A Critical Review On Peptic Ulcer With Pharmacological Screening Models Used In Preclinical Animals Studies

Vivek kumar[1]*, Km. Monika[2], Anil kumar[3], Km. Pinki[4], Geetanjali Mehara[5], Rahul chauhan[6].

[1,3,4,5,6], Department of Pharmacology, Moradabad Educational Trust Group of Institutions, Faculty of Pharmacy Moradabad, India.*

[2]Department of Pharmacology, Pharmacy Academy, IFTM University Lodhipur Rajpoot, Moradabad, India

***Corresponding Author: Vivek Kumar**

Address: *Department of Pharmacology, Moradabad Educational Trust Group of Institutions, Faculty of Pharmacy Moradabad.*

Email: *vivekkumarbph1@gmail.com*

Orchid id-0000-0002-5292-9183

Tel.: *+918979248681*

Abstract

A peptic ulcer is one of greatest typical gastrointestinal problems in people. Here the peptic ulcer has 2 main types i.e., one is the stomach and another is the duodenal ulcer. According to experts, the most frequent causes of this disease are H. pylori infection and nonsteroidal anti-inflammatory drugs. Rather than this, some other causes are cigarette smoking, genetic factors, stress/emotional factors, dietary factors, and other disease states. The ulcer is symptomatic and asymptomatic and many peoples. Epigastric discomfort, diarrhea, nausea, heartburn, flatulence, and bloating are non-specific, recurrent, history-independent symptoms of peptic ulcer disease. According to recent estimates, the average lifetime incidence of the illness peptic ulcer in wide-ranging people is 5–10%, along with the annual occurrence is 0.1-0.3%. A peptic ulcer is treated by a natural and synthetic anti-ulcer agents such as, Proton pump inhibitors, H_2 receptor blockers, antacids, potassium competitive acid blockers, and cytoprotective agents. But these synthetic agents exert some time severe side effects. In Ayurveda, there are lots of medicinal plants having anti-ulcer potential with minimum side effects. These herbal remedies are safer than synthetic drugs. The efficacy of anti-ulcer drugs is evaluated by several animal models such as aspirin-induced ulcer model, acetic acid-induced ulcer method, histamine-induced ulcer model, pyrethrum-lighted ulcer model, stress-induced ulcer model, ethanol-induced ulcer model and cold resistant stress-induced ulcer models. This review article includes the introduction, history, signs and symptoms, epidemiology, Pathophysiology/pathogenesis, etiology, precautions, diagnosis, treatment, and screening model for peptic ulcer, etc. The review paper additionally investigates at plant-based medicines that are more regularly prescribed for peptic ulcers around the world and, when appropriate, their antiulcer efficacy.

Keywords: Peptic ulcer, H. Pylori, NSAIDs, Allopathic drug, Herbal drug, screening models.

1. INTRODUCTION

Gastrointestinal problems are solitary of the excessive lessons of human illnesses inflicting the greatest movement, dissatisfaction and death. A peptic ulcer is one of the most GIT ailments [1]. The word "peptic" comes commencing the Greek word "peptikos," The sense of peptikos is associated with digestion. PUD is a set of illnesses marked by the occurrence of ulcers in either area of the GIT exposed to acid for an extended period [2].

Even though these ulcerations the majority usually take place in the stomach (gastric ulcer) or small intestine, this disorder in addition involves Barrett's ulcer of the esophagus (Barrett's esophagus or Barrett's metaplasia) and along with additional upper GI ulcers (duodenal ulcer) [3]. Due to exposure to pepsin and gastric acid, the stomach and duodenum develop peptic ulcers. Gastric mucus, bicarbonate ions, prostaglandins, and mucosal cells' intrinsic resistance, together with strong substances such pepsin and acid and H. pylori, are out of balance [4]. The gastro-duodenal mucosa employs several defense mechanisms to fend off harsh substances including pepsin and hydrochloric acid [5]. PUD is caused by several variables, the most notable of which are environmental ones like stress and psychological circumstances [6].

1.1. History of peptic ulcer

Even though reports of dyspepsia and heartburn date back 1000 years. The autopsy technique for peptic ulcer ailment diagnosis didn't emerge until the 16th century. Donatus of Mantua investigated one of the earliest autopsy that proved pyloric peptic ulcers in 1586. In 1679, Bauhin concluded that stomach irritation caused a gastric ulcer to burst. In 1704, a gastrointestinal hemorrhage was first noted [7].

With detailed descriptions of acute inflammation (arsenic), ulcer, trichobezoar, scirrhous, pyloric stenosis, perforation and ulcerated cancer, Matthew Baillie provided the first classification of stomach illnesses in 1793. In 1817, Crampton recorded cases of perforated gastric ulcers in Dublin, while Travers reported cases of perforated duodenal ulcers within London. Additionally, Travers noticed instances of stenosing, hemorrhage, and infiltrating stomach ulcers [8-10] In North India, the first epidemiological study on peptic ulcers was conducted in 1963 [11].

2. SIGNS AND SYMPTOMS OF ULCER

The peptic ulcer is asymptomatic and symptomatic [1] Irish surgeon Moynihan was the first to link the pathological discovery and the clinical symptoms of peptic ulcer disease [12,13]. Non-specific, history-independent, recurrent symptoms of peptic ulcer disease include epigastric discomfort, diarrhea, nausea, heartburn, flatulence, and bloating, a posterior ulcer may also cause back pain, and antacids can help with these symptoms [14]. The pain from a gastric ulcer is more prominent in the stomach and may be less severe than duodenal ulcer discomfort. Instead of reducing discomfort, eating may make subjects feel more pain. Nausea, vomiting, and weight loss are possible additional symptoms. Vomiting may be brought on by a partial or whole obstruction of the stomach outlet. Patients who are experiencing duodenal ulcer discomfort may experience upper abdominal burning or gnawing in addition to being awakened from sleep. Periodically, pain in the lower abdomen, lower back, or chest region may develop in the night or two hours after a meal when the stomach is empty. After eating, people commonly feel relieved [15]. Sometimes peptic ulcers have no symptoms. The morbidity and mortality of peptic ulcers are significantly increased by bleeding and perforation complications. The peritoneal cavity may become perforated by an ulcer, the related organ (often the pancreas) may become infected, the artery may erode, and serious blood loss may result. Melena, often known as black tarry stools, is a typical symptom inextricably linked to peptic ulcer illness in elderly people. Melena could be a sign of either acute or ongoing GI hemorrhage [16].

3. TYPES OF PEPTIC ULCER

On the premise of the site, these are the different types of peptic ulcers folloing is–

3.1. ***Gastric ulcer:*** This form of ulcer is found in the stomach. The elder age range is where these ulcers appear more frequently.

3.2. ***Duodenal ulcer:*** Duodenal ulcer refers to an ulcer that develops in the duodenum. These ulcers occur more frequently than stomach ulcers. They are evenly spread across all socioeconomic categories and frequently affect younger people. Patients with duodenal ulcers secrete more acid than is typical [17-19].

Peptic ulcers can also be categorized according to severity:

Acute peptic ulcer**:** These types of ulcers are originated in various sites of the stomach as well as in the few cm of the duodenum portion. They may take place in the type of single or multiple lesions.

Chronic peptic ulcer: This types of ulcer invade the muscular in addition to epithelial layers of the stomach wall, and they may spread to the nearby liver or pancreas. Most often, a single chronic peptic ulcer develops in the duodenum and pyloric antrum of the stomach [20].

4. EPIDEMIOLOGY

According to estimates, the overall population's prolonged incidence of the illness peptic ulcer is around 5–10%, and the annual incidence is between 0–1–3 % [21, 22]. Throughout 1921 and 2004, the likelihood of death through ulcers of the stomach was 10–30 years higher than the likelihood of dying from duodenal ulcers in European nations with varying socioeconomic standings and healthcare systems. Similarly to Europe, Asia, South America, and Central America have seen a drop in stomach and duodenal ulcer-related mortality, with high levels seen in people who were born in the nineteenth century and high death rates for those with duodenal ulcers that prolonged by 10 to 20 years [23]. It has been reported that during the last 20 years, the incidence of peptic ulcer illness has steadily declined across several Asian ethnic groups, especially the Chinese, Indian, as well as Malay people. This drop also marked a reduce in H. pylori-related peptic ulcer illness [24].

