

Pharmacological Screening Model and Its Treatment of Peptic Ulcer Disease

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ABSTRACT

Peptic ulcer is a ceaseless sickness influencing up to 10% of the total population. Peptic ulcer created by the unevenness of gastric juice pH and mucosal protections. Two fundamental components delivered Peptic ulcer. Frist is central point it included bacterial disease, for example, *Helicobacter Pylori* (*H. Pylori*) and medicine non-steroidal anti-inflammatory medication and synthetic E.g., HCL, Ethanol. Second is minor factor it included pressure, smoking, fiery food and nourishment lopsidedness. Ordinary treatment of Peptic ulcer, for example, proton siphon inhibitor (PPI) and Histamine-2 (H₂) Receptor Antagonist. Also, other Hand therapeutic plant and their concoction compound are valuable in the counteraction and treatment of peptic ulcer infection. Various creature models are utilizing to influenced ulcer to identifying the antiulcer activity of many new existed drugs such as Pylorus ligated (shay) rats, Stress ulcers, Restraint ulcer in rats, Water immersion-induced restraint ulcers, Cold and restraint ulcers, Gastric mucosal damage induced by NSAID in rats, Induced solitary chronic gastric ulcer, Acetic acid induced kissing gastric ulcers in rats Histamine induced gastric ulcer in guinea pig, Duodenal anti-ulcer activity, Gastric cytoprotective action.

Keywords- *Helicobacter Pylori*, PPI, Chronic disease, H₂ Receptor Antagonist.

I. INTRODUCTION

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. Gastric corrosive is very much depicted as the reason for peptic ulcer, while *Helicobacter pylori* disease is perceived as the major causative factor in ulcer arrangement. The bacterium causes incitement in the creation of gastric corrosive because of gastritis, and this cycle adds to disintegration of the mucosa and ulcer arrangement. What's more, awkwardness between hostile variables (exorbitant gastric corrosive, *H. pylori*, and gallbladder liquid and raised free radicals) and guarded variables (mucosa, blood liquid, prostaglandins, and

cancer prevention agents) may likewise prompt peptic ulcer. Along these lines, the successful first line treatment is anti-infection treatment. Peptic ulcers are available at around 6%–15% of the population. [1-2] Factors that increase risk of creating peptic ulcer incorporate smoking, more established people, O blood classification, and stress. Peptic ulcers that will in general recuperate longer than duodenal ulcer is at higher danger of creating gastritis and gastric harm. [3-4]

Around 10% of Americans create interminable PUD during their lifetime. The frequency changes with ulcer type, age, sex, and geographic area. Race, occupation, hereditary inclination, and cultural elements may assume a minor function in ulcer pathogenesis yet are lessened by the significance of HP contamination

and NSAID use. The commonness of PUD in the United States has moved from transcendence in men to almost practically identical predominance in people. Late patterns propose a declining rate for more youthful men and an expanding rate for more seasoned ladies. [5-6] Components that have impacted these patterns incorporate the declining smoking rates in more youthful men and the expanded utilization of NSAIDs in more seasoned grown-ups. Since 1960, ulcer-related doctor visits, hospitalizations, activities, and passing's have declined in the United States by over half, essentially as a result of diminished paces of PUD among men. [7-8] The decrease in hospitalizations has come about because of a decrease in emergency clinic confirmations for simple duodenal ulcer. Notwithstanding, hospitalizations of more seasoned grown-ups for ulcer-related inconveniences (draining and hole) have increased. Although the general mortality from PUD has diminished; demise rates have expanded in patient's more established than 75 years old, in all probability a consequence of expanded utilization of NSAIDs and a maturing populace. Patients with gastric ulcer have a higher death rate than those with duodenal ulcer on the grounds that gastric ulcer is more predominant in more established people. [9-10] In spite of these patterns stays one of the most widely recognized GI maladies, bringing about disabled personal satisfaction, work misfortune, and significant expense clinical consideration. [11] Until now, H₂-receptor adversaries (H₂RAs), proton siphon inhibitors (PPIs), and medications that advance mucosal safeguard have not changed PUD confusion rates. Figure 1 speaks to the anatomical structure of the stomach's areas. [12-13]

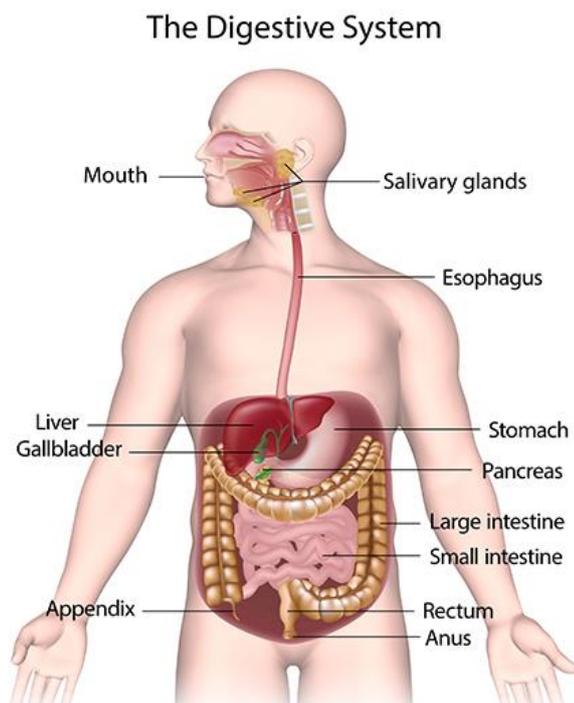


Figure 1: Human Digestive System [14]

