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A COMPREHENSIVE REVIEW ON THE SCREENING MODEL FOR THE PHARMACOLOGICAL ASSESSMENT OF ANTIULCER DRUGS

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ABSTRACT

- *Peptic ulcer disease (PUD), primarily caused by excessive gastric acid secretion, Helicobacter pylori infection, or the use of nonsteroidal anti-inflammatory drugs (NSAIDs), remains a significant global healthconcern. The pharmacological management of PUD relies on the development of antiulcer drugs that targetthe underlying mechanisms of ulcer formation and promote mucosal healing. Screening models play a crucial role in the preclinical assessment of potential antiulcer agents, helping to evaluate their efficacy, safety, and mechanisms of action. This review provides a comprehensive overview of the various in vitro and in vivo screening models used for the pharmacological assessment of antiulcer drugs.*
and high-throughput screening, in advancing drug development is also discussed.
- *This review aims to provide researchers and clinicians with a thorough understanding of the critical role that screening models play in the pharmacological evaluation of antiulcer drugs, highlighti ng both their current applications and future directions in drug development. By improving preclinical testing, more effective and safer antiulcer therapies can be developed forthe management of peptic ulcer disease.*

KEYWORDS: *peptic ulcer disease, antiulcer drugs, screening models, pharmacological assessment, Helicobacter pylori, gastric acid secretion, drug efficacy, pharmacodynamics, pharmacokinetics, toxicity, safety evaluation,*

INRODUCTION

- Gastrointestinal diseases are very serious and common problems, which are causing maximum discomfort, morbidity, and mobility in human beings. It occurs in 10-15% of thepopulation at a time. Apeptic ulcer is a group of disorders which is responsible for the ulcerformation or mucosal lesions formation in the esophageal lining (swallowing pipe), stomachor duodenum (the first part of the small intestine).
- PEPTIC ULCER: It is a chronic inflammatory condition involving a group of disorders characterized by ulceration in regions of upper gastrointestinal tract where parietal cells secret pepsin and hydrochloric acid .
- The symptoms of peptic ulcer are: severe pain and irritation in the upper abdomen. If it is not treated properly, it may result in perforations in the wall of the gastrointestinal tract.
- The small sores are formed due to the imbalance between mucosal defensive factors (bicarbonate, mucin, prostaglandin, nitric oxide, and otherpeptides and growth factors) andinjurious factors (pepsin, helicobacter pylori, nsaids gastric acid). Ulcer in the stomach is known as gastric ulcer while ulcer in thefirst part of the intestine is also known as a duodenalulcer.
- **Aggressive factors:** HCl, pepsin, refluxed bile, NSAIDs, alcohol, pancreatic proteolytic enzymes, ingested irritants, bacterial toxins, physiochemical trauma; all of these factors increase the acid secretion.
- **Digestive factors**: Mucus, bicarbonates, blood flow, resolution of epithelium, the current status of therapy.
- Disruption of the gastrointestinal (GI) mucosa due to gastric acid secretion or pepsin causespeptic ulcerdisease (PUD). It penetrates the gastric epithelium all the way down to the muscularis propria layer. It typically affects the stomach and the first part of the duodenum.
- The jejunum, distal duodenum, and lower oesophagus could be affected. In individuals witha stomach ulcer, epigastric pain typically develops within 15-30 minutes after a meal, but in patients with a duodenal ulcer, the pain typically occurs 2-3 hours after a meal.
- sometimes, people feel that upper abdominal pain may increase after lunch or dinner, and sometimes people vomit materials which looks like coffee grounds , blood comeswith stool, have black or tarry stools, all thesesymptoms cause severe abdominal pain. The gastric ulcer pain may increasewith eating and we feel burning-like sensation in our stomach.
- By vagal postganglionic neurons, a neurocrine transmitter, acetylcholine is released which stimulates hydrogen ion generation directly via a parietal cell m3 muscarinic receptor.
- on parietal cells, paracrine transmitter name histamine binds with h2-specificreceptors. In response to this, adenylate cyclase is activated which increases adenosine 38, 58-cyclic monophosphate (camp) levels, and subsequently stimulates the generation of hydrogen ions.
- Gastrin secretion from astral g-cell which follows the endocrine pathway and stimulates the hydrogenionsecretion both directly or indirectly, in corpus and fundus, increases

