INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Drug Induced Peptic Ulcer in Experimental Animals

Savanth Swetha, Nabila Kulsum Abdul Aleem, Venu Talla*

Department of Pharmacology, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya (Co-Ed.), Tarnaka, Hyderabad, Telangana, India-500017.

ARTICLE INFO

Published: 12 Nov 2026

Keywords:

Drug-Induced Peptic Ulcer (DIPU), Experimental Animal Models, Gastric Mucosal Injury, Oxidative Stress, Gastroprotective Activity

DOI:

10.5281/zenodo.24156173

ABSTRACT

Drug-induced peptic ulcer (DIPU) is an important gastrointestinal disorder that commonly develops due to the prolonged or excessive use of ulcerogenic medications, particularly non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, corticosteroids, antiplatelet agents, and anticoagulants. These drugs cause gastric mucosal damage by inhibiting cyclooxygenase (COX) enzymes, reducing protective prostaglandin synthesis, increasing oxidative stress, and promoting inflammation. Experimental animal models, especially rats and mice, are widely used to investigate the mechanisms of ulcer development and evaluate the gastroprotective effects of different therapeutic agents. Various drugs, including indomethacin, aspirin, ibuprofen, diclofenac, ketorolac, and meloxicam, are commonly employed to induce experimental gastric ulcers. The severity of gastric damage is assessed through macroscopic, biochemical, and histopathological examinations using parameters such as ulcer score, ulcer index, ulcer area, gastric volume, gastric pH, and gastric wall mucus. Biochemical investigations also include oxidative stress markers such as malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT), along with inflammatory mediators such as nitric oxide (NO), prostaglandin E_2 (PGE_2), TNF-α, IL-1β, and IL-6.

***Corresponding Author:** Venu Talla
Address: Department of Pharmacology, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya (Co-Ed.), Tarnaka, Hyderabad, Telangana, India-500017
Email ✉: tallavenu@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

In recent years, medicinal plants, phytochemicals, probiotics, antioxidants, and synthetic compounds have gained considerable attention for their potential gastroprotective properties. Future research should focus on improving experimental ulcer models, understanding chronic gastric injury and healing mechanisms, and exploring advanced techniques such as gastric organoids and computational models. Overall, experimental animal studies provide valuable information about drug-induced gastric injury and contribute to the development of safer and more effective gastroprotective treatments.

INTRODUCTION

A common gastrointestinal condition called peptic ulcer disease (PUD) is defined by a rupture in the duodenum or stomach mucosa that penetrates the muscularis mucosa. Drug-induced peptic ulcers have gained importance due to the widespread use of non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, corticosteroids, antiplatelet agents, anticoagulants, and other ulcerogenic medications, even though the prevalence of Helicobacter pylori-associated ulcers has decreased (1)

NSAIDs are the most common medicine that causes stomach ulcers. Both topical irritation of the stomach epithelium and systemic suppression of cyclooxygenase (COX)-1 and COX-2 enzymes, which results in decreased prostaglandin synthesis, are responsible for their ulcerogenic effects. Depletion of prostaglandins increases vulnerability to oxidative stress and inflammation, decreases mucosal blood flow, inhibits mucus and bicarbonate secretion, and delays epithelial healing. Therefore, long-term NSAID use may cause bleeding, perforation, stomach erosions, and peptic ulcers, especially in older patients and those with a history of gastrointestinal disorders (2,3)

In order to assess the gastroprotective effectiveness of new treatment medicines and to comprehend the pathophysiology of drug-induced peptic ulcers, experimental animal models are essential. Because they offer dependable and repeatable models that closely mimic human stomach ulcers, rats and mice are the most widely utilized laboratory animals (4) NSAID-induced models (indomethacin, ibuprofen, aspirin, diclofenac, and naproxen), ethanol-induced ulcers, stress-induced ulcers, pyloric ligation, and acetic acid-induced chronic ulcers are only a few of the ulcer induction techniques that have been discovered. These models make it easier to study oxidative stress, inflammatory reactions, ulcer healing processes, and stomach mucosal damage (5)

Experimental ulcers are evaluated using both macroscopic and microscopic methods, such as ulcer index, gastric acidity, gastric mucus content, histopathological analysis, and biochemical measurements of oxidative stress markers such as catalase (CAT), superoxide dismutase (SOD), reduced glutathione (GSH), and malondialdehyde (MDA). Additionally, measures of inflammatory cytokines including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are commonly employed to elucidate the molecular mechanisms underlying gastrointestinal injury. (6)

Finding safer pharmaceuticals and natural compounds that can prevent or lessen drug-induced stomach injury without affecting the therapeutic efficacy of NSAIDs has been the subject of extensive research in recent years. Through antioxidant, anti-inflammatory, anti-apoptotic, and cytoprotective processes, a variety of medicinal herbs, phytochemicals, antioxidants, probiotics, and synthetic compounds have shown notable gastroprotective effect in animal experiments (2,4,7) Thus, experimental animal models are still essential for the preclinical assessment of new anti-ulcer treatments and continue to offer insightful information on the mechanisms behind drug-induced peptic ulcers.

2.Epidemiology

Peptic ulcer disease (PUD) has been linked to drug-induced peptic ulcer (DIPU), especially in affluent nations where the prevalence of Helicobacter pylori infection has decreased while the use of ulcerogenic drugs has increased. The epidemiology of PUD has shifted toward medication-associated diseases due to the extensive long-term use of drugs that can harm the gastroduodenal mucosa brought on by the rising frequency of chronic musculoskeletal disorders, cardiovascular diseases, and an aging population (1,11)

Among all the drug classes, NSAID-induced PUD is still a major global public health issue. According to studies, the prevalence of stomach ulcers among NSAID users ranges from 10% to 30% worldwide,

with older people and those with comorbidities bearing a greater burden (8) Gastrointestinal bleeding, perforation, and obstruction are complications linked to NSAID-induced PUD and significantly increase morbidity and death (9) According to a systemic assessment, the annual incidence of PUD complications among NSAID users varies from 3.77 to 14.0 cases per 100,000 people for perforation and from 19.5 to 57.0 cases per 100,000 people for bleeding (10)

Drug-induced peptic ulcer disease is less commonly caused by other drugs. Corticosteroids by themselves only slightly raise the risk of ulcers, but when taken in conjunction with NSAIDs, they greatly increase the incidence of ulcers. Similarly, rather than causing ulcers to form, antiplatelet medications like clopidogrel and anticoagulants mainly raise the risk of gastrointestinal bleeding. Additionally, selective serotonin reuptake inhibitors (SSRIs) raise the risk of upper gastrointestinal bleeding, particularly when used with aspirin or NSAIDs (12)

The strongest predictors of drug-induced peptic ulcers and ulcer complications, according to epidemiological studies, are advanced age, prior peptic ulcer disease, high-dose or multiple NSAID therapy, concurrent use of corticosteroids, anticoagulants, antiplatelet agents, or SSRIs, and Helicobacter pylori infection. According to a meta-analysis, individuals who are exposed to both NSAIDs and H. pylori infection are substantially more likely to develop peptic ulcer disease than those who are only exposed to one of these factors (3,10,12)

