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Review Article

VALIDATION OF SCREENING MODELS OF PEPTIC ULCER: A REVIEW

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ABSTRACT

The stomach plays an important role in the digestion of the things we consume. This part of the body can withstand a wide range of harmful substances, such as hydrochloric acid, alcohol, refluxed bile salts, and other irritants. Upper abdominal pain may be a symptom of a gastrointestinal disorder known as Peptic Ulcer if you eat an unhealthy diet, smoke, drink too much alcohol, or take NSAIDs on a regular basis. You may also have a sedentary lifestyle. Today, gastric hyperacidity and gastroduodenal ulcers are very common problems all over the world. In this article, the author tries to give an overview of the in vivo and in vitro screening models that have been used in different laboratories and their validation during the past few decades to carry out such investigations, along with the underlying mechanisms of ulcer induction in each approach. The goal is to educate of the various experimental models available for conducting novel investigations to gain further knowledge in context to peptic ulcers.

Keywords: Peptic Ulcer, NSAIDs, Screening Model

INTRODUCTION

Gastrointestinal diseases are common and serious issues that cause the greatest amount of discomfort, morbidity, and mobility in humans. It affects 10-15% of the population at any given time[1-2]. One such GIT disorder is peptic ulcer. Peptic ulcer disease is a major health concern with high morbidity and mortality rates, and it is very common in today's world of industrialised and civilised nations[3-4]. In the gastrointestinal tract, peptic ulcer is induced following damage to mucosa as well as sub-mucosa tissues, that arises due to imbalance among invasive factors (secretion of gastric acid, pepsin, bile salts, increase of oxygen free radicals, intake of NSAIDs, and infection with *H. pylori*) and host defensive processes (mucus, bicarbonate, prostaglandin, antioxidant, and blood circulation)[5-8]. Although the incidence, rates of hospital admissions, and mortality associated with peptic ulcer disease are estimated to be 5–10 per cent in the general population, recent epidemiological studies have shown a decrease in the incidence, rates of hospital admissions, and mortality associated with peptic ulcer disease. This is most likely due to the introduction of new therapies and better hygiene, both of which have resulted in a decrease in Helicobacter pylori infections[9-10]. According to reports from Iran's Ministry of Health and Medical Education, one out of every eight Iranians has had a peptic ulcer at some point in their lives; however, duodenal ulcers are more common than gastric ulcers[11]. Risk Factors of Peptic ulcers are given in figure 1[12].

Peptic ulcer symptoms include severe pain and irritation in the upper abdomen. If not treated properly, it can lead to perforations in the gastrointestinal tract's wall. Because of the severity of the problem, the entire world is now waiting for a solution. Before beginning treatment on humans, we must first assess the drugs' effects on animals in order to protect human lives from drug-related disasters[13].

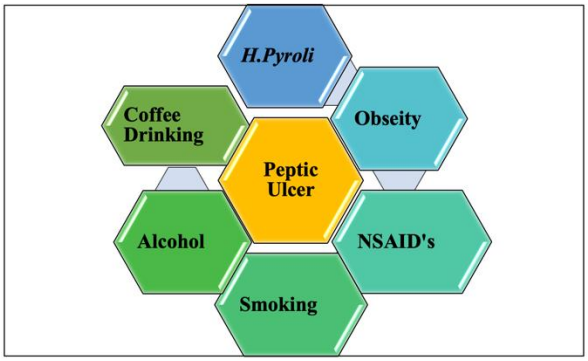

Figure 1: Risk Factors of peptic Ulcers

Different types of in-vivo and in-vitro screening models for the assessment of peptic ulcers will be discussed in our review work. In this article we have discussed about the validation and screening models of peptic ulcers.

Physiology of Gastric Acid Secretion

Gastric acid secretion is a complicated, constant process in which different central and peripheral factors contribute to a prevalent end - point: the secretion of H+ by parietal cells. Under various conditions, this secreted acid plays an etiologic role in causing various forms of discomfort, such as oesophageal and duodenal injury. The human stomach produces/contains approximately 1 billion parietal cells that secrete hydrogen ions into the gastric lumen in response to physiological stimuli, and the generation of these hydrogen ions is mediated by three pathways: endocrine, paracrine, and neurocrine. Acetylcholine is released by vagal postganglionic neurons, a neurocrine transmitter that stimulates hydrogen ion generation directly via a parietal cell M3 muscarinic receptor. Histamine, a paracrine transmitter, binds to H2-specific receptors on parietal cells. Adenylate cyclase is activated in

response, which raises adenosine 38, 58-Cyclic Monophosphate (cAMP) levels and stimulates the production of hydrogen ions. Gastrin secretion from the antral G-cell, which follows the endocrine pathway and stimulates hydrogen ion secretion in the corpus and fundus both directly and indirectly, increases the stimulation of histamine secretion from enterochromaffin-like cells as mentioned in Figure 2[14-16].