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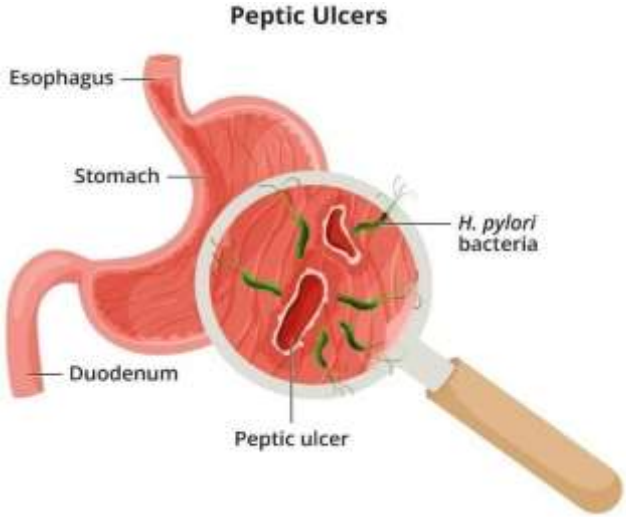
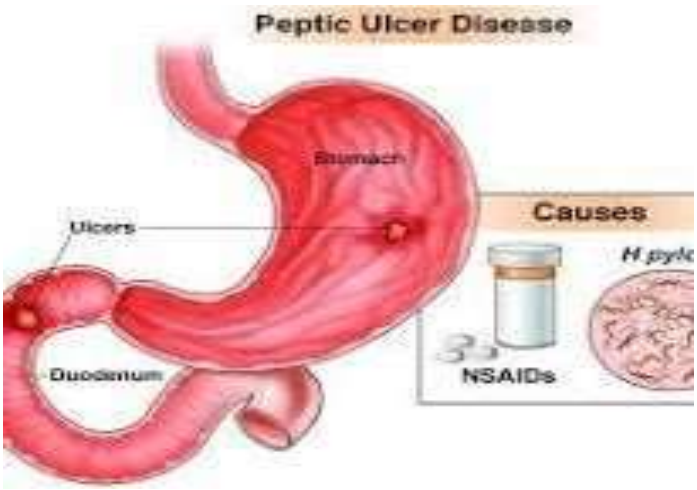
the stimulation of histamine secretion from enterochromaffin-like cells.

- Gastric acid secretions Gastric acid is established as one of the major ulcerogenic factor for the induction of gastric ulcer disease. It has been reported that about 50% of gastric ulcer patients are pepsin and acidhypersecretors. But, on the other hand, gastric acid plays a stringent role in gastric defense. It is the first line of mucosal defense to prevent bacterial colonization and reduced their ability to entrance in the mucosal layer. Acid secretion is suggested to be stimulated by three principlesecretagogues histamine, acetylcholine and gastrin. Gastrin stimulates acid secretion either by directWhile the duodenal ulcer increases with improper sleep or waking up late at night and eating.
- when these types of symptoms are not controlled by the counter drug, then thepatient may be referredtoa specialist called a gastroenterologist.
- The microbe helicobacter pylori (h. Pylori) play a critical role in peptic ulcer disease. This microbe can minimize the complication of this disease. Many studies reveal that more than half of the world's population is affected by chronic h. Pyloriinfection which directly affects. Gastroduodenal mucosa.
- Mammalian stomach has an ability to secrete concentrated hydrochloric acid in a very large quantityas we know that proteolytic enzyme pepsin and gastric acid arerequired to initiate digestion. Gastric aciddoes play a very significant and important role in protein hydrolysis and other digestive processes.