3. Drugs that causing peptic ulcers (13,24,37,41,45,53,57,59)

S.no	Drug class	Drug
1.	Non-steroidal anti-inflammatory drugs	Indomethacin,Aspirin,Ibuprofen, Diclofenac, Ketorolac, Meloxicam
2.	Antiplatelet drugs	Aspirin, Clopidogrel
3.	Antihypertensive agent	Reserpine
4.	Glucocorticoid	Predsisolone,Dexamethasone
5.	Anti-coagulants	Warfarin,Heparin
6.	Antineoplastic drugs	5-Fluorouracil, Methotrexate
7.	Immunosuppressants	Mycophenolate, Azathioprine
8.	Bisphosphonates	Alendronate, Risedronate

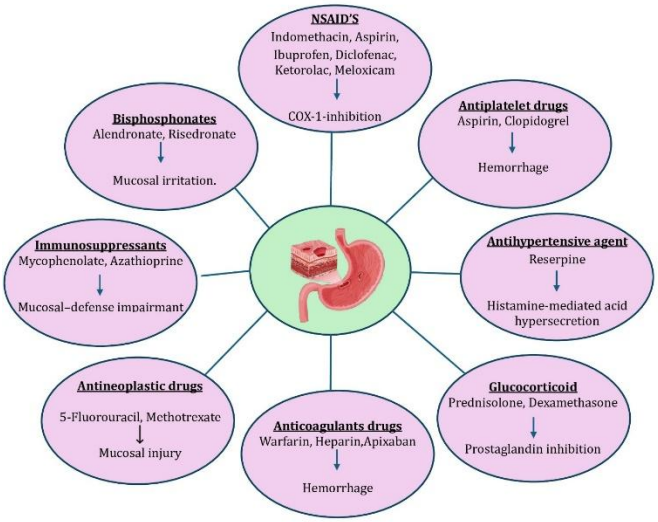


Figure 1: ***Major Mechanisms of Drug-Induced Peptic Ulcer (DIPU) and Representative Ulcerogenic Drugs***

4. Experimental Animal models on Drug induced peptic ulcer

4.1 Indomethacin induced ulcer

Cyclooxygenase (COX) enzymes, which are involved in the manufacture of prostaglandins, are inhibited by indomethacin, an NSAID. Reduced prostaglandin production may exacerbate inflammation and weaken the stomach's protective mucosal barrier, which could result in the development of ulcers (13)

Rats are given 18–60 mg/kg of indomethacin orally or injection. The duration of the investigation is 7–14 days (13,14,15). Indomethacin is injected or given orally to mice at a dose of 18–40 mg/kg, and the study is carried out for 7–14 days (16,17). Indomethacin is injected or given orally to guinea pigs at a dose of 10–100 mg/kg, and the study lasts for seven to fourteen days (18, 19). Indomethacin is given orally or subcutaneously to rabbits at a dose of 20–75 mg/kg, and the trial lasts for seven to fourteen days (20,21).

4.2 Aspirin induced ulcer

Nonsteroidal anti-inflammatory medicines (NSAIDs) like aspirin are frequently prescribed to individuals with peripheral artery disease, coronary heart disease, or cerebrovascular disease.(22) However, research has demonstrated that aspirin exacerbates gastrointestinal (GI) damage by preventing the synthesis of prostaglandins, causing direct cytotoxicity, and producing microvascular damage along with the activation of neutrophils that generate an excess of free radicals obtained from oxygen. Lipid peroxidation and tissue damage are brought on by free radicals.(23)

A popular experimental model for researching NSAID-induced gastrointestinal damage and assessing possible gastroprotective and anti-ulcer medications is aspirin-induced peptic/gastric ulceration. Numerous experimental animals, including rats, mice, guinea pigs, rabbits, and, less frequently, other species, have been used to study it. Rats are the most commonly used of these. The medicine is given orally to rats and mice at a dose of 150–300 mg/kg, and the trial lasts for seven to fourteen days.(24, 25, 26, 27, 28, 29) The drug is given orally to guinea pigs at a dose of 200–500 mg/kg for a duration of 7–14 days.(30, 31) In rabbits, the dose is given orally for 30 days at a level of 150–400 mg/kg.(32, 33, 34).

4.3 Ibuprofen induced ulcer

Ibuprofen's ulcerogenic effect is mainly caused by its inhibition of cyclooxygenase (COX) enzymes, especially COX-1, which reduces the production of protective gastric prostaglandins like PGE_2 and PGI_2. Prostaglandins normally preserve the integrity of the gastric mucosa by promoting mucus and bicarbonate secretion, preserving mucosal blood flow, promoting epithelial restoration, and restricting excessive gastric acid secretion. Therefore, the stomach mucosal defense mechanism is weakened and the mucosa is more vulnerable to damage caused by acid and pepsin when these protective prostaglandins are reduced.(35)

Oxidative stress is also linked to stomach damage caused by ibuprofen. Lipid peroxidation and cellular membrane damage can result from increased reactive oxygen species (ROS) generation. Ibuprofen administration has been linked to increased lipid peroxidation, increased membrane permeability, decreased antioxidant enzyme activity, and increased myeloperoxidase (MPO) activity in experimental rat investigations. These alterations play a role in the formation of stomach ulcers, inflammation, and epithelial damage.(36)

Ibuprofen is given orally or by injection to rats and mice at a dose of 200–400 mg/kg for seven to fourteen days.(37,38,39)

4.4 Diclofenac induced ulcer

A common non-steroidal anti-inflammatory medication (NSAID) for its analgesic and anti-inflammatory properties is diclofenac. On the other hand, erosions, peptic ulcers, and damage to the stomach mucosa might result from prolonged or high-dose administration. Diclofenac-induced stomach damage is mostly linked to the loss of beneficial prostaglandins, suppression of cyclooxygenase (COX) enzymes, and other local irritating effects on the gastric mucosa.(40) Rats and mice are given diclofenac orally or by injection at a dose of 10–100 mg/kg, and the trial is carried out for 7–14 days.(41,42,43**)**

4.5 Ketorolac induced ulcer

Strong NSAIDs like ketorolac are mostly used to treat pain. However, it can result in peptic ulcers and damage to the stomach mucosa. Because ketorolac inhibits COX-1, less protective prostaglandins are produced. This impairs the gastrointestinal mucosal barrier, reduces mucus and bicarbonate secretion, and increases the stomach's susceptibility to gastric acid and digesting enzyme damage. Additionally, ketorolac may induce stomach ulcers via a mitochondrial mechanism. Pyruvate dehydrogenase (PDH), a crucial enzyme that links glycolysis to the Krebs cycle, can be inhibited by it. This disrupts the generation of energy in the mitochondria, lowers the conversion of pyruvate to acetyl-CoA, and may lower ATP levels. Additionally, it may enhance the production of reactive oxygen species (ROS), which can cause oxidative stress and severe harm to the cells lining the stomach.(44)

In rats, the drug is given orally at a dose of 5–50 mg/kg (45,46) The medication is given orally to mice in doses of 10–30 mg/kg (47,48). 0.5% of opthalmic solution of ketorolac is administered in dogs for 28days (49).

4.6 Meloxicam induced ulcer

Meloxicam primarily causes gastrointestinal ulcers by blocking COX enzymes, which lowers PGE_2 production, mucus, bicarbonate secretion, and blood flow to the stomach mucosa.

This makes the stomach mucosal barrier weaker and makes the stomach more vulnerable to damage from pepsin and acid.Additionally, meloxicam increases oxidative stress by raising lipid peroxidation and lowering antioxidants like SOD and GSH.These consequences lead to erosion, bleeding, damage to the stomach epithelium, and eventually the development of ulcers.(50)

Rats are given the drug orally for 28 days at a dose of 3.75–30 mg/kg (50). The medication is given orally and subcutaneously to mice at a dose of 10–20 mg/kg for 7 - 14 days (51,52).

