Journal of Applied Pharmaceutical Research
Volume 13 Issue 2, Year of Publication 2025, Page 39 – 54
DOI: https://doi.org/10.69857/joapr.v13i2.953

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Review Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | JOAPR
www.japtronline.com ***ISSN: 2348 – 0335***

A COMPREHENSIVE REVIEW OF PEPTIC ULCER DISEASE: EPIDEMIOLOGY, EXPERIMENTAL MODELS, AND MECHANISTIC INSIGHTS

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Article Information
Received: 3rd January 2025
Revised: 14th March 2025
Accepted: 8th Aprtil 2025
Published: 30th April 2025

Keywords
Animal Models, Helicobacter pylori, Pathophysiology, Preclinical Models

ABSTRACT

Background: Peptic ulcer disease (PUD) is one of the most common gastrointestinal disorders, resulting from an imbalance between aggressive and protective factors, leading to mucosal erosion. Various factors influence its pathogenesis, including Helicobacter pylori infection, NSAID use, and oxidative stress. **Objective:** We review PUD epidemiology, varying experimental models, and mechanistic insights into PUD and promising therapeutics. **Methodology:** We systematically reviewed previous literature on PUD, including epidemiological trends, commonly used in vivo, and molecular mechanisms. **Results and discussion:** The global prevalence of peptic ulcer disease (PUD) follows an epidemiological pattern influenced by geography, lifestyle, and genetic factors. Experimental models using ethanol, NSAIDs, or *Helicobacter pylori* induction provide valuable insights into disease progression and pathophysiology. **Emerging trends**: Recent research in peptic ulcer disease focuses on molecular mechanisms, gut microbiome interactions, personalized therapies, and novel pharmacological agents. Molecular studies explore genetic and epigenetic factors influencing ulcer formation, while microbiome research examines the role of gut bacteria beyond *H. pylori*. Personalized treatment approaches use genetic profiling and biomarkers to enhance efficacy and reduce toxicity. Additionally, emerging pharmacological agents aim to improve acid suppression, promote mucosal healing, and develop more effective *H. pylori* eradication strategies. **Conclusion:** A deeper understanding of PUD pathophysiology through epidemiological studies and experimental models can aid in developing novel, targeted therapies. Future research should focus on alternative treatments, including phytochemicals and probiotics, to enhance ulcer prevention and management.

INTRODUCTION

Peptic ulcer disease (PUD) is a chronic condition caused by an imbalance between protective and harmful factors in the stomach or duodenum. The main risk factors include *Helicobacter pylori* infection and NSAID use, which impair mucosal defense and promote ulcer formation. Other contributing factors include stress, smoking, and dietary habits [1]. In 2019, approximately 8.09 million cases of peptic ulcer

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disease (PUD) were reported worldwide, reflecting a 25.82% increase from 1990. However, despite the rise in total cases, the age-standardized prevalence has declined over this period. Having understood the global impact of PUD, it's crucial to delve into its pathophysiology to grasp the underlying mechanisms [2] better. Excessive gastric acid secretion by parietal cells plays a vital role in developing gastric ulcers. Since stomach acid is a key factor in ulcer formation, effective management focuses on regulating hydrochloric acid secretion and strengthening the protective mechanisms of the stomach lining [3]. The prevalence of peptic ulcer disease (PUD) varies across populations based on socioeconomic status, healthcare access, and dietary habits. In recent years, developed countries have seen a decline in PUD cases due to improved sanitation and effective *H. pylori* eradication programs. However, the disease remains a significant burden in developing nations [4]. The primary causes of peptic ulcer disease (PUD) are *H. pylori* infection and NSAID use, both of which compromise gastric mucosal integrity. Other contributing factors include excessive gastric acid secretion, oxidative stress, and inflammatory responses that worsen mucosal damage. If left untreated, PUD can lead to severe complications such as bleeding, perforation, and gastric cancer, emphasizing the need for timely and effective treatment [5].

Multiple factors contribute to the development of gastrointestinal ulcers, with *H. pylori* being the primary cause. This bacterium damages the gastric mucosa and, if untreated, can lead to gastric cancer. *H. pylori* is particularly significant in infants, accounting for 80–90% of cases[6]. NSAID use and alcohol dependence weaken the gastric mucosa and impair blood vessel integrity, further exacerbated by dietary habits and lifestyle factors. The rising incidence of peptic ulcers highlights the need for improved prevention and treatment strategies. Animal models play a crucial role in researching and developing anti-ulcer therapies. This study reviews various models used for screening and advancing anti-ulcer treatments [7].

Peptic ulcers are among the most common medical conditions, affecting millions of people worldwide. According to studies, 10-15% of adults in developed countries are susceptible to developing peptic ulcers. However, the incidence and prevalence differ widely depending on the geographic location and demographic factors [8]. Peptic ulcers are a prevalent medical condition, impacting millions globally. Research indicates that 10-15% of adults in developed nations are at risk of developing these ulcers. However, their occurrence and frequency vary significantly based on geographic and demographic factors [9]. Understanding the pathophysiology of peptic ulcer disease (PUD) requires well-established experimental models that replicate disease conditions and evaluate potential treatments. In vivo ulcer models, including those induced by ethanol, NSAIDs, and *H. pylori*, provide valuable insights into ulcer formation, mucosal healing mechanisms, and drug efficacy. These models bridge the gap between preclinical research and clinical application, facilitating the development of new gastroprotective strategies [10-11]. Animal models, e.g., those for ethanol, NSAIDs, and acetic acid, have helped examine mechanisms of ulcer pathogenesis and assess novel therapeutic agents. They assist scientists in investigating the effect of oxidative stress, inflammatory mediators, and gastric acid secretion on ulcer generation and healing. Experimental research is also critical in estimating new gastroprotective compounds like phytochemicals, probiotics, and synthetic agents [12].

PUD can lead to severe complications, including gastrointestinal bleeding, perforation, and obstruction, which occur in a significant proportion of cases and can result in substantial mortality if not promptly treated. [13]. The prevalence of peptic ulcer disease differs across European regions, primarily driven by *Helicobacter pylori* infection and NSAID use. Recent advancements in medical treatments and shifts in lifestyle may have influenced the condition's prevalence. [14]. While discussing the geographic prevalence of PUD, it's interesting to note regional dietary influences, such as capsaicin intake in Asian countries, and their impact on ulcer formation [15].

Pathophysiology of Peptic Ulcer

Peptic ulcer disease (PUD) is defined as mucosal damage in the duodenum or stomach as a result of an imbalance between aggressive forces, like acid, pepsin, *Helicobacter pylori*, and NSAIDs, and defense mechanisms, such as mucus, bicarbonate, prostaglandins, and mucosal blood flow [16]. A key factor in ulcer formation is the excessive production of gastric acids, which erode the stomach's protective mucus lining, leading to ulcers, and pepsin can overwhelm mucosal defense, leading to ulcer formation [16]. *H. pylori* plays a central role in ulcer development by increasing acid production, triggering inflammation, and disrupting the protective mucus layer.

NSAIDs contribute by inhibiting prostaglandin production, reducing bicarbonate and mucus secretion, and making the mucosa more susceptible to acid-induced damage[17] Figure 1. Protective mechanisms, including mucus and bicarbonate secretion, mucosal blood flow, and prostaglandins, help maintain gastric integrity by neutralizing acid and supporting tissue repair. Disruptions in this balance, such as *H. pylori* infection or NSAID use, weaken this defense, leading to cellular injury, inflammation, and ulcer formation [18].

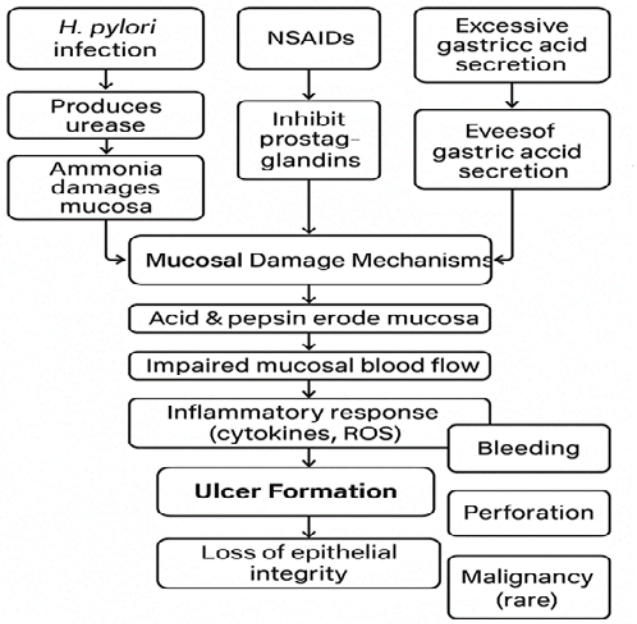

Figure 1: Pathogenesis pathway of peptic ulcer [17]

Experimental Models for Peptic Ulcer

Various experimental models are utilized to study the development of peptic ulcers caused by external factors and to evaluate potential treatments for the condition [19]. These models include animals with Helicobacter pylori (H. pylori) infections as models for creating peptic ulcers in experimental animals. Infecting laboratory animals with *H. pylori* allows studying how *H. pylori* induces ulcers and testing various treatments for *H. pylori* infections. Another such model is of NSAID-induced ulcers, another experimental model to study ulcer induction and therapeutic management in laboratory animals by administering these drugs [20].

***H. pylori* Infection-induced Ulcer in Animals**

Helicobacter pylori easily colonizes human gastric mucosa and is a major contributor to ulcer development, posing a significant global health concern. It causes damage to the gastric mucosa, leading to ulcer formation. More recently, *H. pylori* has been implicated in gastric cancer, with reports indicating its involvement in over 77% of cases [21]. Using animal models has established a platform for researching *H. pylori* induced ulcers. However, it remains tough to cause an ulcer due to the animal's gastric epithelium's reduced susceptibility. It is on this note that scientists have opted to use more advanced models that include transgenic mice, Mongolian gerbils, guinea pigs, and monkeys, among others [22-23]

Mechanism of Action

Helicobacter pylori is a Gram-negative bacterium capable of surviving in the harsh gastric environment. It exists in both spiral and coccoid forms, each serving a distinct function. The spiral shape facilitates movement and invasion, while the coccoid form aids in colonizing the mucous layer of the gastric epithelium. By disrupting this protective barrier in the stomach and duodenum, *H. pylori* exposes underlying tissues to acidic gastric juices, resulting in tissue damage and ulcer formation [24].