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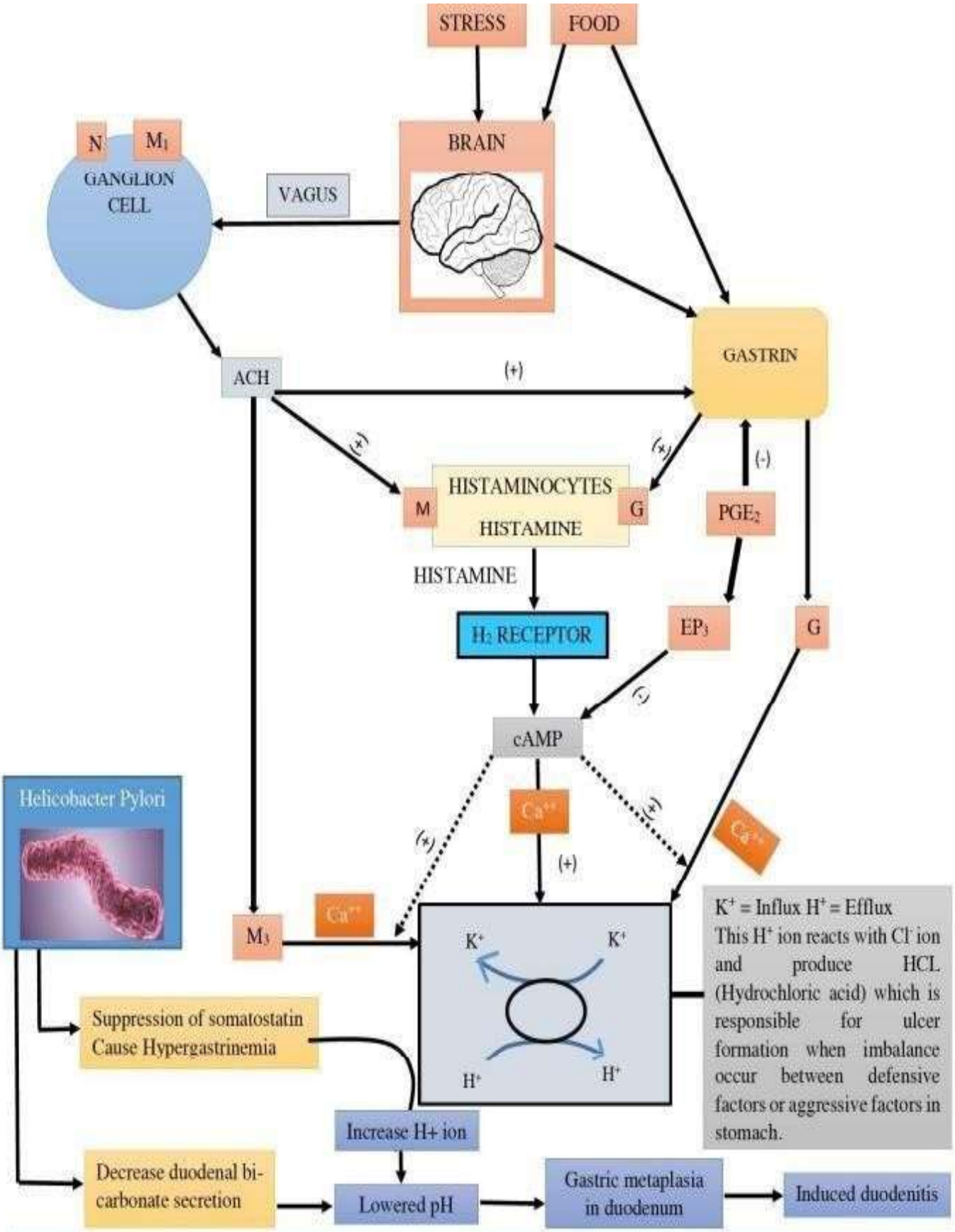
PATHOGENESIS



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SIGN AND SYMPTOMS

- A dull or burning pain in the upper abdomen, between the breastbone and belly button
- Pain that occurs between meals or wakes you up at night
- Pain that worsens with eating
- Feeling full after eating a small amount of food
- Nausea and vomiting
- Bloody or dark stools
- Weight loss or weight gain
- Chest pain
- Fatigue
- Ongoing heartburn

TREATMENT OF PEPTIC ULCER

CLASS	SUBCLASS	DRUGS
RIC ACID SECRETIONINHIBITORS	PROTON PUMP INHIBITORS	1. OMEPRAZOLE 2. LANSOPRAZOLE 3. PANTOPRAZOLE 4. RABEPRAZOLE 5. ESOMEPRAZOLE 6. DEXRABEPRAZOLE
	H2 RECEPTOR ANTAGONIST	1. CIMETIDINE 2. RANITIDINE 3. FAMOTIDINE 4. ROXATIDINE 5. LOXATIDINE
	ANTICHOLINERGICS	1. PIRENZEPINE 2. TELENZEPINE 3. PROPANTHEKLIN 4. OXYPHENONIUM
	PROSTAGLANDINANALOUGE	1. MISOPROSTOL 2. ENPROSTIL 3. RIOPROSTIL
GASTRIC ACIDNEUTRALIZERS(ANTACIDS)	SYSTEMIC	1. SODIUM BICARBONATE , 2. SODIUM CITRATE
ULCER PROTECTIVE		1. SUCRALFATE, 2. COLLOIDAL BISMUTH SUBCITRATE.
ANTI H- PYLORI		1. AMOXICILLIN, 2. CLARITHROMYCIN, 3. METRONIDAZOLE 4. TINIDAZOLE 5. TETRACYCLINE 6. CBS