4.7 Reserpine induced ulcer

Reserpine is a vesicular monoamine transporter (VMAT) inhibitor that causes sympathetic nerve terminals to lose catecholamines and other monoamines. It has long been used to induce experimental gastrointestinal ulcers in rats, especially as a model of stomach mucosal damage brought on by stress. Thru disruptions in autonomic regulation, stomach secretion, mucosal blood flow, and de-granulation of gastric mast cells as a result of histamine release, which is thot to be regulated by the cholinergic system, reserpine treatment causes gastric mucosal ulcers. (53)

Rats are given intraperitoneal and subcutaneous doses of 5-8 mg/kg of reserpine (54,55,56)The drug is given intraperitoneally and subcutaneously to mice at a dose of 5–10 mg/kg (57) and the trial lasts for 7–14 days.

4.8 Prednisolone induced ulcer

A synthetic glucocorticoid with strong anti-inflammatory and immunosuppressive properties is prednisolone. Experimental investigations have shown that repeated or high-dose prednisolone administration can cause stomach mucosal lesions, despite the fact that corticosteroids are often less ulcerogenic than NSAIDs. The primary cause of prednisolone-induced gastric damage is disruption of the stomach mucosa's natural defensive and repair processes. Prednisolone 50 mg/kg administered subcutaneously once daily for four days caused stomach lesions in rats that were not fasting in a traditional rat paradigm (58)

4.9 5-Fluorouracil induced ulcer

By preventing DNA synthesis and the proliferation of rapidly dividing gastric epithelial cells, 5-fluorouracil (5-FU) can cause damage to the gastric mucosa by decreasing epithelial regeneration and repair. Additionally, it reduces the synthesis of mucus and mucin in the stomach, which weakens the gastrointestinal barrier and exposes the mucosa to more gastric acid. Furthermore, 5-FU can lower blood flow to the stomach mucosa, which can hinder the availability of nutrients and oxygen needed for mucosal healing and defense (59). When 5-FU is given to rats at doses of 50–500 mg/kg (60,61), it increases the mucosal susceptibility to damage, leading to erosion and ulceration as well as delayed healing of stomach ulcers.The medication is given intraperitoneally (i.p.) to mice at a dose of 50–450 mg/kg (62).

4.10 Mycophenolate induced ulcer

Mycophenolate mofetil (MMF) is transformed into mycophenolic acid (MPA), which prevents the fast division of gastrointestinal epithelial cells and inhibits inosine monophosphate dehydrogenase. Mucosal regeneration and repair may be hampered by this. Additionally, MMF causes a local inflammatory response that results in oxidative/inflammatory tissue damage due to elevated myeloperoxidase (MPO) activity and nitric oxide (NO). Mucosal erosion and ulceration may develop as a result of the ensuing epithelium damage, inflammation, and poor repair. Rather than a repeatable isolated gastric ulcer model, the best evidence in rats is for intestinal (especially jejunal and ileal) harm (63). The drug is given orally, intraperitoneally, in rat at a dose of 10-300 mg/kg (64,65). Drug doses in mice range from 20 to 500 mg/kg (66).

4.11 Alendronate induced ulcer

When alendronate comes into direct touch with the stomach mucosa, it acts as a topical irritant that damages the epithelium and disrupts the mucosal barrier. It increases the mucosa's susceptibility by reducing the transmucosal potential differential. Then, alendronate increases oxidative stress by lowering antioxidant defenses like SOD and GSH and increasing lipid peroxidation/MDA and MPO activity. Additionally, it inhibits the protective NO/cGMP/KATP pathway by lowering eNOS and iNOS expression, which lowers nitric oxide (NO) production. Antral ulceration and stomach mucosal damage are the results of the ensuing oxidative and inflammatory damage (67,68). Rats are given the medication orally at a dose of 20–700 mg/kg (69).

Drug	Animals	Dose(mg/kg/day)	Route	Duration
Indomethacin	Rats	18–60 mg/kg	P.O , I.P	7-14 days
	Mice	18–40 mg/kg	P.O, I.P	7-14 days
	Guinea pig	10–100 mg/kg	P.O, I.P	7-14 days
	Rabbit	20–75 mg/kg	P.O , S.C	7-14 days
Aspirin	Rats	150–300 mg/kg	P.O	7-14 days
	Mice	150–300 mg/kg	P.O	7-14 days
	Guinea pig	200–500 mg/kg	P.O	7-14 days
	Rabbit	150–400 mg/kg	P.O	30 days
Ibuprofen	Rat	200–400 mg/kg	P.O, I.P	7-14 days
	mice	200–400 mg/kg	P.O, I.P	7-14 days
Diclofenac	Rat	10–100 mg/kg	P.O, I.P	7-14 days
	mice	10–100 mg/kg	P.O, I.P	7-14 days
Ketorolac	Rat	5-50mg/kg	P.O	28 days
	Mice	10-30mg/kg	P.O	28days
	Dog	0.5% Opthalmic solution	Opthalmic	28 days
Meloxicam	Rat	3.75–30 mg/kg	P.O	28 days
	Mice	10–20 mg/kg	P.O , S.C	7-14 days
Reserpine	Rat	5-8 mg/kg	P.O , S.C	7-14 days
	mice	5–10 mg/kg	P.O , S.C	7-14 days
Prednisolone	rat	50 mg/kg	S.C	4 days
	Rat	0.21–0.25 ml/kg of 30% (low dose) to 80% (high dose)	Topical	7-14 days
	Mice	0.1 ml of 20%	Topical	7-14 days
	Rabbit	0.2 ml of 60%	Topical	30 days
5-Fluorouracil	Rat	50-500mg/kg	I.P	7-14 days
	Mice	50-450mg/kg	I.P	7-14 days
Mycophenolate	Rat	10-300mg/kg	I.P	7-14 days
	Mice	20-500mg/kg	I.P	7-14 days

Drug	Animals	Dose(mg/kg/day)	Route	Duration
Alendronate	Rat	20-700mg/kg	P.O	7-14 days

5. Biomarkers of Peptic ulcer

5.1 Macroscopic biomarkers

- **Ulcer score :**In experimental animals, the ulcer score is a macroscopic grading system used to assess the degree of gastrointestinal mucosal damage. Following the induction of an ulcer, the stomach is removed, opened along the larger curvature, cleaned with saline, and checked for erosions, bleeding, and ulcers. A numerical score is given to each lesion based on its quantity, size, and/or severity.(50)

The following are Ulcer Scores (51)

0 = lesions are absent

1 = tiny, spherical hemorrhagic areas

2 = Lesions <2 mm

3 = 2–3 mm lesions

4 = lesions 3–4 mm

5 indicates lesion > 4 mm

- **Ulcer index:** The overall degree of stomach mucosal ulcers in an experimental animal is quantitatively measured macroscopically using the Ulcer Index (UI). Depending on the technique employed, it incorporates data such as the quantity of ulcers, the degree of lesions, and/or the percentage of animals that develop ulcers.It is primarily used to assess a test drug's gastroprotective/anti-ulcer effects and to compare the ulcer-control group with drug-treated groups.(52)

The ulcer index, the percentage protective ratio, and the percentage curative ratio are, respectively, given by the following equation:

