

Gastrointestinal diseases are very serious and common problems, which are causing maximum discomfort, morbidity, and mobility in human beings. It occurs in 10-15% of the population at a time. The group of disorders which is responsible for the ulcer formation or mucosal lesions formation in the oesophageal lining (swallowing pipe), stomach or duodenum is known as Peptic ulcer.The small ulcers are caused by factors that protect the mucous membrane (bicarbonate, mucin, prostaglandin, nitric oxide, and other peptides and growth factors) and harmful factors (pepsin, Helicobacter pylori, NSAIDs gastric acid). The Ulcer that occurs in stomach is known as gastric ulcer while ulcer that occurs in the first part of the intestine is also known as a duodenal ulcer [1]. Sometimes, people feel that upper abdominal pain may increase after lunch or dinner, and sometimes people vomit materials which looks like coffee grounds, blood comes with stool, have black or tarry stools, all these symptoms cause severe abdominal pain. The gastric ulcer pain may increase with eating and we feel burning-like sensation in our stomach. While the duodenal ulcer increases with improper sleep or waking up late at night and eating. These symptoms indicate the severe occurrence of peptic ulcer disease in your body. When these types of symptoms are not controlled by the counter drug, then the patient may be referred to a specialist called a gastroenterologist [2].

The microorganism named (H. pylori) Helicobacter pylori plays an important role in peptic ulcer disease, and eradication of this microbe can minimize the complication of this disease. Many studies explained that more than half of the world's population has been badly affected by this chronic H. pylori infection which directly affects gastro duodenal mucosa.

By using triple chemotherapy i.e. histamine receptor antagonist, proton pump inhibitors and sequential regimen, management of this disease can be done. If the disease condition is severe, we proceed with the surgical approach for the treatment. In the absence of H. pylori\ infection and NSAIDs drugs, a different category of ulcers may occur which are Zollinger-Ellison syndrome, truly idiopathic ulcers, cushing ulcer and high dose upper abdominal radiotherapy that can also lead to a type of ulcer [3]. The drugs covered under NSAIDs category are beneficial agents in treating various diseases like arthritis, musculoskeletal disorders and inflammation, in a variety of clinical scenarios but these agents also cause peptic ulcer [4]. If drugs of class NSAIDs are used in the presence of infection of Helicobacter pylori significantly enhances the complications of peptic ulcer bleeding [5].

Mammalian stomach has an ability to secrete concentrated hydrochloric acid in a very large quantity as we know that proteolysis enzyme pepsin and gastric acid are required to initiate digestion. Gastric acid does play a very significant and important role in protein hydrolysis and other digestive processes [6]. This secreted acid results in causing different forms of complications like oesophageal and duodenal injury under different conditions.

In response of physiological stimuli, human stomach produces/contains approx. 1 billion parietal cells which secrete hydrogen ions into the gastric lumen and the generation of these hydrogen ions is mediated by 3 pathways namely endocrine, paracrine, and neurocrine. By vagal postganglionic neurons, a neurocrine transmitter, acetylcholine is released which cause stimulation of hydrogen ion generation directly via a parietal cell M3 muscarinic receptor. On parietal cells, Paracrine transmitter name Histamine binds with H2 specific receptors. In response to this, activation of Adenylate cyclase results in increasing adenosine 38, 58-Cyclic Monophosphate (cAMP) levels, and subsequently stimulates the generation of hydrogen ions. Gastrin secretion from antral G-cell which follows the endocrine pathway and stimulates the hydrogen ion secretion both directly or indirectly, in corpus and fundus, increases the stimulation of histamine secretion from enterochromaffin like cells [7, 8].

Combination of these three pathways control and regulate hydrogen ion secretion. There is a negative feedback mechanism which is controlling both gastrin release and returning acid secretion to the basal level. Enterochromaffin-like cells are also known as controller cells. Many studies indicate that under different physiological conditions, some of the other neurotransmitters, like galanin, pituitary adenylate cyclase–activating peptide, and Vasoactive Intestinal Peptide (VIP), may play a very important role in regulating gastric acid secretion both directly or indirectly [9]. When gastric acid increases in our stomach, it causes mucosal damage and leads to the formation of gastric lesions.