Types of Ulcer [15-16-17]

1-Peptic Ulcer

- Gastric ulcer - (develop in stomach lining)
- Esophageal ulcer - (develop in esophagus)
- Duodenal ulcer - (develop in small intestine)

2-Arterial Ulcer

- Develop in ankle, feet, toes, heels

3- Venous Ulcer

- Develop in leg, below knee, inner area of ankle

4- Mouth Ulcer

5- Genital Ulcer

- Develop in penis, vagina, anus

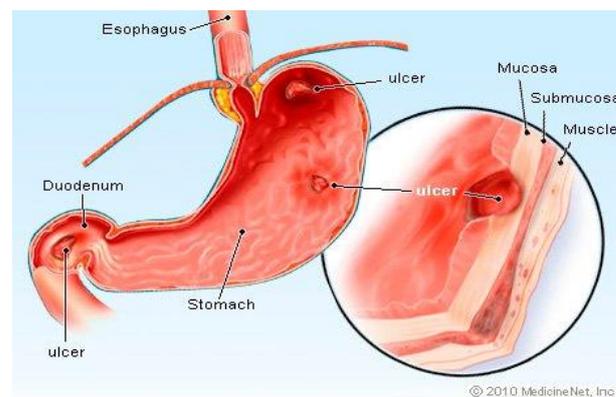


Figure 2: Peptic Ulcer Disease [18-19]

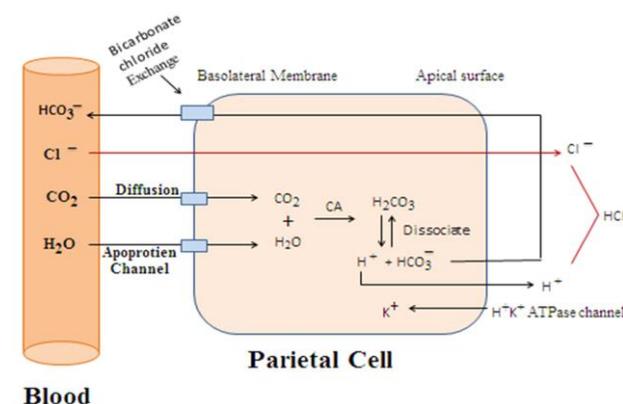


Figure 3: Formation of HCL [20-21]

Peptic Ulcer Disease: CAUSES [22-23]

1. Helicobacter Pylori
2. Nonsteroidal Anti-Inflammatory Drugs (Nsaids)
3. Gastrinoma (Zollinger-Ellison Syndrome)
4. Hereditary Factors
5. Smoking
6. Stress
7. Liquor And Diet

Screening Model for Gastric Ulcer [24-25]

1-Anti-Secretory Activity Screening

- 1-Isolated whole stomach preparation
- 2-Ghosh and shild perfused rat stomach preparation

2- Gastric Anti-Ulcer Activity Screening

- 1-Pylorus ligated (shay) rats
- 2-Stress ulcer

- 3-Restraint ulcer in rats
- 4-Water immersion-induced restraint ulcers
- 5-Cold and restraint ulcers
- 6-Gastric mucosal damage induced by NSAIDs in rats
- 7- Ethanol induced gastric ulcers in rats
- 8-Acetic acid induced kissing gastric ulcers in rats
- 9-Histamine induced gastric ulcer in guinea pig

3- Duodenal Anti-Ulcer Activity

- 1-Dulcerozine induced duodenal ulcer in rats
- 2-Cysteamine induced duodenal ulcer in rats

1-Anti-Secretory Activity Screening Isolated Whole Stomach Preparation

Procedure

Wistar rodents weighing around 40 g are taken for the system. Anesthetize the rodents with 30 mg/kg pentobarbitone controlled intra-peritoneally. The midsection is opened and throat is ligated near the stomach. An entry point is made in the rumen of the stomach and the substance are cleaned out with warm Krebs-Henseleit arrangement. A subsequent cut is made at the pyloric sphincter and polyethylene cannulae are embedded and integrated with the stomach through these entry points. The stomach is dismembered out. Spot promptly into 10 ml organ shower containing Kerbs-Henseleit arrangement at 37°C. The lumen of the stomach is perfused at a pace of 1ml/min with adjusted Kerbs Henseleit arrangement (without Na₂CO₃ and KH₂PO₄) at 37°C. The profluent perfusate from the stomach is disregarded a miniature double anode. The adjustment in pH is changed over to a component of H⁺ particle action. The test mixes or secretogogues are included a volume of 0.5 ml to the Kerb's Henseliet arrangement washing the serosal surface of the stomach. Subsequent to setting up the stomach arrangement, the basal H⁺ yield is permitted to balance out, both leveled out and treated. At that point measure secretogogue reaction by estimating the measure of corrosive discharged at peat reaction over the anticipating basal level. The pace of corrosive discharge is estimated and

communicated as (H⁺) moles * 108 for every minitem Both arrangements are gassed with carbogen (95% O₂ and 5% CO₂) contrast the test and standard and that of the control to get to the counter ulcer action of the medication. [26, 27, 28]

