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REVIEW ARTICLE

Epidemiology, Pathogenesis, and Induction of Peptic Ulcer: A Comprehensive Review

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Abstract:

Peptic ulcers have a significant impact on global mortality and morbidity rates. The primary causative factors explored in this review include *H. pylori* infection, unhealthy lifestyle choices, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Addressing this pressing health issue requires raising awareness and developing novel medications and therapies, which necessitates further research. This article encompasses a wide range of information on peptic ulcers, covering their epidemiology, etiological factors, pathogenesis, antiulcer agents, synthetic compounds, and experimental animal models. It serves as a valuable resource for researchers, healthcare professionals, and policymakers by providing a comprehensive overview of peptic ulcer disease. The review emphasizes the critical role of experimental animal models in advancing our understanding of the disease and facilitating the development of novel treatments. By utilizing these models, researchers can gain deeper insights into the pathogenesis of peptic ulcers and evaluate potential therapeutic interventions. Furthermore, this review highlights the need for continued research efforts to address the challenges posed by peptic ulcer disease. By fostering awareness, promoting research, and encouraging the implementation of effective therapies, we can collectively strive towards reducing the burden of peptic ulcer disease and improving the health and well-being of individuals worldwide.

Keywords: Peptic ulcer, Non-steroidal anti-inflammatory drugs, *H. pylori*, Health issue, Medications, Epidemiology.

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1. INTRODUCTION

Peptic ulcers, which include stomach and duodenal ulcers, are well-known as dangerous, multifunctional gastrointestinal illnesses. The fundamental cause of peptic ulcers is an imbalance between defensive and aggressive components in the gastric and duodenal region that is exposed to gastric chloridopeptic discharge. This leads to the deterioration of the gastric mucosa [1, 2].

Due to the fact that it affects half of the world's population, gastrointestinal dysfunctions are also known as the “plague of the 12th century.” The cost of healthcare is greatly impacted by peptic ulcers, and patient’s quality of life is also reduced [3]. The parietal cell of the digestive system secretes gastric acid in an inappropriate manner. Because stomach acid is recognised as a key contributing factor to gastric ulcers, reducing gastric acid production and strengthening the gastric mucosal barrier are recommended [4, 5]. Stomach acid that is secreted in excess passes through the mucosa layer and into the subcutaneous layer. Because of this, ulcers commonly develop in the stomach and duodenum, though they can also manifest in the oesophagus. In other circumstances, ulcers can also appear in odd places, such as the jejunum because of the Zollinger-Ellison syndrome's excessive acid secretion or the ileum region because of Meckel's diverticulum [6, 7].

1.1. Epidemiology and Etiologic Factors

Peptic ulcer disease's most prevalent symptom is most frequently observed in adults over 60, and 50-170 out of every 100,000 people experience severe consequences. The most prevalent cause of peptic ulcer disease and gastrointestinal bleeding is taking NSAIDs and Helicobacter pylori, which induce infections in the gastrointestinal part of the body [8]. According to reports, peptic ulcer disease (PUD) affects 5–10% of the world's population, with 12% of males and 10% of females reporting lifelong peptic ulcer occurrence [9]. PUD is more common in Iran than in other nations, with a smoking-related prevalence of about 34% [10, 11]. According to reports, the frequency of PUD in Saudi Arabia was 21.9% in 2010 [12]. In another study, it was shown that the prevalence of stomach ulcers in China in the year 2007 was approximately 8.82% in

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men and 5.4% in women and that of duodenal ulcers (DU) was 11.4% and 3.7 in men and women, respectively [13]. According to the most recent WHO data, there were 55,560 or 0.63% more deaths in India in 2018 as a result of PUD. The age-adjusted death rate is 5.58 per 100,000 people, placing the country at number 60 on the global scale.

The annual rate of peptic ulcer disease, as determined by hospitalization records and doctor diagnoses, was 0.10–0.

%. According to doctor diagnoses, the 1-year prevalence was 0.12–1.50%, and the respected hospitalization data showed a stay between 0.10–0.19%. With the introduction of proton pump inhibitors (PPI) and the eradication of *H. pylori*, the management of the PUD is gradually improving. All of this results in a daily decline in PUD prevalence [14].

Due to the effects, they have on the locations, peptic ulcers are also known as "gastric ulcers" and "duodenal ulcers." Both kinds of ulcers are possible in one person. The presence of stomach ulcers is accompanied by symptoms such as discomfort, nausea, vomiting, and weight loss. The majority of patients with this kind of ulceration are elderly adults [15]. Eating while you have ulceration may make the pain worse. Despite the fact that patients with gastric ulcers have normal or decreased stomach acid production, ulcers can still develop even when there is no acid present in gastric areas [16]. Duodenal ulcers are typically seen at the start of the small intestine. This form of ulceration causes intense pain and a burning sensation in the upper region of the abdomen. The intensity of the agony makes it difficult for the patient to get any rest. Usually, pain is worst when the stomach is empty and subsides after eating. Due to daily habits, this form of ulcer can appear on both the anterior and posterior walls and is particularly prevalent in young people, mostly in men [17]. Peptic ulcers occasionally pose a life-threatening threat and present with symptoms like bloody stools, excruciating cramps, and bloody vomiting [18].

The primary pathophysiology of PUD is an imbalance between defensive and offensive factors, including prostaglandin, mucin, nitric oxide, certain growth hormones, and bicarbonate. Offensive factors include acid, pepsin, and *Helicobacter pylori*. However, the main and leading causes of peptic ulcers are bacterial infection (*H. pylori*), NSAIDs medicines (non-steroidal anti-inflammatory drugs), alcohol misuse, emotional stress, and smoking [19, 20].

2. PATHOGENESIS OF PEPTIC ULCER

2.1. *Helicobacter Pylori*

The gram-negative bacillus *H. pylori is spiral-shaped, motile, microaerophilic, and* initially discovered by two Australian researchers in 1982. It is regarded as the main contributor to stomach ulcers. Because they produce the effector protein known as cytotoxin-associated gene A (cagA), Type I strains of *H. pylori* are pathogenic. CagA alters cell shape, boosts cell motility, and interferes with junctional function once it has been translocated into the host cell. The cause of stomach carcinomas and gastric ulcers is this pathogenic activity [21 - 23].