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LITRATURE REVIEW

1. **Bajpai Ankit,et.al. Pharmacological screening on antiulcer agent 2023,** when an imbalance occurs between the defensive factor and aggressive factor of the stomach, ulcer formation in the esophageal lining, stomach, or duodenum takes place. The quantitative assessment of experimentally induced gastric and duodenal ulcers has been a prob lem for investigators in this field of research.
2. **Michael Buenor Adinortey,et.al ,in-vivo model used for antiulcer agent.2022** peptic ulcer diseases comprise heterogeneous disorders, which manifest as a break in the lining of the gastrointestinal mucosa bathed by acidand pepsin.
3. **Raghuvendra Singh, et.al.effect of h-pylori on peptic ulcer,2022,**various creature models are utilizingto influenced ulcer to identifying the antiulcer activity of many new existed drugs such as pylorus ligated (shay) rats.
4. **Mohd. Shahid Khan,et.al a review on antiulcer activity ,2020,** research for a potential anti-ulceragent involves appropriate in vitro or in vivo models. Due to their anatomical,physiological, and genetic similarities to humans, rodents like mice and rats are ideal among the various animal models.
5. **Neetesh K Jain,et.al pharmacological screening of antiulcer agents,2020,** The life time prevalence of peptic ulcer diseases is 5 to 10% in the general population. There are approx 3.9 millionpatients with peptic ulcer diseases in United States with 200,000 to 400,000 new cases reported eachyear. The peak incidence is between 50 to 70 years of age.
6. **Abhinav Prasoon Mishra, et,al A Comprehensive Review on the Screening Models for the Pharmacological Assessment of Antiulcer Drugs,2019,** A literature search was conducted on various database sources (like science direct, PubMed) with the help of the combination of differentkeywords: Anti-ulcer model, In vitro In-vivo models of ulcer activity.
7. **Raghuvendra Singh,et,al, Pharmacological Screening Model and Its Treatment of Peptic Ulcer Disease,2018,** Peptic ulcer, otherwise called stomach ulcer, is a break in the coating of stomach, initial segment of the small digestive tract and at times in the lower throat.

AIM AND OBJECTIVES

AIM: A Comprehensive Review On The Screening Model; For The Pharmacological Assessment Of Antiulcer Drugs**.**

OBJECTIVES

1. TO EVALUATE THE EFFICACY OF ANTIULCER DRUGS

- **Objective:** To assess the ability of antiulcer drugs to reduce or heal ulcers through various in vivo and invitro models (e.g., pyloric ligation, ethanol-induced ulcers, stress-induced ulcers).
- **Purpose:** To determine how well the drug prevents or heals ulcers, which is the primary therapeutic goalfor antiulcer agents.

2. TO ASSESS THE MECHANISMS OF ACTION

- **Objective:** To understand the pharmacodynamics of antiulcer drugs, including how theyaffect gastric acid secretion, mucosal protection, and the healing of damaged gastric tissues.
- **Purpose:** To identify the specific molecular and cellular targets (e.g., proton pump inhibition, H2-receptor antagonism, mucosal cytoprotection) that explain the drug's therapeutic effect.

3. TO EVALUATE THE SAFETY PROFILE

- **Objective:** To identify any potential toxic effects or side effects of antiulcer drugs in preclinical models,such as damage to organs (e.g., kidneys, liver), gastrointestinal effects, or long-term toxicity.
- **Purpose:** To ensure the drug is safe for further clinical trials and eventual human use, minimizing the riskof adverse effects.

4. TO ASSESS THE PHARMACOKINETIC PROPERTIES

- **Objective:** To evaluate how the drug is absorbed, distributed, metabolized, and excreted (ADME) in the body.
- **Purpose:** To understand the drug's bioavailability, half-life, and the most effective dosing regimens, whichare crucial for designing clinical studies and maximizing therapeutic outcomes.

5. TO INVESTIGATE DRUG INTERACTIONS

- **Objective:** To determine whether the antiulcer drug interacts with other commonly used medications, especially those that affect gastric acid secretion (e.g., NSAIDs, corticosteroids).
- **Purpose:** To predict potential drug-drug interactions that could compromise the safety or efficacy of the antiulcer drug.