Ulcer formation occurs due to *H. pylori* invasion and acid-induced damage. The bacterium's virulence factors, including urease and flagella, enable colonization, mobility, and immune system activation. Increased inflammatory mediators weaken the gastric lining and trigger excessive acid production, further contributing to ulcer development [25].

Ulceration Caused by Chemicals:

Ethanol-induced and stress-induced are two experimental models of peptic ulcers. The ethanol-induced model involves administering ethanol to animals, leading to the development of ulcers. This way, researchers can understand how ulcers form and test any treatment. Stress-induced models involve exposure of animals to stress that would provoke ulcers [26]. This enables researchers to examine the connection between stress and peptic ulcer formation while evaluating potential treatments. In the indomethacin-induced ulcer model, the NSAID indomethacin is administered to laboratory animals to stimulate ulcer development [27]. These experimental models are essential for studying how various chemicals cause peptic ulcers and assessing potential treatment options [28].

Mechanism of Action of Cysteamine caused Peptic ulcer:

The widely acknowledged drug cysteamine has been used to induce peptic ulcers experimentally in animal models. High concentrations of this chemical are administered during experiments to test ulcer development or assess potential

therapies. This model helps researchers find factors responsible for ulcer formation, including hypersensitivity, impaired blood supply, and the mucosal protection mechanisms implicated in disease progression [29,30].

Procedure for Animal screening through cysteamine

Male or female rats are used, maintained in a pathogen-free environment, and fed and watered ad libitum. They are kept at 23°C on a 12-hour light/dark cycle. After one week of acclimatization, peptic ulcers are created by intragastric infusion of 500 mg/kg of Cysteamine-HCl. The rats are sacrificed immediately after infusion, and blood samples are collected for further processing [31]. All previous studies on the preclinical effects of Steamine detail the type of animals used, dose, and routes of administration, which is essential for a detailed understanding of these effects. Table 1 summarizes all these details.

Table 1: Peptic Ulcer Caused by Cysteamine-HCl with dose and route of administration

Sr. No.	Animal Used	Dose	Route of Admⁿ	Ref.
1.	Male Wistar Rats.	450mg/kg	Oral	[32]
2.	Male Wistar Rats.	400mg/kg	Oral	[33]
3.	Female Sprague-Dawley Rats.	25mg/100g	Intra-gastric.	[34]
4.	Female Sprague-Dawley Rats.	300mg/kg and after 8hr repeated dose of 100 mg/kg.	*i.p.*	[35]

Mechanism of Action of Aspirin caused Peptic ulcer

Aspirin is a commonly used over-the-counter NSAID (nonsteroidal anti-inflammatory drug) for pain relief, inflammation reduction, and fever management.. Prolonged NSAID use, including aspirin, increases the risk of peptic ulcer development. By inhibiting prostaglandin production, which protects the stomach lining from gastric acid, aspirin weakens this protective barrier, making the stomach more susceptible to ulcer formation [36-37]. Aspirin administration can lead to epithelial erosion and a reduction in mucosal layers. This loss activates apoptosis regulators and iNOS, contributing to gastric damage. Consequently, the IMP pathway is triggered, causing abnormal leukocyte infiltration into the epithelial lining and increased ROS production, further deteriorating the gastric mucosa [38- 39].

Procedure for Animal Screening

Rats are acclimated under controlled conditions, fasted for 24 hours, and administered 200 mg/kg aspirin, followed by a protective treatment after 45 minutes. After ulcer induction, they are euthanized, and their stomachs are examined for ulcer evaluation. Blood samples and organs are collected for biochemical and histopathological analysis (Table 2) [40].

Table 2: Gastric Ulcer Caused by Aspirin with different Routes and doses

Sr. No.	Animal Used	Dose	Routes	Ref.
1.	Male adult albino mice (30-50g)	150mg/kg	Oral	[41]
2.	Wistar albino rats of both sexes (150- 200g)	200mg/kg (45 min after giving the protective dose)	Oral	[42]
3.	Wister albino Rats (150-200 gm)	200mg/kg on the day of sacrifice	Oral	[43]
4.	Adult Wistar Rats of either sex	400mg/kg after one hour of the treatment	Oral	[44]
5.	Adult male Albino Mice (25 g)	A single dose of 500mg/kg	Oral	[45]

Mechanism of action of ethanol as a PUD inducing agent

Ethanol induces peptic ulcers by enhancing gastric acid production and disrupting protective mechanisms such as the mucosal barrier and prostaglandin synthesis. It is widely used in experimental models, causing severe damage to the gastric mucosa, leading to necrotic lesions, reduced bicarbonate secretion, and impaired mucus production [46]. In experiments, ethanol is commonly used in rats and mice to induce gastric ulcers. It causes severe mucosal damage, leading to necrotic lesions, reduced bicarbonate secretion, and decreased mucus production [47].

Procedure for animal screening

For this experiment, rats of either sex may be used. They are kept in clean cages with raised floors and fed a good diet and water ad libitum. Room temperature is maintained at around 22°C.

Fasting for about 48 hours ensures that the rats are presented with an empty stomach [48]. An 8% sucrose solution in 0.2% NaCl can be administered to prevent dehydration [49]. In this experiment, animals receive 10 mg/kg of 50% ethanol to induce stomach ulcers.

After one hour, they are sacrificed, and their stomachs are removed, cleaned, and examined for ulceration, as shown in Table 3. Organs are collected for histological and biochemical analysis, while blood samples are taken for further biochemical studies [50].

Table 3: Gastric Ulcerations by Ethanol with doses and routes of administration.

Sr. No	Animal Used	Dose	Route	Ref.
1.	Male albino Rats (200- 250 g)	10ml/kg	Orally	[51]
2.	Male Albino Rats of Wistar strain(200- 250 g)	5ml/kg for 9 days	Orally	[52]
3.	Adult female Sprague Dawley Rats(150-180 gm)	5ml/kg	Orally	[53]
4.	Albino Mice	0.5ml/100g	Orally	[54]
5.	Male Albino Mice	Acidified ethanol (60% ethanol in saline with 159 mM HCl; 200 μL/mouse)	Orally	[55]
6.	Adult male albino Rats (150-200gm)	80% ethanol (1ml/rat)	GI	[56]
7.	Kunming Mice (18-22 g)	0.1ml ethanol (100%, anhydrous alcohol)	Orally	[57]

Reserpine mechanism of action

Reserpine is a medication formerly used to treat high blood pressure (hypertension) and certain psychiatric disorders, such as schizophrenia and depression [58]. It lowers neurotransmitter levels, such as dopamine and norepinephrine, essential for mood regulation and cardiovascular function [59]. Reserpine is believed to induce peptic ulcers by depleting neurotransmitters like dopamine, which are necessary for regulating gastric function [60]. Reduced dopamine levels may increase gastric acid secretion and decrease prostaglandin synthesis, contributing to peptic ulcer formation [61].

Procedure for animal screening:

In this experiment, ICR mice of 7 weeks of age were subjected to controlled acclimation before the intraperitoneal injection of reserpine at 10 mg/kg daily for three consecutive days to provoke peptic ulcers.

The 24-hour fasted mice were euthanized, and their stomachs were extracted to calculate the ulcer index. Blood samples were also obtained for further study [62]. All procedures are discussed in Table 4.

Table 4: Gastric Ulcers by Reserpine with route of administration and doses.

Sr. No	Animal Used	Dose	Route of Administration	References
1	Male ICR Mice	10 mg/kg	*i.p.*	[63]
2	Cancer Research Male Mice	10mg/kg	*i.p.*	[64]
3	Male Wistar Rats (180-220g)	5mg/kg	*i.p.* 18 hours before sacrifice	[65]
4	Female Sprague-Dawley Rats (115-175 g)	5mg/kg	*i.p.* 4 hours after treatment	[66]
5	Albino Wistar Rats (180-200g)	0.25gm/kg	Intragastric	[67]
6	Albino male Wistar-Bratislava Rats (125-150g)	5mg/kg	*i.p.*	[68]

Mechanism of action of indomethacin causes peptic ulcer

Indomethacin, an NSAID used for pain, fever, and inflammation, inhibits prostaglandin production (Figure 6). This cyclooxygenase inhibition depletes endogenous prostaglandins, contributing to mucosal injury [69].

Indomethacin administration increases inducible nitric oxide synthase (iNOS) production while reducing constitutive nitric oxide synthase (cNOS) activity [70].

Indomethacin-induced gastrointestinal damage is multifactorial, involving white blood cell infiltration, free radical formation, and nitric oxide disruption in gastric tissues.

Preventing gastropathy requires substances with antioxidant properties, the ability to inhibit leukocyte infiltration, and the capacity to regulate nitric oxide levels. Additionally, indomethacin significantly elevates TNF levels [71].

Procedure for animal screening

In this experiment, animals of either sex are fasted for 24 hours before receiving an oral dose of 40 mg/kg indomethacin to induce gastric ulcers. After 8 hours, they are euthanized, and their stomachs are collected for ulcer index evaluation and further analysis (Table 5). The animals are controlled with a standard diet and a 12-hour light/dark cycle [72].

Table 5: Gastric Ulcer by Indomethacin induced their doses and routes of administration

Sr. No	Animal used	Dose	Routes	Ref.
1	Wistar male Rats (150-250g)	40mg/kg	Oral	[73]
2	Female wistar albino Rats (150-180gm)	48mg/kg dissolved in 5% $NaHCO_3$	Oral	[74]
3	Wistar Albino male Rats (230-260gm)	100mg/kg dissolved in Dimethyl Sulfoxide (DMSO)	Oral	[75]
4	Wistar Male Rats (180-200 g)	A single dose of 100mg/kg	Oral	[76]
5	Wistar Male Rats (180-200 g)	A single dose of 100mg/kg	Oral	[77]
6	Adult Wistar Male Rats (200-250 g)	20mg/kg	*i.p.*	[78]
7	Male Sprague-Dawley Rats	30mg/kg	Oral	[79]
8	Swiss albino Mice (25-30 gm)	Single dose of 40mg/kg	*l.p.*	[80]

Acetic acid mechanism of action:

Acetic acid-induced peptic ulceration is a well-established model for studying peptic ulcers in humans. It is thought to cause ulcers by directly damaging the gastric mucosa, leading to ulcer formation [81]. In experimental animal models, acetic acid-induced peptic ulceration is usually induced by administering high doses of acetic acid to the animals for several days. Acetic acid contributes to the formation of ulcers because it causes embolization of the blood vessels in the mucosal layer of the gastric region, which then causes insufficiency in blood oxygen supply and further leads to ischemia [82].