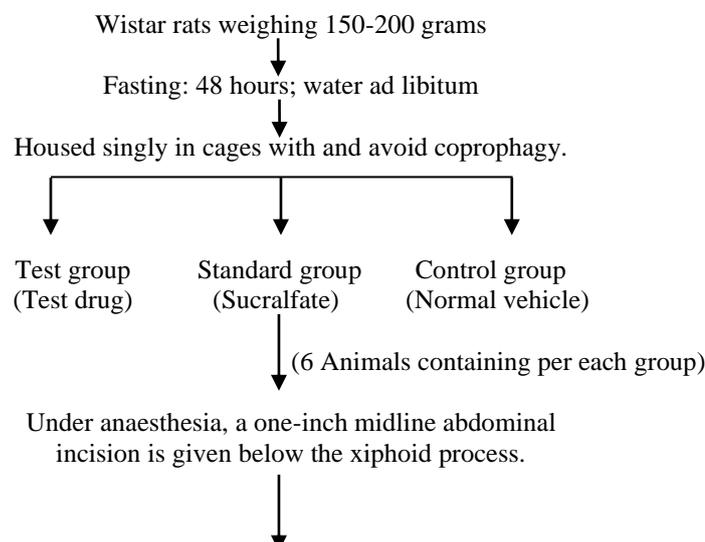
2-Ghosh and Shild Perfused Rat Stomach Preparation Procedure

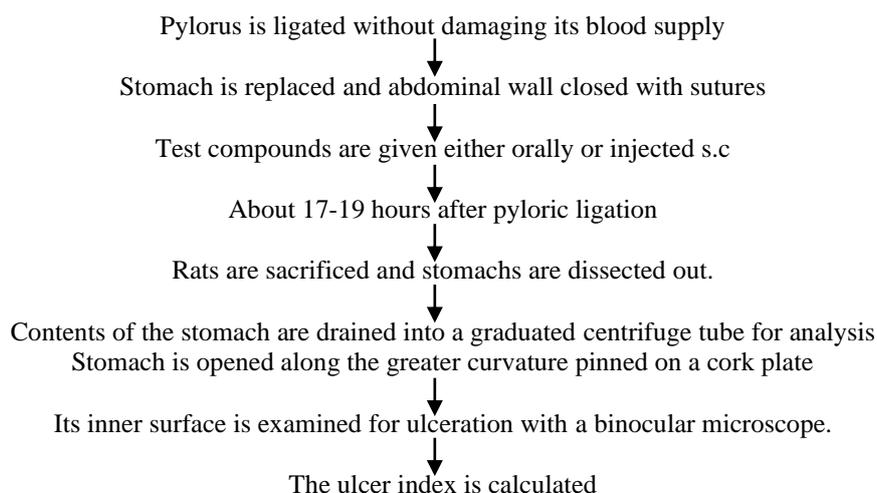
Male Sprague Dawley or Wistar rodents of weighing 180 g are taken for the methodology. Preceding the analyze, starved the creature short-term by pulling back the food. Gathering the rodents haphazardly as four rodents in a gathering. Anesthetize the creatures with 25% urethane arrangement (0.6 ml/100 g, i.m.). The internal heat level is misleadingly settled by methods for a warming loop utilizing a rectal thermometer and furthermore windpipe is uncovered and cannulated for counterfeit breath. The outside jugular vein is uncovered and cannulated with polythene tubes leveled at the tip. The midsection is opened through midline cut, and pyloric finish of the stomach is cannulated. A polythene tube is passed down the oesphagus and tied in the cervical locale. The stomach is cleaned out altogether by passing refined water to the cylinder. Perfuse the stomach with N/4000 sodium hydroxide at a uniform rate. The centralization of sodium hydroxide is balanced so that the perfusate under basal conditions has a pH. The perfusate rises out washes the miniature cathodes which are legitimately associated with the pH meter. Changes in corrosive emission are gotten to by pH changes. The gastric discharge is invigorated by nonstop i.v. implantation of 100 microgram/kg/hr of pentagastrin or 3 mg/kg/h of histamine hydrochloride or 30 microgram/kg/h of carbachol. The test is infused either earlier or after the implantation and measure the hindrance of corrosive discharge and contrast the outcomes and that of standard.[29,30,31]

2-Gastric Anti-Ulcer Activity Screening

1-Pylorus Ligated (Shay) Rats [32,33]

Procedure-





Evaluation of the Test

Ulcer severity

0 = No ulcer

1 = Superficial ulcer

2 = Deep ulcer

3 = Perforation

Ulcer index (UI) : $UI = (UN + US + UP) \times 10^{-1}$

UN = Average number of ulcers per animal

US = Average of severity scores

UP = Percentage of animals with ulcers

Inference-

➤ Ulcer index of test drug compared with control group.