5. PATHOPHYSIOLOGY

Although the precise way whereby Helicobacter pylori causes peptic or gastric ulcers is not understood, it is connected to both hypo and hyperchlorhydria in addition to the site of infection [25]. The consequence of pangastritis H. pylori is hypochlorhydria, which can ultimately lead to a gastric ulcer. It is clearly related to H. pylori or the cytokines it produces that the cells in the parietal region, which release the HCL, have been destroyed. Antral gastritis, which accounts for 10-15% of cases, has an infection mostly within the antrum, that woesen the G- cells that produce gastrin in addition to killing the D- cells that produce somatostatin. It is generally known that when the enterochromaffin-like cells' histaminic receptor activity increases, the result is a rise in acid production. The major increase in the Gastrin hormone causes this. The loss of inhibition and rise in activation in antral H. pylori infection will result in higher levels of stomach acidity and HCL (hyperchlorhydria), which will result in a peptic ulcer. This is also controlled by somatostatin-releasing cell death [26]. On the other hand, when we talk about how aspirin and NSAIDs affect gastric ulcers, it will be directly related to COX1 inhibition (cyclooxygenase 1), which causes a sharp drop in

prostaglandin levels. Prostaglandin protects the mucosal layer by enhancing mucus secretion from the mucosal cells, bicarbonate, and also enhancing the mucosal layer blood supply. As a result, when NSAIDs block the prostaglandin pathway and lessen its protective effect on the mucosal layer, stomach acidity will begin to harm the layers of the stomach. Additionally, it has been demonstrated that inhibiting COX1 has adverse effects on oxidative stress and mitochondrial phosphorylation. As a result, selective COX2 inhibitors exhibit a striking reduction in the risk of developing PUD [27]. The figure 1 indicates the brief mechanism of all pharmacological agent for treating ulcers [28].

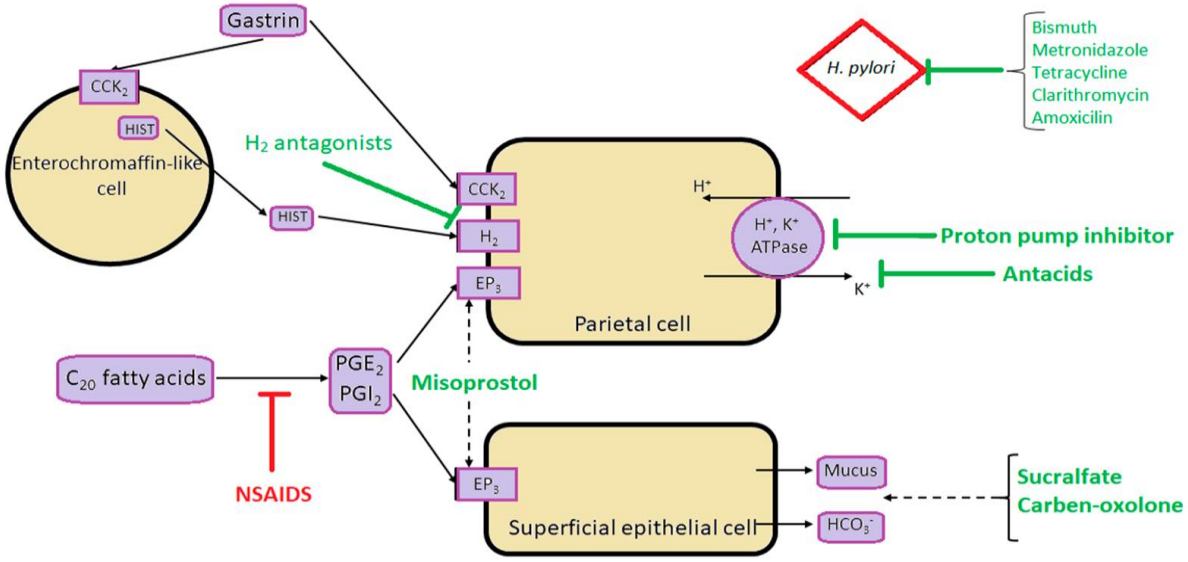

Figure 1. The most often utilized pharmaceutical alternatives for treating peptic ulcer disease are shown schematically, along with the key pathophysiological processes involved in the illness's development.; PGE2 = Prostaglandin E2; CCK2 = Cholecystokinin Receptor; PGI2 = Prostaglandin I2; EP3 = Prostaglandin E receptor 3; HIST = Histamine.

6. ETIOLOGY OF PEPTIC ULCER

The H. Pylori bacteria infection, alcohol and tobacco use, stress, pepsin, NSAIDS, bile acids, steroids, and gastric mucus are some of the causes of peptic ulcer disease (genetic) [29-30].

6.1.Cigarette smoking

The occurrence of peptic ulcer disease (PUD) has been associated with smoking tobacco products. Smoking appears to harm healing rates, therapeutic response, and ulcer-related issues such as perforation, in addition to being demonstrated to have a higher prevalence of ulcers than non-smokers. It is unclear what causes smokers to get ulcer disease more frequently. A significant role in the development of PU is played by theories such as cigarette-induced creation of harmful mucosal-free radicals, delayed stomach emptying, increased risk for H. pylori infection and decreased proximal duodenal bicarbonate production. Acid secretion is not abnormal among smokers. PU diathesis caused by smoking has yet to have a unifying mechanism, despite these intriguing suggestions [31,32]. Emotional trouble because of stress within the pathogenesis of peptic ulcer ailment can't be ignored [33-34]. Although research addressing the involvement of psychological factors in the pathophysiology of PUD has produced mixed results, there has been hypothesis that the

disease may be influenced by emotional strain. Although neuroticism is a personality feature linked to PUD, people with non-ulcer dyspepsia and other functional and biological illnesses also exhibit neuroticism. There hasn't been any research on typical PUD personalities, but more needs to be done in this area. Additionally, it is widely known that night shift workers usually experience more ulcers than daytime workers [35]. Signet ring carcinoma, lymphoma, adenocarcinoma, leiomyosarcoma, and other neoplasms can all be related to an ulcer. More uncommon causes of gastric ulcers include secondary syphilis, sarcoidosis, eosinophilic gastritis, fungal infections, Crohn's disease (which appears in the stomach or duodenum in about 5% of cases), sarcoidosis, TB, and eosinophilic gastritis. Patients with immunological impairment (HIV, post-transplantation) are substantially more likely to develop a stomach ulcer due to an infectious cause [36].

6.2. Dietary factors

In experimental settings, different forms of diet trigger mucosal defense mechanisms [37]. Since the turn of the 20th century, there has been a decline in the prevalence of PUD due to an increase in dietary essential fatty acids [38]. Because fresh rice oil in animal studies prevents stomach ulceration but stored oil is ulcerogenic, rice consumption and handling in different parts of the world could also be a factor in peptic ulcer disease [39].

Salt enhances the mortality from stomach ulcers however now not DU [40]. Peptic disorders are also thought to be influenced by diet. While specific foods can cause dyspepsia, no strong evidence supports a link between a particular diet and the development of ulcers. Alcohol is a well-known mucosal irritant that significantly irritates the stomach mucosa. Alcohol consumption and ulcer disease are only related to patients with portal cirrhosis. Regular and decaffeinated coffee both include peptides that encourage gastrin, a hormone that causes the flow of stomach juice, to be released into the body [41].

However, milk appears to have a negative impact on the DU healing rate [42]. In regions of the world where unprocessed wheat is consumed as the main source of carbohydrates, duodenal ulcers are typically uncommon. Malhotra discovered in 1978 that patients consuming unrefined wheat had a much-reduced rate of duodenal ulcer recurrence than those eating their previous, more refined rice diet [44].