Procedure for animal models

In this procedure, animals are fasted for 20 to 24 hours before surgery to induce ulceration. Acetic acid is applied to the stomach surface, then rinsed, and the stomach is repositioned before suturing the abdomen. After ten days, the animals are sacrificed, and the stomach is excised for ulcer index assessment and further analysis (Table 6) [83].

Table 6: Gastric Ulcers by Acetic Acid and their doses and routes of administration

S No	Animal used	Dose	Routes	Ref.
1	Wistar Rats (200-300gm)	500µl of 80% (v/v) acetic acid	Surface of the stomach line after exposing the stomach	[84]
2	Adult female Wistar Rats (180- 200 g)	500µl of 80% (v/v) acetic acid	Surface of the stomach line after exposing the stomach	[85]
3	Male and female Wistar Rats (150- 200 g)	Acetic acid	Injected into the stomach	[86]
4	Male Wistar Rats (180- 220 g)	70µL of 80%acetic acid	Serosa surface of the stomach area after exposing the stomach	[87]

Mechanism of action of histamine induced peptic ulcer:

Histamine-induced peptic ulceration is one of the best models for studying peptic ulcers in experimental animals. Histamine is mainly present in the skin, stomach, and lungs, but in smaller amounts in the brain and heart [88]. Histamine reduces gastric mucus production, impairing mucosal secretion, microcirculation, and digestive motility. These findings highlight the role of these mechanisms in peptic ulcer formation and the effects of proton pump inhibitors and antibiotic treatments [89].

Procedure for animal models

In this experiment, male Wistar rats are fasted for 24 hours and then stressed by immersing them in a water bath at 23°C for 3.5 hours.

They are pre-treated with histamine phosphate at 2 mg/kg for gastric ulcers. The rats are then euthanized, and their stomachs are examined to count ulceration and subsequent investigation (Table 7) [90].

Table 7: Gastric Ulcers by Histamine induced with route of administration and doses.

Sr. No.	Animal used	Dose	Routes	References
1	Wistar male rats (200- 250 g)	2mg/kg pre-treated dose before inducing stress.	Subcutaneous	[91]
2	Wistar Albino rats	Vary from 40mg/kg- 100mg/kg	Subcutaneous	[92]

Mechanism of action of methyl blue

Methylene blue is a blue dye used in experimental models to cause animal peptic ulcers. It inhibits cyclooxygenase, an enzyme responsible for synthesizing prostaglandins, hormone-like compounds that protect the gastrointestinal tract from acid-induced damage [93-94]. Elevated levels of Thiobarbituric acid, superoxide dismutase, and H+/K+-ATPase contribute to gastric mucosal damage, resulting in lesions and decreased blood supply. Methylene blue activates H+/K+-ATPase, increasing HCl secretion, reducing mucosal blood flow, and inducing oxidative stress (Table 8) [95].

Table 8: Gastric Ulcers by Methylene Blue with routes of administration and different doses.

Sr. No	Animal Used	Dose	Routes	References
1	Rats	100mg/kg	Orally	[96]

Iron Ascorbic Acid

Iron-ascorbic acid, a combination of iron and ascorbic acid, is commonly used to treat iron-deficiency anaemia. However, limited studies have investigated its effects on peptic ulcer formation in experimental animals. High doses of iron-ascorbic acid may contribute to ulcer development by increasing oxidative stress, reducing antioxidant capacity, and decreasing prostaglandin synthesis. This process leads to ulceration in a dose-dependent manner through elevated ROS formation [97].

Serotonin

Serotonin is a neurotransmitter that acts as a chemical messenger for transmitting signals in the brain and other parts of the body. This neurotransmitter regulates mood, appetite, sleep, and behaviour [98]. Experimental studies suggest elevated serotonin in the gastrointestinal tract may be associated with animal peptic ulcer formation. Serotonin is a neurotransmitter involved in the contraction of smooth muscle in the wall of the gastrointestinal tract [99]. Elevated serotonin levels can intensify smooth muscle contractions, potentially leading to peptic ulcer formation. Additionally, serotonin stimulates hydrochloric acid production in the stomach, further exacerbating ulcer development [100]. Animal studies suggest that inhibiting serotonin activity in the gut can lower the occurrence of peptic ulcers, emphasizing its role in ulcer development [101].

Induction of Peptic Ulcer other than Chemicals

Water Immersion Restraint Stress (WRS)

It has been one of the most utilized experimental methods used to induce peptic ulcers in animals- the WRS; this method of experimentation involves subjecting the animal to a duration of time under water, restraining it physiologically while psychologically stressing the animal [102]. WRS has been shown to increase gastric HCl secretion while reducing mucosal blood flow, raising the risk of peptic ulcer formation. The combined effects of physical and psychological stress elevate stress hormones like cortisol, further contributing to ulcer development. This model is primarily used to study the mechanisms of PUD formation and evaluate the effectiveness of various treatments [103].

Induction of Peptic Ulcers by Surgical Methods:

Various surgical techniques are available to induce peptic ulcers in experimental animals. These methods generally involve creating gastric mucosal lesions or modifying the gastrointestinal anatomy to enhance the risk of PUD development [104]. A widely used surgical approach is chronic gastric vagotomy, which increases HCl secretion and reduces mucosal blood flow, thereby elevating the risk of peptic ulcer formation [105]. Another method is making a ligated pylorus- a tied-off opening from the stomach to the small intestine; however, this blocks the food and digestive juices from flowing into the small intestine, increasing gastric pressure and leading to peptic ulcer [106]. These surgical methods are utilized in experimental animal studies to investigate the mechanisms of peptic ulcer formation and evaluate potential treatments for PUD. Additionally, all surgical procedures must comply with ethical guidelines for humanely treating experimental animals [107].

Pylorus ligation method

This is one of the most widely accepted surgical methods for inducing gastrointestinal ulcers in rats. In this procedure, the animals are appropriately anesthetized, fasted for at least 24 hours before the operation, and housed in cages [99]. An incision is performed in the region of the xiphoid process through which to open the abdomen and ligate the pylorus with ordinary

anesthesia. The stomach was replaced in the abdominal cavity with utmost care, and catgut was sutured in place [108]. Immediately after surgery, food and water are supplied in limited quantities. At the end of four hours, these animals are sacrificed by a suitable method under anesthesia. After sacrifice, the stomach is opened; the gastric juice is collected [109]. Ligation of the pylorus increases the volume of gastrointestinal fluid, which causes injuries due to the self-digestion of the gastric mucosal layer due to the accumulation of pepsin and hydrochloric acid [110-112].

Gastric Ulcer by Ischemia-Reperfusion (IR) Method

The ischemia-reperfusion (IR) method is a surgical technique used in experimental animal studies to induce peptic ulcers by temporarily restricting blood flow to the stomach (ischemia) followed by its restoration (reperfusion) [113]. In this model, rats are fasted for at least 16 hours before IR induction. Anaesthesia is carefully administered throughout the procedure. The stomach is identified, delicately exposed, and isolated from surrounding muscles after shaving the area beneath the thoracic cage [114-115]. Following the laparotomy, the celiac artery is carefully isolated, and a microvascular clamp is applied to obstruct blood flow for 60 minutes [116-117]. In the IR method, rats are fasted for 16 hours before undergoing surgery, during which the celiac artery is clamped to induce ischemia for 60 minutes. Following clamp removal, reperfusion is allowed for 20 minutes. The abdomen is then sutured, and the rats are returned to their cages. After the treatment period, the animals are sacrificed, and their stomachs are analyzed for morphological and biochemical changes, with ulcer indexes assessed [118].

Epidemiology

Recent estimates indicate that peptic ulcer disease (PUD) affects 5–10% of the global population. While its prevalence has declined in industrialized nations, it remains high in developing countries due to widespread *H. pylori* infection and increased NSAID use [119-120]. The World Health Organization (WHO) reports that *H. pylori* infection remains a primary risk factor, affecting over 50% of individuals in many parts of Africa, Asia, and Latin America [121]. Additionally, the Centers for Disease Control and Prevention (CDC) highlights an increasing trend of NSAID-related ulcers, particularly among the elderly and those with chronic illnesses [122]. Demographic patterns indicate a higher prevalence of PUD in males compared to females, with incidence rising in older adults due to increased NSAID consumption and weakened mucosal defense [123]. Socioeconomic disparities also contribute, as limited healthcare access leads to delayed diagnosis and higher rates of complications such as bleeding and perforation [124]. Regional differences remain significant, with East and South Asia experiencing the highest burden due to dietary habits, high *H. pylori* prevalence, and inadequate eradication strategies. At the same time, North America and Europe show declining trends due to improved healthcare infrastructure and antibiotic use [125-126].

Limitations of the PUD screening model

Experimental models that screen anti-ulcer agents prove beneficial but fail to receive a proper assessment of their specific limitations. The absence of appropriate critical evaluation of these individual models leads researchers to interpret the data excessively, decreasing the ability to translate preclinical data into human clinical practices effectively. Each commonly used experimental model, such as ethanol-, NSAID-, stress-, and pylorus ligation-induced ulcers, shows limited application by representing individual ulcer pathophysiological features but not the complete range of human peptic ulcer disease aspects [127-129]. This model of ulcer formation primarily leads to mucosal tissue damage and oxidative stress without triggering acid production or Helicobacter pylori infection, which are dominant factors in human peptic ulcers [130]. Similarly, NSAID-induced ulcer models emphasize prostaglandin inhibition but do not account for other pathogenic mechanisms such as impaired mucosal blood flow or delayed epithelial repair [131]. Ulcer models created with cold-restraint methods release ulcers through sympathetic hyperactivation and reduced blood supply, yet remain distant from human stress conditions [132]. Furthermore, models like acetic acid-induced ulcers are better suited for evaluating healing rather than ulcerogenesis and might not reflect the initial pathogenic events [133]. The absence of systematic analysis between different ulcer models has caused researchers to generalize anti-ulcer agent effectiveness across all types of ulcers. Still, this approach may misinterpret the results and restrict their practical clinical use [134].