6. TO EVALUATE THE LONG-TERM EFFICACY AND HEALING

Objective: To assess whether the drug promotes long-term healing and prevents recurrence of ulcers,which is essential for chronic ulcer treatment.

- **Purpose:** To simulate long-term clinical treatment and determine the drug's potential for preventingrelapse and healing ulcers permanently.

7. TO ANALYZE THE IMPACT ON GASTRIC MUCOSAL DEFENSE

- **Objective:** To assess the drug's effect on enhancing mucosal defenses, such as stimulating mucussecretion, improving blood flow, or promoting the repair of damaged epithelial cells.
- **Purpose:** To evaluate how the drug supportsthe natural healing and protection mechanisms ofthe stomachlining, which is critical for ulcer treatment.

8. TO SIMULATE HUMAN-LIKE CONDITIONS

- **Objective:** To use animal models or in vitro systems that mimic human ulcer conditions, including acidsecretion, infection (e.g., *H. pylori*), and stress.
- **Purpose:** To ensure that the screening model reflects real-world clinical situations, improving thepredictive accuracy of preclinical findings.

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9. TO IDENTIFY POTENTIAL FOR COMBINATION THERAPY

- **Objective:** To explore whether the antiulcer drug can be used in combination with other treatments (e.g., antibiotics for *H. pylori* or proton pump inhibitors with cytoprotective agents).
- **Purpose:** To identify synergistic effects that may improve treatment outcomes or reduce treatment duration for patients with complex ulcer conditions.

10. TO INVESTIGATE THE EFFECT ON GASTRIC ACID SECRETION

- **Objective:** To evaluate the drug's role in modulating gastric acid secretion, either by reducing excess acid production or by balancing acid levels.
- **Purpose:** To determine if the drug is effective in lowering gastric acidity, which is a major contributing factor in ulcer formation.

11. TO INVESTIGATE THE DRUG'S EFFECTIVENESS AGAINST H. PYLORI

- **Objective:** To assess whether the antiulcer drug is effective against *Helicobacter pylori* infections, which are a major cause of peptic ulcers.
- **Purpose:** To determine if the drug has antibacterial properties and can treat ulcers caused by *H. pylori*,either alone or in combination with other antibiotics.

- **TYPE OF SCREENING MODEL FOR ANTIULCER ACTIVITY:**
  ANIMAL MODELS IN EXPERIMENTAL PEPTIC ULCER:
  Studies on animal models helps to understanding the etiology and screening of anti-ulcer agents.
  1. Ethanol-Induced Ulcers
  2. Cold Restraint Stress-Induced Ulcers
  3. Stress-Induced Gastric Ulceration
  4. Pylorus Ligated (PL)-Induced Ulcers
  5. Acetic Acid-Induced Ulcers
  6. Histamine- Induced Ulcers
  7. Indomethacin-Induced Ulcers
  8. Serotonin- Induced Ulcer
  9. Aspirin-Induced Ulcers
  10. Reserpine - Induced Ulcers Alcohol Induced Gastric Ulcer

1. ALCOHOL INDUCED GASTRIC ULCER

- **Principle:** Alcohol causes secretion of gastric juice and decrease mucosal resistance due to which protein content of gastric juice is significantly increased by ethanol. This could be leakage because of plasma protein inthe gastric juice with weakening of mucosal resistance barrier of gastric mucosa,this leading to peptic ulcer.
- **Procedure**: Albino rats of either sex weighing between (150-200 gms) are divided into six groups of animals in each group. The animals are fasted for 24 hours with free access water. Animals are given test drugs or standard drug. 1 hour later 1ml/200gm of 99.80% alcohol is administered p.o to each animal.
- Animal are sacrificed 1 hour after alcohol administration, stomach is isolated and cut open along the greater curvature and pinned on a soft board. The length of each gastric lesion is measure in mm. The %inhibition is expressed as sum of the length of the control-mean lesion index of text / mean lesion indexof control × 10.