6.3. Uses of NSAIDs

Reduced protective mucosal endogenous PGs and intestinal mucus, disruption of intercellular junctions that allow enterobacteria, viruses, and NSAIDs to infiltrate, and intestinal motility that results in PU generation are all caused by decreased protective mucosal endogenous PGs and intestinal mucus. As a result, all of these variables cause Proteolytic enzymes, gut microbes, and bile acid, and toxins to penetrate, resulting in epithelial cell damage and ulceration. Heme oxygenase protein (HO-1) is elevated in the intestinal mucosa by proton pump inhibitors (PPIs), which are beneficial for the growth and proliferation of the tissues. Additionally, it prevents neutrophil activation and inflammatory cytokines [45]. A common misconception regarding the pathophysiology of these lesions is that acid is not involved because NSAID-induced ulcers occur in achlorhydric people [46]. Therefore, attributed gastropathy to NSAIDs, prevention is a crucial medical problem, and treatment approaches for both initial and subsequent detrimental avoidance are constantly changing [47]. Numerous studies showing that H2 receptor for histaminic antagonist therapy

did not lower the frequency of ulcers brought on by NSAIDs support this theory even further [48].

6.4. Probiotics

A live microorganism called probiotics has the potential to interact with the GI system when taken [49]. They have been promoted for the preservation of GI microbiota homeostasis and the treatment of GI diseases, and are widely utilized as functional foods [50]. Lactic acid bacteria and *Saccharomyces boulardii* yeast, such as *Lactobacillus* and *Bifidobacterium* species are examples of probiotics. Lactic acid bacteria and *Saccharomyces bouldardii* yeast, such as probiotics include, for instance, the species of *Lactobacillus* and *Bifidobacterium* [51]. Proteomics is essential because of their capacity to destroy H. pylori and because of their significant contribution to the exacerbation of the effects of several antibiotic regimens used to treat the infection of H. pylori. Sulforaphane is an abundant isothiocyanate that is present in some types of broccoli and broccoli sprouts as its glucosinolate precursor. In addition to preventing stomach cancer caused by benzopyrene, broccoli shoots contain a specific component that prevents intracellular, extracellular, and antibiotic-resistant strains of Helicobacter pylori [52].

6.5. Genetic factors

The formation of ulcers has also been linked to genetic susceptibility. The possibility of increasing an ulcer in first-degree associations of duodenal ulcer individuals is three times higher, but H. pylori infection in contacts may also play a significant effect. As hereditary risk factors for peptic diathesis, an increased prevalence of blood group "O" and the nonsecretor status have also been mentioned. H. pylori, however, attaches to group "O" antigens preferentially. As a result, it is unknown if genetic predisposition plays a role in common PUD [53].

Advanced age

Dysfunction of the pylorus allows bile to reflux into the stomach, which fosters the growth of ulcers. Despite the lack of a defined "antiulcer diet," the patient need to steer clear of anything that can aggravate their ulcer symptoms or make them worse, such as spicy foods, alcohol, and caffeine [54].

7. DIAGNOSTIC TESTS FOR PEPTIC ULCER

The identification of a peptic ulcer was done on a scientific basis up to the early 20th century. The direct visualization of ulcer disease underwent a revolution in the 1950s thanks to numerous flexible endoscopies.

The following text provides a summary of the many diagnostic procedures that gastroenterologists regularly use in response to patient symptoms [55].

7.1. Esophagogastroduodenoscopy

There is a small tube along among a camera at the end. It enters the GI tract by way of the mouth. It is ingested into the GI tract by the mouth for a particular test carried out by gastroenterologists to view the stomach and small intestine. The physician could take take a sample from the stomach's wall to determine H. Pylori [56].

7.2. *X- Ray*

The patient throughout this technique is prepared to ingest barium, it is a white, crystalline material that is detectable on X-rays before even being instructed to lie on the

floor on inclined examination table. The barium is equally distributed across the upper digestive system by tilting, and several angles may be captured by the X-ray machine. This enables the medical professional to find the ulcer with assess its form and harshness [57].

7.3. Computed tomography (CT)

CT is a quick method to verify a perforation and penetration diagnosis linked to peptic ulcer disease that was previously deemed to be unclear. The results of stomach CT scan in patients having peptic ulcer illness were analyzed in this retrospective study, and they were contrasted to the clinical history, the results of the upper GIT and endoscopic series, and the results of any surgery that had been done [57,58].

7.4. Diagnosis of H. Pylori

Before starting treatment, it is necessary to confirm if the patient has H. pylori in the case of a peptic ulcer. Tests that are invasive or noninvasive can be used to do this [59].

Urea breath testing, stool antigen testing, and serology testing are between the noninvasive examinations.. Radioisotopes 13C or 14C are used in urea breath tests to help identify the formation of urease by H. pylori. The patent breathes out tagged carbon dioxide after ingesting 13C or 14C-labeled urea. Since H. pylori generate urease, which breaks urea, the presence of the bacteria can be determined if it is present. If H. pylori are inhibited but not entirely eradicated with therapy, false negative tests may happen [60].

There are also numerous viable stool antigen tests accessible. This examination determines whether chemicals cause the immune system to combat an infection of H.pylori that is found in individuals who have the bacterium infections in their stool [61,62].

The existence of human IgG antibodies against H. pylori is tested using serology. Since antibody levels drop after infection-related therapy, a positive antibody level could point to a recent or prior illness. Serum, plasma, or whole blood can all be used to measure H. Pylori antibodies [63-64].

A clinician can identify the organism by culturing, endoscopy with subsequent histology, and urease production testing. Giemsa, Warthin-Starry, or Hematoxylin-Eosin stains can be used to detect bacteria and make them easier to see. As a result, if the test of urease is negative or if verification of the urease is sought, many gastroenterologists use the urease test first, followed by histology. Although culture is challenging to do, it is useful for assessing therapy failure since antibiotic sensitivity may be determined [65-66]. The table 1 showed the diagnostic test for detecting the H. pylori [67].

Table 1. The H. pylori diagnostic tests are listed together with their advantages

S. no	Test	Advantages
1	NON- INVASIVE Urea breath tests Stool antigen test Serology	 High Specificity and sensitivity Accurate and cheap Rapid office kits were useful for persons examination.
2	INVASIVE (ANTRAL BIOPSY) Histology Rapid urease test	 Sensitivity and specificity Cheap, quick specificity

	Microbiological culture	Drug sensitivity is defined by the "gold standard."

8. Precautions during peptic ulcer

8.1.Taking meals on time

It is crucial for ulcer patients to eat all of their meals on schedule and to refrain from snacking between meals. To aid in the digestion of food, the stomach secretes acid. By eating on schedule, the body learns when and how much digestive juice to release. On the other hand, eating irregularly, such as in between meals, causes an excess of stomach acid to be produced. As a result, ulcer patients are counseled to watch their mealtimes and curb their desires [68].

9. GUIDELINES FOR THERAPY

Treatment of the ulcer's underlying etiology and acid suppression are the two fundamental tenets of therapy for established PUD. The first-line acid-suppressing medication of preference in PUD is PPI medication. Histamine-2 receptor antagonists (H2RAs), however effective, are less effective acid-suppressing medications and may be used as second-line therapy in some patients. As long as the underlying cause is found and properly addressed, 4-8 weeks of acid suppression medication is sufficient to promote healing for the majority of ulcers [69]. It is crucial to get rid of the bacteria when H. pylori are found in a patient with PUD. H. pylori can be effectively treated with several triple and quadruple regimens (antibiotics plus PPI, with or without bismuth) [70]. Eliminating H. pylori is known to improve ulcer healing and stop recurrence in the great majority of individuals with simple PUD [71,72]. Eradication of H. pylori essentially decreases the risk of re-bleeding in gastrointestinal hemorrhage caused by PUD [73]. Early research on the effectiveness of triple therapy for treating H. pylori indicated eradication rates of about 80–90% [74,75]. However, H. pylori are becoming more resistant to first-line treatments, particularly clarithromycin [76,77]. Therefore, after receiving first-line antibiotic therapy (usually administered after a 4–8 week course of PPI therapy), confirmation of eradication with a stool or breath test should be completed in all peoples who have PUD associated with H. pylori [78,70,75]. Retreatment is necessary for patients who still have H. pylori [79]. PPI medication can be discontinued permanently once H. pylori eradication has been established [75]. When possible, drug withdrawal is the basis of treatment for NSAID-associated PUD. Acid suppression with a PPI should be provided when the NSAID/aspirin is started and continued continuously to prevent the development of new ulcers if the patient has a disease that requires ongoing NSAID or aspirin treatment. Both the synthetic prostaglandin misoprostol and H2RAs may be effective for treating stomach ulcers, while misoprostol is frequently poorly tolerated and does not advise pregnant women to use it due to the possibility of causing an abortion [80,27]. PPI medication ought to be used as the first option for patients who have a history of duodenal ulcers [81]. For patients aged 70 and older or those who also use aspirin, corticosteroids, or anticoagulants concurrently, proton pump inhibitor medication is also advised [82].