Discussion of human studies in Peptic Ulcer disease

The pathogenesis of human ulcer development surpasses experimental models since these models neglect multiple human-triggering factors like *H. pylori* infections, NSAID

consumption, genetic vulnerabilities, and emotional stress elements [135-136]. Research data from clinical trials regarding anti-ulcer therapy effectiveness remains scarce, even though numerous trials have generated beneficial findings. Clinical research by the European Helicobacter pylori Study Group demonstrated that anti-ulcer therapy proved better than acid suppression in discouraging ulcer recurrence [137]. The results of randomized controlled trials indicate that proton pump inhibitors successfully treat and sustain ulcer remission better than H2-receptor antagonists, particularly for NSAID-associated ulcers [138-139]. Failure to integrate such clinical evidence may overstate the applicability of preclinical outcomes, as many experimental models do not account for comorbidities, drug interactions, or long-term outcomes assessed in human populations [140].

DISCUSSION

Recent advancements in peptic ulcer disease (PUD) research include molecular discoveries, microbiome studies, and novel therapeutic approaches. Genetic and epigenetic insights have deepened the understanding of ulcer pathogenesis, while microbiome research highlights the role of non *H. pylori* bacteria in mucosal health and disease progression [141-142]. Personalized medicine approaches, including biomarker-driven therapies and precision drug targeting, are also gaining traction [143]. Despite these advancements, a significant translational gap remains between human PUD and preclinical models. While animal models are invaluable for studying ulcer development and healing, they often fail to fully replicate the complexity of human gastric physiology, immune responses, and disease progression.[144]. Differences in gastric acid secretion, mucosal repair mechanisms, and microbial interactions limit the direct applicability of preclinical findings to clinical practice [145]. Current models of PUD, including rodent and non-human primate studies, have limitations such as differences in gastric anatomy, healing processes, and responses to therapeutic agents [146]. In vitro models also lack the dynamic interactions in a living system, further hindering accurate translation to human disease [147].

Future research should improve model accuracy through advanced techniques such as 3D organoid cultures, patient-derived cell systems, and computational models to bridge the translational gap. Key areas for advancing PUD management include understanding host-microbiome interactions, developing targeted therapies based on molecular signatures, and discovering new drug candidates with improved efficacy and safety profiles [148-149].

CONCLUSION

Experimental models have been central to the progress of peptic ulcer disease (PUD) knowledge, contributing enormously to drug discovery and *Helicobacter pylori* studies. Yet, their limitations in mimicking human gastric physiology, host immune responses, and microbiome interactions have provided a wide translational gap between preclinical observations and clinical results. Traditional rodent and in vitro models are ineffective in replicating human ulcer pathology, causing therapeutic efficacy and safety prediction issues. Future studies must emphasize novel techniques like human-derived 3D organoid models that resemble gastric architecture and function to address this deficiency. Also, including precision medicine by genomic and epigenetic profiling will facilitate individualized treatment plans catering to individual patient variations. Pharmacologic treatments based on innovative mucosal healing, inflammation modulation, and microbiome restoration will be pivotal in optimizing treatment effectiveness. Developing these fronts will enhance model accuracy and provide a way to treat PUD more effectively and patient-specifically.

ACKNOWLEDGEMENTS

The authors thank the Narayan Institute of Pharmacy, Sasaram, Bihar, for cooperation and support.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Laliteshwar Pratap Singh contributed to conceptualization, investigation, and data curation. Sandip Chatterjee wrote the draft and contributed to data collection and revision. Sanjeeb Kumar Kar analysed and reviewed the draft and contributed to the literature survey.

ABBREVIATIONS

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; **PUD:** Peptic Ulcer Disease; **CDC:** Center for Disease Control and Prevention; **GU:** Gastric Ulcer; **PU:** Peptic Ulcer; **DU**:

Duodenal Ulcer; **PPIs**: Proton Pump Inhibitors; **cNOS**: Constitutive Nitric acid Synthesis; **iNOS**: Inducible Nitric acid Synthesis; **HCl**: Hydrochloric acid; **WRS**: Water Immersion Restraint Stress; **IR**: Ischemia-Reperfusion; **WRS**: Water Immersion Restraint Stress; **3D**- three dimension

REFERENCES

[1] Okabe S, Amagase K. An overview of acetic acid ulcer models--the history and state of the art of peptic ulcer research. *Biol Pharm Bul.l*, **28 (8)**, 1321-41 (2005) https://doi.org/10.1248/bpb.28.1321

[2] Xie X, Ren K, Zhou Z, Dang C, Zhang H. The global, regional and national burden of peptic ulcer disease from 1990 to 2019: a population-based study. *BMC Gastroenterol*, **22 (1)**, 58 (2022) https://doi.org/10.1186/s12876-022-02130-2

[3] Zhang Q, Huang N, Wang J, Luo H, He H, Ding M, Deng WQ, Zou K. The H+/K+-ATPase inhibitory activities of Trametenolic acid B from Trametes lactinea (Berk.) Pat, and its effects on gastric cancer cells. *Fitoterapia*, **89**, 210-7 (2013) https://doi.org/10.1016/j.fitote.2013.05.021

[4] Wang S, Zhang T, Li D, Cao X. The global, regional and national burden of peptic ulcer disease attributable to smoking from 1990 to 2021: A population-based study. *Preventive Medicine Reports*, **51**, 103019 (2025) https://doi.org/10.1016/j.pmedr.2025.103019

[5] Ameen AA, El-Masry HG, Bashatly MYMHE. The effect of licorice (Glycyrrhiza glabra) on peptic ulcer in rats. *International Journal of Health Sciences*, **6 (S4)**, 12173-83 (2022) https://doi.org/10.53730/ijhs.v6nS4.11829International

[6] Shell EJ. Pathophysiology of peptic ulcer disease. *Physician Assistant Clinics*, **6 (4)**, 603-11 (2006) https://doi.org/10.1016/j.cpha.2021.05.005

[7] Kang, D.W, Lee, JW., Park, M.Y. *et al.* Impact of *Helicobacter pylori* eradication on age-specific risk of incident dementia in patients with peptic ulcer disease: a nationwide population-based cohort study. *GeroScience* , **47**, 1161–1174 (2025). https://doi.org/10.1007/s11357-024-01284-z

[8] Nejati S, Karkhah A, Darvish H, Validi M, Ebrahimpour S, Nouri HR. Influence of *Helicobacter pylori* virulence factors CagA and VacA on pathogenesis of gastrointestinal disorders. *Microbial pathogenesis*, **117**, 43-8 (2018) https://doi.org/10.1016/j.micpath.2018.02.016

[9] Fang B, Yang S, Liu H, Zhang Y, Xu R, Chen G. Association between depression and subsequent peptic ulcer occurrence among older people living alone: A prospective study investigating the role of change in social engagement. *Journal of Psychosomatic Research*, **122**, 94-103 (2019) https://doi.org/10.1016/j.jpsychores.2019.04.002

[10] Satapathy T, Sen K, Sahu S, et al. Experimental animal models for gastric ulcer/peptic ulcer: an overview. *J Drug Deliv Ther*, **14 (1)**, 204-212 (2022) http://dx.doi.org/10.22270/jddt.v14i1.6258

[11] Silen W. Experimental models of gastric ulceration and injury. *Am J Physiol Gastrointest Liver Physiol*, **255 (4)**, G395-G401 (1988) https://doi.org/10.1152/ajpgi.1988.255.4.G395

[12] Suleyman H, Küçükler S, Kandemir FM, Yıldırım S. Protective effect of chrysin on indomethacin induced gastric ulcer in rats: Role of multi-pathway regulation. *Biotechnic & Histochemistry*, **97 (7)**, 490-503 (2022) https://doi.org/10.1080/10520295.2021.2014569

[13] Salari, N., Darvishi, N., Shohaimi, S. *et al.* The Global Prevalence of Peptic Ulcer in the World: a Systematic Review and Meta-analysis. *Indian J Surg*, **84**, 913–921 (2022) https://doi.org/10.1007/s12262-021-03189-z

[14] Bardhan KD, Royston C. Time, change and peptic ulcer disease in Rotherham, UK. *Digestive and Liver Disease*, **40 (7)**, 540-6 (2008) https://doi.org/10.s1016/j.dld.2008.02.024

[15] Dugani, A.M, and Glavin, G.B. Capsaicin effects on stress pathology and gastric acid secretion in rats. *Life Sci*, **39**, 1531–1538 (1986) https://doi.org/10.1016/0024-3205(86)90383-8

[16] Sonnenberg A. Pathogenesis of peptic ulcer disease. *Clin Gastroenterol Hepatol*, **11 (8)**, 936–42 (2013) https://doi.org/10.1016/B978-0-12-821232-5.00021-5

[17] Soll AH. Jaiswal F, Rai AK, Wal P, Wal A, Singh SP. Peptic ulcer: a review on etiology, pathogenesis and treatment. *Asian Journal of Pharmaceutical Education and Research*, **10 (4)**, 1 (2021) https://dx.doi.org/10.38164/AJPER/9.4.2021.01-17

[18] Schubert ML, Peura DA. Control of gastric acid secretion in health and disease. *Gastroenterology*, **134 (7)**, 1842–60 (2008) https://doi.org/10.1053/j.gastro.2008.05.021

[19] Megraud, F.; Brouter, N. Review article: Have we found the source of Helicobacter pylori? *Aliment. Pharmacol Ther*, **14 (Suppl. 3)**, 7–12 (2000) https://doi.org/10.1046/j.1365-2036.2000.00095.x

[20] Stolte M, Meining A. The updated Sydney system classification and grading of gastritis as the basis diagnosis and treatment. *Can. J. Gastroenterol*, **12**, 591–598 (2001) https://doi.org/10.1155/2001/367832

[21] Salleh KL, Iversen E, Ibsen B, Fehsenfeld M. Exploring the impact of stressful life events on quality of life: meaning making and narrative reconstruction. *International journal of qualitative studies on health and well-being*, **19 (1)**, 2330117 (2024) https://doi.org/10.1080/17482631.2024.2330117

[22] Glavin GB, Szabo S. Experimental gastric mucosal injury: laboratory models reveal mechanisms of pathogenesis and new therapeutic strategies. *The FASEB journal*, **6 (3)**, 825-31 (1992) https://doi.org/10.1096/fasebj.6.3.1740232

[23] Musumba C, Pritchard DM, Pirmohamed M. cellular and molecular mechanisms of NSAID-induced peptic ulcers.