2. H. PYLORI- INDUCED GASTRIC ULCER:

- **Principle:** It is a gram negative bacteria found in gastric an duodenal mucosa of most persons particularly the elderly. They, while in the mucosa, split into ammonia and thus elevates the local region of the mucosa by high alkalinity. In this way they strongly help the peptic ulcer development.
- **Procedure:** Albino Wistar rats of either sex weighing between (150-200 gms) are divided into fivegroups of six animals in group. In this method albino rats are fasted in individual cages for 24 hours.Care was being taken to avoid coprology. Test drug or standard drug or control vehicle is administered 30 minute prior to pyloric ligation. Under light ether anaesthesia, the abdomen is openedand the pyloruswas ligated. The abdomen is then sutured. At the end of 4 hours after ligation the animals are sacrificedwith excess of anaesthetic ether , and the stomach is dissected out gastric juiceis collected were drained into tubes and were centrifuged at 1000 rpm for 10 minutes and the volumeis noted. The pH of gastric juice is recorded by pH meter. Then the contents are subjected to analysis for free and total acidity. The stomachs are then washed with running water to see for ulcers in the glandular portion of the stomach.
- The numbers of ulcers per stomach are noted and severity of the ulcers scored microscopically with thehelp of hand lens (10x) and scoring was done as per Kulkarni (1987).
  - ❖ 0 = Normal stomach
  - ❖ 0.5 = Red coloration
  - ❖ 1 = Spot ulcers
  - ❖ 1.5 = Haemorrhagic streaks
  - ❖ 2 = Ulcer > 3 mm but > 5 m
  - ❖ 3 = ulcers > 5 mm
  - ❖ Percentage protection = 100- ut / uc × 100 Mean ulcer score for each is expressed as ulcer index. The percentage protection is calculated using the above formula.
  - ❖ where, ut = ulcer index of treated group.
  - ❖ uc = ulcer index of control group.

3. STRESS- INDUCED GASTRIC ULCER

- **Principle :** Stress can arise from prolonged anxiety, tension, and emotion, severe physical discomfort, haemorrhage and surgical shock, burns and trauma, thereby resulting in severe gastric ulceration. The mechanism of gastric ulceration is poorly understood. Recently research has shownthat resistant cold stress causes severe haemorrhage ulcer through derangement of the mucosal antioxidant enzyme such as super oxide,dismutase and peroxides. This is the stress condition arising mainly from physiology discomfort and themechanism of ulceration caused in this case should be different from ulcer caused due to

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other factors. The stress generate highly reactive OH* radicals thatcauses oxidative damage of the gastric mucosa andthat the radicals is formed by metal catalysed. Herber weiss reaction between O2 – and H2O2 followinginduction of the superoxide dimutase andoxidative damage of gastric peroxides.

- **Procedure:** Albino Wistar rats of either sex weighing between (150-200 gms) are divided into fivegroups of six animals in group.
- Cold resistance stress (CRS) induced ulcer-to 18 hours fasted rats, cold resistance stress is given by strapping the rats on a wooden plank and keeping them for 2 hours at 4o -6oc. The animals are then sacrificed by cervical dislocation and ulcers are scored on the dissected stomachs.

4. ASPIRIN- INDUCED GASTRIC ULCER

- **Principle:** NSAIDs inhibits the PG synthesis of gastric mucosa, PG gives cytoprotection. Enhancement of leukotriene synthesis, exhibits damage effect. Aspirin also inhibit gastric peroxidase&may increase mucosal H2O2 & hydroxyl ions level to cause oxidative mucosal damage.
- **Procedure:** Albino rats of either sex weighing between 150-200 gms are divided into five groups of sixanimals in group. The animals are fasted for 24 hours. The test drug in varying concentrations based onthe design of the experiment is administered orally in 2% gum acacia solution 30 minute prior to aspirinat dose of 200 mg/kg. 4 hours later the rats are sacrificed by using anaesthetic ether and their stomachs dissected. for the determination of gastric lesions.
- **Parameter studied - ulcer index:** The numbers of ulcers per stomach is noted and severity of the ulcersscored microscopically with the help of hand lens (10x) and scoring is done as per Kulkarni (1987).

❖ 0 = Normal stomach
❖ 0.5 = Red coloration
❖ 1 = Spot ulcers
❖ 1.5 = Haemorrhagic streaks
❖ 2 = Ulcer > 3 mm but ‹ 5 mm
❖ 3 = ulcers > 5 mm
❖ Percentage protection = 100- ut / uc × 100 Mean ulcer score for each is expressed as ulcer index. The percentage protection is calculated using the formula.
❖ Where, ut = ulcer index of treated group.
❖ Use = ulcer index of control group.