Ulcer Index = Total ulcer score

No. of animals ulcerated

- **Ulcer area:** After the stomach is removed, opened along its larger curvature, cleaned, and examined macroscopically, the entire surface area of visible gastric mucosal ulcerative/hemorrhagic lesions is quantified. Ulcer area is typically calculated as follows: mm^2 per stomach. The gastric ulcer area (mm2) of the stomach sample was measured using the image J program. Using a ruler, the ulcer's length and width were measured in order to determine the overall ulcer area. The percentage of ulcer inhibition (%) by the treatment was calculated using the following formula, and the resulting ulcer index was expressed as the mean score value for each animal.(53,54,55)

Protection inhibition (%) = [(UA control − UA treated) / UA control] × 100

5.2 Gastric secretion biomarkers

- **Gastric volume:** The measured amount of gastric juice extracted from an experimental animal's stomach during a predetermined therapy or ulcer-induction time, which represents gastric secretory activity, is known as gastric volume.Typically, it is stated in milliliters (mL) (56,57).
- **Gastric pH:** The hydrogen-ion concentration (acidity) of gastric juice taken from an experimental animal's stomach is measured. Whereas a higher pH denotes less acidity, a lower pH denotes more acidity. An significant aggressive factor in damage to the stomach mucosa is gastric acid. As a result, pH measurement is useful in determining whether an ulcerogenic medication has changed the acidity of the stomach and whether a test treatment may preserve or repair the stomach mucosa. A digital pH meter was used to assess the pH of the supernatant after the stomach contents were collected into centrifuge tubes and spun at 4,000 rpm for 10 minutes. (55,56,57,59).
- **Free acidity:** Gastric acid secretion and acid-related aggressive behavior in experimental gastric ulceration are measured using free acidity, which is the concentration of unbound/free hydrochloric acid in the stomach juice. The contents of the stomach were transferred into centrifuge tubes and spun at 4,000 rpm for 10 minutes. The free acidity of the centrifuged gastric juice was measured by titrating

it against 0.1 N NaOH using the Topfer reagent.(55, 58, 59)

- **Total Acidity:** The total amount of acid in stomach juice is known as total acidity. It is frequently employed in experimental gastro-ulcer research to evaluate hyperacidity and gastric acid secretion as well as to ascertain whether an anti-ulcer medication lowers gastric acid output.Centrifuged stomach juice was titrated against 0.1 N NaOH by adding two to three drops of Topfer's reagent until the solution turned yellowish orange and all traces of red were gone. It was observed the volume of the alkali that corresponded to free acidity. After adding two to three drops of the indicator phenolphthalein solution, the titration was carried out until a distinct red tint emerged. Once more, the total alkali volume that matched the overall acidity was recorded. (58,59)

Acidity (meq/l/100 g) was calculated by the equation (acidity = $Volume_{NaOH}$ ×$Normality_{NaOH}$ × 100/0.1).

Gastric wall mucus: Gastric wall mucus was determined using the Alcian blue binding method. Briefly, the glandular part of the stomach was separated after opening it along the greater curvature and weighed. The tissue was then immersed in 10 mL of 0.1% (w/v) Alcian blue solution prepared in 0.16 M sucrose and buffered with 0.05 M sodium acetate. The pH of the solution was adjusted using hydrochloric acid (HCl), and the tissue was allowed to remain in the dye solution for 2 hours. Following incubation, the tissue was washed twice with 10 mL of 0.25 M sucrose solution for 15 and 45 minutes, respectively, to eliminate unbound dye. The mucus-bound Alcian blue was subsequently extracted using 10 mL of 0.5 M magnesium chloride ($MgCl_2$), with the mixture being shaken for one minute at 30-minute intervals over a period of 2 hours. An equal volume of diethyl ether was then added, and the mixture was shaken thoroughly before centrifugation at 3000 rpm for 10 minutes. The absorbance of the separated aqueous layer was measured at 580 nm against a magnesium chloride blank using a spectrophotometer. The concentration of Alcian blue was determined with the help of a standard calibration curve, and the gastric wall mucus content was expressed as micrograms of Alcian blue per gram of glandular stomach tissue (µg/g).(60)

5.3 Oxidative strees biomarkers :

- **Malondialdehyde (MDA):** A common indicator of oxidative stress in experimental gastric ulcer research, MDA is a significant secondary product of lipid peroxidation. When stomach mucosal damage occurs, increased creation of reactive oxygen species encourages membrane polyunsaturated fatty acid peroxidation, which increases the formation of MDA. Consequently, increased lipid peroxidation and oxidative damage are indicated by increasing gastric-tissue MDA. This causes damage to the stomach mucosa and the development of ulcers.(55, 14)
- **Glutathione (GSH):** Glutamate, cysteine, and glycine make up the tripeptide GSH. In the stomach mucosa, it serves as a significant endogenous antioxidant. Reactive oxygen species (ROS) are increased by ulcerogenic factors during the development of peptic ulcers. GSH neutralizes ROS and, via glutathione peroxidase, decreases hydrogen peroxide and lipid peroxidation. This preserves the stomach mucosal barrier and offers gastroprotection by reducing MDA production, oxidative damage, and gastric epithelial cell injury. Therefore, while GSH depletion is linked to higher stomach mucosal damage and ulceration, increasing GSH signals enhanced antioxidant defense.[37]
- **Superoxide Dismutase (SOD) and Catalase (CAT):** These two crucial antioxidant enzymes shield the stomach mucosa from oxidative stress during the development of peptic ulcers. In order to stop additional ROS-mediated cellular damage, SOD turns the dangerous superoxide radicals ($O_2•^-$) into hydrogen peroxide (H_2O_2), which CAT then further reduces into water and oxygen. When combined, they lessen oxidative damage, lipid peroxidation, and damage to the stomach mucosa. Thus, better antioxidant defense and gastroprotection are shown by elevated or restored SOD and CAT activity in experimental ulcer studies.(38)

5.4 Inflammatory biomarkers:

- **Nitric oxide (NO)**: By boosting stomach mucosal blood flow, nitric oxide (NO) functions as a crucial gastroprotective mediator in peptic ulcers, improving the delivery of oxygen and nutrients to injured tissue and accelerating ulcer healing. Additionally, NO fortifies the stomach mucosal barrier, promotes the secretion of mucus and bicarbonate, and aids in the preservation of epithelial integrity.Furthermore, it can minimize oxidative damage and decrease inflammation and leukocyte adhesion. Thus, sufficient NO availability aids in shielding the stomach mucosa from ulcer-causing substances including ethanol, NSAIDs, and other irritants.(58,61,63)
- **Prostaglandin E2:** The integrity of the stomach mucosa is preserved by prostaglandin E_2 (PGE_2), a crucial gastroprotective mediator. By boosting mucus and bicarbonate secretion, preserving mucosal blood flow, lowering gastric acid output, and encouraging epithelial repair and ulcer healing, it shields the stomach. Inhibition of COX enzymes weakens these protective mechanisms and increases stomach mucosal damage in NSAID-induced peptic ulcer models by reducing PGE_2 synthesis. Consequently, elevated gastric PGE_2 levels following therapy are typically regarded as a sign of enhanced gastroprotection and mucosal defense.(62,63)

5.5 Pro Inflammatory cytokines:

- **Tumor Necrosis Factor-α (TNF-α), Interleukin-1β (IL-1β), and IL-6 :** Tissue damage and oxidative stress trigger inflammatory pathways, especially NF-κB, which increases the production of TNF-α, IL-1β, and IL-6 during the development of stomach ulcers. These cytokines encourage the recruitment of inflammatory cells, oxidative damage, mucosal damage, and delayed repair. As a result, increased levels of these cytokines are frequently employed as indicators of the severity of ulcers and stomach inflammation.(58,63)