Alimentary pharmacology & therapeutics, **30 (6)**, 517-31**,** (2009) https://doi.org/10.1111/j.1365-2036.2009.04086.x

[24] Miller, A.K., Williams, S.M. *Helicobacter pylori* infection causes both protective and deleterious effects in human health and disease. *Genes Immun*, **22**, 218–226 (2021). https://doi.org/10.1038/s41435-021-00146-4

[25] Nrayanan M, Reddy KM, Marsicano E. Peptic Ulcer Disease and Helicobacter pylori infection. *MoMed*, **115 (3)**, 219-224 (2018) https://pmc.ncbi.nlm.nih.gov/articles/PMC6140150/

[26] Adinortey MB, Ansah C, Galyuon I, Nyarko A. In vivo models used for evaluation of potential antigastroduodenal ulcer agents. *Ulcers*, **2013 (1)**, 796405 (2013) https://doi.org/10.1155/2013/796405

[27] Bertleff MJ, Lange JF. Perforated peptic ulcer disease: a review of history and treatment. *Digestive surgery*, **27 (3)**, 161-9 (2010) https://doi.org/10.1159/000264653

[28] Beiranvand M. A review of the most common in vivo models of stomach ulcers and natural and synthetic anti-ulcer compounds: a comparative systematic study. *Phytomedicine Plus*, **2 (2),** 100264 (2022) https://doi.org/10.1016/j.phyplu.2022.100264

[29] Cherqui S. Cysteamine therapy: a treatment for cystinosis, not a cure. *Kidney international*, **81 (2),** 127-9 (2012) https://doi.org/10.1038/ki.2011.301

[30] Robert A, Nezamis JE, Lancaster C, Badalamenti JN. Cysteamine-induced duodenal ulcers: a new model to test antiulcer agents. *Digestion*, **11 (3-4)**, 199-214 (1974) https://doi.org/10.1159/000197584

[31] Minaiyan M, Ghannadi A, Salehi E. Antiulcerogenic effect of Zataria multiflora Boiss. on cysteamine induced duodenal ulcer in rats. *Iranian journal of pharmaceutical sciences*, **1 (4)**, 223-9 (2005**)** https://doi.org/10.22037/ijps.v1.39542

[32] Choi KS, Kim EH, Hong H, Ock CY, Lee JS, Kim JH, Hahm KB. Attenuation of cysteamine-induced duodenal ulcer with Cochinchina momordica seed extract through inhibiting cytoplasmic phospholipase A2/5-lipoxygenase and activating γ-glutamylcysteine synthetase. *Journal of Gastroenterology and Hepatology*, **27**, 13-22 (2012) https://doi.org/10.1111/j.1440-1746.2012.07065.x

[33] Fukuhara S, Suzuki H, Masaoka T, Arakawa M, Hosoda H, Minegishi Y, Kangawa K, Ishii H, Kitajima M, Hibi T. Enhanced ghrelin secretion in rats with cysteamine-induced duodenal ulcers. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **289 (1),** G138-45 (2005) https://doi.org/10.1152/ajpgi.00298.2004

[34] Khomenko T, Szabo S, Deng X, Ishikawa H, Anderson GJ, McLaren GD. Role of iron in the pathogenesis of cysteamine-induced duodenal ulceration in rats. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **296 (6),** G1277-86 (2009) https://doi.org/10.1152/ajpgi.90257.2008

[35] Sikiric P, Boban BA, Krezic I, Zizek H, Kalogjera L, Smoday IM, Vukovic V, Oroz K, Chiddenton HM, Buric S, Antunovic M. From Selye's and Szabo's Cysteamine-Duodenal Ulcer in Rats to Dopamine in the Stomach: Therapy Significance and Possibilities. *Pharmaceuticals*, **16 (12)**, 1699 (2023) https://doi.org/10.3390/ph16121699

[36] Martins Prizão V, de Moura de Souza M, de Athayde De Hollanda Morais BA, Ximenes Mendes B, Cosendey Martins O, Defante ML, Queiroz Vasconcelos Muniz J, Francisco Buzetti Spinelli B. Impact of low-dose aspirin on the prevalence of anemia in elderly patients: a systematic review and meta-analysis. *Postgraduate medicine*; **137(2)**, 148-54 (2025) https://doi.org/10.1080/00325481.2024.2446010

[37] Wang X, Kong Y, Li Z. Advantages of Chinese herbal medicine in treating rheumatoid arthritis: a focus on its anti-inflammatory and anti-oxidative effects. *Frontiers in Medicine*, **11**, 1371461 (2024) https://doi.org/10.3389/fmed.2024.1371461

[38] Mahmoud YI, Abd El-Ghffar EA. Spirulina ameliorates aspirin-induced gastric ulcer in albino mice by alleviating oxidative stress and inflammation. *Biomedicine & Pharmacotherapy*, **109**, 314-21 (2019) https://doi.org/10.1016/j.biopha.2018.10.118

[39] Odashima Nehlig A. Effects of coffee on the gastro-intestinal tract: a narrative review and literature update. *Nutrients*,**14(2)**, 399 (2022) https://doi.org/10.3390/nu14020399

[40] Bora M, Mandal S, Singh PK, Das H, Bora GK, Bora D, Baruah D, Gautam MK. Phytochemical and pharmacological profile of Desmodium gangeticum (L.) DC.: a comprehensive review. *Current Traditional Medicine*, **10 (4)**, 52-9 (2024) https://doi.org/10.2174/2215083810666230523145738

[41] Arefpour H, Sadeghi A, Zayeri F, Hekmatdoost A. The application of ginger supplementation on peptic ulcer disease management: A randomized, double blind, placebo-controlled clinical trial. *Clinical Nutrition Open Science*, **57**, 231-40 (2024) https://doi.org/10.1016/j.nutos.2024.08.008

[42] Badapanda SS, Kaur A, Jain D, Bhatia D. Epidemiology, Pathogenesis, and Induction of Peptic Ulcer: A Comprehensive Review. *New Emirates Medical Journal*, **5 (1)**, e02506882348139 (2024) https://doi.org/10.2174/0102506882348139241210080210

[43] Altyar AE, Munir A, Ishtiaq S, Rizwan M, Abbas K, Kensara O, Elhady SS, Rizg WY, Youssef FS, Ashour ML. Malva parviflora leaves and fruits mucilage as natural sources of anti-inflammatory, antitussive and gastro-protective agents: A comparative study using rat models and Gas chromatography. *Pharmaceuticals*, **15 (4)**, 427 (2022) https://doi.org/10.3390/ph15040427

[44] Cherrada N, Chemsa AE, Gheraissa N, Laib I, Gueboudji Z, EL-Shazly M, Zaater A, Abid A, Sweilam SH, Emran TB, Nani S. Gastroprotective Efficacy of North African Medicinal Plants: A Review on Their Therapeutic Potential for Peptic Ulcers. *Food*

Science & Nutrition, **12 (11)**, 8793-824 (2024) https://doi.org/10.1002/fsn3.4536

[45] Kamar SA, Bayoumi AH, Rady HY. Spirulina supplements: An approach moderating aspirin persuaded histological and ultra-structural alterations in albino rats gastric mucosa. *Ultrastructural Pathology*, **46(2)**, 204-16 (2022) https://doi.org/10.1080/01913123.2022.2052779

[46] Marhuenda E, Martin MJ, Alarcon Lastra CD. Antiulcerogenic activity of aescine in different experimental models. *Phytotherapy Research*, **7 (1),** 13-6 (1993) https://doi.org/10.1002/ptr.2650070105

[47] Akhtar MS, Malik A, Arshad H, Batool S, Raza AR, Tabassum T, Murtaza MA, Riaz M, Noreen M, Rasool G. Protective effect of newly synthesized indole imines against ethanol-induced gastric ulcer in rats. *Biotechnology & Biotechnological Equipment*, **35(1)**, 231-7 (2021) https://doi.org/10.1080/13102818.2020.1868330

[48] Wylie MR, Merrell DS. The antimicrobial potential of the neem tree Azadirachta indica. *Frontiers in pharmacology*, **13**, 891535 (2022) https://doi.org/10.3389/fphar.2022.891535

[49] Glavin GB, Mikhail AA. Stress and ulcer etiology in the rat. *Physiology & behavior*, **16 (2)**, 135-9 (1976) https://doi.org/10.1089/neu.2023.0314

[50] Alkofahi A, Atta AH. Pharmacological screening of the anti-ulcerogenic effects of some Jordanian medicinal plants in rats. *Journal of Ethnopharmacology*, **67 (3)**, 341-5 (1999) https://doi.org/10.1016/S0378-8741(98)00126-3

[51] Chen J, Wang H, Zhu J. Extract from Falcaria vulgaris loaded with exosomes for the treatment of hypertension in pregnant mice: In vitro and In vivo investigations. *Bio-Medical Materials and Engineering*, **35(6)**, 509-21 (2024) https://doi.org/10.3233/BME-240053

[52] Keyvanara AH, Yegdaneh A, Talebi A. Evaluating anti-inflammatory effect of hydroalcoholic extracts of Citrus medica L. pulp and peel on rat model of acute colitis. *Research Journal of Pharmacognosy*, **10 (2)**, 29-38 (2023) https://doi.org/10.22127/rjp.2023.377466.2027

[53] Balaky ST. Anti H. pylori, anti-secretory and gastroprotective effects of Thymus vulgaris on ethanol-induced gastric ulcer in Sprague Dawley rats. *Plos one*, **19(1)**, e0287569 (2024) https://doi.org/10.1371/journal.pone.0287569

[54] Li W, Huang H, Niu X, Fan T, Mu Q, Li H. Protective effect of tetrahydrocoptisine against ethanol-induced gastric ulcer in mice. *Toxicology and applied pharmacology*, **272 (1)**, 21-9 (2013) https://doi.org/10.1016/j.taap.2013.05.035