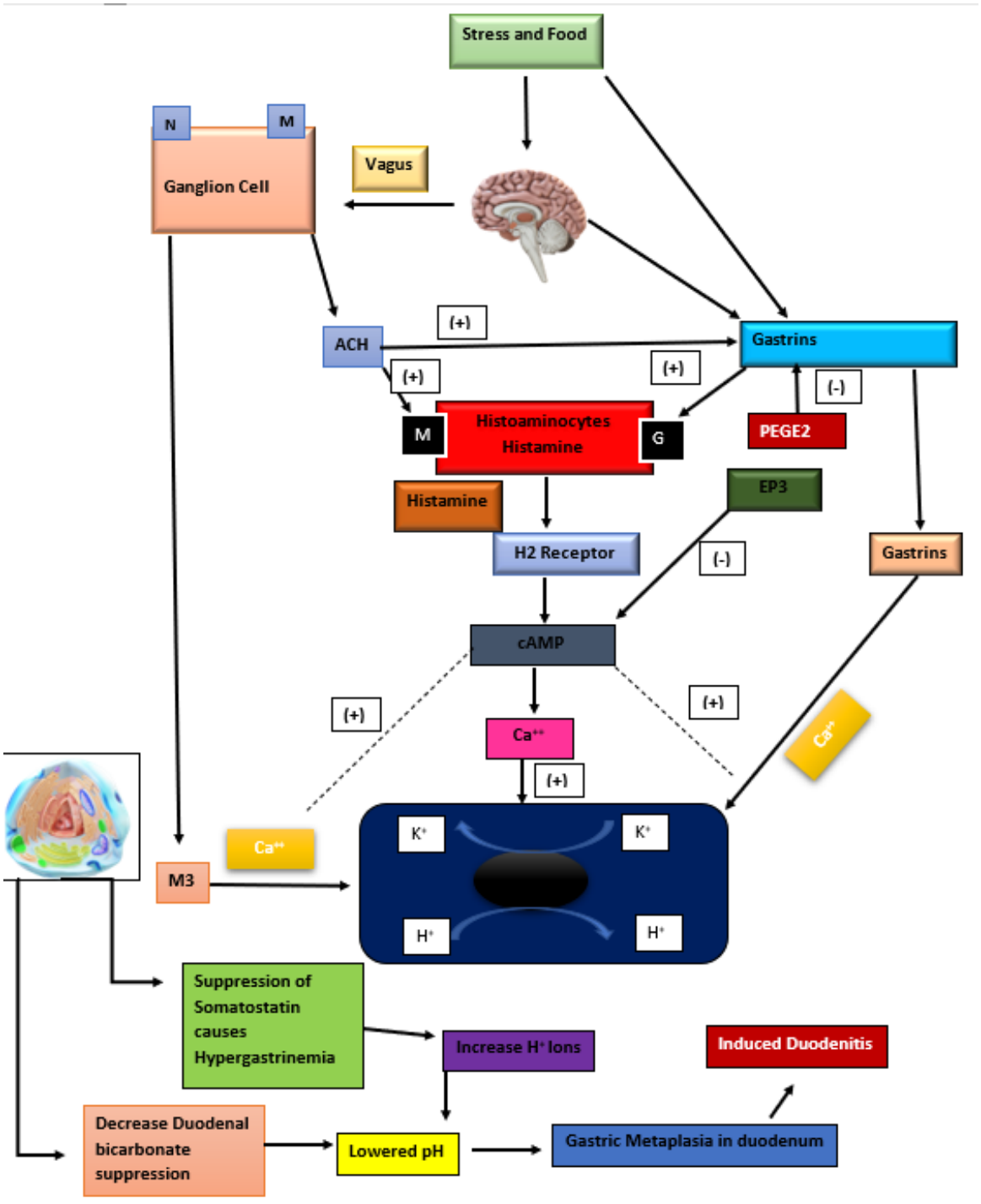

Figure 2: Physiology of peptic ulcer

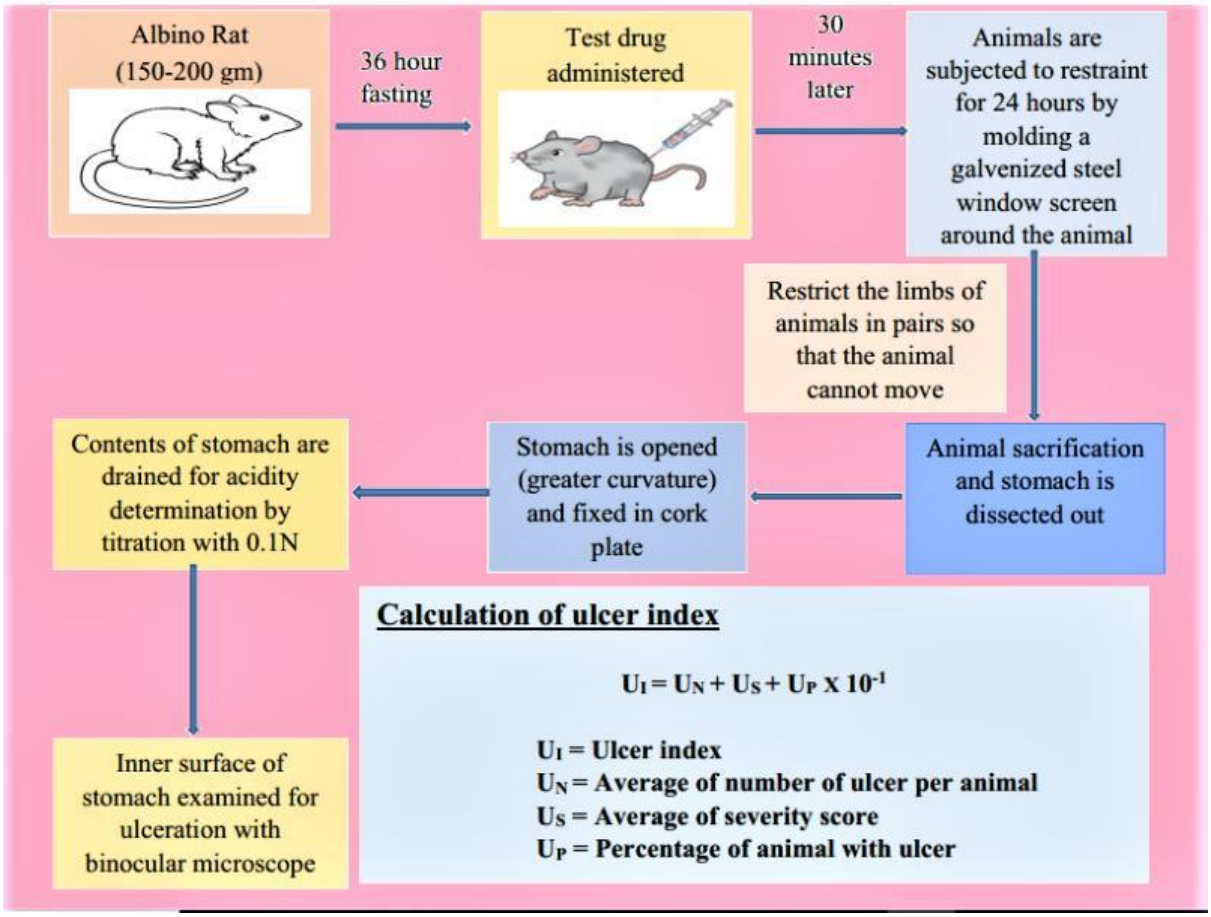

Figure 3: Approach of restrain induced ulcers

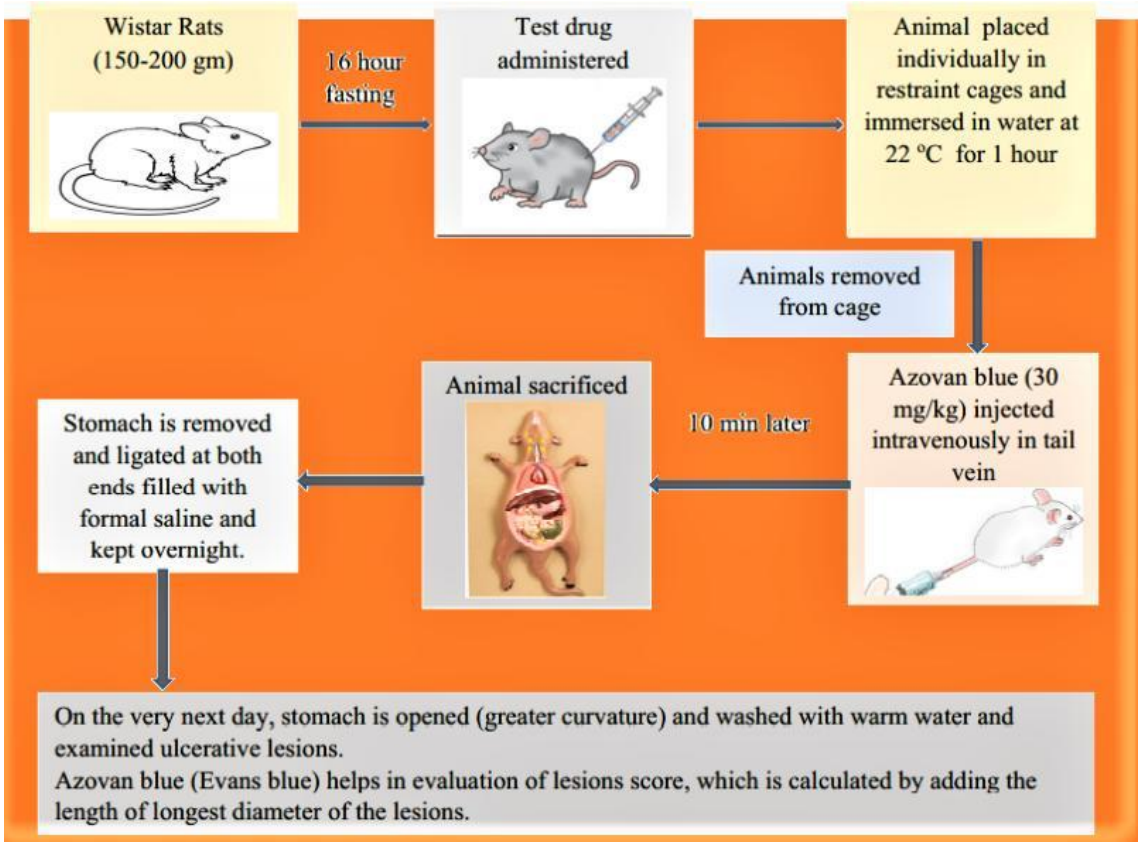

Figure 4: Approach of Coldwater Immersion Induced Ulcer

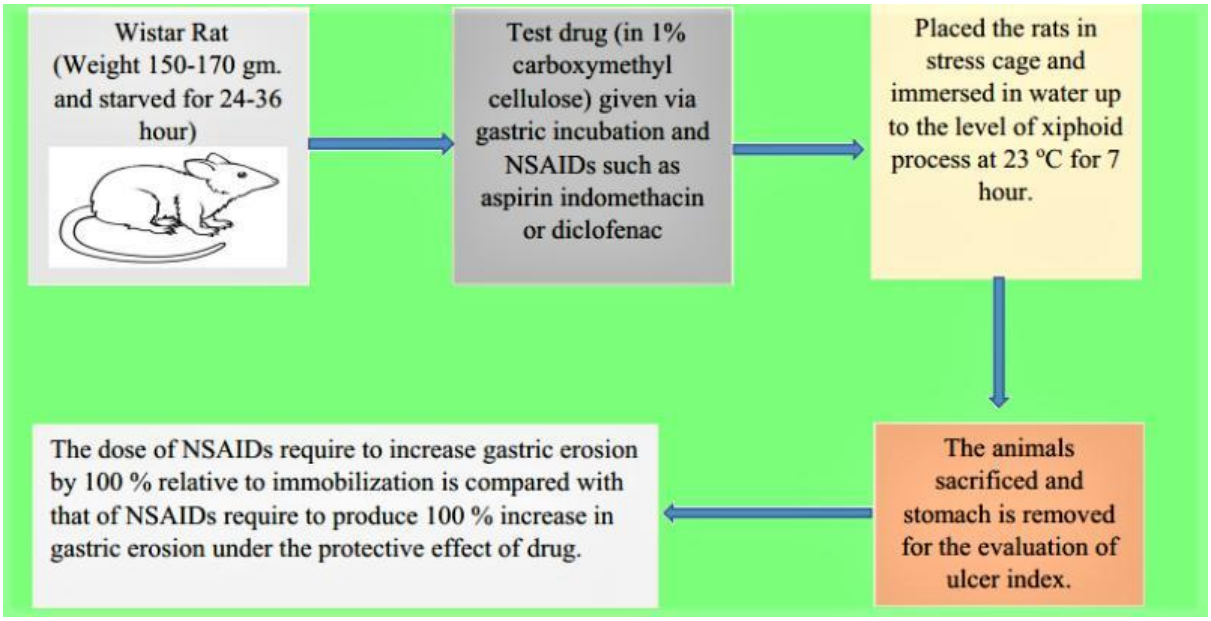

Figure 5: Methodology of Stress and NSAIDs Immersion Induced Ulcer

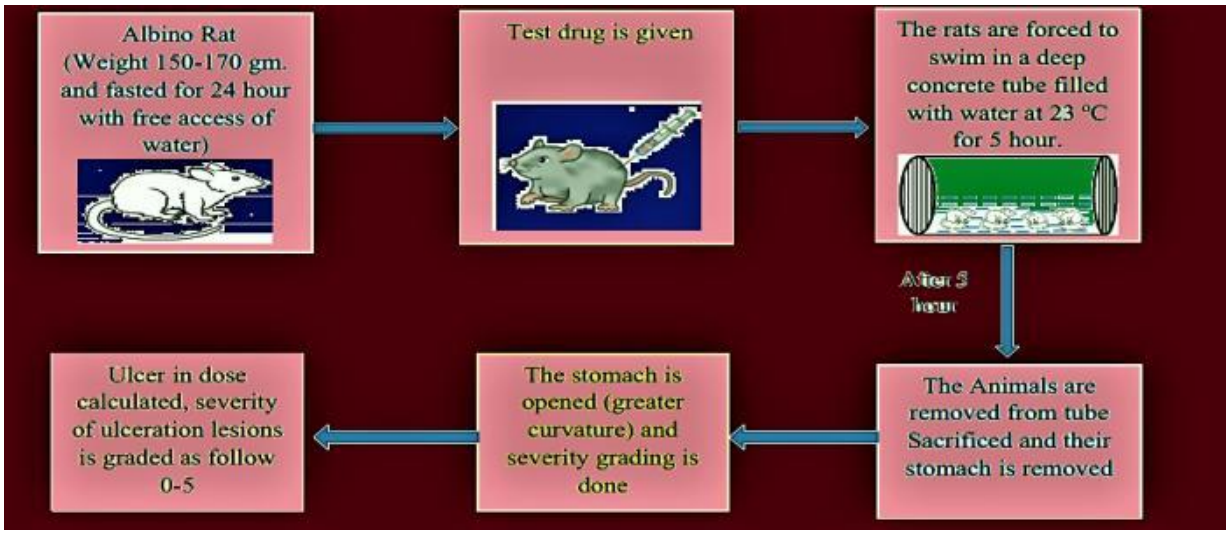

Figure 6: Method of Swimming Stress Ulcers

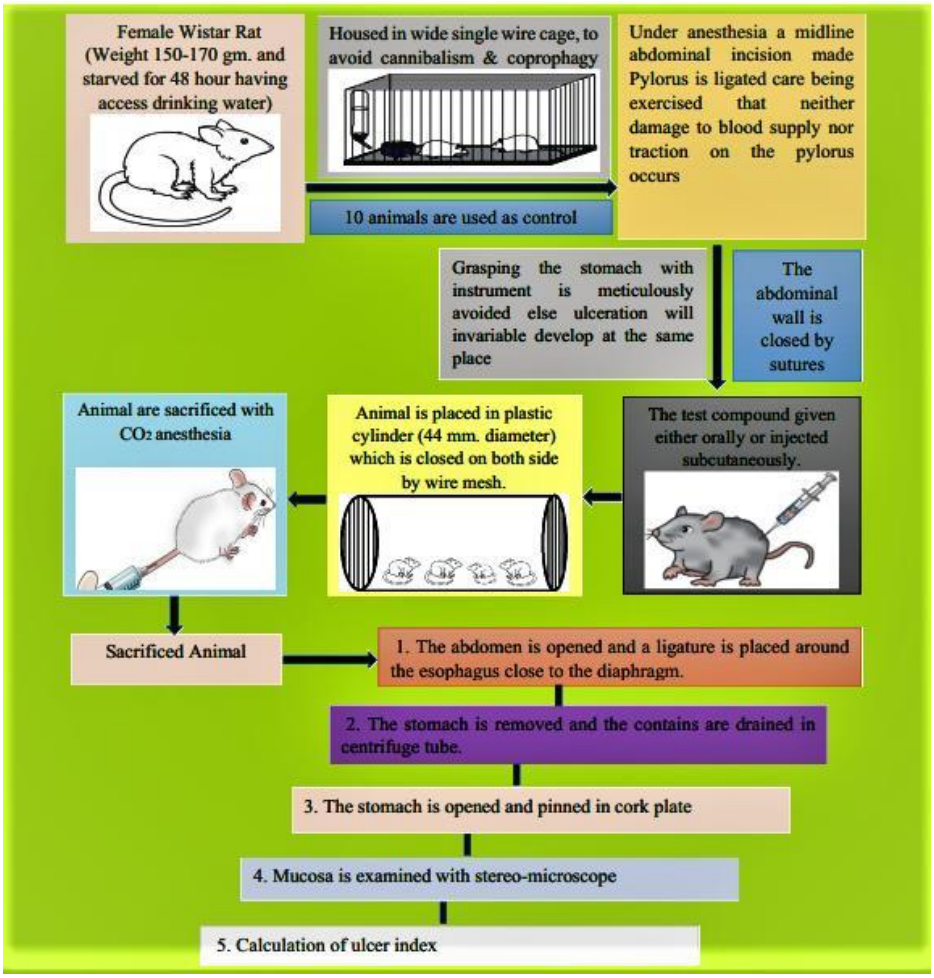