Gastric lesions are one of the most important tools for the determination of an antiulcer property of drug molecule because the size changes constitute useful information like if a drug is effective in the case of ulcer or not, and if the size of the lesion is small and less in number, then we can say that the prepared preparation is an effective antiulcer agent [10].

The process of measurement of gastric ulcer or gastric lesions is done after dissection of the stomach along its greater curvature from the rat and fixed on a plane board or transparent glass. After fixing it into board or glass, the gastric lesions are examined by microscopes like light or scanning microscope. Another examination method is performed by hand lens, though it is an old method of examination and ulcer investigation, later the size of lesions are measured. Nowadays, the stomach is also scanned by using the camera in ulcer investigation and later investigated by suitable or appropriate software programs like Scion, Image J and others. After examination, the investigator can calculate the ulcer index by different methods as per their vantage [10, 11]. The choice of screening model is also influenced by local resources, study objective, the hypothesis being tested or researcher's questions. Preclinical experiments were carried out in in-vivo models. Colours for all the figures in this review are prepared according to the guidelines of "Guidelines for preparing colour figures for everyone including the colour-blind" given by Robert Roskoski Jr. [12].Ulcers are an open sore of the skin or mucus membrane characterized by sloughing of inflamed dead tissue. A gastric ulcer results in epigastric pain during the meal, as acid production is increased when food enters the stomach.Symptoms of duodenal ulcers would initially be relieved by a meal, as the pyloric sphincter closes to concentrate the stomach contents therefore acid does not reach the duodenum [13]. Peptic ulcer is a disease that affects a considerable number of people worldwide. It occurs as the result of imbalance between ''aggressive'' and ''protective'' factors at the luminal surface of the epithelial cells. An aggressive factor includes Helicobacter pylori, HCl, pepsins, NSAIDs, bile acids, ischemia, hypoxia, smoking and alcohol. Although protective factors includes

bicarbonate, mucus layer, mucosal blood flow, PG's and growth factors[14] .Ulcers are usually accompanied by burning or gnawing sensation in the abdomen lasting 30 minutes -3 hrs[15].

HISTORY

The ancient description of ulcer belongs to a period of 3000 BC and even before that. Hippocrates (460 360 BC) known as "father of medicine", described an ulcer while defining, Cancer and termed it as carcinos and carcinoma referring them as non-ulcer forming and ulcer forming tumours. [16]

By the 16th century, Hippocrates himself had studied and explained peptic ulcers and their associated symptoms. He even described the treatment of and ulcer which can be seen in the Corpus Hippocratum, a collection of Hippocratic works by his followers. [17] The great Arabic physician Avicenna (980- 1037) studied the relationship between gastric pain and the mealtimes. [18] An Italian physician named Marcello Donati (1538-1602) first recorded and described a case of peptic ulcer and the case was reported in 1586. At that time, it was clear that stomach pain and peptic ulcer were very closely related and often depends on lifestyle and diet of the human beings. The first clear description of the symptoms and morbid anatomy of gastric ulcers was attributed to an English physician, Matthew Baillie in 1793, followed by his publication on ulceration in 1799. I 1875, G. Bottcher and M. Letulle presented their hypothesis that the ulcer was caused by bacteria , but no one believe them at the time. As it was thought that bacteria couldn't survive the acidic conditions and the use of antibiotics was deemed as quackery. In 1834 T Schwann (1810-1882) devised Pepsin and it was stated as another known cause of peptic ulcer. During the period 1889 spiral-shaped bacteria were found both in the mucosa and in the contents of stomach of ulcer patients, this was followed by observation of Helicobacterpylori by Howard steer in the biopsies of patient with the ulcer in the year 1971. The two Australian physicians John Robin Warren and Barry Marshal, brought revolution in the medical science in the year 1982, when Helicobacter pylori was first identified and cultured separately and was revealed as one of the known cause for peptic ulcer ,for which they were also awarded Nobel prize in 2005, which proved Koch's 3rd postulate that the pathogenesis of ulcer and many diseases including cancer lied in the presence of a bacteria. As we look at the dawn of history related to ulcer, the scientific investigations were followed by treatment methodologies applied by medical practitioners, the treatment goals and management of diseases have seen drastic changes including proper management and cure of ulcer. During 1920's, milk was considered to cure gastritis andproblems linked with gastric region.