Increased expression of cytokines like TNF-alpha is brought on by *H. pylori* infection in gastritis. IL-1B is also overexpressed in gastritis brought on by *H. pylori*. The infected gastric mucosa exhibits lamina propria infiltration of polymorphonuclear leukocytes, lymphocytes, monocytes, and plasma cells as well as significant epithelial neutrophil infiltration [24]. In order to properly eliminate *H. pylori* infection and ensure complete resolution of mucosal inflammation with minimum possibilities of ulcer recurrence, appropriate antibiotic regimens are used. The recommended course of treatment for *H. pylori* infection is triple therapy, which includes two antibiotics (often amoxicillin and clarithromycin), a proton pump inhibitor, or ranitidine bismuth citrate [25].

2.2. Non-steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are valuable therapeutic agents used for their anti-inflammatory, analgesic, and antipyretic properties [26]. They are commonly prescribed for conditions such as arthritis and musculoskeletal disorders. However, the use of NSAIDs is directly linked with the development of gastric ulcers, with approximately 25% of chronic users experiencing gastric ulcer disease [27]. The development of ulcers caused by NSAIDs is associated with their ability to inhibit the enzyme cyclooxygenase (COX). Normally, COX prevents the conversion of arachidonic acid (AA) into prostaglandins (PGs). By inhibiting COX, NSAIDs disrupt the protective mucosal barrier, allowing pepsin to cause corrosive damage and leading to the progression of peptic ulcers. Moreover, NSAIDs specifically inhibit COX-1, which results in the release of endothelin-1 (ET-1), a potent vasoconstrictor that can contribute to mucosal injury [28].

NSAIDs have an additional impact on gastric health by interfering with the synthesis of prostaglandins, which normally play a role in activating neutrophils and facilitating the local release of reactive oxygen species (ROS). This interference disrupts the natural defence mechanisms of the stomach and initiates gastric injury. Additionally, NSAIDs significantly reduce mucosal blood flow and impair the secretion of mucus and bicarbonate, which are crucial for maintaining a protective barrier. They also negatively affect platelet aggregation, impair epithelial cell renewal, and increase leukocyte adherence. All of these factors collectively contribute to the development of ulceration [29]. Exacerbating superficial lesions, interfering with platelet aggregation, and hindering ulcer healing are further negative effects of NSAIDs on stomach acid. Elevated ROS levels result in the oxidation of lipids, proteins, and DNA, contributing to mucosal injury [30].

2.3. Gastric Acid Secretion

Gastric acid secretion is recognized as a major factor in the development of gastric ulcer disease. Approximately 50% of gastric ulcer patients have been reported to exhibit increased secretion of pepsin and acid. However, gastric acid also plays a crucial role in gastric defence. It serves as the first line of defence against bacterial colonization and helps prevent bacteria entry into the mucosal layer [31]. The stimulation of acid secretion is attributed to three primary secretagogues: histamine, acetylcholine, and gastrin. Parietal cells, which are

responsible for acid secretion, possess specific receptors that respond to these secretagogues. Histamine binds to H2 receptors on parietal cells and is released from specialized mast cells. Acetylcholine, released from the vagus nerve, acts on receptors sensitive to its muscarinic effects [32].

Gastrin can stimulate acid secretion directly on parietal cells or by promoting the release of histamine from enterochromaffin-like (ECL) cells. Research studies have demonstrated the existence of histamine and histidine decarboxylase (HDC), the enzyme accountable for histamine synthesis, in multiple epithelial cells positioned at the base of pyloric glands. Acetylcholine (ACh), which can directly influence parietal cells, is solely derived from the postganglionic fibres of the enteric nervous system [33, 34]. In summary, gastric acid secretion, mediated by the actions of histamine, acetylcholine, and gastrin, plays a dual role in gastric defence and ulcerogenesis.

2.4. VEGF (Vascular endothelial growth factor)

VEGF, a glycoprotein consisting of homodimeric subunits with a molecular weight of approximately 46 kDa, plays a critical role as a potent stimulator of angiogenesis. It is synthesized by various cell types, including macrophages, smooth muscle cells, fibroblasts, megakaryocytes, and neoplastic cells [35, 36].

The process of angiogenesis, which is regulated by VEGF, plays a crucial role in various reparative mechanisms, including the healing of gastric ulcers caused by an imbalance between factors that damage the gastric mucosa barrier and those that have a protective role. Numerous studies have provided evidence supporting the involvement of VEGF in the healing of gastric ulcers. In summary, VEGF acts as a potent stimulator of angiogenesis and plays a vital role in the healing process of gastric ulcers. Research has demonstrated its beneficial effects on ulcer healing, suggesting its potential as a therapeutic target for promoting the recovery of gastric ulcers [37].

2.5. NO (Nitric oxide)

NO is synthesized from L-arginine through the action of NO synthases (NOS) enzymes. It has been extensively studied for its role in GI mucosal defence and the development of mucosal injury [38]. NO also influences muscle tone and secretion, both endocrine and exocrine. NOS enzymes, including nNOS, iNOS, and eNOS, are crucial for normal GI tract function, affecting motility, blood flow, and secretion. Inhibiting these enzymes can lead to disturbances in GI function [39, 40]. Conversely, inducible nitric oxide synthase (iNOS), which is responsible for producing higher levels of nitric oxide (NO) under specific pathological conditions, plays a role in mucosal injury and dysfunction. Inhibition of NO synthesis increases the susceptibility of the gastric mucosa to injury. Moreover, NO hinders the recruitment of neutrophils to inflammatory sites [41].

2.6. Prostaglandins

Prostaglandins are fatty acids with 20 carbon atoms derived from arachidonic acid through the action of cyclooxygenase. These molecules have cytoprotective properties, as demonstrated by Hawkey and Rampton. Prostaglandins stimulate mucus and bicarbonate secretion, maintain mucosal blood flow, and enhance the resistance of epithelial cells against injury caused by cytotoxins [42, 43]. Prostaglandins also have inhibitory effects on leukocyte recruitment, which can be beneficial in situations where the gastrointestinal (GI) mucosa is inflamed. Prostaglandin E2 (PGE2) is particularly potent in suppressing the release of platelet-activating factor (PAF), histamine, and tumor necrosis factor-alpha (TNF-a) from mast cells found in the peritoneum and intestinal mucosa. Furthermore, prostaglandins have been shown to suppress the production of reactive oxygen metabolites by neutrophils, providing additional protective effects [44, 45].

2.7. Apoptosis

Apoptosis is a well-defined process that involves distinctive morphological changes in dying cells. These changes include chromatin condensation, cytoplasmic and nuclear blebbing, and ultimate cellular demise without compromising the integrity of the cell membrane. In the gastric mucosa, it is essential to maintain a balance between epithelial cell proliferation and cell death to preserve the integrity of the mucosal layer [45 - 47]. Under normal physiological conditions, gastric epithelial cells proliferate in the lower part of the glandular neck, migrate upward along the crypt, and are eventually shed into the lumen through apoptosis. This balanced process ensures the healthy turnover of cells in the gastric mucosa. Disruption of this delicate balance can lead to either excessive cell loss, resulting in mucosal damage and ulcer formation, or abnormal cell accumulation, which can contribute to the development of gastric cancer [48].