[55] Byeon S, Oh J, Lim JS, Lee JS, Kim JS. Protective effects of Dioscorea batatas flesh and peel extracts against ethanol-induced gastric ulcer in mice. *Nutrients*, **10 (11)**, 1680 (2018) https://doi.org/10.3390/nu10111680

[56] Al-Qarawi AA, Abdel-Rahman H, Ali BH, Mousa HM, El-Mougy SA. The ameliorative effect of dates (Phoenix dactylifera L.) on ethanol-induced gastric ulcer in rats. *Journal of ethnopharmacology*, **98 (3)**, 313-7 (2005) https://doi.org/10.1016/j.jep.2005.01.023

[57] Pan LR, Tang Q, Fu Q, Hu BR, Xiang JZ, Qian JQ. Roles of nitric oxide in protective effect of berberine in ethanol-induced gastric ulcer mice. *Acta Pharmacologica Sinica*, **26 (11),** 1334-8 (2005) https://doi.org/10.1111/j.1745-7254.2005.00186.x

[58] Bremshey S, Groß J, Renken K, Masseck OA. The role of serotonin in depression—A historical roundup and future directions. *Journal of Neurochemistry*, **168 (9)**, 1751-79 (2024) https://doi.org/10.1111/jnc.16097

[59] Mózsik G, Past T, Abdel Salam OM, Kuzma M, Perjési P. Interdisciplinary review for correlation between the plant origin capsaicinoids, non-steroidal anti-inflammatory drugs, gastrointestinal mucosal damage and prevention in animals and human beings. *Inflammopharmacology*, **17**, 113-50 (2009) https://doi.org/10.1007/s10787-009-0002-3

[60] Li T, Shi M, Zhao Y, He Z, Zong Y, Chen W, Du R. Mechanism of action of vinegared Cornu Cervi Degelatinatum in suppressing spleen kidney yang deficient ulcerative colitis through NCK2-JNK pathway. *Heliyon*, **10 (2)** (2024) https://doi.org/10.1016/j.heliyon.2024.e24782

[61] Glavin GB, Szabo S. Experimental gastric mucosal injury: laboratory models reveal mechanisms of pathogenesis and new therapeutic strategies. *The FASEB journal*, **6 (3)**, 825-31 (1992) https://doi.org/10.1096/fasebj.6.3.1740232

[62] Qian Y, Li GJ, Zhu K, Suo HY, Sun P, Zhao X. Effects of three types of resistant starch on intestine and their gastric ulcer preventive activities in vivo. *Journal of the Korean Society for Applied Biological Chemistry*, **56 (6)**, 739-46 (2013) https://doi.org/10.1007/s13765-013-3229-z

[63] Zhou YL, Wang R, Feng X, Zhao X. Preventive effect of insect tea against reserpine-induced gastric ulcers in mice. *Experimental and Therapeutic Medicine*, **8 (4)**, 1318-24 (2014) https://doi.org/10.3892/etm.2014.1859

[64] Yi R, Wang R, Sun P, Zhao X. Antioxidant-mediated preventative effect of Dragon-pearl tea crude polyphenol extract on reserpine-induced gastric ulcers. *Experimental and Therapeutic Medicine*, **10 (1)**, 338-44 (2015) https://doi.org/10.3892/etm.2015.2473

[65] Pfeiffer CJ, Cho CH, Cheema A, Saltman D. Reserpine-induced gastric ulcers: protection by lysosomal stabilization due to zinc. *European Journal of Pharmacology*, **61 (4)**, 347-53 (1980) https://doi.org/10.1016/0014-2999(80)90073-4

[66] Ogle CW, Cho CH. Protection by zinc sulphate against reserpine-induced ulceration and other gastric effects in the rat. *Pharmacology*, **17 (5)**, 254-61 (1978) https://doi.org/10.1159/000136864

[67] Li T, Shi M, Zhao Y, He Z, Zong Y, Chen W, Du R. Mechanism of action of vinegared Cornu Cervi Degelatinatum in suppressing spleen kidney yang deficient ulcerative colitis through NCK2-JNK pathway. *Heliyon*, **10 (2)** (2024) https://doi.org/10.1016/j.heliyon.2024.e24782

[68] Sandu, R., Singh, J. A comprehensive review on calcitonin gene-related peptide in the management of gastrointestinal disorders. *Inflammopharmacol*, **33**, 1043–1059 (2025) https://doi.org/10.1007/s10787-025-01657-6

[69] Vane JR, Botting RM. Anti-inflammatory drugs and their mechanism of action. *Inflammation Research*, **47**, 78-87 (1998) https://doi.org/10.1007/s000110050284

[70] Simmons DL, Botting RM, Hla T. Cyclooxygenase isozymes: the biology of prostaglandin synthesis and inhibition. *Pharmacological reviews*, **56 (3)**, 387-437 (2004) https://doi.org/10.1124/pr.56.3.3

[71] Slomiany BL, Slomiany A. Role of endothelin-converting enzyme-1 in the suppression of constitutive nitric oxide synthase in rat gastric mucosal injury by indomethacin. *Scandinavian journal of gastroenterology*, **35 (11),** 1131 (2004) https://doi.org/10.1080/00365200750056583

[72] Maity B, Banerjee D, Bandyopadhyay SK, Chattopadhyay S. Regulation of arginase/nitric oxide synthesis axis via cytokine balance contributes to the healing action of malabaricone B against indomethacin-induced gastric ulceration in mice. *International immunopharmacology*, **9 (4)**, 491-8 (2004) https://doi.org/10.1016/j.intimp.2009.01.028

[73] Suzuki T, Yoshida N, Nakabe N, Isozaki Y, Kajikawa H, Takagi T, Handa O, Kokura S, Ichikawa H, Naito Y, Matsui H. Prophylactic effect of rebamipide on aspirin-induced gastric lesions and disruption of tight junctional protein zonula occludens-1 distribution. *Journal of pharmacological sciences*, **106 (3)**, 469-77 (2008) https://doi.org/10.1254/jphs.FP0071422

[74] Doma I, Haruna I, Hamza A. Antipyretic and Antinociceptive Effect of the Methanol Leaf Extract of Ficus asperifolia in Murine Models. *Journal of Current Biomedical Research*, **4 (1),** 1436-53 (2024) https://doi.org/10.54117/jcbr.v4i1.2

[75] Abdel-Raheem IT. Gastroprotective effect of rutin against indomethacin-induced ulcers in rats. *Basic & clinical pharmacology & toxicology*, **107 (3)**, 742-50 (2010) https://doi.org/10.1111/j.1742-7843.2010.00568.x

[76] Eraslan E, Tanyeli A, Güler MC, Kurt N, Yetim Z. Agomelatine prevents indomethacin-induced gastric ulcer in rats. *Pharmacological Reports.*, **72 (4)**, 984-91 (2020) https://doi.org/10.1007/s43440-019-00049-2

[77] El-Ashmawy NE, Khedr EG, El-Bahrawy HA, Selim HM. Nebivolol prevents indomethacin-induced gastric ulcer in rats. *Journal of immunotoxicology*, **13 (4),** 580-9 (2016) https://doi.org/10.3109/1547691X.2016.1142488

[78] Tiwari D, Alam A, Dhoundiyal S, Sharma S, Yadav S. Medicinal Herbs for the Treatment of Peptic Ulcers. *Current Traditional Medicine*, **10 (7),** 106-18 (2024) https://doi.org/10.2174/0122150838262681230920054706

[79] Bhattacharya S, Chaudhuri SR, Chattopadhyay S, Bandyopadhyay SK. Healing properties of some Indian medicinal plants against indomethacin-induced gastric ulceration of rats. *Journal of Clinical Biochemistry and Nutrition.*, **41 (2)**, 106-14 (2007) https://doi.org/10.3164/jcbn.2007015

[80] Aleid IS, Alfheeaid HA, Aljutaily T, Alhomaid RM, Alharbi HF, Althwab SA, Abdel-Rahman HA, AlGeffari MA, Barakat H. Gastroprotective effects of spirulina platensis, golden kiwifruit flesh, and golden kiwifruit peel extracts individually or in combination against indomethacin-induced gastric ulcer in rats. *Nutrients.*, **13 (10)**, 3499 (2021) https://doi.org/10.3390/nu13103499

[81] Wang XY, Wang M, Yin JY, Song YH, Wang YX, Nie SP, Xie MY. Gastroprotective activity of polysaccharide from the fruiting body of Hericium erinaceus against acetic acid-induced gastric ulcer in rats and structure of one bioactive fraction. *International Journal of Biological Macromolecules*, **210**, 455-64 (2022) https://doi.org/10.1016/j.ijbiomac.2022.04.153

[82] Shen C, Zhang S, Di H, Wang S, Wang Y, Guan F. The Role of Triterpenoids in Gastric Ulcer: Mechanisms and Therapeutic Potentials. *International Journal of Molecular Sciences*, **26 (7)**, 3237 (2025) https://doi.org/10.3390/ijms26073237

[83] Devaraj VC, Krishna BG, Viswanatha GL, Prasad VS, Babu SV. Protective effect of leaves of Raphinus sativus Linn on experimentally induced gastric ulcers in rats. *Saudi Pharmaceutical Journal*, **19 (3)**, 171-6 (2011) https://doi.org/10.1016/j.jsps.2011.03.003

[84] da Silva LM, Pezzini BC, Somensi LB, Mariano LN, Mariott M, Boeing T, Dos Santos AC, Longo B, Cechinel-Filho V, de Souza P, de Andrade SF. Hesperidin, a citrus flavanone glycoside, accelerates the gastric healing process of acetic acid-induced ulcer in rats. *Chemico-biological interactions*, **308**, 45-50 (2019) https://doi.org/10.1016/j.cbi.2019.05.011

[85] da Silva LM, Allemand A, Mendes DA, Dos Santos AC, André E, de Souza LM, Cipriani TR, Dartora N, Marques MC, Baggio CH, Werner MF. Ethanolic extract of roots from Arctium lappa L. accelerates the healing of acetic acid-induced gastric ulcer in rats: Involvement of the antioxidant system. *Food and chemical toxicology*, **51**, 179-87 (2013) https://doi.org/10.1016/j.fct.2012.09.026