10. TREATMENT OF PEPTIC ULCER

Additionally, two varieties of treatments in favor of ulcer are available in the modern era as are the Allopathic and Plant-based herbal treatments.

10.1. Allopathoc or synthetic drugs

These are the totally man made agent that treat the ulcers in effective manner but the produced the no of side effects. The table 2 indicates the mechanism of action and side effects of allopathic antiulcer agents [83-93].

Table 2. List of antiulcer drugs together with their Mode of action and side effects.

Class	Medicine	MOA	Side effects	Reference
Proton-Pump Inhibitors	Omeprazole Lansoprazole Rabeprazole Esmoprazole Pentoprazole	Inhibition of the gastric H^+/K^+ATPase (proton pump) enzyme system.	Nausea Vomiting Headache Diarrhea Abdominal pain Flatulence Constipation Vit. B_{12} deficiency Osteoporosis	[83-84]
H_2 Receptor Blockers	Ranitidine Cimetidine Famotidine Nizatidine	preventing histamine from acting on parietal cells histaminic H2 receptors	Dizziness Headache Depression Thrombocytopenia Anxiety Cardiovascular events	[85]
Antacid	Aluminum hydroxide	Enhance the pH of the stomach to more than 4, and stop pepsin's proteolytic action.	Nausea Vomiting Low K level Constipation Chalky taste	[86]
	Magnesium hydroxide	Cause fluid osmotic retention.	Diarrhea Electrolyte imbalance Abdominal cramping	
Potassium Competitive Acid Blocker	Vonoprazan	Stop the H^+, K^+-ATPase In the stomach parietal cell the latter phase of the acid secretory process.	Diarrhea Inflammation in the upper respiratory tract Nasopharyngitis	[87-91]

Cytoprotective agents	Misoprostol	Increase blood flow and trigger the production of mucus in the GI tract's lining.	Diarrhea Headache Abdominal pain Constipation	[92-93]

The table 3 indicate the treatment strategies for destroying H. Pylori in patents [94-97].

Table 3. Treatment strategies for destroying H. Pylori: effectiveness and duration

Type	Drug combination	Effectiveness	Duration	References
Ist Line	**Standard triple therapy:** PPI+two antibiotics (Clarithromycin+Metronidazole or Amoxicillin)	70–85%	7-14 days	[94]
IInd Line	**Bismuth-containing quadruple therapy:** PPI+Bismuth salt+Tetracycline+ Metronidazole **Non-bismuth-based concomitant therapy:** PPI+ Clarithromycin+ Amoxicillin + Metronidazole **Levofloxacin triple therapy:** PPI+ Amoxicillin + Levofloxacin	77-93% 75-90% 74-81%	14 days 14 days 14 days	[95,96]
Salvage regimen	**Rifabutin-based triple therapy:** PPI+ Rifabutin+ Amoxicillin	66-70%	10 days	[97]

10.11.Herbal plants therapy used in Peptic Ulcer

Various studies have investigated the antiulcer capacity of a wide variety of herbs and spices, with promising results. Many food components and medicinal plants have been found to offer gastro-protective properties [98]. As old as humans, the practice of using medicinal plants to treat a variety of illnesses is well-known as phototherapy. Additionally, there has been an increase in interest in herbal products, particularly those made from medicinal plants, over the past few years [99,100]. Additionally, medicinal plants are regarded as the main source of potential new medications, as a result of the development of numerous adverse consequences from the utilization of traditional drugs for a wide range of illnesses. The essential resources for new drugs are plant extracts as well as their compounds, which have been discovered to establish remarkable results when used to treat gastric ulcers [101]. The H_2 -receptor antagonist, PPI, antacids, antibiotics, anticholinergics, bismuth, and sucralfate are just a few examples of medications that aren't completely effective and can have a variety of various adverse effects, including hematopoietic change, gynecomastia, impotence, hypersensitivity and arrhythmia [102]. Thus, by testing a variety of plant extracts for novel biologically potent compounds, researchers have discovered effective and safe drugs with

gastro-protective qualities. For the treatment of ulcer disease, plants having antioxidant capacity as the primary process are utilized in particular [103]. The therapeutic capabilities of medicinal plants are a result of their possibility of producing a large variety of additional metabolites, or phytochemical ingredients, which are renewable and diverse. These phytochemical have thus been utilized by many plants as a defense strategy against diseases [104]. The emergence of resistant bacteria, on the other hand, has significantly influenced pharmaceutical industries to alter their approach to the production of traditional antibiotics and create novel antimicrobial medications obtained from medicinal plant life [105]. However, when it comes to antimicrobial medications, synthetic antibiotics continue to rule. Because they are more socially acceptable, more compatible using the human body, and have less adverse effects than other types of medicine, about 75–80% of the world's population still uses plant remedies intended for chief healthcare today, mostly within less developed countries [106]. Histopathological investigations demonstrated that these therapeutic plants or herbs failed to display any acute toxicity. The existence of important secondary metabolites including tannins and flavonoids that are the main essential parts of the antiulcer effects was discovered throughout a primary photochemical screening of this medicinal plant [107]. The present study aimed at discovering to evaluate the medicinal plants that are regarded in Ayurvedic literature as gastro-protective and ulcer-healing agents, as well as to collect data on their efficacy and biological mechanisms for modern research.

This goal was accomplished by researching most of herbal plants utilized in peptic ulcer in the Materia Medica an Indian Ayurvedic book and electronic records such as science direct, Scopus, google scholar and Pubmed. The efficacy and probable mechanisms of all collected publications were then evaluated for any existing in vitro, in vivo, or clinical records. The research found either directly or indirectly shows that these herbs are beneficial in treating peptic ulcers by influencing the mechanisms involved. Numerous researchers have investigated and demonstrated the antiulcer activity of ethnomedicinal herbs used in experimentation, which are valuable as antiulcer agents, in Meteria Medica. According to accumulated data, there are medicinal plants that are known for their antiulcer efficacy [108].

Ocimum sanctum

Ocimum sanctum, a part of the Lamiaceae family, is significant for its therapeutic action. Ocimum sanctum comes in two colors: green (Rama Tulsi) and black (Krishna Tulsi), and their chemical components are comparable. The entire Indian subcontinent is covered by the *Ocimum sanctum*, which is widely cultivated. An essential part of the Hindu religious culture is tulsi. Ayurveda and Siddha systems of medicine employ various plant parts for the treatment and prevention of numerous ailments. Tulsi is a well-known natural treatment for a wide range of illnesses, including bronchitis, liver problems, wounds, lumbago, catarrhal fever, otalgia, skin diseases, stomach disorders, hiccough, ophthalmia, genitourinary disorders, psychological stress disorders and different poisonings [109-111].

Furthermore, it contains qualities that are aromatic, carminative, diaphoretic, demulcent, stomachic, diuretic, alexiteric, vermifuge, expectorant, and febrifuge [112]. Because of lipoxygenase inhibitory, anti-secretory, and histamine antagonistic properties of *Ocimum sanctum*, the fixed oil considerably exhibited antiulcer activity [113]. The plant is said to have pharmacological properties that include anti-oxidant, anti-inflammatory, cardioprotective, anti-bacterial, anti-hypertensive, antidepressant, hepatoprotective,

antipyretic immunomodulatory, analgesic, anti-stress, anti-cataract, anti-fertility, radioprotective, anticoagulant and anti-arthritic properties [114].