2.8. Endothelin

Endothelin, a 21-amino acid peptide produced by vascular endothelial cells, has been implicated in the pathophysiology of conditions characterized by vascular spasm. It is suggested to play a role in regulating vascular tone, exhibiting actions that are opposite to endothelium-derived relaxing factors (EDRF) and prostacyclin (PGI2). In gastric ulceration induced by substances like ethanol and aspirin, vascular congestion is a notable characteristic. The gastric mucosa is influenced by several lipid mediators that have ulcerogenic effects. These mediators exert specific actions that contribute to the development of gastric ulcers [49, 50].

2.9. Anti-ulcer Agents

There are several agents that are reported to cure ulcers as mentioned in Table **1** [32].

The formation of peptic ulcers depends on the presence of gastric juice pH and the decrease in mucosal defences. Non-steroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori (H. pylori)* infection are the two major factors disrupting mucosal resistance to injury. Conventional treatments of peptic ulcers, such as proton pump inhibitors (PPIs) and histamine-2 (H2) receptor antagonists, have demonstrated effect as shown in Fig. (**1**) [20, 21].

Table 1. Different classes of drugs are used for the treatment of peptic ulcer and their side effect.

Class	Example	Side Effects	Refs.
Acid pump (H^+/K^+atpase) inhibitor	Pantaprozole, Lansoprozole, Omiprazole, Rabeprazole	Abdominal pain, constipation, nausea, diarrhoea	[51, 52]
Antacids	Aluminium hydroxide, Sodium bicarbonate, Aluminium hydroxide+ Magnesium hydroxide (Combination)	Prevent acid secretion	
h2 receptor agonist	Nizatidine, cimetidine, ranitidine, roxatidine, lafutidine, famotidine	Blurred vision, dry mouth, bladder dysfunction, tachycardia	
Cholecystokinin-2-receptor antagonist	PD 136450, YM 022, YF476, Proglumide, S 0509, Z 360, L 365260	Under clinical trial	
Mucosal defensive agent	Sucralfate, prostaglandin analogue (Misoprostol)	Constipation, contraindicated in pregnancy, diarrhoea	

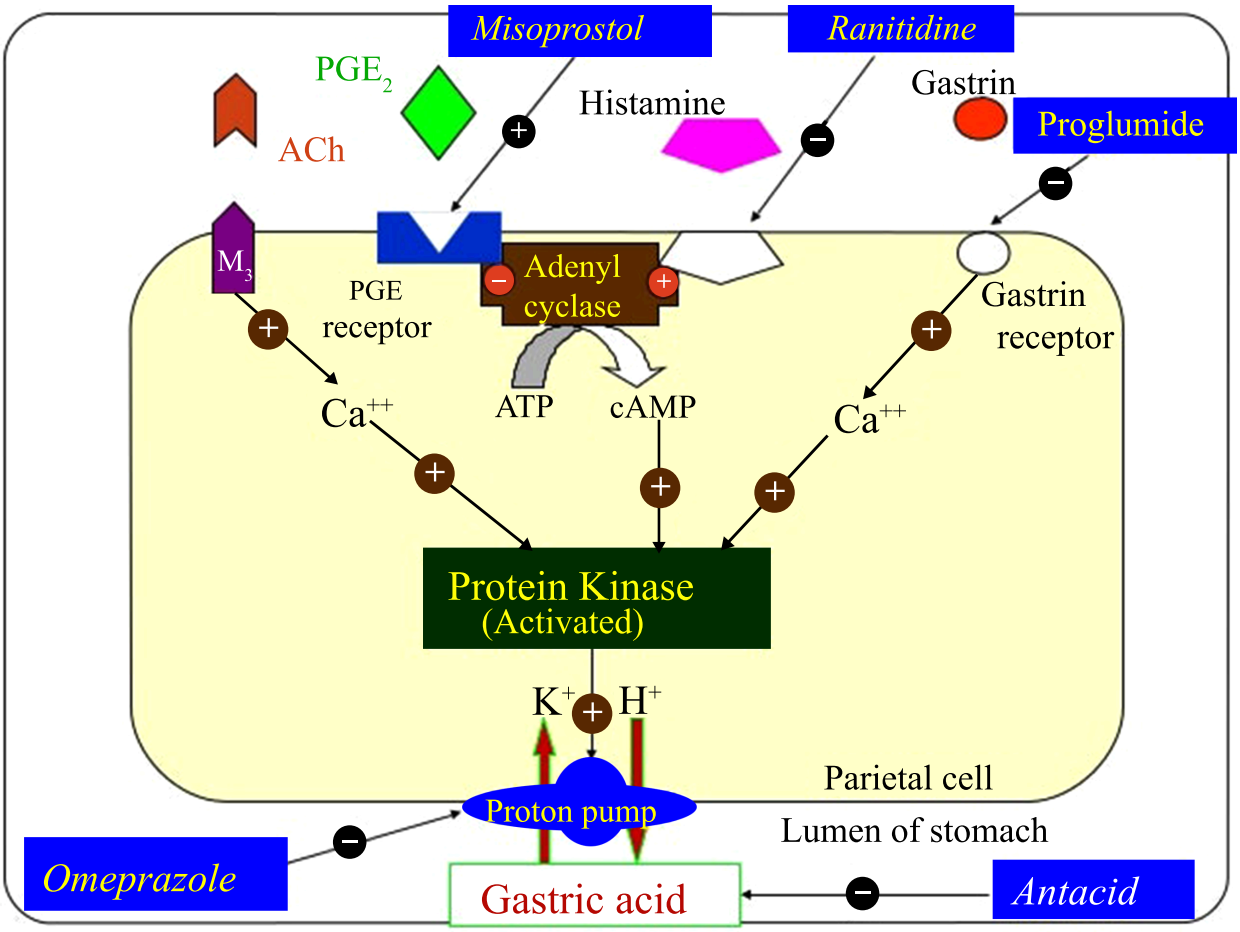
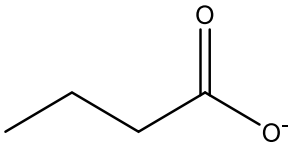
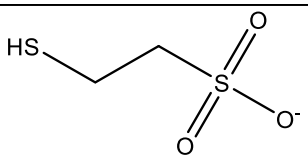
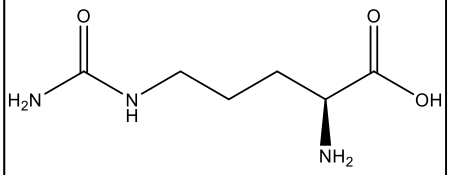
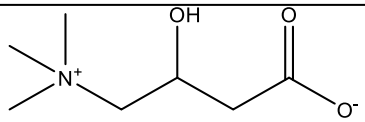
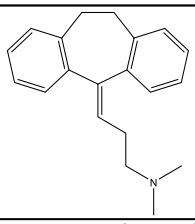
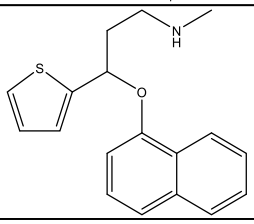
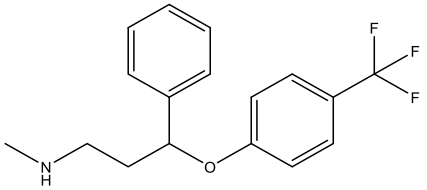
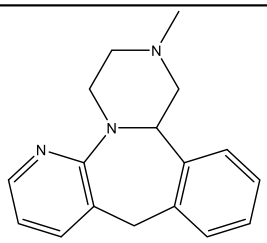