Figure 7: Methodology of Pylorus ligated induced ulcer model

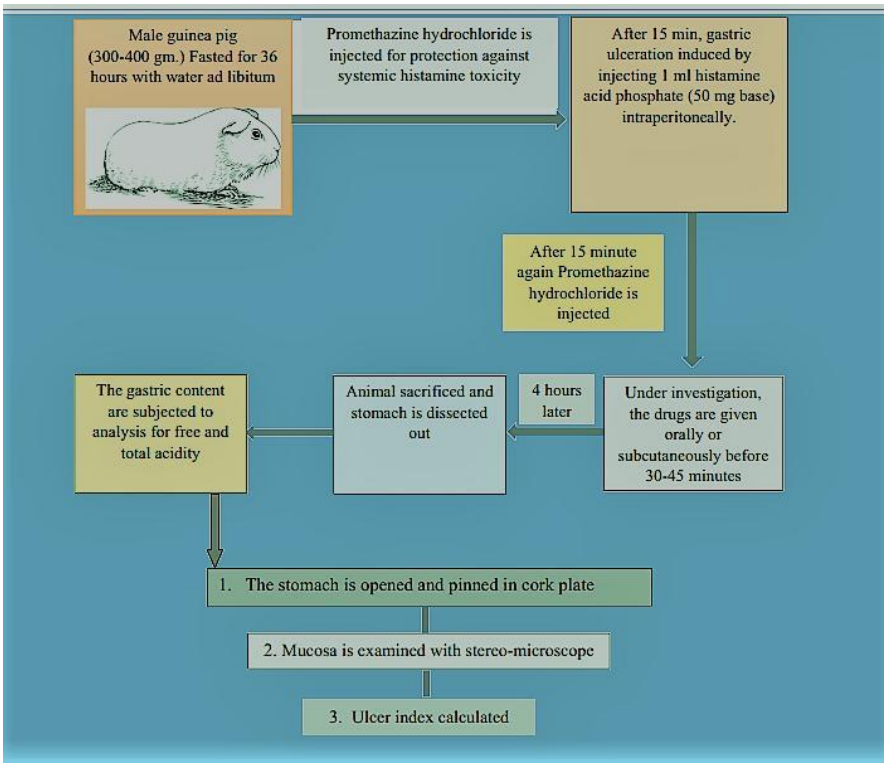

Figure 8: Approach of Histamine-induced Gastric Ulcer

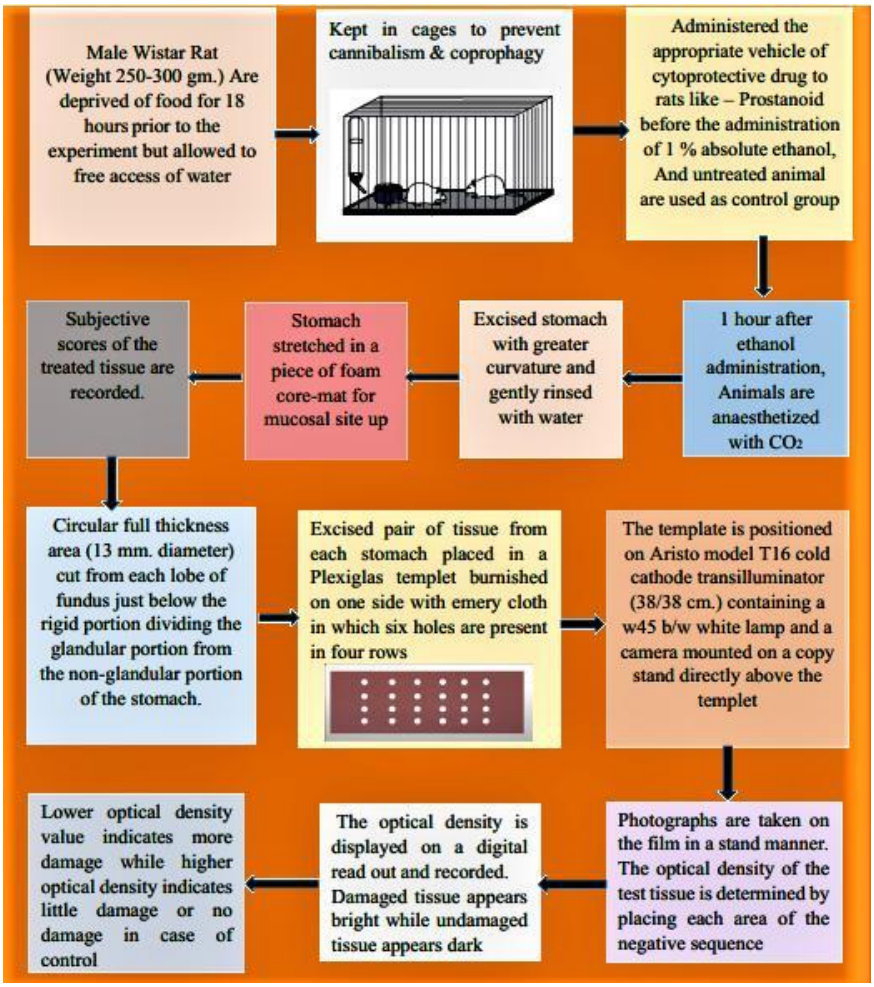

Figure 9: Methodology of Ethanol induced gastric ulcer model

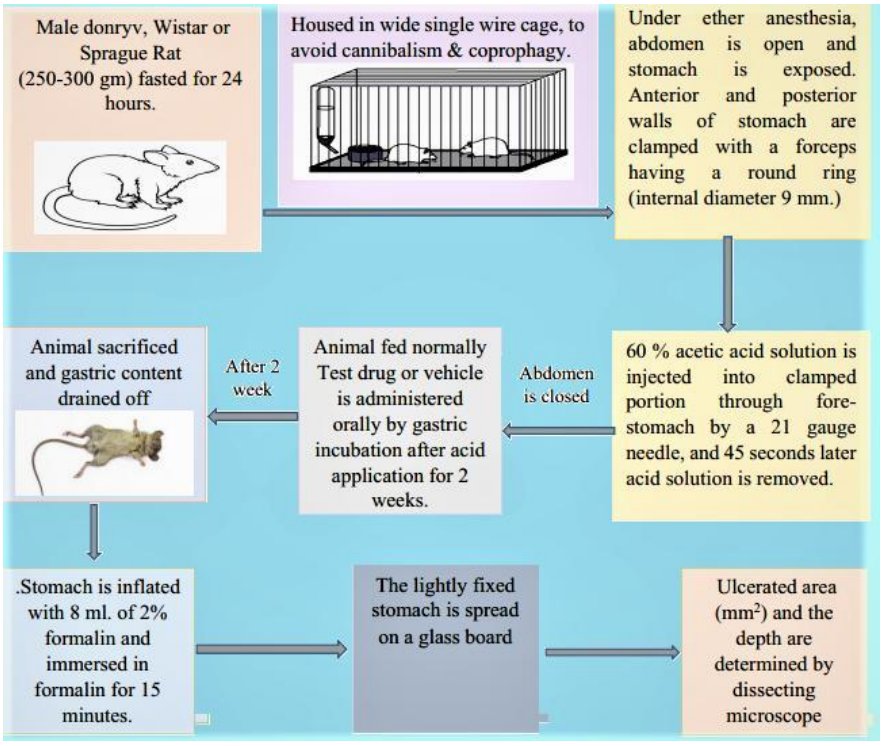

Figure 10: Procedure of Ethanol induced gastric ulcer model

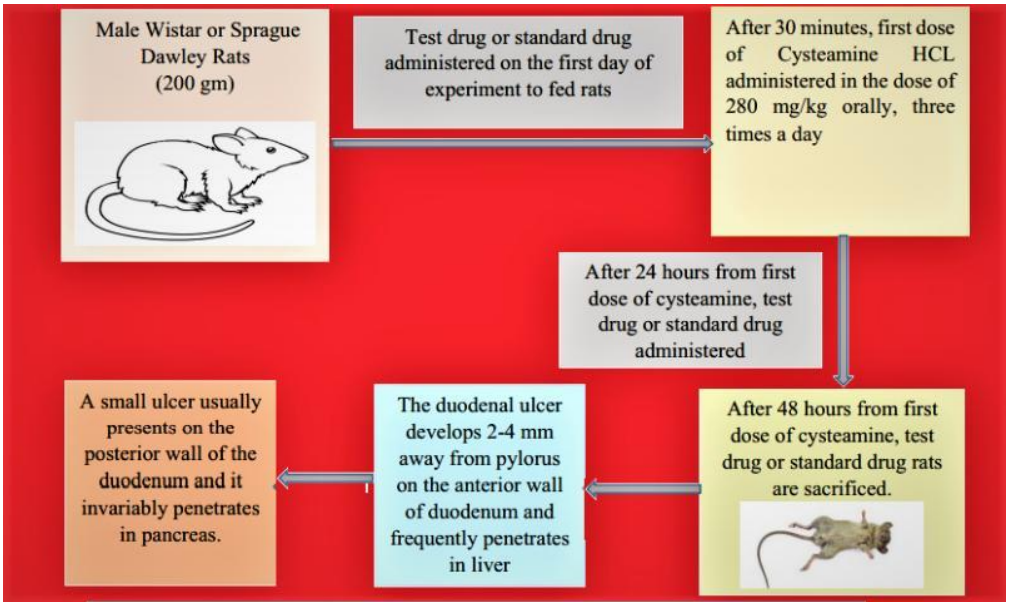

Figure 11 : Methodology of Cysteamine Induced Duodenal Ulcer

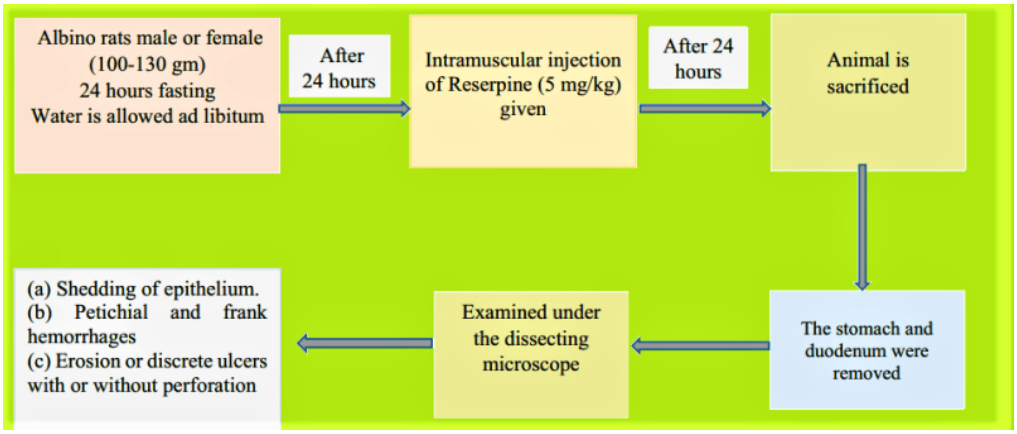