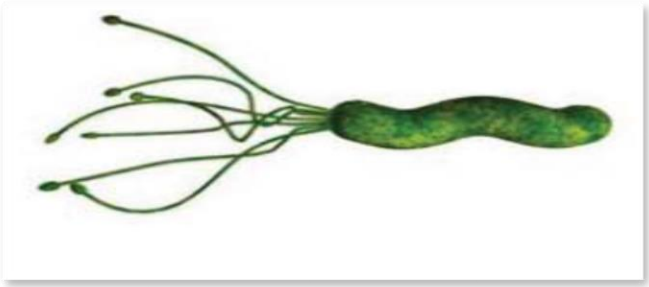

Figure 1: Helicobacter pylori

At the time, it was believed that giving milk through nasogastric tube could treat or cure an ulcer. Soon this was changed to surgical options during 1930's to 1960's when vagotomy or surgical removal of parts of stomach were thought to be the treatment options to eliminate ulcer from the diseased individual. During 1980's cimetidine was discovered to cure gastric ulcer and who had more knowledge about the origin of the ulcer i.e. acid, cimetidine and ranitidine were used to heal the ulcer, because then it was the clear that the acid was the main cause of the ulcer in most cases. After the revolutionary discovery of pathogen i.e. Helicobacter pylori the treatment goals changed to the use of antibiotics and bismuth followed by use of acid blockers. [19] After the introduction of Helicobacter pylori during the period of 1995, almost 75 % patients with ulcer were treated with anti-secretory agents or medications and only 5 % got antibiotic therapy. This was followed by national campaign to educate the masses about the known cause of ulcer i.e. H.pylori and changed the treatment options available with the medical fraternity. [19] It took two decades to understand that H. pylori was causative agent for an ulcer, numerous investigations and animal models were established to come up with the mechanism via which Helicobacter pylori establishes itself in gastric environment and is

responsible for the pathogenesis of gastric ulcer. More than half of the population of world is affected by H. pylori, only 5-10 % develop ulcer. [19]

Etiology and Pathogenesis of Peptic Ulcer

The etiology of peptic ulcer is not clearly recognized. Peptic ulcer occurs in that part of the gastrointestinal tract (GIT) which is exposed to gastric acid and pepsin i.e. the stomach and duodenum. It it probably caused by imbalance between the aggressive (acid, pepsin, bile and Helicobacter pylori) and the protective (secretion of gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, innate resistance of the mucosal cells) factors [20]. Many psychosomatic, humoral and vascular diseases are associated with Helicobacter pylori infection to ulcer formation and recurrence has been identified [21]. In gastric ulcer; acid secretion is normal or low. In duodenal ulcer; acid secretion is high in half of the patients but normal in the rest.

Whether the acid production is normal or high, it contributes to the development of ulcers as an aggressive factor, the reduction of which is the most important approach in ulcer treatment.

The development of antiulcer disorders is multifactorial, involving several contributing factors. The major etiological factors include:

1. Helicobacter pylori infection: H. pylori is a gram-negative bacteria that causes infection in the stomach. It is the main cause of peptic ulcers, and it can also cause gastritis and stomach cancer.It is estimated that around 70-90% of duodenal ulcers and 60-80% of gastric ulcers are associated with H. pylori infection. The bacterium damages the protective mucosal layer of the stomach, leading to increased vulnerability to acid and digestive enzymes.[22]

2. Nonsteroidal anti-inflammatory drugs (NSAIDs): NSAIDs, such as aspirin, ibuprofen, and naproxen, are commonly used medications for pain relief and inflammation. Prolonged use of NSAIDs can disrupt the stomach's natural defence mechanisms, impair mucosal blood flow, and inhibit prostaglandin synthesis, leading to an increased risk of ulcer formation. The risk is further amplified when combined with H. pylori infection [23].

3. Stress and lifestyle factors: Psychological stress, smoking, excessive alcohol consumption, and irregular eating patterns results in increasing complications of antiulcer disorders. While the exact mechanisms are not fully understood, these factors are thought to disrupt the normal balance between mucosal protective factors and damaging factors [24].

The pathogenesis of antiulcer disorders involves complex interactions between the aforementioned etiological factors and the body's physiological responses. The key pathogenic mechanisms include:

1. Disruption of mucosal defense mechanisms: H. pylori infection and NSAIDs impair the integrity of the gastric mucosal barrier, which normally protects the underlying tissues from acid and other noxious agents. H. pylori release virulence factors that weaken the mucosal barrier, while NSAIDs inhibit the synthesis of protective prostaglandins [25-29].