Fig. (1). Mechanism of action of ulcer protective drugs.

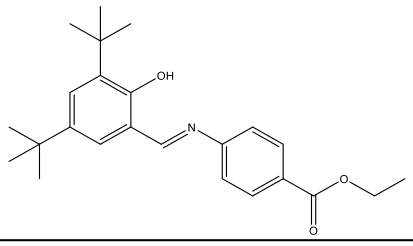
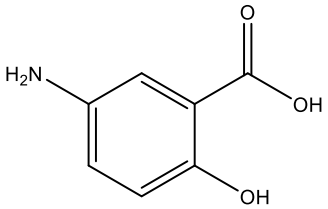
2.10. Synthetic Compounds

Synthetic compounds have revolutionized the field of medicine, and their application as anti-ulcer agents is a remarkable example of their effectiveness. Antiulcer agents are designed to combat ulcers, which are open sores that develop in the lining of the stomach or the upper part of the small intestine. Synthetic compounds developed for this purpose work by inhibiting the production or neutralizing the effects of gastric acid, the primary culprit behind ulcer formation. These compounds are carefully engineered to selectively target specific molecules or receptors involved in acid secretion, such as proton pump inhibitors (PPIs) or histamine H2 receptor antagonists. By blocking or reducing the production of gastric acid, synthetic antiulcer agents help promote the healing of existing ulcers and prevent the formation of new ones [51 - 53]. Their use has significantly improved the treatment outcomes for patients suffering from ulcers, offering relief and a chance for full recovery and listed in Table **2**.

Table 2. Various synthetic compounds and their mechanism of action [53 - 58].

Synthetic Compounds	Ulcer Model	Animal Used	Doses	Mechanism of Gastroprotection	Chemical Structure	Refs.
Butyrate	Stomach ulcer induced by ethanol	Mice	50, 100, 200, 400 and 600 mg/kg	In the gastric wall mucus, there is an increase in MDA level, a decrease in PCO level, and a reduction in the levels of IL-1β, TNF-α, and IL-6. This is associated with the downregulation of NF-κB, p38, and ERK signalling pathways.		[53]
2 mercaptoethane sulfonate	Acute ethanol/HCl-induced injury to the stomach mucosa	Mice	400 mg/kg	The MDA level decreases, while the GSH level increases. MPO activity decreases, while SOD and CAT activities increase. TNF-α, IL-1β, IL-6, and MCP-1 levels decrease.		[54]
L-citrulline	stomach ulcer induced on by ethanol	Rats	300, 600 and 900 mg/kg	SOD and GPx activities increase, cNOS levels increase, TNOS levels decrease, iNOS levels decrease, MPO activity decreases, NO levels increase, MDA delevels decrease, GSH levels increase, IL-6 levels decrease, and IL-10 levels increase.		[55]
L-carnitine	Ethanol induced Ulceration	-	500 mg/kg	TBARS levels decrease while GSH levels increase		[56]
Amitriptyline	Indomethacin, reserpine, water immersion, and constraint stress-induced stomach ulcer model	Rats	5, 10 and 20 mg/kg	Ulcer Index and intraluminal bleeding decrease.		[55]
Duloxetine	Indomethacin, reserpine, water immersion, and constraint stress-induced stomach ulcer model	Rats	5, 10 and 20 mg/kg	In reserpine-induced gastric ulcer models, the Ulcer Index increases and there is an increase in intraluminal bleeding.		[55]
Fluoxetine	Indomethacin, reserpine, water immersion, and constraint stress-induced stomach ulcer model	Rats	5, 10 and 20 mg/kg	In water-immersion plus restraint stress-induced gastric ulcer models, there is an increase in the Ulcer Index, while intraluminal bleeding decreases. As for reserpine-induced gastric ulcer models, the Ulcer Index increases.		
Mirtazapine	Indomethacin, reserpine, water immersion, and constraint stress-induced stomach ulcer model	Rats	5, 10 and 20 mg/kg	In other models, the Ulcer Index decreases, and there is a decrease in intraluminal bleeding. However, in the case of reserpine-induced gastric ulcer, the Ulcer Index increases, while the level of intraluminal bleeding remains unchanged.		-

(Table 2) contd.....

Synthetic Compounds	Ulcer Model	Animal Used	Doses	Mechanism of Gastroprotection	Chemical Structure	Refs.
Ethyl-4-[(3,5-di-tert-butyl2-hydroxybenzylidene) Amino]benzoate	Ulcer induced by Ethanol	Rats	5, 10 and 20 mg/kg	The pH level increases, mucus weight increases, SOD (superoxide dismutase) activity increases, MDA (malondialdehyde) level decreases, Hsp70 expression increases, and Bax expression decreases		[57]
Mesalazine	stomach ulcer induced on by ethanol	Rats	50 and 100 mg/kg	The pH level increases, gastric juice volume decreases, MDA (malondialdehyde) level decreases, tissue NO (nitric oxide) level increases, serum NO level decreases, GSH (glutathione) level increases, CAT (catalase) activity increases, PCO (prostaglandin E2) level decreases, and ROS (reactive oxygen species) level decreases.		[58]

2.11. Experimental Models for Peptic Ulcer

Many animal models are used in ulcerative experiments because these animals have similar functions compared to the human body. Due to this, animals play a vital role in the experiments. Peptic ulcers can be introduced to an animal by chemicals, drugs and some experimental surgical procedures. Among all the drugs, NSAIDs are more commonly causing ulceration in patients because this medication is prescribed in patients as a painkiller for many conditions like acute musculoskeletal disorder, inflammatory conditions, arthritis and many other painful conditions.