5. ACETIC ACID- INDUCED GASTRIC ULCER

- **Principle:** Acetic acid is reported to produce ulcers by gastric obstruction leading to increase in acidicgastric juice.
- **Procedure:** The rats were anesthetized with phenobarbitone (35 mg/kg, i.p.). the abdomen was openedand the stomach was visualized. Gastric ulcers were produced in rats at the anterior serosal surface of the glandular portionof the stomach 1 cm away from the pyloric end by 50% acetic acid (0.06ml/animal).Test drug and standard drug was given on day 1,orally, 4h after the application of acetic acid and continued for either up to 3 or 7 days after induction of ulcer. The animals were sacrificed after 18 h of the last dose of test drug either on 4th day or 8th day of experiment to assessthe ulcer size and healing.

6. INDOMETHACIN (IND)-INDUCED GASTRIC ULCERS

- **Principle:** Oral administrations of indomethacin (20 mg/kg) resulted in production of gastric lesions predominantly on glandular segment of the stomach and few or non in the antrum.lesions were producedlinearly on mucosal folds and had appearance of mucosal erosions.
- **Procedure:** IND (20mg/kg b.w.) suspended in 0.5% carboxymethyl cellulose was given as a singlei.p.dose to induce gastric ulcers after 30 min of test or standard drug treatment. After 5h, the animalswere killed and lesions in the gastric mucosa were scored. After identification of ulcer areas, the length of the ulcer was measured along the greater diameter. Number of haemorrhagic spots was considered equivalent to 1mm of ulcer. The mean ulcer size was calculated by dividing the total length (in mm) of ulcers for all the animals divided by total number of animals.

7. HISTAMINE-INDUCED GASTRIC ULCER

- **Principle:** Histamine-induced gastric ulceration is recognised to be mediated through both enhance gastric acid secretion and vasosplastic action of histamine
- **Procedure:** Guinea pigs weighing 300-400 g were fasted for 36 hr. with water ad libitum prior to the experiment and were divided into two groups of six animals each. Gastric ulceration was induced by i.p. administration of histamine acid phosphate (Sigma USA) (50 mg. base.). To protect the animals againsthistamine toxicity, 5 mg. of promethazine hydrochloride was injected i.p. to each animal 15 min after histamine administration. The test drug or control vehicles (Dist. water) were given orally 45 min beforehistamine administration.

8. RESERPINE-INDUCED GASTRIC ULCER

- **Principle:** Reserpine-induced gastric ulceration has been attributed to the degranulation of gastric mast cells and consequent liberation of histamine which is believed to be a cholinergacally mediated10.
- **Procedure:** Adult albino rats were fasted for 24 hr. following water ad libitum. Reserpine (5mg/kg) administered intramuscularly to four groups of six rats each. 30 min after the administration of the test drug or control vehicle (Distilled water) intraperitoneally. All the animals were sacrificed after 18 hr, there stomachs were removed, opened along the greater curvature and sum of lengths(mm) ofall lesions for each rat was used as “ulcer index”10.

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9. SEROTONIN-INDUCED GASTRIC ULCER

- **Principle**: Serotonin-induced gastric ulceration is believed to arise from a disturbance of gastric mucosal microcirculation. The development of ulcers by serotonin and reserpine usually takes about18 hr10.
- **Procedure:** Serotonin creatinine sulphate (Sigma USA) (20mg/kg) were administered subcutaneously to four groups of rats (24 hr. fasted). The test drug or control vehicle
- (Distilled water) was administered intraperitoneally after 30 min prior to the serotonin injection. The animals were sacrificed after 18 hr, their stomachs were removed, and the ulcer index was determined as described earlier.

CONCLUSION

- For validation of the presence of antiulcer activity in the newly synthesized drug which is going tobe used by the practitioner to treat gastric mucosal lesions or ulcer, then it is essential to investigatethe antiulcer property of the synthesized drug.
- The various number of antiulcer screening model have been developed over the past years in a different part of the world in which some are very good and some are not.
- Each and every model has its own pros and cons. The main objective for doing this review is to present an overview of antiulcer models which can be most frequently used by investigators for their gastrointestinal protection studies.
- After the study of antiulcer models, we found that the above mention models are widely used nowadays as per drug requirement and choice of the model also depends upon their result and timing.
- In-vitro models are less used in comparison with in-vivo but as per our study, we suggest that if bothin-vitro and in-vivo models are used together then there is a chance to increase the efficacy of result
  and it will help to find the better antiulcer activity of new drug molecules.

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