Figure 12 : Methodology of Reserpine-induced Duodenal Ulcer

Screening Models In Peptic Ulcer

Following an exhaustive literature review, we discovered that there are an 'n' number of models available, some of which are no longer in use due to procedural difficulties or poor results, while others provide good results in a short period of time. So, in general, these models are used in the laboratory with the aid of instruments and chemicals, while in some cases, animals are required. We divide antiulcer models into in-vitro and in-vivo categories based on the methodology[17].

Conditions for the Ideal Model

- During the observation period, the ulcers should not heal on their own.
- It should include a variety of mechanisms that cause ulceration.
- Should cause distinctive ulceration in specific areas.
- Allow for easy quantification of results by being simple, reproducible, and AMP [18]

***In-Vivo* models for peptic Ulcers**

The term in-vivo refers to the testing of drugs in a living organism, and testing of anti-ulcer drugs would be incomplete without using an in-vivo model, because ulcer is a disease that affects the body's internal environment and causes lesions in humans. Induced peptic ulcer [19]. Following In-Vivo models are associated with the screening of peptic ulcer.

Stress Ulcer Models

Stress can result in severe gastric ulceration as a result of prolonged anxiety, tension, and emotion, severe physical discomfort, haemorrhage and surgical shock, burns, and trauma[20]. Stress causes intestine lining lesions in the mucosal layer of the stomach oesophagus. This type of ulcer is common in critically ill patients in the intensive care unit, and it can also cause bleeding, which has been linked to a high rate of morbidity and mortality despite aggressive acid suppression treatment. A better understanding of the mechanisms underlying the development of stress ulcers will aid in the development of useful prophylactics or therapeutic interventions that may reduce morbidity and mortality[21-22]. For in-vivo studies, there are four stress ulcer methods available.