ULCERS TYPES

Different types of ulcers have been delineated by medical scientists and they are known by their origin or location in the human body. So far, the known types of ulcers are pressure ulcers, genital ulcers, ulcerative dermatitis (which means inflammation), anal fissure, diabetic foot ulcer, corneal ulcer (according to the specific area of occurrence), Mouth ulcer also known as Aphthous ulcer (Canker sores), Peptic ulcer, Venous ulcer, Stress ulcer, Ulcerative sarcoidosis, Ulcerative lichen planus, Ulcerative colitis, Ulcerative disposition. However, the most common types of ulcers are-

1. Peptic Ulcer: This type of ulcer is related to pepsin and can appear at different regions.

2. Gastric Ulcer: Ulcer arises in the stomach region and is often known as Stomach ulcer.

3. Duodenal Ulcers: This type of Ulcer occurs in the duodenal region of the GIT tract or Gastro intestinal tract [30].

CHEMOTHERAPY OF ULCER

Ulcer is a chronic remitting and relapsing disease lasting several years. The goals of anti-ulcer therapy are, relief of pain, ulcer healing, prevention of complications and prevention of relapse.

Anti-ulcer drugs are classified as

1) Agents which help in reduction of gastric acid secretion

2) Agents which neutralize the gastric acid

3) Ulcer protective agents

4) Anti-helicobacter pylori agents.

Table 1 describes the chemotherapeutic options available for medical practitioners in dealing with ulcer and proper management of peptic ulcer. As Helicobacter pylori has been known as one reason behind the pathogenesis of Ulcer, new treatment therapies are available for proper management of Helicobacter pylori induced ulcers.It includes, Triple therapy for 14 days: Proton pump inhibitors + clarithromycin 500 mg plus metronidazole 500 mg or Amoxicillin 1 g twice a day (tetracycline 500 mg can be substituted for amoxicillin or metronidazole).Quadruple therapy for 14 days: Proton pump inhibitors twice a day + metronidazole 500 mg three times daily plus bismuth subsalicylate 525 mg + tetracycline 500 mg four times a day.

Table 1: Anti-Ulcer Drugs Classification

Classification	Drugs
1. Reduction of Gastric acid secretion	
H2 Histamines	Cimetidine, Ranitidine, Famotidine, Roxatidine
Proton Pump Inhibitors	Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole,
Anticholinergic drugs	Pirenzepine, Propantheline, Oxyphenonium
Prostagladin analogue	Misoprostol
2. Neutralization of Gastric acid	
Systemic	Sodium bicarbonate
Non-systemic	Magnesium hydroxide
3. Ulcer Protective	Sucralfate, Colloidal bismuth subcitrate
4. Anti H.pylori drugs	Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline

Table 2: Medicinal Plants having Anti Ulcer property

S.No	Herbal Drug	Reference
`1	*Ocimum Sanctum*	[31]
2	*Desmodium Gangeticum*	[32]
3	*Azadirachta Indica*	[33]
4	*Hemidesmus Indicus*	[34]
5	*Asparagus Racemosus*	[35]
6	*Terminalia pallida Brandis*	[36]
7	*Embilica officinalis*	[37]
8	*Centella asiatica*	[38]
9	*Bacopa monniera*	[39]
10	*Musa sapiento*	[40]
11	*Carica papaya*	[41]
12	*Kielmeyera coriacea*	[42]
13	*Garcinia cambogia*	[43]
14	*Banincasa hispida*	[44]
15	*Ficus Arnottiana*	[45]
16	*Alstonia Scholaris*	[46]
17	*Morinda Citrifolia*	[47]
18	*Plectranthus Amboinicus*	[48]
19	*Allium Sativum*	[49-50]
20	*Adansonia Digitata*	[51]
21	*Aegle Marmelos*	[52]
22	*Emblica officinalis*	[53]
23	*Aloe Barbadensis*	[53]
24	*Careya Arborea*	[54]

25	*Ficus Religosa*	[55]