➤ To detect anti-ulcer effect of test drug. Other parameters help to infer the mechanism of ulcer protection.

➤ Decrease in volume, free & total acidity: antisecretory action Rise in pH: acid neutralising action Increase in mucin, PGs: cytoprotective effect.

2-Stress Induced Ulcer in Rats ^[34,35]

Wistar or Sprague Dawley rats Weighing 250 – 300 g are taken for the procedure. Drugs (control, standard, test) administered once daily for 2 days & AMP; 30 mins prior to applying restraint. Fasted & AMP; lightly anesthetized rats placed on galvanized steel window screen. Limbs are held together in pairs & AMP; tightened with adhesives. After 24 hrs, animal removed, sacrificed and degree of ulceration noted

3-Restraint Ulcer in Rats ^[36, 37]

Restraint ulcer model was developed by **Hanson and Brodie in 1960** for the exploration of antiulcer activity in rats.

Procedure

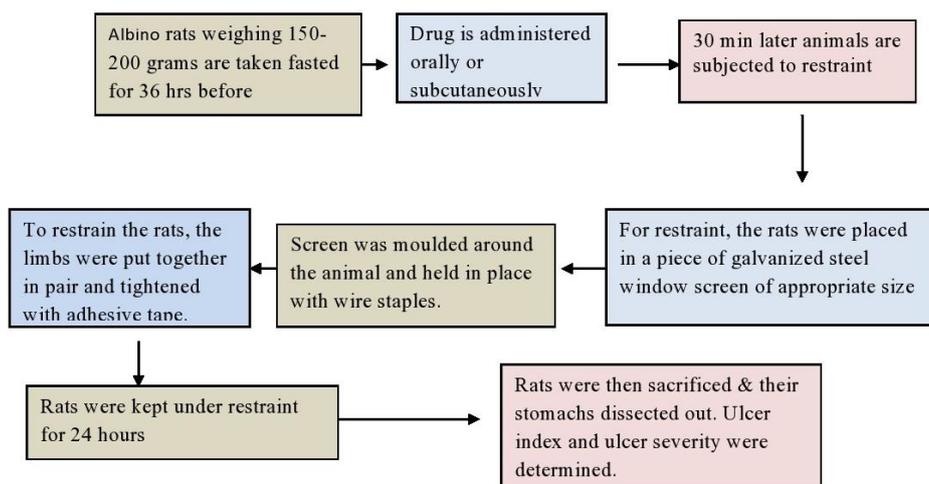


Figure 4: Restraint ulcer in rat ^[38]

4-Cold and Restraint Ulcers

Cold Restraint ulcer model was developed by **Vincent et al.1997** for the exploration of antiulcer activity

Procedure

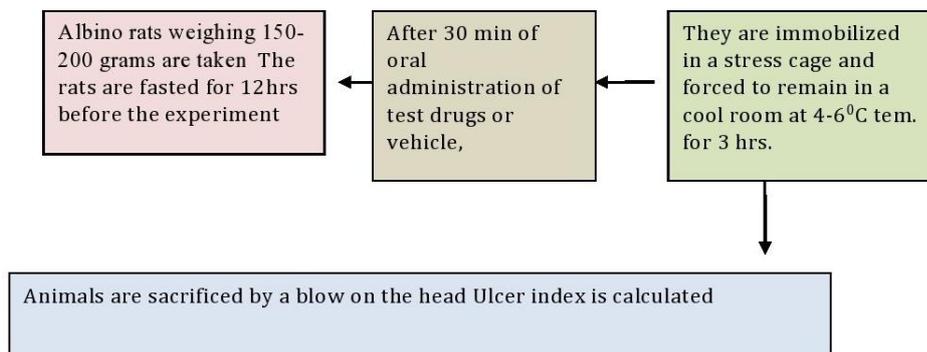


Figure 5: Cold restraint ulcer in rat [39]

5-Water Immersion-Induced Restraint Ulcers

Procedure-

Water immersion induced restraint ulcer model was developed by **Takagi et al, 1964** for the exploration of antiulcer activity