Table 3: ***Changes in biomarkers commonly reported in experimental Drug-Induced Peptic ulcer (DIPU).***

Biomarker	Change in DIPU	Range in DIPU animal studies	Ref
Ulcer score	Increased	29.0 + 1.7	50
Ulcer index	Increased	22.57 + 6.86 mm	65
Ulcer area	Increased	mm^2	53,54,55
Gastric volume	Increased	4.69 + 0.37 mL	56,57
Gastric pH	Decreased	2.78+0.25 pH	55,56,57,59
Free acidity	Increased	9.6 + 0.6 mEq/L	55,58,59
Total Acidity	Increased	20.8 + 2.5 mEq/L	58,59
Gastric wall mucus	Decreased	100.33 + 0.76 µg	60
MDA	Increased	59.73 + 11.20 nmol/mg tissue	14,55
GSH	Decreased	22.18 + 5.42 mmol/mg tissue	37
SOD	Decreased	1.003 + 0.19 U/mg tissue	38
CAT	Decreased	14.29 + 0.48 µmol/L	*38*
Nitric oxide	Decreased	8.02 + 2.75 nmol/mg tissue	58,61,63
PGE_2	Decreased	72.50 + 0.593 ng/mg protein	62,63
TNF-α	Increased	796.5 + 13.7	58,63
IL-1β	Increased	-	58,63
IL-6	Increased	-	58,63

6. Future Perspective on drug induced peptic ulcer in experimental animals.

6.1 Development of Advanced Animal Models

Future research should focus on developing advanced experimental animal models that closely resemble clinical drug-induced peptic ulcers. Most conventional

studies use a single ulcer-inducing drug, such as indomethacin or aspirin, to produce acute gastric injury. However, future studies should investigate combination-drug models, such as NSAIDs with corticosteroids or antiplatelet agents, to understand the effects of multiple medications on gastric mucosal damage. Such models may provide better insights into drug interactions and ulcer complications.(7)

6.2 Investigation of Chronic Ulcer Formation and Healing

Most experimental studies focus on acute gastric ulcer formation. Future investigations should emphasize chronic ulcer development, delayed healing, recurrence, and tissue regeneration. Acetic acid-induced chronic gastric ulcer models in rats can be used to investigate ulcer healing, angiogenesis, mucosal regeneration, and recurrence. Researchers should also examine the effects of prolonged NSAID exposure on matrix metalloproteinases (MMPs), growth factors, and tissue remodeling.(7)

6.3 Identification of Novel Molecular and Biochemical Biomarkers

Future studies should investigate additional molecular pathways involved in drug-induced gastric injury. Apart from conventional oxidative stress markers such as MDA, GSH, SOD, and CAT, researchers should evaluate inflammatory cytokines, apoptosis-related proteins, and angiogenic factors. Particular attention should be given to NF-κB, Nrf2, COX-1, COX-2, caspases, VEGF, and matrix metalloproteinases. These investigations may help identify new therapeutic targets for gastroprotection.(84)

6.4 Development of Gastric Organoid and Stomach-on-a-Chip Models

Gastric organoids and stomach-on-a-chip technologies may provide additional platforms for investigating drug-induced gastric mucosal injury. These models can help study epithelial barrier damage, cellular responses, and drug toxicity before conducting animal experiments. In the future, combining these techniques with rat and mouse models may improve the reliability of preclinical research and reduce unnecessary animal use.(85)

6.5 Translational Research and Development of Safer Gastroprotective Agents

Future investigations should focus on translating experimental findings into clinically useful gastroprotective treatments. Newly developed compounds should be evaluated for their ability to prevent gastric mucosal injury without interfering with the therapeutic activity of NSAIDs. Standardized experimental protocols, reproducible results, and comprehensive toxicological evaluations will be important for successful translation into clinical applications.(84)

CONCLUSION

Drug-induced peptic ulcer is an important gastrointestinal disorder commonly associated with the use of NSAIDs and other ulcerogenic medications. Experimental animal models, particularly rats and mice, play a significant role in understanding the mechanisms involved in gastric mucosal damage and evaluating the gastroprotective potential of various therapeutic agents. Different ulcer induction models, including indomethacin, aspirin, ibuprofen, diclofenac, ketorolac, and other drugs, help researchers investigate the pathophysiology of gastric ulceration. Assessment of macroscopic, biochemical, and histopathological parameters provides valuable information regarding ulcer severity, oxidative stress, inflammation, and mucosal protection. Recent studies have highlighted the potential of medicinal plants, phytochemicals, antioxidants, probiotics, and synthetic compounds in preventing and treating gastric ulcers. Future research should focus on developing advanced experimental models, identifying novel molecular biomarkers, investigating chronic ulcer healing, and exploring alternative technologies such as gastric organoids. Overall, experimental animal studies provide a strong foundation for discovering safer and more effective gastroprotective agents and translating preclinical findings into potential clinical applications.

REFERENCES

1. Dawood HA. Peptic ulcer disease (Doctoral dissertation, College of Medicine A Review Article in: Peptic ulcer disease Submitted to the Council of the College of Medicine, Diyala University).

2. Melcarne L, García-Iglesias P, Calvet X. Management of NSAID-associated peptic ulcer disease. Expert Review of Gastroenterology & Hepatology. 2016 Jun 2;10 (6):723-33.
3. Wallace JL. How do NSAIDs cause ulcer disease? Best Pract Res Clin Gastroenterol. 2000;14 (1):147-159.
4. Adinortey MB, Ansah C, Galyuon I, Nyarko A. In Vivo Models Used for Evaluation of Potential Antigastroduodenal Ulcer Agents. [190] CODEN (USA): JDDTAO Satapathy et al Hindawi Publishing Corporation Ulcer. 2013; 2013:12. https://doi.org/10.1155/2013/796405 .open the file
5. Satapathy T, Sen K, Sahu S, Pradhan B, Gupta A, Khan MA, et al. Experimental animal models for gastric ulcer/peptic ulcer: An overview. J Drug Deliv Ther. 2024;14 (1):182-189.
6. Akbaş N, Süleyman B, Mammadov R, et al. Effect of felodipine on indomethacin-induced gastric ulcers in rats. Exp Anim. 2023;72 (4):505-512.
7. Okabe S, Amagase K. An overview of acetic acid ulcer models—the history and state of the art of peptic ulcer research. Biol Pharm Bull. 2005;28 (8):1321-1341.
8. Laine L. Nonsteroidal anti-inflammatory drug gastropathy. Gastrointest Endosc Clin N Am. 1996;6:489 –504.
9. Yuan JQ, Tsoi KK, Yang M, et al. Systematic review with network meta-analysis: comparative effectiveness and safety of strategies for preventing NSAID-associated gastrointestinal toxicity. Aliment Pharmacol Ther 2016;43:1262–1275. doi: 10.1111/apt.13642
10. Lau JY, Sung J, Hill C, Henderson C, Howden CW, Metz DC. Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality. Digestion. 2011;84:102–113. doi: 10.1159/000323958.
11. Malfertheiner P, Chan FKL, McColl KEL. Peptic ulcer disease. *Lancet.* 2009;374 (9699):1449–1461.
12. Jung HK, et al. Clinical Guidelines for Drug-Related Peptic Ulcer, 2020 Revised Edition. *Gut Liver.* 2020.
13. Tamaddonfard E, Erfanparast A, Farshid AA,Imani M,Navideh M, SalighedarR et.al. Safranal, a constituent of saffron, exerts gastroprotective effects against indomethacin-induced gastric ulcer. Life Sciences. 2019;224:88-94.
14. Mahmoud MF, Abdo W, Mohamed N, Drissi B, Abdelfattah M AO, Sobeh M et.al. Apple (MalusdomesticaBorkh) leaves attenuate indomethacin-induced gastric ulcer in rats. Biomedicine & Pharmacotherapy. 2023;160.
15. Feng L,BaoT,BaiL, Mu X, Ta Na, BaoM et.al. Mongolian medicine formulae Ruda-6 alleviates indomethacin-induced gastric ulcer by regulating gut microbiome and serum metabolomics in rats. Journal of Ethnopharmacology. 2023;314.
16. Jiang GL, Im WB, Donde Y, Wheeler LA. EP4 agonist alleviates indomethacin-induced gastric lesions and promotes chronic gastric ulcer healing. *World J Gastroenterol*. 2009;15 (41):5149–5156. doi:10.3748/wjg.15.5149. PMID:19891013.
17. Aly MH, Said AK, Farghaly AM, Abd El Aziz RM, El-Sayed NS. Protective effect of astaxanthin on indomethacin-induced gastric ulcerations in mice. *Naunyn Schmiedebergs Arch Pharmacol*. 2024;397 (12):9897–9907. doi:10.1007/s00210-024-03206-4.
18. Albaser N, Ghanem N, Shehab M, Al-Adhal A, Al-Kamarany MA. Investigation of Pharmacological Activity of *Caralluma penicillata*: Anti-Inflammatory Properties and Gastritis Protection against Indomethacin in Adult Guinea Pigs. *International Scholarly Research Notices*. 2014;2014:738493. doi:10.1155/2014/738493.
19. Sugita R, Kubota K, Sugimoto K, Tachida Y, Shibayama T, Kiho T, et al. A novel selective prostaglandin E2 synthesis inhibitor relieves pyrexia and arthritis in guinea pigs inflammatory models. J Pharmacol Sci. 2016;130 (2):128-135. doi:10.1016/j.jphs.2016.01.009.
20. Lee M, Kallal SM, Feldman M. Omeprazole prevents indomethacin-induced gastric ulcers in