2.11.1. Ulceration Caused by Chemicals

Some chemicals like ethanol, acetic acid and cysteamine HCl have major roles to induce gastric ulcer in the experimental animal, as shown in Fig. (**2**).

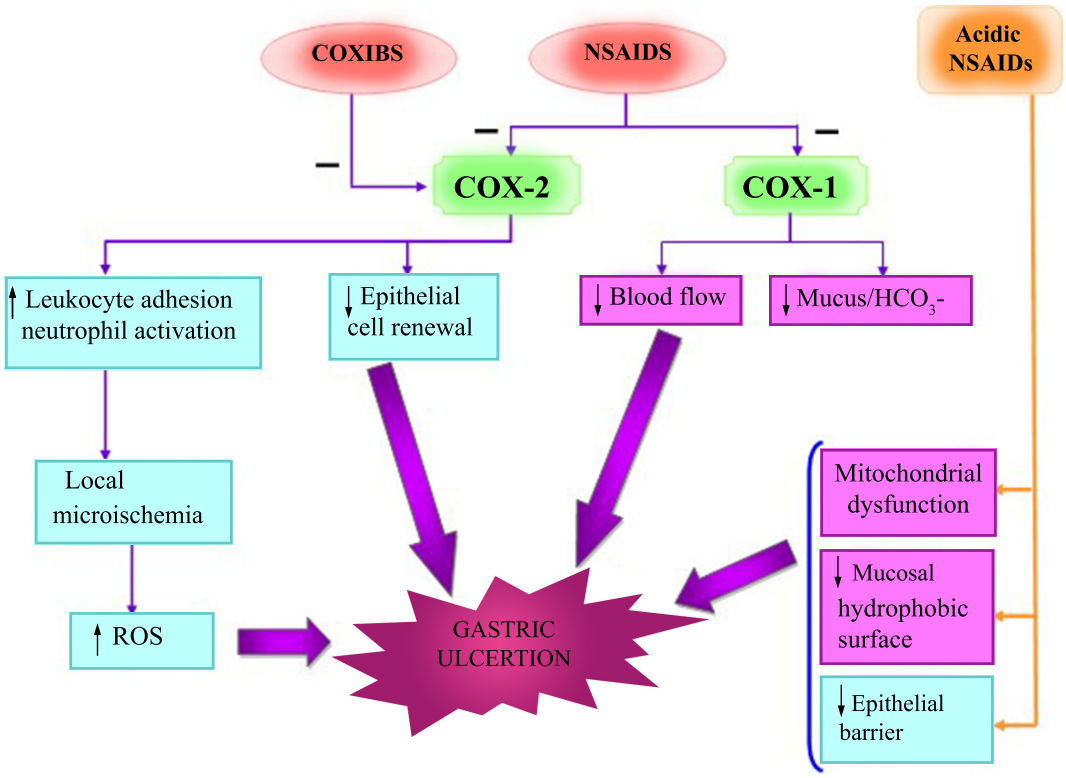


Fig. (2). Mechanism of ulceration caused by chemicals.

Table 3. Peptic ulcer caused by cysteamine-HCl [64 - 67].

Animal Used	Dose	Route of Administration	Refs.
Male Sprague-Dawley rats	500mg/kg	Intragastric	[64]
Male Wistar rats	400mg/kg	Oral	[65]
Female Sprague-Dawley rats	25mg/100g	Intragastric	[66]
Female Sprague-Dawley rats	300mg/kg and after 8hr repeated dose of 100mg/kg.	Two injections	[67]

Table 4. Gastric ulcer caused by aspirin [70 - 73].

Animal Used	Dose	Route of Administration	Refs.
Male adult albino mice (30-50g)	150mg/kg	Oral	[70]
Wistar albino rats of either sex (150-200gm)	200mg/kg (45min after giving the protective dose)	Oral	[71]
Wister albino rats (150-200 gm)	200mg/kg on the day of sacrifice	Oral	[72]
Adult Wistar rats of either sex	400mg/kg after one hour of the treatment	Oral	[67]
Adult male albino mice (25gm)	A single dose of 500mg/kg	Oral	[73]

2.11.2. Cysteamine

2.11.2.1. Mechanism of Action

Cysteamine is known as a metabolized natural product of coenzyme A; low level of cysteamine in the mucosa of the small intestinal parts leads to resistance to oxidative stress [59]. Some laboratory studies show that this cysteamine is responsible for the reduction of somatostatin bioavailability and elevation of gastric acid levels, increasing gastric acid secretion, respectively [60, 61]. Additionally, it is to blame for the decline in acid neutralisation in the proximal duodenum, which inhibits gastric motility and emptying [62, 63]. However, it is still fully unclear how cysteamine-induced duodenal ulcers are caused.

2.11.2.2. Procedure

Rats of any gender are chosen, provided with unrestricted access to food and water, and housed in a cage at a constant 23°C with a 12h/12 h light/dark cycle in a pathogen-free environment. Peptic ulcers are brought on after a week by giving 500mg/kg of cysteamine-HCl intragastrically. Rats are euthanized for use in additional experimental procedures after the medication is administered, and blood samples are obtained for further analysis (Table **3**).

2.12. Aspirin

2.12.1. Mechanism of Action

Aspirin belongs to the NSAIDs, which has the main role to induce gastric ulcers in lab experiments. Induction of Aspirin causes erosion in the surface of epithelial cells, and due to this, it results in the decrement or thinning of the mucosal layer inside the stomach. This loss of the mucosal layer leads to enhancement of the apoptosis regulator and inducible nitric oxide synthesis (iNOS), which can cause gastric damage, lead to activate the interleukin pathway, which causes the entry of leukocytes into the gastric epithelial lining in an abnormal way and reactive oxygen species generated which damage the gastric mucosa [68, 69].

2.12.2. Procedure

Rats of any gender are selected and acclimated in an air-conditioned, clean, hygienic room at 25˚C and 55% humidity before surgery. Rats are fasted for around 24 h and full access is given to food and water.200 mg/kg aspirin was administered to the rat 45min after giving the extract or protective treatment. After inducing the gastric ulcer, the experimental animals are sacrificed and their stomach is widely opened to calculate the ulcer index. Before sacrifice, the animal's blood was collected for further biochemical analysis and the organ was collected for the study of the histopathological and biochemical parameters (Table **4**).