Morus alba Linn

The Moraceae family includes the white mulberry or *Morus alba* Linn White mulberry is cultivated in every area of the world silkworm is raised. The white mulberry leaves are the main feeding source for silkworms. The mulberry fruit has long been used as a treatment for anemia, weakness, and early hair greying as well as a blood tonic and kidney tonic. The fruit of the mulberry has long been used as a drug to strengthen the blood, help the kidneys and treat anemia, weakness, and premature greying of the hair [115]. Additionally, it is utilized to treat older patients' constipation, dizziness, tinnitus and urine incontinence [116]. Additionally, it stated that the regeneration of cells led to a decrease in blood glucose levels [117]. Rats with experimentally produced stomach ulcers were treated with plant leaf extracts that showed antiulcer efficacy [118]. In Chinese medicine, the white mulberry has a long history of use; nearly every part of the plant is used as a drug [119]. The most abundant resource of phytochemicals, which are beneficial to health and can be taken as vegetables, is found in mulberry leaves. The mulberry leaves have larger concentrations of quercetin, which both in vivo and in vitro slows down the oxidation process.

Muca acuminata

The plant *Musa acuminata* is a part of the Liliaceae family, which also involves lilies and orchids. Along with *M. balbisiana*, *Musa acuminata* is one of two species that served as the wild ancestors of the intricate hybrids that make up contemporary plantains and bananas. Glucose and fructose, Malic acid, pectin potassium, vitamin B-complex and carotene (provitamin) are all significant components in banana fruit. Potassium, a vital mineral that supports healthy cardiac function, functioning cells, blood pressure, neurons, and muscles, is abundant in bananas. Several previous types of research studies have shown that a diet rich in dietary fiber, magnesium, and potassium reduces the chance of heart attack. One study found that combining milk and banana considerably lowers stomach acid output. It also has hypoglycemic, anti-ulcerogenic and hyperlipidemic properties, and is used to treat intestinal lesions in colitis, inflammation, pain and snakebites [120-123]. Activating the stomach's lining epithelial cells to form a thick layer of mucus that acts as an acid obstruction and eradicating microorganisms from the stomach, particularly the ulcer-causing H. Pylori, are two ways that substances found in ripe bananas work. For the treatment of diarrhea and dysentery, plant parts from banana plants such as fruits, peels, root, stalks and leaves have been taken topically or orally. The presence of natural flavonoids, though, is what gives bananas their anti-ulcerative properties, and the concentrations of these flavonoids may change between banana verities [124,125].

Mangifera indica Linn

The mango plant, *Mangifera indica* L., is well-known. It is a member of the Anacardiaceae family. Different portions of the mango plant are used as a stomachic, dentifrice, diaphoretic, astringent, antiseptic, vermifuge, diuretic, tonic, and laxative as well as for the treatment of piles, leucorrhoea, piles, asthma, bronchitis, cough, hypertension, and sleeplessness. The Leaf extracts from the ethanol and Pt. ether showed antiulcer efficacy of the plant.[126] The actions of mangiferin on gastric epithelium injury were evaluated by assessing variations in the average gastric lesion region or ulcer score in mice and acid

content and the stomach secretory volume in four-hour pylorus-ligated rats [126]. These data demonstrate that mangiferin protects against stomach injury brought on by ethanol and indomethacin, most likely via antioxidant and antisecretory MOA [127].

Zingiber officinalis Rosceo

Zingiber Officinalis, which is also well-known as ginger and is used as a flavoring component, is a member of the Zingiberaceae family. The plant is said to have anti-osteoarthritic, anti-microbial, anti-inflammatory, anti-thrombotic, anti-analgesic, anti-proliferative and hepatoprotective pharmacological effects [128]. Even though ginger stimulates stomach secretions, its powdered rhizome has been used traditionally to treat gastrointestinal ailments, including peptic ulcers [129]. Ginger contains several anti-ulcer substances, counting 6-gingesulphonic acid [130], 6- shogaol, and ar-curcumin [131].

The main remarkable is 6-gingesulphonic acid which demonstrated stronger anti-ulcer action and less pungency than 6-gingerol and 6-shogaol [132-134]. The strong thromboxane synthetase inhibition present in ginger may also contribute to its antiulcer properties [135].

Acacia arabica

Acacia Arabica belongs to the Mimosaceae family. This family is widespread throughout India in sandy as well as dry areas. Both locally and generally, it is referred to as "babul tree" or "karuvelam." This plant's chemical makeup has been identified as gum with Arabic acid mixed with magnesium, potassium and calcium as well as a minor amount of sugar, malic acid, ash 3-4%, and moisture 14%. Tannin is abundant in bark, and pods have a tannin content of around 22.44%.In Ayurveda, gargling is used as a wash for wounds and hemorrhagic ulcers. A poultice made from bruised, sensitive leaves that are put to ulcers acts as an astringent and stimulant [108]. According to recent research, rats' stomach ulcers caused by cold confinement stress may have been prevented by *Acacia senegal* gum [136]. The intestinal damage caused by meloxicam was prevented by an aqueous extract of *A. arabica* gum, and intestinal enzyme activity was reduced [137].

Adansonia digitata.

The *Adansonia digitata* is a member of Malvaceae. It is referred to as the "boabab or monkey-bread tree of Africa." Locally, it is referred to as "paparapuli." Among the world's biggest and longest-living trees, it is mostly found in Bombay, the Coromandal Coast, Gujarat and Ceylon. This plant's chemical components include phobaphene-containing pulp, glucose, mucilage, gum, and acetate of potash, tartrate, along with additional salts. Albuminoids, gum, glucose salt and wax can all be found in leaves. Insoluble and soluble tannins, acid gum, wax, albuminous carbonate, potassium and sodium chloride and glucoside adansonin are all present in the bark. Indolent syphilitic ulcers respond favorably to the fresh juice of *Salvadora indica's* leaves combined with powdered ginger and the fresh root's expressed juice. For irritable inflammatory ulcers, leaves are applied topically and utilized in poultices [138]. The Kani tribes of Tamil Nadu, India's Kanyakumari area, customarily treat ulcers with the fruit of the *A. marmelos* plant [139]. Recent Studies revealed that the Aspirin and pylorus ligation models cause stomach ulcers in rats, and aqueous leaf extract must be taken at least 21 days (p.o) at a rate of 1000mg/kg every day. In comparison to control [140] the outcome showed a substantial diminish in the number of ulcer lesions. Pyranocoumarin and luvangetin phytoconstituents isolated from seeds of the plant [141].

Allium sativum.

The plant *Allium sativum*, a part of the family Liliaceae, is sometimes referred to as "vellapundu" in some regions and as "garlic" in general. *A. sativum* is grown everywhere in India. The active ingredient found in *A. sativum* is an acrid volatile oil. Other chemical components include mucilage, sugar, starch and albumen. Aromatic oil comes from seeds. Along with other vital nutrients and supportive compounds containing vitamins, the juice, and especially its oil contents, is rich in combinations of salicylic acid, iodine, and sulfur that are organically bound. Applying fried garlic in mustard or coconut oil is a great way to get rid of maggots that are infesting wounds, ulcers, and ulcerated surfaces. A lotion made of garlic juice and three to four parts plain or distilled water has been used to wash wounds and treat nasty ulcers [142]. Rats were given oral doses of the *A. sativum* bulb juice extract at 250 and 500 mg/kg to treat cysteamine-induced stomach ulcer. The extract greatly speeds up the curing of gastric ulcers in rats and inhibits the growth of experimentally produced duodenal and gastric ulcers. The plant's alliin, allicin and volatile oil and are thought to contain active constituents [143].

Aloe vera

Aloe vera is belongs to the family Lilaceae. It is commonly commonly known as “aloe gel”. It is known as "kattalai" locally, and it is common throughout India. This plant contains the chemicals aloin, emodin, and isobarbaloin. In America, leaves are used successfully to cure recurrent ulcers. Within the initial pain relief, the ulcers begin to heal after a few weeks [144]. The gum acacia and powder of *Aloe vera* were combined, and 200mg/kg of the resulting solution was given orally to rats to treat stomach ulcers brought on by indomethacin. Significant antiulcer activity comparable to control was demonstrated by the extract. The plant contains isobarbolin, saponins and barbalin as phytoconstituents [145].