rabbits. *Aliment Pharmacol Ther.* 1996;10 (4):571-576. doi:10.1046/j.1365-2036.1996.34176000.x.

21. Al-Saeed MH, Al-Masoudi EA, Abdul-Razak AS. Study the effect of proanthocyanidin and ranitidine on haematology and biochemical parameters in adult female rabbits with gastric ulceration induced by indomethacin. *Basrah J Vet Res.* 2016;15 (1):132-160. doi:10.33762/bvetr.2016.124262.
22. Kleindorfer DO, Towfighi A, Chaturvedi S et al. Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2021;52:e364–467
23. Yeomans ND, Lanas AI, Talley NJ, et al. Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin. Aliment Pharm Ther. 2005;22:795–801.
24. Abdelatif BS, El-Safty FNA, Zolfakar AS, Essawy A. The Potential Curative and Prophylactic Effects of Grape Seed Extract on Aspirin Induced Gastric Ulcer in Adult Male Albino Rats. *Journal of Clinical and Diagnostic Research*. 2019;13 (7):AF01-AF06. doi:10.7860/JCDR/2019/41620.13016.
25. Weng J, Song Y, Kuai D, Dai W, Yao Y, Xu W, et al. Omeprazole taken once every other day can effectively prevent aspirin-induced gastrointestinal mucosal damage in rats. *BMC Gastroenterol.* 2024;24:187. doi:10.1186/s12876-024-03265-0.
26. Moke EG, Umukoro EK, Akponah E, Chinwuba P, Demaki WE. Gastro-protective activities of misoprostol and omeprazole on aspirin-induced gastric ulceration in rat model. *Trop J Pharm Res.* 2025;24 (12). doi:10.4314/tjpr.v24i12.5.
27. Jha DK, Rajashekhar U, Yadav N. Gastro-protective effect of root extract of *Barleria buxifolia* on aspirin induced gastric ulcer in rats. *Int J Pharm Sci Drug Res.* 2024;16 (2):157-162. doi:10.25004/IJPSDR.2024.160204.
28. Yue P, Hou J, Shi J, Wu Q, Han L, Peng D, Zhang P. *Protective Effects and Underlying Mechanisms of Isoschaftoside Against Aspirin-Induced Gastric Mucosal Injury in Mice.* International Journal of Pharmacology. 2025/2026;21 (7):46588. DOI: 10.31083/IJP46588.
29. Hemamalini K, Ramulu Y, Rambabu B. *Protective Effect of Raphanus sativus Using by Phytochemical and Antiulcer Activity by Aspirin Induced Gastric Ulcer.* Journal of Pharmaceutical Research International. 2025;37 (1):83–89. DOI: 10.9734/jpri/2025/v37i17650.
30. Singh AK, Kavitha B. Comparative Study of Anti Ulcer Effect of Aloe Vera, Omeprazole and Rabeprazole in Aspirin Induced Peptic Ulcers in Guinea Pigs. *International Journal of Scientific Research.* 2014;3 (10).
31. Kadhem MA, Abdul-Niby AA, Khassaf HK. Study the effect of Ethanolic extract of *Anethum graveolens* L. on Aspirin induced Gastric Ulcer in Male Guinea Pigs. *Research Journal of Pharmacy and Technology.* 2018;11 (9):3793–3798. doi:10.5958/0974-360X.2018.00695.9.
32. Pasha I, Arshad A, Ahmad F, Raza A. Antiulcerative potential of sweet potato (*Ipomoea batatas*) against aspirin-induced gastric ulcers in a rabbit model. Nutrition. 2022;98:111799. doi:10.1016/j.nut.2022.111799.
33. Zaidi SU, Khan MWA, Yaseen S, Gul M, Rashid Z, Saqib M. Novel protective role of montelukast against aspirin induced gastric ulceration in rabbits – Montelukast; a revolutionary aspect. Pak Armed Forces Med J. 2019;69 (5):1088–1093.
34. Al-Saeed MH. Study the effect of aqueous extract of *Piper nigrum* on some physiological parameters and histopathological changes in female rabbits induced gastric ulceration by aspirin. Journal of Kerbala University. 2011;4 (12).
35. Santhosh S, Anandan R, Sini TK, Mathew PT. Protective effect of glucosamine against ibuprofen-induced peptic ulcer in rats. *Journal of Gastroenterology and Hepatology.* 2007;22 (6):949–953. doi:10.1111/j.1440-1746.2007.04840.x.
36. Liu J, Sun D, He J, Yang C, Hu T, Zhang L, et al. Gastroprotective effects of several H2RAs on

ibuprofen-induced gastric ulcer in rats. *Life Sciences.* 2016;149:65–71. doi:10.1016/j.lfs.2016.02.045.