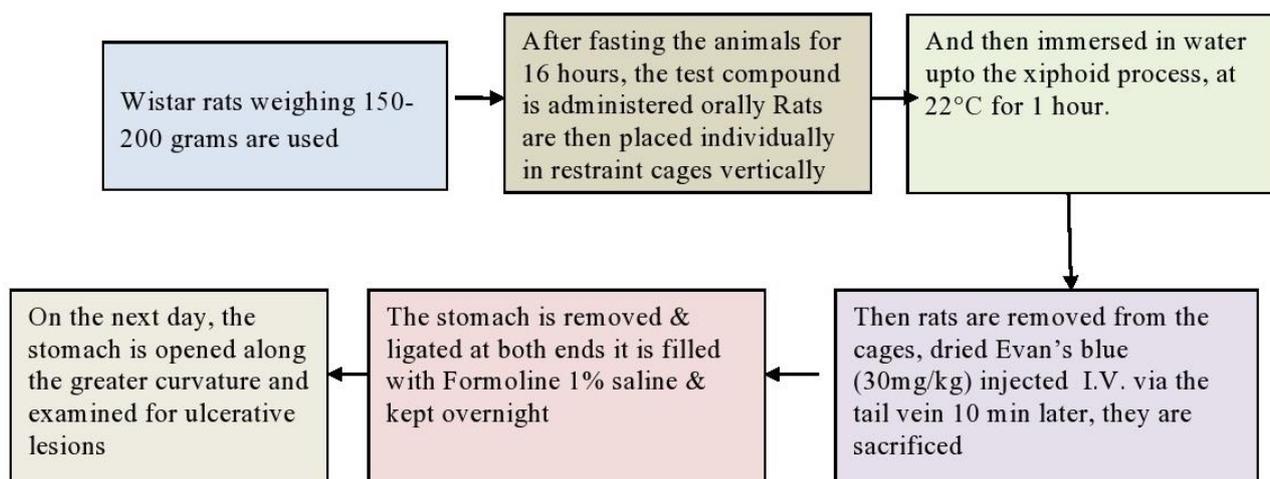
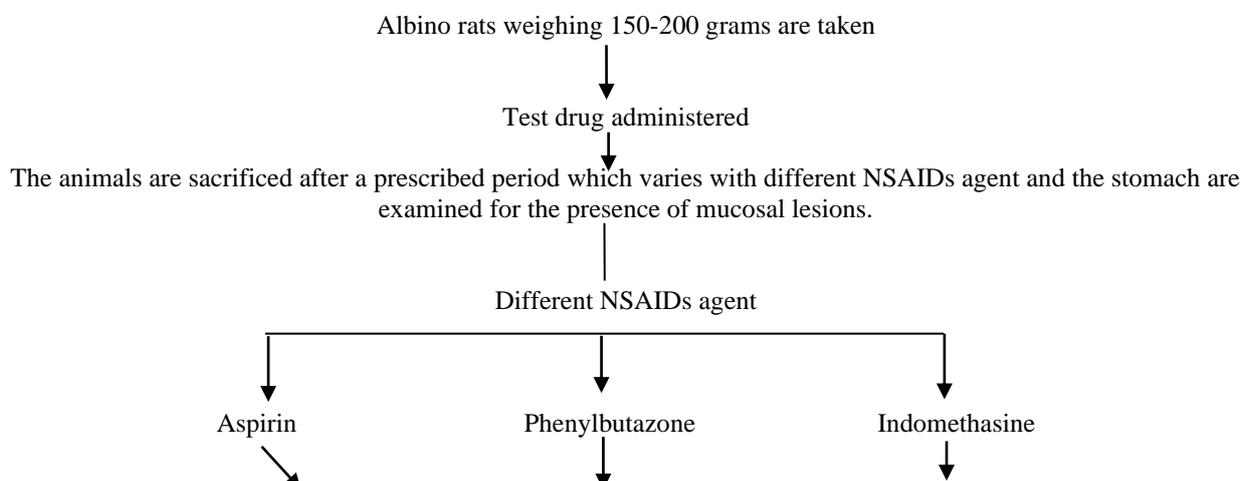


Figure 6: Water immersion restraint ulcer in rat [40]