Annona squamosa.

Custard apple, or *Annona squamosa* (Annonaceae), is a common name for this plant. In gardens, it is raised across India and is recognized there as "sitapalam." Tannins, alkaloids, saponins and flavonoids are some of the phytochemicals present in this plant. Seeds produce resin and oil, and immature fruit, leaves, and seeds all have an acrid principle. In Ayurveda, unhealthy ulcers are treated using leaves that have been ground into a paste without the addition of water [146]. Recent research revealed that the leaves aqueous extract protected rats against ethanol-induced stomach ulcers and pylorus ligation. Tannic acid is one of the plant's active ingredients [147].

Azadirachta indica.

Neem (*Azadirachta indica)* is a member of the Meliaceae family. It is native to found in many regions of India. Both locally and generally, it is referred to as "neem" or "vembu." Phenolic compounds, flavonoids, saponin, and nimbidin, are the phytoconstituents of this plant that have been identified. It includes margosine, a bitter alkaloid. Seeds contain 10–31% of a yellow, bitter fixed oil. The oil contains fatty acids that are volatile, free, and present. The mixture of stearic, lauric and oleic acids, which make up the volatile fatty acids is most likely the case. Ayurveda recommends using a poultice made of leaves and sesame seeds for unhealthy ulcerations [148]. Neem leaves extract in rats prevented the development of stomach ulcers brought on by pylorus ligation and cold restraint stress [149]. Palmitic acid

and stearic acid are active components. They are taken out of the neem seed oil's nimbidin fraction [150].

Balsamodendron mukul.

The botanical name for *Balsamodendron mukul* (Burseraceae) is "gum-gugul." Locally *Balsamodendron mukul* known as "gukkulu". It is grown in Assam, Khandesh, Eastern Bengal, Mysore, Sind and Berars. This plant contains bitter principles, gum-resin volatile oil and chemical components. In Ayurveda, guggul gum is combined with coconut oil or lime juice and put on indolent ulcers as a plaster or lotion. When combined with borax, catechu, gum and sulfur from another variety, *B. pubescens,* which is originate in Karachi, Baluchistan and send and, is applied as an cream to severe ulcer like Delhi sores [151].

Bauhinia variegate

B. variegate belongs to a family Caesalpiniaceae. *B. variegate* belongs to the family Caesalpiniaceae. It originates from found on the sub-Himalayan region, as well as the forests in Burma and India. Its local name is "shemmandarai" and its common name is "orchid tree." The phytoconstituents quercetin, 7-0-glucoside, rutin, apigenin and apigenin have been identified in this plant. The bark of the plant contains glucose, a brownish gum, and tannin (tannic acid). The bark's formulation of the plant is a helpful wash for ulcers in Ayurveda. The following substances are used in a remedy called "kanchanara guggula," which is beneficial for ulcers: Take 10 parts of the *Bauhinia variegate* bark, 3 parts of each of the three myrobalans, black pepper, ginger, long pepper, *Crataeva nurvala* bark, cardamoms, Tejpatra and cinnamon, leaves. To produce a pill mass, powder everything altogether and add guggula (15 part) and add 15 parts of guggula. Half a tola of this is used each morning together with a decoction of *Sphaeranthus mollis*, Triphala, or catechu [152]. A recent study found that aspirin, ethanol–induced ulcer, and pylorus ligation-induced stomach ulcers may be prevented in rats by administering the aqueous and ethanolic extract of the *Bauhinia variegate* root at doses of 200 and 400mg/kg by oral route. Flavonoids are the active constituents of the plant. The extract considerably lowered basal stomach acid secretion and inhibited gastric mucosal damage [153].

Berberis aristata

Berberis aristata is a member of Berberidaceae family. It originates in the Nilgiris and throughout the temperature Himalayans from Bhutan to Kunawer. In the region, it is referred to as "kasturimanjal" and is also referred to as "Indian or Nepal barberry." Chemical components of *B. aristata* include wood and root, so they are abundant in the bitter yellow alkaloid yellow "berberine," that composing of the acid to obtain alkaloid salts. Two more alkaloids are present in root [154].

Beta vulgaris

Beta vulgaris is a member of the family Chenopodiaceae. It is normally well-known as "Sugar beet or beetroot”. It is now widely farmed in America and Europe. In various regions of India, it is also grown in gardens for its fleshy roots and leaves. Red and white are the two colors available for *Beta vulgaris*. This plant's chemical components include the "betin" active principle. Using Ayurveda all types of ulcers and running sores respond well to the root's decoction when a little vinegar is added [155].

Careya arborea

Locally, it is known as "pailacputatammi." In the Sub-Himalayan tract, it is common. The thick red bark of this shrub, which contains 8% tannin, is one of its chemical components. Large simple crystals of calcium oxalate can be seen in liber. In Ayurveda, obstinate ulcers are quickly healed by applying a poultice made of pulped leaves three to four times per day [156]. According to a recent study, to treat ethanol, pylorus ligation and cold stress strain-induced ulcer in experimental rats, the stem bark ethanolic extract of *Careya arbora* was given at doses of 300 and 600mg/kg for 5 days by oral route. In comparison to controls, the plant extract dramatically speeds up the healing of stomach ulcers. Tannins and saponins, which are active phytoconstituents, are taken into account [156,157].

Carica papaya.

Papaya, or *Carica papaya* (Caricaceae), is a common name for this fruit. Locally, it is known as "papali-pazham." It flourishes throughout the world's subtropical and tropical climates. Antheraxanthin, pectin, carpaine, chymopapain, carposide, papain, and carotenoids are some of the chemical components of this plant. The majority of tropical folk remedies employ it. The mature fruit of the plant is not poisonous and raw fruit can be cocked and consumed for treating indolent ulcers. Consumption of the raw fruit of *C. papaya* has been associated with an antiulcer effect [158]. Rats were treated orally with *C. papaya* aqueous seed extract at doses of 50 and 100 mg/kg to treat ethanol-induced stomach ulcers. The extract defended the stomach mucosa from the effects of ethanol. The amount of gastric juice and stomach acidity was dramatically lowered by *C. papaya* extract [159]. The plant contains chymopapain and papain. The benefits of chymopapain and papain for gastrointestinal disturbances and digestive problems are well documented [160].

Euphorbia neriifolia

The popular name for the Euphorbia neriifolia (Euphorbiaceae) plant is "common milk hedge." Locally, *E. neriifolia* referred to as "ilaikkalli." This shrub is grown in Bengal in addition to can be found throughout Central India. The plant contains caoutchouc, gum, euphorbon, resin, calcium malate, and other chemical components. In Ayurveda, plant juice is frequently applied to diseased ulcers and scabies along with clarified or fresh butter [161].

Eclipta alba

Eclipta alba is a perennial shrub that is primarily found in humid tropical regions. Triterpenoids, Alkaloids, glycosides, flavonoids and polyacetylenes are typically found in *Eclipta alba* (L.). No flavonoids such luteolin-7-0-glucoside, apigenin different types of triterpene like –amyrin, sulphur compounds, cinnaroside and echolalia-saponins I–VI are present in the aerial section. The hepatotoxic effects caused by paracetamol are effectively treated by the *Eclipta alba* (EA) extract. According to numerous types of research, *E. alba* (ethanolic extract) exhibits an effect on the paracetamol-induced hepatotoxic model in mice at different dosages, such as 100 mg and 250 mg/kg b.w. The normalization of increased serum transaminase levels brought on by liver damage, poor blood flow, etc. is greatly aided by this herbal extract. It was determined through a microscopic study of the tissue that the medication lessens centrizonal necrosis and fatty degeneration [162,163].