37. Aliouche N, Sifour M, Kebsa W, Khennouf T, Ercan F, Ouled-Haddar H. Prophylactic Effect and Antiulcerogenic Potential of Probiotic *Lactiplantibacillus plantarum* E1K2R2 and its Exopolysaccharide Against Ibuprofen-Induced Acute Gastric Ulcer. *Probiotics and Antimicrobial Proteins*. 2025;17 (6):3887–3902. doi:10.1007/s12602-024-10321-4.
38. Adebayo-Gege G, et al. Molecular docking and anti-ulcerative potential of *Cucumis* (L. Inodorous) on ibuprofen induced gastric ulceration in male Wistar animals. *Biomedicine & Pharmacotherapy*. 2023;161:114531. doi:10.1016/j.biopha.2023.114531.
39. Machado FDF, Silva FV, Fernandes HB, et al. Gastroprotective effect of an ethanolic extract from *Neoglaziovia variegata* (Arruda) Mez (Bromeliaceae) in rats and mice. Zeitschrift für Naturforschung C. 2013;68 (3–4):97–107.
40. Khan MI, Khan MR. Gastroprotective potential of *Dalbergia sissoo* Roxb. stem bark against diclofenac-induced gastric damage in rats. Osong Public Health Res Perspect. 2013;4 (5):271-277. doi:10.1016/j.phrp.2013.09.006.
41. Ghoneim ME, Noureldin MH, El Sayed I, El Banna YY, El Sayed NF. Novel gastroprotective role of Alogliptin: Modulating the GDNF/PI3K/Akt/GSK3β, SDF-1/CXCR4, and CREB/COX-2/PGE2 signalling pathways to ameliorate diclofenac-induced peptic ulcer in rats. *European Journal of Pharmacology.* 2026;1029:179066. doi: 10.1016/j.ejphar.2026.179066.
42. Sharif SJ, Kadhim HM, Ahmed BS, Ridha-Salman H. Gastroprotective and therapeutic effects of emodin on rat model of diclofenac-induced gastric ulceration. *Naunyn-Schmiedeberg's Archives of Pharmacology.* 2026;399 (3):4519–4536. doi: 10.1007/s00210-025-04701-y.
43. Goswami SK, Rand AA, Wan D, Yang J, Inceoglu B, Thomas M, Morisseau C, Yang GY, Hammock BD. Pharmacological inhibition of soluble epoxide hydrolase or genetic deletion reduces diclofenac-induced gastric ulcers. *Life Sciences.* 2017;180:114-122. doi:10.1016/j.lfs.2017.05.018.
44. Majumder R, Datta M, Banerjee A, Roy T, Bandyopadhyay A, Bandyopadhyay D, Chattopadhyay A. Possible role of the mitochondrial pyruvate dehydrogenase in ketorolac mediated onset and progression of gastric ulcers in male Wistar rats: Protection by melatonin. Biochim Biophys Acta Mol Basis Dis. 2025;1871 (6):167908. doi:10.1016/j.bbadis.2025.167908.
45. El-Gizawy SA, et al. In vivo Evaluation of Ulcerogenic Activity of Ketorolac, its Solid Dispersion Systems, as Well as its Microcapsules in Rats. *Research & Reviews: A Journal of Pharmaceutical Science.* 2015;4 (3):26–32.
46. Majumder R, Datta M, Banerjee A, Bandyopadhyay D, Chattopadhyay A. Melatonin protects against ketorolac induced gastric mucosal toxic injuries through molecular mechanism associated with the modulation of Arylakylamine N-Acetyltransferase (AANAT) activity. *Chemico-Biological Interactions.* 2023;382:110611. doi: 10.1016/j.cbi.2023.110611
47. Russo R, De Caro C, Avallone B, Magliocca S, Nieddu M, Boatto G, Troiano R, Cuomo R, Cirillo C, Avagliano C, Cristiano C, La Rana G, Sarnelli G, Calignano A, Rimoli MG.Ketogal: A Derivative Ketorolac Molecule with Minor Ulcerogenic and Renal Toxicity. *Frontiers in Pharmacology.* 2017;8:757.
48. Darkazally AZ, Alnour A, Homsi S. Troxerutin effect on gastric ulcers induced by ketorolac in rats: Relation with oxidative stress. *Heliyon.* 2024;10 (19):e38893.
49. Van Vertloo LR, et al. Systemic absorption and gastrointestinal adverse effects from topical ketorolac and diclofenac ophthalmic solutions in healthy dogs. J Am Vet Med Assoc. 2024;262 (7):940–949. doi:10.2460/javma.23.12.0707.
50. Villegas I, Martín MJ, La Casa C, Motilva V. Effects of meloxicam on oxygen radical generation

in rat gastric mucosa. *Inflammopharmacology.* 2000;8:209–216. DOI: 10.1007/PL00000217.

51. Kim J, Cannon BA, Freeman LE, et al. High-dose meloxicam provides improved analgesia in female CD1 mice. J Am Assoc Lab Anim Sci. 2023;62 (1):74-80.
52. Kendall LV, Bailey AL, Singh B, McGee WK. Toxic effects of high-dose meloxicam and carprofen on female CD1 mice. J Am Assoc Lab Anim Sci. 2022;61 (1):75-80. doi:10.30802/AALAS-JAALAS-21-000071
53. Gupta MB, Tangri KK, Bhargava KP. Mechanism of ulcerogenic activity of reserpine in albino rats. *European Journal of Pharmacology.* 1974;27 (2):269–271. doi:10.1016/0014-2999 (74)90159-9.
54. Pfeiffer CJ, Cho CH, Cheema A, Saltman D. Reserpine-induced gastric ulcers: protection by lysosomal stabilization due to zinc. *European Journal of Pharmacology.* 1980;61 (4):347–353. doi:10.1016/0014-2999 (80)90073-4.
55. Kagoshima M, Suguro N. Gastric movement of the rat in reserpine-induced ulcer. *Folia Pharmacologica Japonica.* 1982;80 (3):231–238. doi:10.1254/fpj.80.231
56. Adinortey MB, Ansah C, Galyuon I, Nyarko A. In vivo models used for evaluation of potential antigastroduodenal ulcer agents. *Ulcers.* 2013;2013:796405. doi:10.1155/2013/796405.
57. Zhou YL, Wang R, Feng X, Zhao X. Preventive effect of insect tea against reserpine-induced gastric ulcers in mice. *Experimental and Therapeutic Medicine.* 2014;8 (4):1318–1324.
58. Nobuhara Y, Takeuchi K, Okabe S. *Effects of Various Agents on Prednisolone-Induced Gastric Lesions in Rats.* Japanese Journal of Pharmacology. 1985;38 (2):219–222. DOI: 10.1254/jjp.38.219.
59. Saegusa Y, Ichikawa T, Iwai T, Goso Y, Ikezawa T, Nakano M, Shikama N, Saigenji K, Ishihara K. Effects of acid antisecretory drugs on mucus barrier of the rat against 5-fluorouracil-induced gastrointestinal mucositis. *Scandinavian Journal of Gastroenterology.* 2008;43 (5):531–537. doi:10.1080/00365520701811693
60. Medeiros ADC, Azevedo ÍM, Lima ML, Araújo Filho I, Moreira MD. *Effects of simvastatin on 5-fluorouracil-induced gastrointestinal mucositis in rats.* Rev Col Bras Cir. 2018;45 (5):e20181968. doi:10.1590/0100-6991e-20181968
61. Ciobanu L, Tantau M, Valean S, Parau A, Bedecean I, Mîrleneanu R, Berce C, Catoi C, Taulescu M. Rifaximin modulates 5-fluorouracil-induced gastrointestinal mucositis in rats. Eur Rev Med Pharmacol Sci. 2016;20 (23):4993–5001
62. Soares PMG, Lima-Junior RCP, Mota JMSCM, Justino PFC, Brito GAC, Ribeiro RA, Cunha FQ, Souza MHLP. Role of platelet-activating factor in the pathogenesis of 5-fluorouracil-induced intestinal mucositis in mice. European Journal of Pharmacology. 2011;652 (1–3): 223–230. doi:10.1016/j.ejphar.2010.11.004
63. Deng Y, et al. Mycophenolic Acid Induces the Intestinal Epithelial Barrier Damage through Mitochondrial ROS. *Oxidative Medicine and Cellular Longevity.* 2022;2022:4195699
64. Malekinejad H, Cheraghi H, Alizadeh A, et al. Nitric oxide and acute phase proteins are involved in pathogenesis of mycophenolate mofetil-induced gastrointestinal disorders in rats. *Transplantation Proceedings.* 2011;43 (7):2741–2746. doi:10.1016/j.transproceed.2011.04.016.
65. Dridi I, Ben-Cherif W, Haouas Z, Aouam K, Ben-Attia M, Reinberg A, Boughattas NA. *Gastrointestinal toxicity of mycophenolate mofetil in rats: Effect of administration time.* Chronobiology International. 2015;32 (10):1373–1384. doi: 10.3109/07420528.2015.1082481
66. Song Y, Hu W, Xiao Y, et al. Keratinocyte growth factor ameliorates mycophenolate mofetil-induced intestinal barrier disruption in mice. *Molecular Immunology.* 2020;124:61–69. doi:10.1016/j.molimm.2020.04.012.
67. Takeuchi K, Kato S, Amagase K. Gastric ulcerogenic and healing impairment actions of alendronate, a nitrogen-containing bisphosphonate—prophylactic effects of rebamipide. *Current Pharmaceutical Design.* 2011;17 (16):1602–1611. doi:10.2174/138161211796196927.