6-Gastric Mucosal Damage Induced by Nsaids in Rats

Procedure-



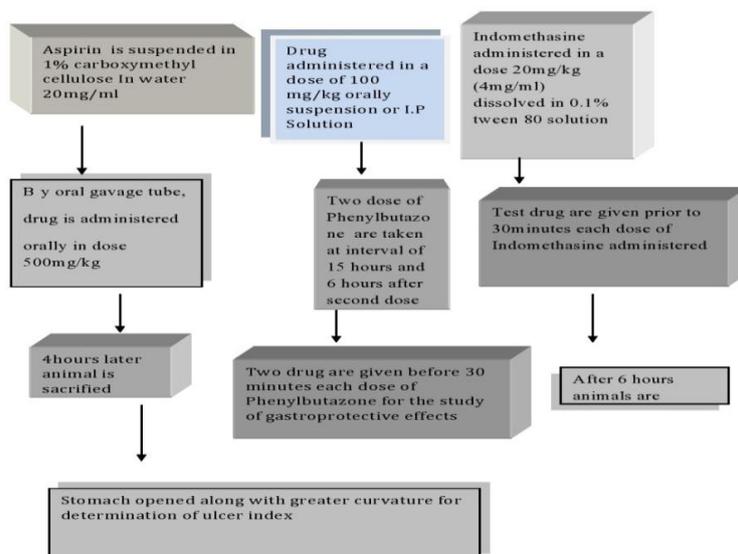
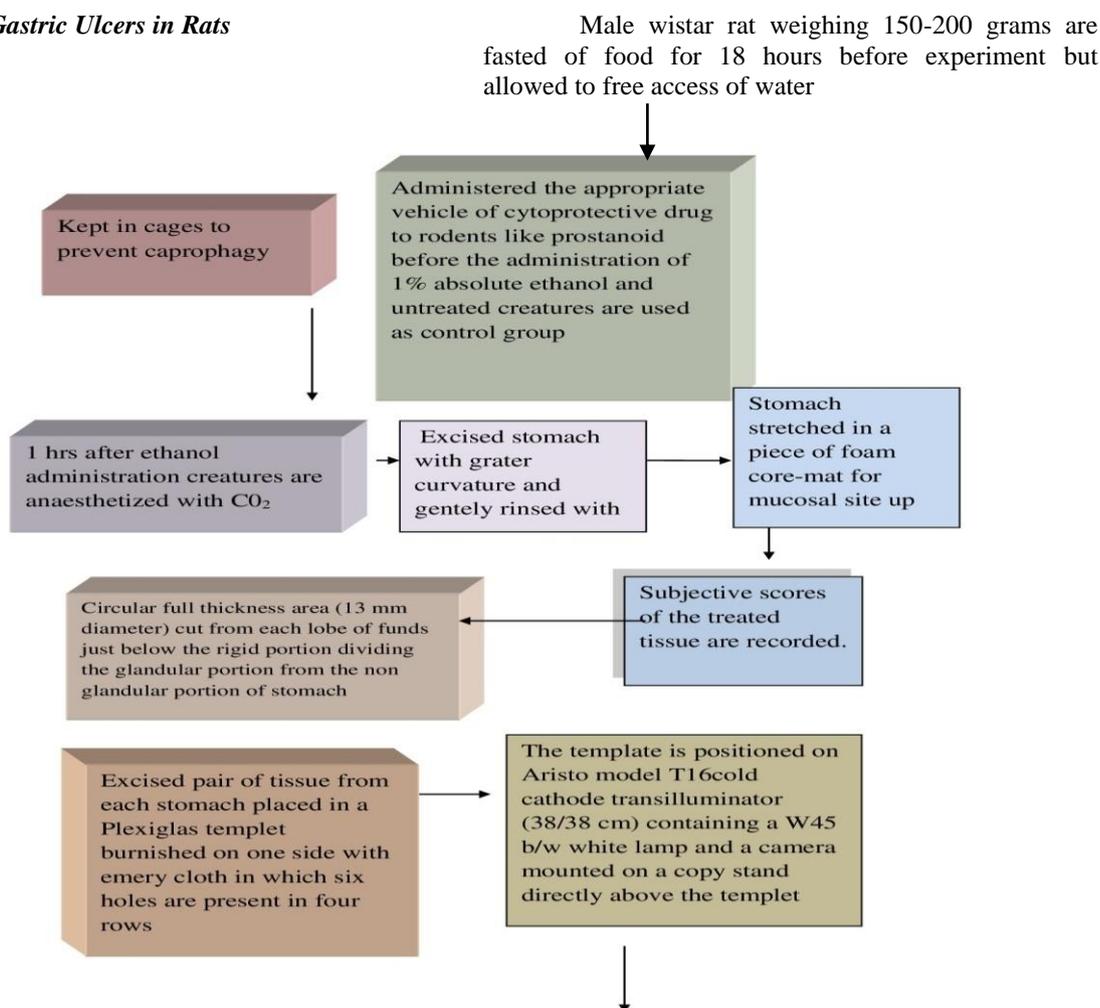


Figure 6: Gastric mucosal damage induced by NSAIDs in rats [41]