Picrorhiza kurroa

It is a very popular plant in Ayurvedic medicine used traditionally in India. *Picrorhiza kurro* has been utilized as a crucial medication for liver disorders and as a highly important

element in many Ayurvedic formulations for the treatment of liver toxicity, according to a variety of literature reviews. According to a different study, *P. kurroa* has excellent antioxidant capabilities. The experiment demonstrated that the drug lowers glutathione levels while increasing the activity of an enzyme that is beneficial for antioxidant activity, such as glutathione peroxidase. After 50 days of treatment with 50 mg/kg of *picrorhiza kurroa* extract on the rat group (an antitubercular drug-induced model), the raised body serum level was significantly normalized [164].

Schouwia thebica

Schouwia thebica extracts perform a significant function as a hepatoprotective medication, according to numerous studies. Rats were given several solvent extracts of *S. thebica* Webb as a hepatoprotective medication. It was discovered as a result that these extracts successfully normalize the raised body serum level [165].

Syzygium aromaticum L

Clove is the common name for the herbal drug *Syzygium aromaticum* L. (Family Myrtaceae), which is used as a flavoring. This plant is said to include tannins, triterpenes, flavonoids, sterols, and among other chemical components. According to various literature reviews, dried clove flower buds extracted in n-butanol are particularly successful at treating stomach disorders and ulcers in rats. According to the original study, eugenol, one of the key ingredients in this plant, is what causes it to have ulcer-causing properties. According to the pharmacological study, eugenol stimulates the production of mucus, which causes the mucus layer to thicken. Eugenol, therefore, functions as a gastroprotective medication [16, 167].

11. PHARMACOLOGICAL SCREENING MODEL FOR PEPTIC ULCER IN EXPERIMENTAL ANIMALS

Understanding the etiology and screening of anti-ulcer medicines is aided by studies using animal models.

1. Alcohol (Ethanol)-induced ulcers
2. Pylorus ligated (PL)-induced ulcers
3. Stress-induced gastric ulceration
4. Aspirin-induced ulcers
5. Acetic acid-induced ulcer
6. Indomethacin-induced ulcer
7. Histamine-induced ulcer
8. Reserpine-induced ulcer
9. Serotonin-induced ulcer
10. Cold restraint stress-induced ulcer

11.1. Alcohol (Ethanol)-induced gastric ulcer:

Principle: Ethanol makes stomach fluid secrete along with reducing the mucosal barrier; as a result, ethanol greatly raises the gastric juice's protein level. This could be a leak caused by gastric juice containing plasma proteins and a weakened mucosal barrier [168].

Procedure: The 150–200g male albino rats are placed into six groups. The 3- experimental rats are kept in every one of the groups. The animals are given free access to water during their 24-h fast. Test substances or standard drugs are administered to animals. Each animal

receives 1ml/200g of 99.80% alcohol orally an hour later. One h after the administration of alcohol, the animal is sacrificed. The stomach is separated, ripped open across its larger curvature, and fixed to a flexible board. Every stomach ulcer is measured in mm.

The % reduction is represented as the sum of the duration of the control-mean lesion index test/mean lesion index of control X 10 [169].

11.2. Pylorus ligated (PL)-induced ulcers

Principle: The majority of people, especially the elderly, have these gram-negative bacteria in their stomach and duodenal mucosa. They divide into ammonia while inside the mucosa, which increases the local mucosa's alkalinity. They significantly aid the development of peptic ulcers in this way [170].

Procedure: Wistar albino rats of either sex about 150-200g are separated into 5 groups**.** Albino rats have fasted in individual cages for 24 h using this technique. Coprology was being avoided with care. Thirty minutes before pyloric ligation, a test drug or a reference drug, or a control vehicle is provided. The pylorus was tied while the abdomen was opened under a light ether anesthetic. Next, the abdomen is stitched. After 4 hours of ligation, anesthetic ether in an excessive amount is used to kill the experimental animal. The abdomen is then cut, and the stomach juice is taken in the tubes. After that, the tubes are centrifuged at 1000 rpm to measure the volume. A pH meter is used to record the pH of the stomach juice. Then the contents are examined for total and free acidity. The glandular regions of the stomach are then cleansed under flowing water to examine for ulcers.

Ulcer Index*:* The number of stomach ulcers is documented, along with the degree of the ulcer is graded by a microscope utilizing the help of a hand lens (10x), with scoring carried out by Kulkarni.

0= Normal stomach
0.5 = Red coloration
1 = Spot ulcer
1.5 = Hemorrhagic streaks
2= Ulcers > 3 mm but > 5 mm
3= Ulcers > 5 mm
% Protection =100-ut/uc x100

The average ulcer score for every animal is represented as the ulcer index. The percentage protection is calculated using the above formula. The % protection determines by using the formula mentioned above.

Where,
Ut = Treated group ulcer index.
Uc = Control group ulcer index.

11.3. Stress-induced gastric ulcer

Principle: Stress or anxiety can result in severe stomach ulcers from long-term anxiety, stress, and emotion as well as from physical pain, hemorrhage, surgical shock, burns, and trauma. Gastric ulceration's mechanism is not well understood.

According to recent studies, resistive cold stress damages mucosal antioxidant enzymes such as superoxide, dismutase, and peroxides, which leads to severe bleeding ulcers.

This is a stress condition brought on primarily by physiologic distress, and the method causing the ulceration in this situation is supposed to be distinct from ulcers brought on by other reasons. The stress produces highly reactive OH* radicals that are metal-catalyzed and induce oxidative damage to the stomach mucosa. Following the stimulation of superoxide dismutase and oxidative damage to gastric peroxides, there occurs a Herber-Weiss reaction between O_2^- and H_2O_2 [171,172].

Procedure: Five groups of albino Wistar rats, of either sex, were created and the weight of the animal should be between 150-200g. Each group contains six animals. 18-hour fasting mice were subjected to cold resistance stress (CRS), which is administered by tying the animals and the rats to a wooden board and storing them at 4°-6°C for two h. After that, the animals are killed by cervical dislocation, and their dissected stomachs are marked with sores [173].

11.4. Aspirin-induced gastric ulcer

Principle: NSAIDs prevent the stomach mucosa from producing prostaglandins, which provide cytoprotection. Increased leukotriene production has a damaging effect. Aspirin can increase mucosal levels of H_2O_2 and hydroxyl ions, which can lead to oxidative mucosal damage. It can also block gastric peroxidase.

Procedure: Five groups of albino Wistar rats, of either sex, were created and the weight of the animal should be between 150-200g. Each group contains six animals. The rats go without food for a full day. 30 min before aspirin, the test substance is administered by oral route in 2% gum acacia solution at a dosage of 200mg/kg in different concentrations based on the experiment's design. The rats are slain using anesthetic ether 4 h later, and their stomachs are examined to identify any gastrointestinal lesions.

Parameter studied

Ulcer index: The number of stomach ulcers is documented, along with the degree of the ulcer is graded by microscope using the help of a hand lens (10x), with scoring carried out in accordance with Kulkarni.

0= Normal stomach
0.5 = Red coloration
1 = Spot ulcer
1.5 = Hemorrhagic streaks
2= Ulcers > 3 mm but > 5 mm
3= Ulcers > 5 mm
% Protection =100-ut/uc x100

The average ulcer score for every animal is represented as the ulcer index. The percentage protection is calculated using the above formula. The % protection determines by using the formula mentioned above.

Where,
Ut = Ulcer index of treated group.
Uc = Ulcer index of control group [171].

11.5. Acetic acid-induced ulcer

Principle: According to reports, acetic acid causes ulcers by obstructing the stomach and increasing the amount of acidic gastric fluid.

Procedure: A 35 mg/kg intravenous dose of phenobarbitone was used to anesthetize the rats. The stomach was seen once the abdomen was opened. Rats were given 0.06 ml of 50% acetic acid, which caused gastric ulcers on the forward submucosal outside of the secretory 1 cm from the pyloric end of the stomach. After the development of an ulcer on day one, four hrs just after the introduction of acetic acid, both the test and the reference drug treatment were given orally for up to three or seven days. To measure the size and curing of the ulcer, the rats were slaughtered following 18-hours after the last dose administration of the test substance test, also on the fourth or eighth day of the experimentation [169].