68. Işeri SO, Şener G, Yüksel M, Contuk G, Çetinel S, Gedik N, Yeğen BC.Ghrelin against alendronate-induced gastric damage in rats. *Journal of Endocrinology.* 2005;187 (3):399–406. DOI: 10.1677/joe.1.06432.)
69. Brzozowski T, et al. Hydrogen Sulfide and Carbon Monoxide Protect Gastric Mucosa Compromised by Mild Stress Against Alendronate Injury. *Digestive Diseases and Sciences.* 2016;61:3176–3189.)
70. Arab HH, Salama SA, Omar HA, Arafa EA, Maghrabi IA. Diosmin protects against ethanol-induced gastric injury in rats: novel anti-ulcer actions. PLoS One. 2015;10 (3):e0122417. doi:10.1371/journal.pone.0122417.
71. Nwafor PA, Okwuasaba FK, Binda LG. Antidiarrhoeal and antiulcerogenic effects of methanolic extract of Asparagus pubescens root in rats. J Ethnopharmacol. 2000;72 (3):421–427. pmid:10996281
72. Adinortey MB, Ansah C, Galyuon I, Nyarko A. In vivo models used for evaluation of potential antigastroduodenal ulcer agents. *Ulcers*. 2013;2013:796405. doi:10.1155/2013/796405.
73. Halabi MF, Shakir RM, Bardi DA, Al-Wajeeh NS, Ablat A, Hassandarvish P, Hajrezaie M, Norazit A, Abdulla MA. Gastroprotective activity of ethyl-4-[(3,5-di-tert-butyl-2-hydroxybenzylidene)amino]benzoate against ethanol-induced gastric mucosal ulcer in rats. *PLoS One.* 2014;9 (5):e95908. doi:10.1371/journal.pone.0095908.
74. Hajrezaie M, Salehen N, Karimian H, Zahedifard M, Shams K, Al Batran R, Abdul Majid N, Khalifa SAM, Mohd Ali H, El-Seedi H, Abdulla MA. Biochanin A gastroprotective effects in ethanol-induced gastric mucosal ulceration in rats. *PLoS One.* 2015;10 (3):e0121527. doi:10.1371/journal.pone.0121527. PubMed
75. Gong G, Zhao R, Zhu Y, Yu J, Wei B, Xu Y, Cui Z, Liang G. Gastroprotective effect of cirsilineol against hydrochloric acid/ethanol-induced gastric ulcer in rats. *Korean J Physiol Pharmacol.* 2021;25 (5):403–411. doi:10.4196/kjpp.2021.25.5.403
76. Kangwan N, Pintha K, Lekawanvijit S, Suttajit M. Rosmarinic acid enriched fraction from *Perilla frutescens* leaves strongly protects indomethacin-induced gastric ulcer in rats. *BioMed Res Int.* 2019;2019:9514703. doi:10.1155/2019/9514703.
77. Sabiu S, Garuba T, Sunmonu T, Ajani E, Sulyman A, Nurain I, Balogun A. Indomethacin-induced gastric ulceration in rats: Protective roles of *Spondias mombin* and *Ficus exasperata*. *Toxicol Rep.* 2015;2:261-267. doi:10.1016/j.toxrep.2015.01.002.
78. Raish M, Shahid M, Bin Jardan YA, Ansari MA, Alkharfy KM, Ahad A, Abdelrahman IA, Ahmad A, Al-Jenoobi FI. Gastroprotective effect of sinapic acid on ethanol-induced gastric ulcers in rats: involvement of Nrf2/HO-1 and NF-κB signaling and antiapoptotic role. *Front Pharmacol.* 2021;12:622815. doi:10.3389/fphar.2021.622815
79. Tarique M, Siddiqui HH, Khushtar M, Rahman MA. Protective effect of hydro-alcoholic extract of *Ruta graveolens* Linn. leaves on indomethacin and pylorus ligation-induced gastric ulcer in rats. J Ayurveda Integr Med. 2016;7 (1):38-43. doi:10.1016/j.jaim.2015.09.002.
80. *Corne S.J., Morrissey S.M., Woods R.J. Proceedings: a method for the quantitative estimation of gastric barrier mucus. J Physiol. 1974;242:116P–117P.*
81. Heeba GH, Hassan MKA, Amin RS. Gastroprotective effect of simvastatin against indomethacin-induced gastric ulcer in rats: Role of nitric oxide and prostaglandins. *European Journal of Pharmacology*. 2009;607 (1–3):188–193. doi:10.1016/j.ejphar.2009.02.008.
82. AlRashdi AS, Salama SM, Alkiyumi SS, Abdulla MA, Hadi AHA, Abdelwahab SI, Taha MM, Hussiani J, Asykin N. Mechanisms of gastroprotective effects of ethanolic leaf extract of *Jasminum sambac* against HCl/ethanol-induced gastric mucosal injury in rats. *Evidence-Based Complementary and Alternative Medicine.* 2012;2012:786426. doi:10.1155/2012/786426.
83. Almasaudi SB, El-Shitany NA, Abbas AT, Abdel-Dayem UA, Ali SS, Al Jaouni SK, Harakeh S.

Antioxidant, anti-inflammatory, and antiulcer potential of Manuka honey against gastric ulcer in rats. Oxid Med Cell Longev. 2016;2016:3643824. doi:10.1155/2016/3643824.

84. Seidlitz T, Koo BK, Stange DE. (2021). Gastric organoids—an in vitro model system for the study of gastric development and road to personalized medicine. Cell Death & Differentiation, 28, 68–83.

85. Carvalho MR, Yan LP, Li B, et al. (2023). Gastrointestinal organs and organoids-on-a-chip: advances and translation into the clinics. Biofabrication, 15 (4). https://doi.org/10.1088/1758-5090/acf8fb

HOW TO CITE: Savanth Swetha, Nabila Kulsum Abdul Aleem, Venu Talla, Drug Induced Peptic Ulcer in Experimental Animals, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 11, 1995-2010. https://doi.org/10.5281/zenodo.24156173