2.13. Ethanol

2.13.1. Mechanism of Action

Ethanol is a commonly used chemical to induce gastric ulcers in experimental animals, especially in rats and mice. Ethanol can cause intense gastric mucosal damage. According to many studies, it suggested that gastrointestinal mucosa damage can be caused by using ethanol as an inducing agent. It produces necrotic gastrointestinal lesions in the gastric mucosa due to the toxic effect of ethanol. It leads to reduce the bicarbonate secretion followed by the production of mucus [74]. Specifically, in rats and mice, ethanol is a frequently utilised substance to cause gastric ulcers in experimental animals. Ethanol can seriously harm the gastric mucosa. Numerous studies have demonstrated that employing ethanol as an inducing agent can damage gastrointestinal mucosa. Due to the harmful effects of ethanol, it causes necrotic gastrointestinal lesions in the stomach mucosa. It causes a decrease in bicarbonate secretion, which is followed by a decrement in mucus production [75].

2.13.2. Procedure

In this experiment, rats of either sex may be utilised. The cages where the animals are housed are clean and have elevated floors. With a healthy diet and unrestricted access to water, the temperature is kept at about 22°C. To ensure an empty stomach, all rats fast for about 48 hours. It is possible to

administer an 8% sucrose solution in 0.2% NaCl to prevent dehydration. Then, 10 mg/kg of 50% (v/v) ethanol is given to all of the animals in order to cause a stomach ulcer. The animals were anaesthetized and sacrificed after an hour, and their stomachs were swiftly removed and quickly cleaned under running water, and the degree of ulceration was measured. The organ was removed for the investigation of the histological and biochemical characteristics, and blood was collected for additional biochemical research [76 - 78] (Table **5**).

2.14. Reserpine

2.14.1. Mechanism of Action

Reserpine in the injectable dose induces gastric glandular ulceration and free glucuronidase release from lysosomes within the stomach mucosa. In rodents, reserpine can also cause Parkinson's disease, depression, and cognitive decline [86 - 88].

2.14.2. Procedure

Generally, in this model, 7 week old ICR mice are taken for the experiment and they were maintained in a properly controlled environment where the temp was maintained around 23-24˚C with 50-55% of relative humidity in the animal house with a 12h light/dark cycle and the proper diet was maintained for all of the animals. The experiment was run following the acclimation phase. In order to create ulcers in the mucosal layer, mice are injected intraperitoneally (*i.p*) with 10 mg/kg reserpine for three days. The animals then fasted for 24 hours, were sacrificed and the stomach was removed, and the ulcer index was calculated [89]. To determine the additional parameters, blood was drawn from the mice and centrifuged for 10 minutes at 1,100 x g at 4°C (Table **6**).

2.15. Indomethacin

2.15.1. Mechanism of Action

Indomethacin is a drug of Non-Steroidal Anti-Inflammatory (NSAIDs) class of medications, which is frequently used to cause Gastrointestinal Ulcers. This is thought to be one of the contributing factors to mucosal injury since the inhibition of cyclooxygenase led to the depletion of endogenous prostaglandins [97]. Indomethacin administration results in an increase in inducible nitric oxide synthesis (iNOS) and a decrease in constitutive nitric oxide synthesis (cNOS) activity [98, 99]. It is clear that the gastrointestinal damage caused by indomethacin is multifactorial and involves white blood cell infiltration, the creation of free radicals, and the disruption of nitric oxide in the gastric tissues. To prevent indomethacin-induced gastropathy, it is beneficial to use substances with antioxidant capabilities, the ability to prevent leucocyte infiltration, and the ability to alter nitric oxide levels. Additionally, indomethacin significantly raises TNF levels.

2.15.2. Procedure

In this method, animals of either sex can be used; before the experiment, they are placed in a clean place in the laboratory and at a maintained suitable temperature inside the animal house. The laboratory animals are fed a standard diet and during the study, the animals are maintained at a twelve-hour light: dark cycle. Animals fasted at least for 24hr before the experiment with free excess drinking water [100]. Gastric ulcers were introduced by giving 40 mg/kg of indomethacin orally. After induction of gastric ulcer, the animals are sacrificed under anaesthesia with cervical dislocation method after 8 hours. The abdomen of each rat was opened and the stomach was collected to judge the ulcer index and further experimental procedures (Table **7**).

Table 5. Gastric ulcerations by ethanol [79 - 85].

Animal Used	Dose	Route of Administration	Ref.
Male albino rats (200-250gm)	10ml/kg	Oral	[79]
Male Albino rats of Wistar strain (200-250gm)	5ml/kg for 9 days	Oral	[80]
Adult female Sprague Dawley rats (150-180 gm)	5ml/kg	Oral	[81]
Albino mice	0.5ml/100g	Oral	[82]
Male Albino mice	Acidified ethanol (60% ethanol in saline with 159 mM HCl; 200 µL/mouse)	Oral	[83]
Adult male albino rats (150-200gm)	80% ethanol (1ml/rat)	Gastric intubation	[84]
Kunming mice (18-22 gm)	0.1ml ethanol (100%, anhydrous alcohol)	Orally	[85]

Table 6. Gastric ulcers by reserpine [90 - 96].

Animal Used	Dose	Route of Administration	Refs.
Male ICR mice	10mg/kg	*i.p.*	[90]
Cancer Research Male Mice	10mg/kg	*i.p.*	[91]
Male Wistar rats (180-220 g)	5mg/kg	*i.p.* 18hr before sacrifice	[92]
Female Sprague-Dawley rats (115-175 g)	5mg/kg	*i.p.* 4hr after treatment	[93]
Albino Wistar Rats (180-200 g)	0.25 gm/kg	Intragastric	[95]
Albino male Wistar-Bratislava rats (125-150g)	5mg/kg	*i.p*	[96]

Table 7. Gastric ulcer by indomethacin [101 - 108].