12.5. Indomethacin (IND)-induced gastric ulcers

Principle: When indomethacin (20 mg/kg) was administered orally, it mostly caused lesions on the secretory portion of the stomach and only some or no lesions in the antrum. The lesion appeared as mucosal erosions and was generated linearly on mucosal folds [174].

Procedure: After 30 min of testing or receiving the usual medication, indomethacin (20mg/kg, b.w.) dissolved in 0.5% CMC was administered as only one i.p. dosage to induce stomach ulcer. i.p. dosage to cause gastric ulcers. The animals were put to death after five hours, and the stomach mucosa lesions were scored. The size of the ulcer was determined along the larger diameter once the ulcer regions had been identified. It was determined that one hemorrhagic patch was equal to one mm of an ulcer. The overall distance end to end (in mm) of the entire ulcer for each of the experimental animals was separated via the overall figure of animals to get the mean ulcer size [175].

11.5. Histamine-induced gastric ulcer

Principle: It is known that both increased stomach acid output and histamine's vasospastic activity contribute to histamine-induced gastric ulceration.

Procedure: Before the experiment, guinea pigs weighing 300-400g were separated into two groups of six animals each, who went 36 hours without food, while being given access to water as needed. Histamine acid phosphate was given intravenously (i.v.) to cause gastric ulcers (Sigma USA) (50 mg base). To prevent histamine toxicity, each animal received an intraperitoneal injection of 5mg of promethazine hydrochloride 15 min following histamine therapy. 45 min before the delivery of histamine, the test medication or the control vehicle (Dist. water) was taken orally.

12.5. Reserpine-induced gastric ulcer

Principle: Reserpine-induced stomach ulceration has been associated with the degranulation of stomach mast cell and subsequent release of histamine, which is assumed to be cholinergically mediated.

Procedure: Healthy albino rats were given free access to water after a 24 h fast. Four groups of six rats each received an intramuscular injection of reserpine (5mg/kg). 30 minutes following intraperitoneal management of the control (distilled water) and test substance, the stomachs of every rat were taken and opened along the more curved portion, and the total

lengths (mm) of all the lesions for every one rat served as the "ulcer index" when they were all sacrificed after 18 h.

13.5. Serotonin-induced gastric ulcer:

Principle: Gastric mucosal microcirculation is thought to be disturbed in serotonin-induced gastric ulceration. It typically takes around 18 h for serotonin and reserpine to cause ulcers.

Procedure: Four groups of rats received subcutaneous injections of serotonin creatine sulphate (20mg/kg; Sigma USA) (24 h fasted). After 30 min before the serotonin injection, the control vehicle (distilled water) was given by i.p. After 18 h, the experimental animals were slaughtered, their stomachs were taken out, and the ulcer index was calculated as previously said [176].

Parameters to be calculated

Seven indicators including pH, gastric content, total and free acidity volume, ulcer index, lipid peroxidation, and percentage of curative ratio and percentage of protection ratio, are determined utilizing a technique devised via several scientists to assess the ulcer-protective action of a substance *in-vivo* model.

pH: The pH of the stomach juice is measured by immersing the electrode of the pH meter inside a beaker filled with the contents of the stomach [177-178].

The volume of gastric contents: Gastric contents are measured by carefully pouring them into a graduated container [179].

Free Total and acidity: Take 1 mL of stomach content, centrifuged the content and filter it before using the Topfers reagent to titrate it against 0.1 sodium hydroxide solution. The free acidity of a solution can be determined using this reagent as an indicator. For verified total acidity, a 1% solution of phenolphthalein indicator is used. Total acidity will be calculated as the sum of two titrations [180].

Lipid Peroxidation: The stomach's secretory tissue will be homogenized with trichloro acetic acid (TCA), and the mixture will be utilized to calculate malondialdehyde levels. To cause lipid peroxidation, stomach homogenate (0.3 ml) in phosphate buffer solution will be combined with ferric chloride (10 1d. 400mM) and 1-ascorbic acid (10d. 400mM) (5 ml pH 7.4. 0.2 M). The process will be halted by introducing hydrochloric acid (2ml. 0.25 N) containing TCA (1 ml. 15% w/v) and TBA (0.5 ml, 0.375% w/v) heated for IS mm after one hour of incubation at 37 °C. Cooling, centrifuging and measuring the % supernatant's absorbance at 532 nm [181].

Scoring of ulcers according to their severity

The table 4 indicate the of score of ulcer with their severity [182].

Table 4. Representation of ulcer score with sevirity

Score	Severity of ulcer
0	No lesion
1	Mucosal edema
2	1-5 small lesions (1-2 mm in size)
3	> 5 small or intermediate (3-4 mm in size)
4	≥ 2 intermediate lesions or 1 gross (> mm in size) lesion
5	Perforated ulcers.

Ulcer index (UI) calculation based on ulcer score

Using the previously given ulcer score, the following formula may be used to determine the ulcer index:

$$\textbf{Ulcer Index (UI)} = \frac{\text{Total ulcer score}}{\text{No of animal ulcerated}}$$

Utilizing the ulcer index, calculate the percentages of protection and curative ratio

The % protection and percentage curative ratios can be calculated using the formula below [183].

$$\%\ \textbf{Protection Ratio} = \frac{\text{UI of ulcerogen treated group}}{\text{UI of ulcerogen treated}} - \frac{\text{UI of drug pre treated group}}{\text{UI of ulcerogen treated}}$$

$$\%\ \textbf{Curative Ratio} = \frac{\text{UI of ulcerogen treated group}}{\text{UI of ulcerogen treated}} - \frac{\text{UI of drug treatd group}}{\text{UI of ulcerogen treated}}$$

12. IDEAL ANIMAL FOR SCREENING ANTI-ULCER AGENTS

Rats are frequently employed as animal models because of their continual acid secretion, the glandular region of their stomachs, which is anatomically and physiologically similar to the human stomach, and their omnivorous diet, which is similar to that of humans. When histamine is employed to cause ulcers, Guinea pigs and rats are also utilized [184].

13. QUESTION FOR FUTURE RESEARCH IN ULCER

Many different stomach lesions linked to H. pylori still have their pathophysiology unclear. Even though the specific relationship between H. pylori elements and also the genomic characteristic is yet unknown, likely, a arrangement of H. pylori pathogenic elements and also the host immune response is what causes the formation of such lesion. By locating genetic variants linked to peptic ulcer illness in particular populations, technological advancements in genome-wide related studies may offer a number of insight. The reason why a number of individuals are much more susceptible compared to others to the GI toxic effects of NSAIDs and aspirin is unclear. Antibiotic resistance is still a significant obstacle to effectively treating H. pylori infection. In reality, new treatments are merely old ones that have been given a longer course of treatment and various drug regimens. The identification of molecular targets against essential bacterial proteins may be crucial to combating antibiotic resistance [185].

14. DISCUSSION

One of the most prevalent GIT conditions in the world is a peptic ulcer. This disease mostly affects the stomach and duodenum in the body. There are several factors responsible for the development of peptic ulcers like- H.pylori infection, smoking, emotional factors, dietary factor, genetic factor and use of NSAIDs.

The ulcer is evaluated in the experimental animals by various models/methods. Aspirin-induced ulcer model, acetic acid-induced ulcer model, histamine-induced ulcer model, pyrethrum-lighted ulcer model, stress-induced ulcer model, ethanol- induced ulcer

model and cold-resistant stress- induced ulcer model etc are the most commonly used anti-ulcer models/technique in experimental animals. For the screening model of anti-ulcer action, both the guinea pig and rat are frequently used. The aforementioned methods can be used to evaluate the therapeutic efficacy of natural and synthetic products.

15. CONCLUSION

As a result of literature, this review paper proved the scientific information related to the peptic ulcer such as the etiology, signs and symptoms, epidemiology, pathogenesis and treatments well as the screening model for ulcers in experimental animals. This article also provides information on medicinal plant/herbs which has the potential antiulcer activity due to the presence of phytoconstituents the medicinal plants or herbs might be better and safe option for the treatment and management of ulcer.

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AUTHORCONTRIBUTION

All other have the equal contribution.

CONFLICT OF INTEREST

No conflict of interest related to this review work.

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