Conclusion

Ulcers have a documented history of causing morbidity and mortality in humans. From the era of Hippocrates to the present day, significant transformations have occurred in the understanding of disease pathophysiology and treatment objectives. Chemotherapy has undergone considerable evolution, with ongoing advancements driven by global scientific discoveries. Despite extensive research aimed at identifying effective molecules, the potential for side effects or adverse reactions remains a concern. Therefore, there is a growing emphasis on developing traditional medicines or herbal remedies. Numerous clinical developments are unfolding worldwide. Future progress in molecular biology and genetic engineering is anticipated to play a pivotal role in managing peptic ulcer disease. As the prevalence of this condition rises with age, it is expected to exert a substantial global impact on healthcare delivery, health economics, and patients' quality of life. Combining herbal products with standard anti-gastric ulcer drugs may yield a synergistic effect against H. pylori and gastric ulcer disease, potentially enhancing outcomes for patients. Despite limited human studies, it is recommended to conduct further clinical research with larger sample sizes to assess the efficacy and safety of medicinal plants with antiulcer properties. Additionally, investigating and elucidating the mechanisms of action of medicinal plants used for peptic ulcer treatment or prevention should be a focus of future studies. Licensing herbal products for medicinal use is essential to enhance their safety and quality, ensuring that randomized controlled investigations validate potential efficacy claims. The escalating reports of herb–drug interactions underscore the need for more comprehensive research in this area, with measures to address this deficiency. Pharmacists and doctors should remain vigilant, particularly regarding the risks associated with the use of herbal preparations, whether standalone or in combination with other herbal or conventional therapies. The author envisions a transformative future in the overall management of ulcers and other diseases, anticipating advancements in treatment strategies.

References

1. Kaur A, Singh R, Sharma R, Kumar S. Peptic Ulcer: A Review On Etiology And Pathogenesis. Int Res J Pharm, 2012;3(6): 34-8.
2. Vomero ND, Colpo E.Nutritional Care In Peptic Ulcer. Arq Bras Cir Dig, 2014;27(4): 298-302.
3. Prabhu V, Shivani A. An Overview Of History, Pathogenesis And Treatment Of Perforated Peptic Ulcer Disease With Evaluation Of Prognostic Scoring In Adults. Ann Med Health Sci Res, 2014;4(1):22-9.
4. Lanza FL, Chan FKL, Quigley EMM, Parameters P.Practice.Guidelines for Prevention Of NSAID-Related Ulcer Complications. Am J Gastroenterol, 2009;104(3): 728-38.
5. Malfertheiner P, Megraud F, O'Morain C, *et al.* Current Conceptsin The Management of Helicobacter Pylori Infection: The Maastricht III Consensus Report. Gut,2007;56(6): 772-81.
6. Wolfe MM, Soll AH. The Physiology of Gastric Acid Secretion. N Engl J Med,1986;319(26): 1707-15.
7. Waldum HL, Sandvik AK, Syversen U, Brenna E.The Entero- Chromaffin-Like (ECL) Cell. Physiological and Pathophysiological Role. Acta Oncol, 1993;32(2): 141-7.
8. Andersson N, Rhedin M, Peteri-Brunback B, Andersson K, Cabero JL.Gastrin Effects On Isolated Rat Enterochromaffin-Like Cells Following Long-Term Hypergastrinaemia In Vivo Biochim Biophysacta,1999;1451(2-3): 297-304.
9. Wolfe MM, Sachs G.Acid Suppression: Optimizing Therapy For Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, And Stress-Related Erosive Syndrome. Gastroenterology 2000;118(2)(Suppl. 1): S9-S31.
10. Oka K, Seki T, Akatsu T, Wakabayashi T, Inui K, Yoshino J. Clinical Study Using Novel Endoscopic System For Measuring Size Of Gastrointestinal Lesion. World J Gastroenterol 2014;20(14): 4050-8.
11. Adinortey MB, Ansah C, Galyuon I, Nyarko A. In-Vivo Models Used For Evaluation Of Potential Antigastroduodenal Ulcer Agents. Ulcer, 2013: 1-12.
12. Roskoski R Jr. Guidelines for Preparing Color Figures For Everyone Including The Color Blind. Pharmacol Res,2017;119: 240-1.
13. Harsh Mohan. 2009.Text Book of Pathology .Sixth Edition, Jaypee Publishers., 549-555.
14. Harold, Kalant, Grant, Denis M., Mitchel, Jane, 2007. In: Principles of Medical Pharmacology, Seventh Ed. Elsevier Canad Ltd., P. 557, 558, 559.
15. Mahajan N, Sanghai D. Evaluation of Anti-Uler Potential of Leaves of *Jasminum Grandiflorum* L.