Animal Used	Dose	Route of Administration	Refs.
Wistar male rats (150-250g)	40 mg/kg	Oral	[101]
Female wistar albino rats (150-180gm)	48 mg/kg dissolved in 5% $NaHCO_3$	Oral	[102]
Wistar Albino male rats (230-260gm)	100 mg/kg dissolved in Dimethyl sulfoxide (DMOS)	Oral	[103]
Male Wistar rats (180-200 gm)	A single dose of 100 mg/kg	Oral	[104]
Male Wistar rats (180-200 gm)	A single dose of 100 mg/kg	Oral	[105]
Adult male Wistar rats (200-250 gm)	20 mg/kg	*i.p*	[106]
Male Sprague-Dawley rats	30 mg/kg	Oral	[107]
Swiss albino mice (25-30 gm)	Single dose of 40 mg/kg	*l.p*	[108]

2.16. Acetic Acid

2.16.1. Mechanism of Action

Acetic acid plays a key role in this sort of ulcer model in the embolization of blood vessels inside the mucosa layer in the body's gastric region. As a result, the mucosal blood flow becomes blocked. This discrepancy between the mucosal part's inadequate oxygen supply and the need for oxygen causes ischemia, necrosis, and loss of the mucosal tissue, which results in ulceration [109].

2.16.2. Procedure

In this technique, either male or female animals can be utilised to cause ulceration. They are housed in polypropylene boxes in a chamber that is 22°C and has 12-hour cycles of light and dark periods. Every animal has unrestricted access to food and water to ensure they are eating a well-balanced, healthy diet. The animals were allowed free access to water and were fasted for at least 20 to 24 hours before the experiment. After making a midline epigastric incision and exposing the stomach under a light anaesthetic, the surgical operation was carried out. Acetic acid (0.05ml) was then administered to the stomach's surface using a cylindrical mold with a diameter of around 6mm for 60 seconds. To avoid harming the other tissues, the acid was removed after application by repeatedly rinsing the mold in a normal saline solution [110]. Following this treatment, the stomachs are gently pushed back into position, and the abdominal walls are stitched shut. Ten days following the surgical procedure, the rats are sacrificed, and the stomach is taken out and opened to determine the ulcer index and conduct additional experimental procedures (Table **8**).

2.17. Histamine

Histamine is a neurotransmitter that affects blood vessel permeability, the contraction of the cerebral and muscular systems, and the regulation of stomach acidity.

2.17.1. Mechanism of Action

Histamine is mostly found in the skin, stomach, and lungs area and a minimal level of histamine is found in the brain and heart. Histamine is responsible for the reduction in the production of gastric mucous which leads to disturbances in the normal mucosal secretion of the microcirculation and digestive motility.

Table 8. Gastric ulcers by acetic acid [111 - 114].

Animal Used	Dose	Route of Administration	Refs.
Wistar rats (200-300 gm)	500 µl of 80% (v/v) acetic acid	Serosal surface of the stomach line	[111]
Adult female Wistar rats (180-200 gm)	500 µl of 80% (v/v) acetic acid	Serosal surface of the stomach line	[112]
Male and female Wistar rats (150-200 gm)	Acetic acid	Injected into the stomach	[113]
Male Wistar Rats (180-220gm)	70µL of 80% acetic acid	Serosal surface of the stomach area	[114]

Table 9. Gastric ulcer by histamine [115, 116].

Animal Used	Dose	Route of Administration	Refs.
Wistar male rats (200-250gm)	2 mg/kg pre-treated dose before inducing stress.	Subcutaneous	[115]
Wistar Albino rats	Vary from 40mg/kg- 100 mg/kg	Subcutaneous	[116]

Table 10. Gastric ulceration by methylene blue [117].

Animal Used	Dose	Route of Administration	Refs.
Rats	100 mg/kg	Orally	[117]

2.17.2. Procedure

Wistar male rats are taken for this experiment weighing around 200-250 gm. Animals are acclimated in an air-conditioned, clean, hygienic room and they are fasted 24 hours before the experiment. Stress-induced gastric lesion damage is done by placing the rats in individual cages. After some time, the rats are immersed in the water at 23°c and this process is continued for 3.5 h. To induce gastric ulcers, the rats are pre-treated with 2mg/kg histamine phosphate before inducing stress. After 3.5 hours, the animal is sacrificed under the anaesthetic condition and the abdomen part is opened by a midline incision. The stomach is exposed and the gastric ulcer was counted by using a laser Doppler flowmeter and other further experimental procedures (Table **9**).

2.18. Methylene Blue

2.18.1. Mechanism of Action

Induction of high levels of thiobarbituric acid, superoxide dismutase and H^+/K^+ -ATPase as a reactive substance leads to damage to the gastric mucosal area and causes gastric lesions. The blood flow to the gastric mucosa is reduced. Reduction of glutathione is also seen combined with catalase activity. Methylene blue helps to activate H+/K+ -ATPase, which is one of the leading causes to increase HCl secretion and reduction of blood flow to the gastric mucosa and local oxidative stress (Table **10**).

2.19. Iron-ascorbic Acid

Due to free oxygen radicals, iron ascorbic acid inside the stomach can lead to ulceration in a dose-dependent way. By injecting a local solution of ascorbic acid and ferrous iron into the gastrointestinal mucosal walls of the animal, gastric ulcers are generated. Ferrous iron or ascorbic acid cannot cause a stomach ulcer on its own [118, 119].

2.20. Serotonin

Serotonin is a monoamine in the central nervous system's serotonergic neurons and serves as a neurotransmitter. Tryptophan, an essential amino acid, is used to produce it. Serotonin causes vasoconstriction in the chromaffin cells of the digestive system, which decreases blood flow at the gastric mucosa. Internal mucosal layer lesions are brought on by this reduction in blood supply [120].

2.21. Diethyldithiocarbamate

Diethyldithiocarbamate is frequently used in this ulcer-inducing paradigm to assess the antioxidant properties of medications in avoiding stomach damage. It is also employed to evaluate the cytoprotective qualities of new drugs. By causing the generation of superoxide and hydroxyl radicals, which are known to aid in the development of ulcers, diethyldithiocarbamate has been demonstrated to produce antral lesions [121]. To induce acute glandular lesions in this model, an 800 mg/kg body weight dose of diethyl-dithiocarbamate in saline is administered subcutaneously (1 mL), followed by an oral dose of 0.1N HCl (1 mL). Additionally, food is withheld for 24 hours, and water is withdrawn for 2 hours before the start of the experiment [122].

3. INDUCTION OF PEPTIC ULCER BY WATER IMMERSION RESTRAINT STRESS (WRS)

By using an acute invasive factor (surgery or trauma), an infection, or both, the water immersion restraint stress model is used to cause lesions in the gastric mucosa region. Multiple variables, including oxidative stress and inflammation, are implicated in this model to cause a stomach ulcer, and this model is acknowledged in the research for stress-induced ulcers [122, 123]. This model is very useful in determining how the new medicine affects the healing of stomach ulcers in test animals. Although the animals are given unrestricted access to the water and the water temperature is strictly maintained before immersion, they must fast for at least 24 hours before the experiment's start [124]. In this model, rats are exposed to a variety of stressors in combination, such as simple resistance, free swimming, conscious or anaesthetized WRS, non-water fluid immersion, immersion without water contact, or confinement in a cage with sand. In some circumstances, the eyes are closed to study the sensitive areas of the body that respond to stress in addition to skin stimulation. The length of the stress exposure has a clear correlation with stomach lesions [125, 126].