7-Ethanol Induced Gastric Ulcers in Rats
Procedure



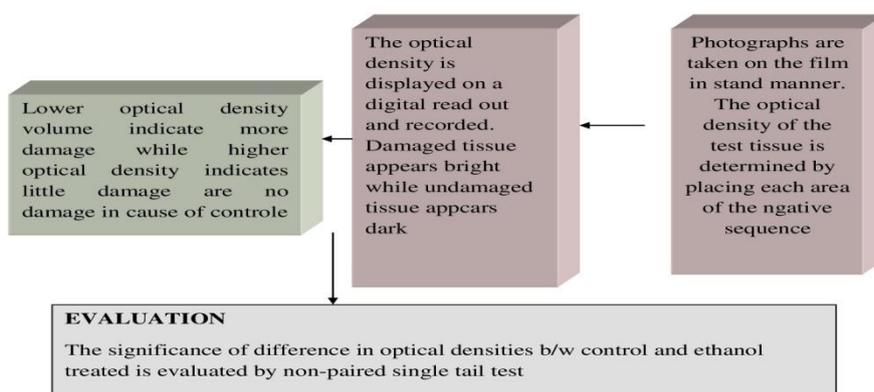


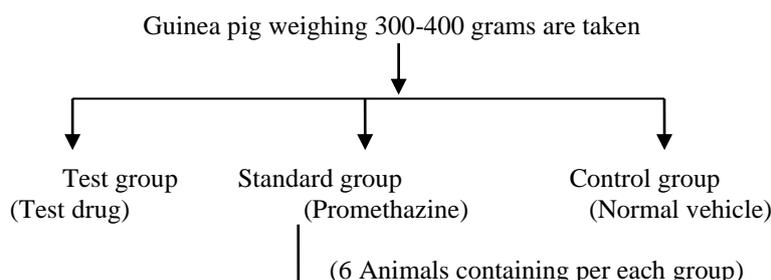
Figure 7: Ethanol induced gastric ulcers in rats [41]

8-Acetic Acid Induced Gastric Ulcers in Rats Procedure

Male Donryv, Wistar or Sprague Dawley rats Weighing 250 – 300 g are taken for the procedure. Overnight fasted rats operated under ether anesthesia. Anterior & AMP; posterior walls of stomach clamped with forceps. 0.2 ml of 40% acetic acid injected into

clamped portion. After 45 secs, acid removed. Deep round ulcers develop on the anterior & AMP; posterior walls. Respective treatments (control, standard and test) started from 3rd to 10th day. Rats sacrificed on 10th day. Ulcers respond well to most anti ulcer drugs like PPI, H2 blockers, cytoprotectives[42].

9-Histamine Induced Gastric Ulcer in Guinea Pig [43]



Fasted for 36 hours before experiment; water ad libitum 1 ml of histamine acid phosphate (50 mg base) was administered i.p.

Promethazine hydrochloride 5 mg was injected i.p. 15 min before and 15 min after histamine to protect the animals against histamine toxicity.

The standard/test drugs were administered p.o. or s.c 45 minutes before histamine injection. 4 hours after histamine injection, guinea pigs were sacrificed and stomach dissected out.

The gastric contents were subjected to analysis

Stomach was opened along the greater curvature, ulcers were identified.

Estimation Of Parameters:

- Estimation of free radical generation
- Lipid peroxides (LPO)
- Super oxide dismutase (SOD) activity
- Estimation of mucosal glycoprotein's
- Estimation of free acidity and total acidity
- Estimation of DNA in gastric mucosa
- Estimation of glandular weights of stomach

Estimation of Ulcer Index (UI):

$Ui = \text{mean degree of ulceration} \times \% \text{ group of ulceration} / 100$
 $\% \text{ inhibition} = (\text{ulcer index in control} - \text{ulcer index in test}) / \text{ulcer index in control} \times 100$

3- Duodenal Anti-Ulcer Activity [44,45]

1-Dulcerozine Induced Duodenal Ulcer In Rats

➤ **Procedure-**

Male wistar or Sprague dawley rats weighing around 200 g are taken for the procedure. Duclerozine 300 mg/kg, suspended in 5% gum acacia solution, is

administered orally as a single dose. The drugs (test/standard) are given 30 min prior to the administration of Duclerozine. The animals are sacrificed after 18 hr of administration.

➤ **Scoring**

- 0 – No ulcer
- 1 – Superficial mucosal erosion
- 2 – Deep ulcer usually with transmural
- 3 – Perforated or penetrated ulcer

Applications

- The lesions developed are analogous to themclinical disease with respect to location and histology.
- The factors responsible for producing the pathological changes are similar in man and animal used.
- The drugs effective against experimental ulcer could be clinically useful.
- The method is dependable, reproducible and easy to perform and results are obtained with in 24hrs.

2-Cysteamine Induced Duodenal Ulcer in Rat [46,47]

Procedure-

Male Wistar or Sprague Dawley rats weighing around 200 g are taken for the procedure. Administer cysteamine Hcl of dose 280 mg/kg orally tree times in a day on the first day of experiment to the fed rats. For the treated animals: Administer the drugs before 30 min of first dose and again after 24 hrs on the second day. The rats are sacrificed after 48hrs of the first dose of cysteamine Hcl. The duodenal ulcers are developed 2 -4 mm away from the pylorus on the anterior wall of the duodenum and frequently perforate the liver. A small ulcer present on the posterior wall (kissing ulcer) of the duodenum and it is invariably penetrates the pancreas.