International Journal of Pharmaceutical Sciences. 2009;1(2): 247-249.
16. A Brief History of Cancer: Age Old Milestones Underlying Our Current Knowledge Database [Online]. 2014 April 22 ,assesd on 29 november,2023.
17. https://www.ucl.ac.uk/~ucgajpd/medicina%20antiqua/sa_hippint.html ,assessed on 1October, 2023.
18. Moradi Z, Besharat M, Minaiee B, Aliasl J, Parsa Yekta Z, Nasiri Toosi M. Avicenna's View on the Etiologies of Intestinal Obstruction. Iran Red Crescent Med J. 2016 Jan 1;18
19. Anwar Jamal, Aisha Siddiqui, Tajuddin And M A Jafri. A Review On Gastric Ulcer Remedies Used In Unani System Of Medicine. 2006; 5 (2) 153-159.
20. Richard M Peek, Martin J Blasser. Pathophysiology of Helicobacter Pylori-Induced Gastritis And Peptic Ulcer Disease.The American Journal Of Medicine, 1997;102(2):200-207.
21. Marshall BJ, Warren JR. Unidentified Curved Bacilli in the Stomach Of Patients With Gastritis And Peptic Ulceration. Lancet. 1984;1(8390):1311-1315.
22. Lanas A, Chan FKL. Peptic Ulcer Disease. Lancet. 2017; 390 (10094):613-624.
23. Cryer B, Feldman M. Effects Of Very Low Dose Daily, Long-Term Aspirin Therapy On Gastric, Duodenal, And Rectal Prostaglandin Levels And On Mucosal Injury In Healthy Humans. Gastroenterology. 1999;117(1):17-25.
24. Amarapurkar AD, Amarapurkar DN, Rane PS. Risk Factors for Peptic Ulcer Disease In A Large Prospective Cohort Study Of Indian Patients. Indian J Gastroenterol. 2005;24(6):248-251. Sugano K, Tack J, Kuipers EJ, Et Al. Kyoto Global Consensus Report On Helicobacter Pylori Gastritis. Gut. 2015;64(9):1353-1367.
25. Suerbaum S, Michetti P. Helicobacter Pylori Infection. N Engl J Med. 2002;347(15):1175-86.
26. Http://Www.Webmd.Com/Digestive-Disorders/Tc/Types-Ofpeptic- Ulcers-Topic-Overview. on Accessed 28november 2023.
27. Https://Www.Carilionclinic.Org/Sites/Default/Files/164748951.Jpg.assessd on 5 November 2023.
28. Mertz H R, Walsh J H. Peptic Ulcer Pathophysiology. Med Clin North Am, 1991;75(4):799-814.
29. Tripathy K D. Essentials of Medical Pharmacology. Jaypee Brothers Publishers, Newdelhi, 17th Edition, 647, 2014
30. Ghangale G R, Mahale Tushar and Jadhav N D. Evaluation Of Antiulcer Activity Of Ocimum Sanctum In Rats. Veterinary World, 2009;2(12):465-466.
31. 24. Dharmani P, Mishra P K, Maurya R, Singh Chauhan V, Palit G. Allophylus Serratus: A Plant With Potential Anti-Ulcerogenic Activity. J Ethnopharmacol, 2005;99(3):361-6.
32. Dharmani P. Desmodium ,Gangeticum: A Potent Anti-Ulcer Agent. Indian Journal Of Experimental Biology, 2005;43:517-521..
33. Chattopadhyay I, Nandi B, Chatterjee R, Biswas K, Bandyopadhyay U, Banerjee R K. Mechanism Of Antiulcer Effect Of Neem (*Azadirachta Indica*) Leaf Extract: Effect On H+-K+- Atpase, Oxidative Damage And Apoptosis. Inflammopharmacology, 2004;12(2):153-76.
34. Shalini R, Rajan S. Antiulcer Activity of Hemidesmus Indicus Root on Ethanol-Hcl Induced Ulcer In Rats. Indo Am J Pharm Res, 2015;5(05): 1995- 2001.
35. Bhatnagar M, Sisodia S S. Antisecretory And Antiulcer Activity of *Asparagus Racemosus* Wild Against Indomethacin Plus Phyloric Ligation-Induced Gastric Ulcer In Rats. J Herb Pharmacother, 2006;6(1):13-20.
36. Gupta M, Mazumder U K. Anti-Ulcer Activity Of Ethanol Extract of Terminalia pallida Brandis. In Swiss Albino Rats. J Ethnopharmacol, 2005;97(2):405-8.
37. Sairam K. Antiulcerogenic Effect of Methanolic Extract of *Emblica Officinalis*: An Experimental Study. J Ethnopharmacol, 2002;82(1):1-9.
38. Abdulla M A. Antiulcer Activity of *Centella Asiatica* Leaf Extract Against Ethanol-Induced Gastric Mucosal Injury In Rats. Journal 2009;70-77.
39. Dorababu M, Prabha T, Priyambada S, Agrawal V K, Aryya NC, Goel R K. Effect of *Bacopa Monniera* And *Azadirachta Indicaon* Gastric Ulceration And Healing In Experimental NIDDM Rats.Indian J Exp Biol, 2004;42(4):389-97.
40. Prabha P, Karpagam T, Varalakshmi B, Packiavathy A S.Indigenous Anti-Ulcer Activity of *Musa*