4. INDUCTION OF PEPTIC ULCERS BY SURGICAL METHODS

4.1. Pylorus Ligation Method

This is one of the most accepted surgical methods to induce gastric ulcers in rats. In this method, animals were anaesthetized in a proper manner and before the experiment, the animals were fasted for at least 24 hours before the operation in the cages [127]. The abdomen was opened below the xiphoid process and the ligation of the pyloric part was done under anaesthesia. Then stomach was placed back into the abdominal area and stitched by catgut. Food and water were limited in the post-operational time and at the end of four hours, animals were sacrificed by using a suitable method under the anaesthetic condition. After sacrificing the animal, their stomach was wide opened and procured gastric juice [128, 129]. Ligation of the pylori part helps to increase the gastric fluid volume, which resulting injuries due to self-digestion of the gastric mucosal layer by the accumulation of pepsin and hydrochloric acid [130 - 133].

4.2. Gastric Ulcer by Ischemia-reperfusion (IR) Method

Another way of surgically inducing stomach ulcers in rats includes creating mucosal lesions by shutting the celiac artery: the ischemia-reperfusion method. Rats are fasted for at least 16 hours before to the induction of IR. The anaesthesia needs to be appropriately maintained during the surgical procedure. The stomach was found, brought out, and freed of fast and surrounding muscles after shaving the rat below the thoracic cage area [134, 135].

Following laparotomy, the celiac artery was isolated, and a microvascular clamp was put to block the blood flow and was left in place for 60 minutes. Following artery clamping, the bulldog clip (microvascular clamp) was withdrawn to allow for around 20 minutes of gastric tissue re-oxygenation (reperfusion

stage). The abdomen was then stitched back together, and the animals were then placed back into their individual cages. Period animals were sacrificed once the course of treatment was complete, and the stomachs were removed for morphological and biochemical examination. Software is used to calculate ulcer indexes [136 - 139]. The pathophysiological mechanisms behind the formation of gastric ulcers can be studied using this surgical experimental model, as well as potential new therapeutic medicine [140].

4.3. Measurement of Gastric Lesion

To measure gastric ulcerations after their induction, various methods can be employed. One approach involves dissecting the stomach along its greater curvature and fixing it on a board or transparent glass. A macroscopic examination can be performed using a hand lens, and the ulcers can be traced on transparent paper [141, 142]. The ulcer sizes are measured when the paper is put on a graph sheet. A light or scanning microscope can also be used for microscopic investigation. Additionally, cameras can be used to scan stomachs, and computer-assisted image analysis tools like Scion, Image J, EARP Image analysis software, or other suitable software can be used to quantify the existence of ulcers.

Different methods have been developed to assess the extent of ulcerations and calculate an ulcer index, as well as protective and/or curative ratios for the ulcers. Takagi and Okabe described scores or ratings that can be used to evaluate gastric lesions' ulcer index and severity:

0= no injury.
1= indicates petechiae and mucosal oedema.
2 = 1 to 5 minor lesions.
3 = One middle lesion (3-4 mm) or more than five tiny lesions.
4 = One big lesion (more than 4 mm) or two to more intermediate lesions.
5 = A perforated ulcer.

The ulcer index, percentage protective ratio, and percentage curative ratio can be calculated using the following formulas:

$$\text{Ulcer index (UI): } = \frac{Total\ Ulcer\ Score}{No.of\ animals\ Ulcerated}$$

Percentage Protective ratio:

$$= \left(\frac{UI\ of\ Ulcerogen\ treated\ group}{UI\ of\ Ulcerogen\ treated} - \frac{UI\ of\ drug\ pretreted\ group}{UI\ of\ Ulcdrogen\ treated}\right)$$

Percentage Curative ratio

$$= \left(\frac{UI\ of\ Ulcerogen\ trearted\ group}{UI\ of\ Ulcerogen\ treated} - \frac{UI\ of\ drug\ treated\ group}{UI\ of\ Ulcerogen\ treated}\right)$$

5. DISCUSSION

People of all ages suffer from peptic ulcer disease, which is a prevalent clinical issue in society. As the disease's prevalence increases with age, peptic ulcers are predicted to continue to have a significant worldwide influence on patient quality of life and the delivery of healthcare. Medical appointments are still plagued by peptic ulcer disease. Most patients with dyspepsia should have a peptic ulcer disease examination. Determining which area of the stomach is most affected by the etiologic agent of peptic ulcer disease requires an understanding of gastric acid secretion. Up until recently, *H. pylori* has continued to be a risk factor for the onset of peptic ulcer disease. The clinical prognosis of this bacterium is determined by its preferred site.

CONCLUSION AND FUTURE PERSPECTIVE

This paper provides a comprehensive review of experimental ulcer models that serve as valuable tools for testing potential antiulcer agents, particularly plant medicines with reported ethnomedicinal uses against ulcers. Each model is carefully examined, shedding light on the underlying pathophysiological mechanisms that contribute to ulcer formation. This in-depth understanding enables researchers to make informed decisions when selecting a suitable model for evaluating a test agent. The paper also discusses the existing methods for scoring ulcers, highlighting the limitations and challenges associated with different approaches. By offering critical insights and considerations, this resource proves valuable for scientists interested in the evaluation of antiulcer agents.

AUTHORS' CONTRIBUTION

S.S.B. & A.K.: Writing-original draft preparation, data curation, resources; D.J.: Writing-review and editing; D.B.: Conceptualization, investigation, supervision, project administration. All authors have read and agreed to the published version of the manuscript.

LIST OF ABBREVIATIONS

NSAID	=	Non-Steroidal Anti-Inflammatory Drugs
PUD	=	Peptic Ulcer Disease
GU	=	Gastric Ulcer
PU	=	Peptic Ulcer
DU	=	Duodenal Ulcer
PPI	=	Proton Pump Inhibitors
cNOS	=	Constitutive Nitric Acid Synthesis
iNOS	=	Inducible nitric acid synthesis
HCL	=	Hydrochloric acid
WRS	=	Water immersion restraint stress
IR	=	Ischemia-reperfusion

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