[86] Garabadu D, Singh S, Gautam T. Manilkara hexandra (Roxb.) Dubard Ameliorates Acetic Acid-induced Rat Gastric Ulcer. *Journal of Dietary Supplements*, **18 (3),** 278-92 (2021) https://doi.org/10.1080/19390211.2020.1770393

[87] Viana AF, Lopes MT, Oliveira FT, Nunes PI, Santos VG, Braga AD, Silva AC, Sousa DP, Viana DA, Rao VS, Rita de Cássia

MO. (−)-Myrtenol accelerates healing of acetic acid-induced gastric ulcers in rats and in human gastric adenocarcinoma cells. *European Journal of Pharmacology*, **854**, 139-48 (2019) https://doi.org/10.1016/j.ejphar.2019.04.025

[88] Fan HP, Zhou Y, Chen ML, Qiu KH, Feng X, Zhou C, Zhu ML, Huang RZ, Hu TY. Effect of proton pump inhibitors versus histamine-2 receptor antagonists on acute kidney injury in septic patients at high risk for developing stress ulcers. Pharmacotherapy: *The Journal of Human Pharmacology and Drug Therapy*, **44 (7)**, 539-48 (2024) https://doi.org/10.1002/phar.2947

[89] Jily J. Noor A, Qazi NG, Nadeem H, Khan AU, Paracha RZ, Ali F, Saeed A. Synthesis, characterization, anti-ulcer action and molecular docking evaluation of novel benzimidazole-pyrazole hybrids. *Chemistry Central Journal*, **11**, 1-3 (2017) https://doi.org/10.1186/s13065-017-0314-0

[90] Hosoda S, Ikedo H, Saito T. Praomys (Mastomys) natalensis: Animal model for study of histamine-induced duodenal ulcers. *Gastroenterology*, **80 (1)**, 16-21 (1981) https://doi.org/10.1016/0016-5085(81)90184-0

[91] Pu L, Jia T, Su S, Yang L, Yao H, Su Y, Chen Z. Proton Pump Inhibitors Versus Histamine-2 Receptor Blockers for Stress Ulcer Prophylaxis on In-Hospital Mortality Among Intensive Care Unit Patients Hospitalized for Major Adverse Cardiovascular and Cerebrovascular Events: Retrospective Cohort Study. *Clinical Therapeutics*, **46 (9)**,677-82 (2024) https://doi.org/10.1016/j.clinthera.2024.06.020

[92] Fulga S, Pelin AM, Ghiciuc CM, Lupușoru EC. Particularities of experimental models used to induce gastric ulcer. *ARS Medica Tomitana*, **25 (4),** 179-84 (2020) https://doi.org/10.32819/2021.94026

[93] Yin R, R Hamblin M. Antimicrobial photosensitizers: drug discovery under the spotlight. *Current medicinal chemistry*, **22 (18)**, 2159-85 (2015) https://doi.org/10.2174/0929867322666150319120134

[94] Chrétien NM, Zenab Linda FN, Brice Junior NN, Marcelle Olga FY, Vanessa Mba MM, Stephanie Flore DN, Yacine Karelle MK, Elvira NA, Marius M, Gilbert A. Anti-inflammatory, anti-oxidant and anti-ulcer activities of aqueous lyophilizate of Markhamia lutea (Bignoniaceae). *Journal of Complementary and Integrative Medicine*, **10 (0)** (2024) https://doi.org/10.1515/jcim-2024-0059

[95] Anderson G, Noorian AR, Taylor G, Anitha M, Bernhard D, Srinivasan S, Greene JG. Loss of enteric dopaminergic neurons and associated changes in colon motility in an MPTP mouse model of Parkinson's disease. *Experimental neurology*, **207 (1)**, 4-12 (2007) https://doi.org/10.1016/j.expneurol.2007.05.010

[96] Shah DI, Santani DD, Goswami SS. A novel use of methylene blue as a pharmacological tool. *Journal of pharmacological and toxicological methods*, **54 (3)**, 273-7 (2006) https://doi.org/10.1016/j.vascn.2005.12.003

[97] Lynch SR, Stoltzfus RJ. Iron and ascorbic acid: proposed fortification levels and recommended iron compounds. *The Journal of nutrition*, **133 (9)**, 2978S-84S (2003) https://doi.org/10.1093/jn/133.9.2978S

[98] Teleanu RI, Niculescu AG, Roza E, Vladâcenco O, Grumezescu AM, Teleanu DM. Neurotransmitters—key factors in neurological and neurodegenerative disorders of the central nervous system. *International journal of molecular sciences*, **23 (11)**, 5954 (2022) https://doi.org/10.3390/ijms23115954

[99] Thanoon TB, Althanoon ZA. Ketamine role in the treatment of Maternal depression: effects on offspring behaviour.Research square, **28 (2)**, (2024) https://doi.org/10.21203/rs.3.rs-3969981/v1

[100] Lüscher TF, Vanhoutte PM. Endothelium-dependent responses to platelets and serotonin in spontaneously hypertensive rats. *Hypertension*, **8 (6_pt_2)**, II55 (1986) https://doi.org/10.1161/01.HYP.8.6_Pt_2.II55

[101] Boakye-Yiadom M, Kumadoh D, Adase E, Woode E. Medicinal plants with prospective benefits in the management of peptic ulcer diseases in Ghana. *BioMed Research International*, **2021 (1)**, 5574041 (2021) https://doi.org/10.1155/2021/5574041

[102] Buynitsky T, Mostofsky DI. Restraint stress in biobehavioral research: recent developments. *Neuroscience & Biobehavioral Reviews*., **33 (7)**, 1089-98 (2009) https://doi.org/10.1016/j.neubiorev.2009.05.004

[103] Guo Jiang Q, Guo M, Guo L, Ling Q, Xie C, Li X, Zhao G, Tu W. Electroacupuncture pretreatment at ST36 alleviates acute gastric mucosal lesions induced by water immersion restraint stress through the TRPV1/SP/CGRP/NO pathway in rats. *Acupuncture in Medicine*, **43 (1)**, 3-13 (2025) https://doi.org/10.1177/09645284241300177

[104] Fulga S, Pelin AM, Ghiciuc CM, Lupușoru EC. Particularities of experimental models used to induce gastric ulcer. *ARS Medica Tomitana*, **25 (4),** 179-84 (2020) https://doi.org/10.2478/arsm-2019-0035

[105] Janssen, H.J.B., Geraedts, T.C.M., Fransen, L.F.C. *et al.* Electrical vagus nerve stimulation is a promising approach to reducing pulmonary complications after an esophagectomy: an experimental rodent model. *Immunol Res*, **72**, 1247–1258 (2024) https://doi.org/10.1007/s12026-024-09523-3

[106] Khan N, Khushtar M, Rahman MA, Kaish M, Ajmal M. Amelioration of gastric ulcer using a hydro-alcoholic extract of Mangifera indica in Sprague Dawley rats by prevention of muco-oxidative stress. *Pharmacological Research-Modern Chinese Medicine*, **11**, 100442 (2024) https://doi.org/10.1016/j.prmcm.2024.100442

[107] Clark JD, Gebhart GF, Gonder JC, Keeling ME, Kohn DF. The 1996 guide for the care and use of laboratory animals. *ILAR journal*, **38 (1)**, 41-8 (1997) https://doi.org/10.1093/ilar.38.1.41

[108] Al-Gabri N, Elnagar GM, Saghir SA, El-Shaibany A, Alnomasy SF, Althafar ZM, Elkomy NM, Elaasser MM, Abdoh MS, Yosri M. Preliminary Study of Gastroprotective Effect of Aloe perryi and Date Palm Extracts on Pyloric Ligation-Induced Gastric Ulcer in Experimental Rats. *BioMed Research International*, **2022 (1),** 9246785 (2022) https://doi.org/10.1155/2022/9246785

[109] Yismaw Haritha M, Leena Lavanya D, Muthukumar T. Morphological, Anatomical, and Histochemical Study of Cordia diffusa KC Jacob—*A Steno Endemic Plant. Microscopy Research and Technique*, **88 (5),** 1273-91 (2025) https://doi.org/10.1002/jemt.24791

[110] Rajakrishnan R, Alfarhan AH, Al-Ansari AM, Lekshmi R, Sreelakshmi R, Benil PB, Kim YO, Tack JC, Na SW, Kim HJ. Therapeutic efficacy of the root tubers of Aconitum heterophyllum and its substitute Cyperus rotundus in the amelioration of pylorus ligation induced ulcerogenic and oxidative damage in rats. *Saudi Journal of Biological Sciences*, **27 (4)**, 1124-9 (2020) https://doi.org/10.1016/j.sjbs.2019.12.025

[111] Elazab ST, Hsu WH. α-Bisabolol alleviates doxorubicin-induced cognitive dysfunction in rats via enhancing the hippocampal BDNF/TrKB signaling and inhibiting neuroinflammation. *Frontiers in Pharmacology*, **16**, 1549009 (2025) https://doi.org/10.3389/fphar.2025.1549009

[112] Andargie Y, Sisay W, Molla M, Norahun A, Singh P. Evaluation of the antiulcer activity of methanolic extract and solvent fractions of the leaves of Calpurnia aurea (Ait.) Benth.(Fabaceae) in rats. *Evidence-Based Complementary and Alternative Medicine*, **2022 (1),** 4199284 (2022) https://doi.org/10.1155/2022/4199284

[113] Odukanmi OA, Salami AT, Ashaolu OP, Adegoke AG, Olaleye SB. Kolaviron attenuates ischemia/reperfusion injury in the stomach of rats. *Applied Physiology, Nutrition, and Metabolism*, **43 (1)**, 30-7 (2018) https://doi.org/10.1139/apnm-2017-0138

[114] Fagundes FL, Piffer GD, Périco LL, Rodrigues VP, Hiruma-Lima CA, Dos Santos RD. Chrysin modulates genes related to inflammation, tissue remodeling, and cell proliferation in the gastric ulcer healing. *International Journal of Molecular Sciences*, **21 (3)**, 760 (2020) https://doi.org/10.3390/ijms21030760

[115] Ohara R, Périco LL, Rodrigues VP, Bueno G, Zanatta AC, Dos Santos LC, Vilegas W, Constatino FB, Justulin LA, Hiruma-Lima CA. Terminalia catappa L. infusion accelerates the healing process of gastric ischemia-reperfusion injury in rats. Journal of ethnopharmacology, **256**, 112793 (2020) https://doi.org/10.1016/j.jep.2020.112793