Sapientum On Peptic Ulcer. Pharmacognosy Res, 2011; 3(4):232-8.
41. Oloyede H O, Adaja M C, Ajiboye T O, Salawu M O. Antiulcerogenic Activity of Aqueous Extract of Carica Papaya Seed On Indomethacin-Induced Peptic Ulcer In Male Albino Rats. J Integr Med, 2015;13(2):105-14.
42. Goulart Y C F. Evaluation of Gastric Anti-Ulcer Activity In A Hydro-Ethanolic Extract From Kielmeyera Coriacea. Braz Archbiol Technol, 2005;48(2):1.
43. Mahendran P, Vanisree A J, Shyamala Devi C S. The Antiulcer Activity Of Garcinia Cambogia Extract Against Indomethacininduced Gastric Ulcer In Rats. Phytother Res, 2002;16(1):80-3.
44. Rachchh M A. Gastro-Protective Effect of Benincasa Hispida Fruit Extract. Indian J Pharmacol, 20058;40(6):271-275.
45. Gregory M. Anti-Ulcer (Ulcer-Preventive) Activity of *Ficus arnottiana* Miq. (Moraceae) Leaf Methanolic Extract. American Journal of Pharmacology And Toxicology, 2009;4(3):89-93.
46. Bhano P. Complete Aspects of Alstonia Scholaris. International Journal of Pharmtech Research, 2013;5(1):17-26.
47. Muralidharan P, Srikanth J. Antiulcer Activity of Morinda Citrifolia Linn Fruit Extract. J Sci Res, 2006;1(2):345-352.
48. Devi M R. Anti-Gastric Ulcer Activity of Plectranthus Amboinicus (Lour) In Wistar Albino Rats. J Chem Pharm Res, 2010;2(3):374-380.
49. Vimala G, Shoba F G. A Review on Antiulcer Activity of few Indian Medicinal Plants. Int J of Microbio, 2014: 1-14.
50. Azamthulla M. Anti-Ulcer Activity of *Allium Sativum* Bulb Juice. Saudi Pharm J, 2009;17(1):70-77.
51. Karumi Y. Gastroprotective Effects of Aqueous Extract of *Adansonia Digitata* Leaf On Ethanol-Induced Ulceration In Rats. Journal of Biological Sciences, 2008;8(1):225.
52. Shenoy A M. Evaluation of Anti-Ulcer Activity of Aegle Marmelos Leaves Extract. IJPSR,2012; 3(05):1498-1501.
53. Gopinathan S. Anti-Ulcer Activity of *Aloe Vera* Juice And *Aloe Vera* And Amla Fruit Combined Juice In Ethanol Induced Ulcerated Rats. Int J of Pharmacy And Pharm Sci, 2014;6(6):190-197.
54. Goyal K K. Phytochemical and Anti-Ulcer Activity of Careya Arborea Roxb. Lap Lambart Publishing, Germany, 2013.
55. Gregory M. Anti-Ulcer Activity of *Ficus religosa* Leaf Ethanolic Extract. Asian Pac J Trop Biomed, 2013; 3(7):554-556.

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