The intensity of the duodenal ulcers is evaluated as 0 – No ulcer

- 1 – Superficial mucosal erosion
- 2 – Deep ulcer usually with transmural
- 3 – Perforated or penetrated ulcer

Applications:

- Suitable method for studying the pathogenesis of duodenal ulcer
- An effective method for anti-ulcerogenic regimes detection.
- Since some of such chemicals might have a role in the etiology of human duodenal ulcers as well, the structure activity conclusions may helps in the identification of ulcerogenic chemicals in our diet and environment

Medications

In the event that you have H. pylori, you will presumably be recommended three unique meds. "Triple treatment" (counting a proton siphon inhibitor, for example, omeprazole or Prilosec, to diminish corrosive creation and two anti-microbials to dispose of the creature) is ordinarily used to treat H. pylori - related ulcers. A medication called bismuth salicylate might be suggested instead of one anti-infection. This medication, accessible over the counter, covers and calms the stomach, shielding it from the harming impacts of corrosive. Two medication regimens are presently being created. A portion of similar medications are utilized for non-H. pylori ulcers just as for manifestations (like acid reflux) because of ulcers of any reason [48,49,50]

CLASS	DRUG
Antacids	Aluminum hydroxide, Magnesium hydroxide, Carbonate and Sodium bicarbonate
H2 blockers,	Cimetidine, Ranitidine, Nizatidine, Famotidine
Proton-pump inhibitors,	Esomeprazole, Lansoprazole Omeprazole Pantoprazole, Rabeprazole.
Ulcer-protective	Sucralfate

II. SURGERY AND OTHER PROCEDURES

Once hospitalized, if seeping from a ulcer doesn't stop by utilizing drugs and steady consideration (like liquids and, perhaps, blood bonding), it can quite often be halted through endoscopy. The doctor (a gastroenterologist) who plays out the strategy initially recognizes the ulcer and the territory that is dying. The doctor will at that point infuse adrenaline and different drugs to stop the draining and invigorate the development of a blood coagulation. In the event that the draining repeats after that system or you have a punctured ulcer or an impediment, medical procedure might be required. In the event that you don't show signs of improvement from clinical or endoscopic treatment,

medical procedure might be thought of. About 30% of individuals who go to the medical clinic with a draining ulcer need endoscopy or medical procedure. [51, 52]

Herbs

Herbs are commonly a sheltered method to fortify and condition the body's frameworks. Similarly as with any treatment, you should work with your medical services supplier to get your concern analyzed before beginning any therapy. You may utilize spices as dried concentrates (cases, powders, teas), glycerites (glycerine concentrates), or colors (liquor extricates). Except if in any case demonstrated, you should make teas with 1 tsp. spice per cup of high temp water. Steep secured 5 - 10 minutes for leaf or blossoms, and 10 - 20 minutes for roots. Drink 2 - 4 cups for every day. You may utilize colors alone or in mix as noted. [53, 54]

Herbal Drug	Biological Name	Dose
Green tea	Camelia sinensis	250 - 500 Milligram daily
Cat's claw	Uncaria tomentosa	20 Milligram 3 times a day
Reishi mushroom	Ganoderma lucidum	150 - 300 Milligram 2 - 3 times daily,
Olive leaf	Olea europaea	250 - 500 Milligram 1 - 3 times daily,
DGL-licorice	Glycyrrhiza glabra	250 - 500 Milligram 3 times daily,
Mastic	Pistacia lentiscus	1,000 - 2,000 Milligram daily
Peppermint	Mentha piperita	1 tablet 2 - 3 times daily

Homeopathy-

Albeit not many investigations have inspected the adequacy of explicit homeopathic treatments, proficient homeopaths may think about the accompanying solutions for the treatment of ulcers or its side effects, in view of their insight and experience. Before endorsing a cure, homeopaths consider an

individual's sacred sort - your physical enthusiastic, and scholarly cosmetics. An accomplished homeopath evaluates these elements while deciding the most proper treatment for you separately. For the treatment of ulcers, regardless of whether you do look for homeopathic cures as adjunctive consideration, ordinary treatment proposals must be followed ^[55,56 57]

Homeopathic- Drug	Use
Argentum nitricum	Pain
Arsenicum album	Intense burning pains and nausea
Kali bichromicum	Burning or shooting abdominal pain
Lycopodium	Bloating after eating with burning
Nux vomica	Digestive disturbances
Pulsatilla	Burning stomach pain

III. ACUPUNCTURE

Acupuncture therapy has been utilized customarily for an assortment of conditions identified with the gastrointestinal plot, including peptic ulcers. A developing collection of logical proof recommends that needle therapy can help decrease torment related with endoscopy (the methodology utilized, as depicted prior, to make an analysis of ulcer or to treat its difficulties). ^[58-59]

IV. CONCLUSION

Peptic ulcer infection is a typical stomach related turmoil in which corrosive and pepsin (a significant stomach related protein) cause the covering of the stomach or the initial segment of the small digestive tract, known as the duodenum, to disintegrate. This prompts bruises known as peptic ulcers. All the more explicitly, a peptic ulcer that is situated in the stomach is known as a gastric ulcer. On the off chance that a sore is in the duodenum, it is known as a duodenal ulcer. Peptic ulcer illness can cause noteworthy upper stomach torment, however manifestations, overall, may shift to some degree between the two kinds of peptic ulcers, and your PCP may treat each somewhat better. Dealing with your case is significant, as genuine results, for example, draining and weakness, can happen. ^[60]

AUTHOR CONTRIBUTION

All author participated Equally

CONFLICT OF INTEREST

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