[116] Bajramagic S, Sever M, Rasic F, Staresinic M, Skrtic A, Beketic Oreskovic L, Oreskovic I, Strbe S, Loga Zec S, Hrabar J, Coric L. Stable Gastric Pentadecapeptide BPC 157 and Intestinal Anastomoses Therapy in Rats—A Review. *Pharmaceuticals*, **17 (8)**, 1081 (2024) https://doi.org/10.3390/ph17081081

[117] Dos Santos RD, Bonamin F, Périco LL, Rodrigues VP, Zanatta AC, Rodrigues CM, Sannomiya M, dos Santos Ramos MA, Bonifácio BV, Bauab TM, Tamashiro J. Byrsonima intermedia A. Juss partitions promote gastroprotection against peptic ulcers and improve healing through antioxidant and anti-inflammatory activities. *Biomedicine & pharmacotherapy*, **111**, 1112-23 (2019) https://doi.org/10.1016/j.biopha.2018.12.132

[118] Salami AT, Odukanmi OA, Faniyan OF, Omayone TP, Olaleye SB. Seeds of Buchholzia coriacea in diet mitigate ischemic reperfusion–induced gastric ulceration in experimental rats. Journal of dietary supplements, **15 (6)**, 842-59 (2018) https://doi.org/10.1080/19390211.2017.1404544

[119] Sung JJY, Kuipers EJ, El-Serag HB. Systematic review: The global incidence and prevalence of peptic ulcer disease. *Aliment Pharmacol Ther*, **29 (9)**, 938–46 (2009) https://doi.org/10.1111/j.1365-2036.2009.03960.x

[120] Borao Laguna C, Lanas A. Advances in the pharmacotherapeutic management of refractory peptic ulcers. *Expert Opinion on Pharmacotherapy*, **24 (7)**, 825-33 (2023) https://doi.org/10.1080/14656566.2023.2199922

[121] Wu, Y., Murray, G.K., Byrne, E.M. *et al.* GWAS of peptic ulcer disease implicates *Helicobacter pylori* infection, other gastrointestinal disorders and depression. *Nat Commun*, **12**, 1146 (2021) https://doi.org/10.1038/s41467-021-21280-7

[122] Mozaffari S, Mousavi T, Nikfar S, Abdollahi M. Common gastrointestinal drug-drug interactions in geriatrics and the importance of careful planning. *Expert Opinion on Drug Metabolism & Toxicology*, **19 (11)**, 807-28 (2023) https://doi.org/10.1080/17425255.2023.2273384

[123] Tang B, Li P, Mao X. Precision Diagnosis of Helicobacter pylori Infection and Its Drug Resistance. *iLABMED*, **3 (1),** 106-23 (2025) https://doi.org/10.1002/ila2.73

[124] Yuan Y, Dong SX. Social and natural environmental factors cause the birth-cohort phenomenon of peptic ulcers by superposition mechanism. *International Journal of Environmental Health Research*, **35 (2)**, 424-38 (2025) https://doi.org/10.1080/09603123.2024.2359069

[125] Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of *Helicobacter pylori* infection: Systematic review and meta-analysis. *Gastroenterology*, **153 (2),** 420–9 (2017) https://doi.org/10.1053/j.gastro.2017.04.022

[126] Ford AC, Yuan Y, Moayyedi P. Helicobacter pylori eradication therapy to prevent gastric cancer: Systematic review and meta-analysis. *Gut*, **69 (12)**, 2113–21 (2020) https://doi.org/10.1136/gutjnl-2020-320839

[127] Bafna PA, Balaraman R. Anti-ulcer and antioxidant activity of *DHC-1*, a herbal formulation. *J Ethnopharmacol*, **97 (2)**, 273–80 (2005) https://doi.org/10.1016/j.jep.2003.09.036

[128] Szabo S, Hollander D. Pathways of gastrointestinal protection and repair: mechanisms of action of sucralfate. *Am J Med*, **86 (6A)**, 23–31 (1989) https://doi.org/10.1016/0002-9343(89)90153-8

[129] Mamache W, Amira S, Benchikh F, Benabdallah H, Bencheikh A, Amira H, Ounis R, Torki MA, Kaoudoune C. The therapeutic potential of Salvia aegyptiaca extracts in ethanol-induced gastric ulcer: insights into macroscopic, histopathological, and biochemical mechanisms. *Turkish Journal of Biology*, **49 (1)**, 40-51 (2025) https://doi.org/10.55730/1300-0152.2722

[130] Suden A. Management of Ulcerative Colitis Vis-À-Vis Atisara and Its Manifestations: An Ayurvedic Review. International research journal of ayurveda and yoga, **3 (8)** (2020) https://doi.org/10.47223/IRJAY.2020.3818

[131] Wang X, Tang Q, Hou H, Zhang W, Li M, Chen D, Gu Y, Wang B, Hou J, Liu Y, Cao H. Gut microbiota in NSAID enteropathy: new insights from inside. *Frontiers in cellular and infection microbiology*, **11**, 679396 (2021) https://doi.org/10.3389/fcimb.2021.679396

[132] Muayad HA, AlQadhi HI. The Cytoprotective Effects of Melatonin on Gastric Ulcer: A Rat Model. *Journal of the Faculty of Medicine Baghdad*, **67 (1)**, 78-84 (2025) https://doi.org/10.32007/jfacmedbaghdad2467

[133] Okabe S, Pfeiffer CJ. Chronicity of acetic acid ulcer in the rat stomach. *Am J Dig Dis*, **17 (7)**, 619–29 (1972**)** https://doi.org/10.1007/BF02231748

[134] Fokou PV, Nyarko AK, Appiah-Opong R, Yamthe LR, Addo P, Asante IK, Boyom FF. Ethnopharmacological reports on anti-Buruli ulcer medicinal plants in three West African countries. *Journal of ethnopharmacology*, **172**, 297-311 (2015) https://doi.org/10.1016/j.jep.2015.06.024

[135] Kavitt RT, Lipowska AM, Anyane-Yeboa A, Gralnek IM. Diagnosis and treatment of peptic ulcer disease. *The American journal of medicine*, **132 (4),** 447-56 (2019) https://doi.org/10.1016/j.amjmed.2018.12.009

[136] Sung JJ, Kuipers EJ, El-Serag HB. Systematic review: the global incidence and prevalence of peptic ulcer disease. *Aliment Pharmacol Ther*, **29 (9)**, 938–46 (2009) https://doi.org/10.1111/j.1365-2036.2009.03960.x

[137] Nyssen OP, Bordin D, Tepes B, Pérez-Aisa Á, Vaira D, Caldas M, Bujanda L, Castro-Fernandez M, Lerang F, Leja M, Rodrigo L. European Registry on Helicobacter pylori management (Hp-EuReg): patterns and trends in first-line empirical eradication prescription and outcomes of 5 years and 21 533 patients. *Gut*, **70 (1)**, 40-54 (2021) https://doi.org/10.1136/gutjnl-2020-321372

[138] Bardhan KD, Strugala V, Dettmar PW. Reflux revisited: advancing the role of pepsin. *Int J Otolaryngol*, **2012**, 646901 (2012) https://doi.org/10.1155/2012/646901

[139] Ko KA, Lee DK. Nonsteroidal Anti-Inflammatory Drug-Induced Peptic Ulcer Disease. The Korean *Journal of Helicobacter and Upper Gastrointestinal Research*, **25 (1),** 34-41 (2025) https://doi.org/10.7704/kjhugr.2025.0004

[140] Wallace JL, Syer S, Denou E, et al. Proton pump inhibitors exacerbate NSAID-induced small intestinal injury by inducing dysbiosis. *Gastroenterology*., **141 (4)**, 1314–22 (2011) https://doi.org/10.1053/j.gastro.2011.06.075

[141] Tourrette E, Torres RC, Svensson SL, Matsumoto T, Miftahussurur M, Fauzia KA, Alfaray RI, Vilaichone RK, Tuan VP, Helicobacter GenomicsConsortium, Wang D. An ancient ecospecies of Helicobacter pylori found in Indigenous populations and animal adapted lineages. *bioRxiv*, **2023 (04)** (2023) https://doi.org/10.1101/2023.04.28.538659

[142] Shanahan F, Ghosh TS, O'Toole PW. The gut microbiome in health and disease: A clinical perspective. *Lancet Gastroenterol Hepatol*, **6 (3)**, 260–70 (2021) https://doi.org/10.1146/annurev-med-051223-031809

[143] Liu JZ, Öztekin M, Yılmaz B, Ağagündüz D, Capasso R. Overview of Helicobacter pylori infection: clinical features, treatment, and nutritional aspects. *Diseases*, **9 (4)**, 66 (2021) https://doi.org/10.3390/diseases9040066

[144] Tarnawski AS, Ahluwalia A. Molecular mechanisms of epithelial regeneration and neovascularization during healing of gastric and esophageal ulcers. *Curr Med Chem*, **19 (1),** 16–27 (2012) atoon A, Sachan V, Kori P, Khushtar M, Pujari NM. Current Practices and Emerging Technologies in Animal Models for Gastric Ulcer Research. *Journal of Drug Discovery and Health Sciences*, **1 (3)**, 153-60 (2024) https://doi.org/10.21590/jddhs.01.03.05

[145] Wallace JL, Sharkey KA. Pharmacotherapy of gastric acid-related disorders: Pathways of gastric protection and healing. *Trends Pharmacol Sci*, **42 (4)**, 276–88 (2021) https://doi.org/10.3390/ijms25021311

[146] Zatorski H, Mukherjee P, Roy S, Ghosh D. *et al.* Role of animal models in biomedical research: a review. *Lab Anim Res*, **38**, 18 (2022) https://doi.org/10.1186/s42826-022-00128-1

[147] Mills JC, Shivdasani RA. Gastric epithelial stem cells and their roles in cancer and mucosal regeneration. *Gastroenterology*, **140 (2)**, 412–24 (2011) https://doi.org/10.1053/j.gastro.2010.12.001

[148] Malfertheiner P, Schulz C, Hunt RH. Helicobacter pylori Infection: A 40-year journey through shifting the paradigm to transforming the management. *Digestive Diseases*, **42 (4)**, 299-308 (2024) https://doi.org/10.1159/000538079