Restrain Induced Ulcer

Restraint ulcers are created using the method described by 2 scientists. Albino rats of either sex, weighing 150-200 g, are

separated into groups and housed in separate cages. Before the experiment, the animals are starved for 36 hours. Each rat is then placed in an appropriate-sized piece of galvanised steel window screen. The screen is stapled in place after being moulded around the animal. The animals' limbs are taped together and tightened to prevent them from moving. The drugs under investigation are given to the animal 30 minutes before it is restrained. The animals are removed from the screen after 24 hours and killed with an overdose of ether. The stomach is opened along its greater curvature, drained, and the ulcers are examined and scored using a suitable method. Total areas of stomach mucosa and ulcers are measured in one of the methods for calculating the ulcer index. The stomach is taken out of the body, opened along the greater curvature, cleaned, and spread on card board with the mucous surface facing up to avoid corrugation. The outline of the stomach and the areas of erosions of ulceration are traced on tracing paper placed over the stomach. This method has also been successfully used to investigate ulcer healing and its methodology is well elaborated in Figure 3[23].

Coldwater Immersion Induced Ulcer

Gastric ulcers are induced in rats and mice in this model by water immersion stress or cold restraint stress. Stress causes ulcers by releasing histamine, which causes increased gastric acid secretion, reduced mucous production, pancreatic juice reflux, decreased gastric blood flow, and increased gastro-intestinal motility. In restraint animals, cold water immersion quickens the development of ulcers. For experimental purposes, Wister rates are used. Animals are fasted for 16 hours before the experiments in this model. Orally, the test compound is given. After an hour, the animals are individually restrained in vertical restraint cages for two hours. Animals are submerged in 22°C water for 1 hour. Evans' blue is injected intravenously into the tail vein at a dose of 30mg/kg. After 10 minutes, the animals are sacrificed. Stomach is removed and both ends are ligated. The stomach is saline-filled and kept overnight. The stomach is opened along the greater curvature the next day, washed in warm water, and examined for ulcer lesions the next day[24-25]. Following Figure 4 well explain this peptic ulcer model.

Stress and NSAIDs Immersion Induced Ulcer

The second most common cause of gastric ulcer is nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, indomethacin, and ibuprofen[26].

NSAIDs cause ulcers by inhibiting prostaglandin synthesis via the COX pathway's cyclooxygenase enzyme. Prostaglandins protect the body by stimulating the secretion of bicarbonates and mucous, regulating mucous cell turnover and repair, and maintaining blood flow. Animals are fasted for 24 to 36 hours in this model. Orally, an NSAID (aspirin or indomethacin) is given in the appropriate vehicle (water or 1% carboxymethylcellulose). The animals are given the test drug after an hour. Animals are sacrificed 4 hours later, the stomach is removed, and the severity of the ulcer is measured. NSAID dose used to cause ulcers: Aspirin is 150 milligrams per kilogramme of body weight, and Indomethacin is 40 to 100 milligrams per kilogramme of body weight[27]. This method has also been successfully used to investigate ulcer healing and its methodology is well elaborated in Figure 5.

Swimming Stress Ulcers

Swimming stress ulcer method causes more ulcer formation in the animal than other stress methods because it is a more distressed strain, and a highly positive correlation is found between depression and ulcer severity scores. Animals are forced to swim in deep water using this method. Each animal is placed in a cylindrical chamber that is sealed on both sides. Rats are forced to swim in 30 cm of water at 23-28 degrees Celsius so that their feet do not touch the cylinder's surface. A minimum of two swimming sessions were completed, with a drug administered in between. Acid concentration in the stomach rises as a result of histamine release, causing an ulcer. The gastrointestinal motility increases as a result of stress-induced folds in the stomach, and when this gastrointestinal motility comes into contact with acid, the risk of damage increases. Stress reduces the quality and quantity of mucus, causing damage to the mucosal layer[28-29]. This method has also been successfully used to investigate ulcer healing and its methodology is well elaborated in Figure 6.

Pylorus ligated induced ulcer model

Researchers demonstrated this method for the first time in 1945. In rats, pyloric ligation causes a build-up of gastric acid in the stomach, resulting in acute gastric ulceration. The rats used in the experiment are Wrister rats weighing between 150 and 180 gm. For 48 hours, the animals are fasted. A 1-inch midline abdominal incision is made below the xyphoid process after the animals have been anaesthetized. Without damaging the pylorus' blood supply, the pylorus is carefully lifted out and ligated. Sutures are used to close the abdominal wall and replace the stomach. Orally or subcutaneously, the test compound is administered. Animals are sacrificed and stomachs are dissected 10 to 19 hours later. The contents of the stomach are drained into a graduated centrifuge tube, and the acidity of the contents is determined using 0.1N NaOH titration. The ulcer index is calculated after the stomach is opened along its greater curvature[30]. This method has also been successfully used to investigate ulcer healing and its methodology is well elaborated in Figure 7

Histamine-induced Gastric Ulcer

Histamine is released by mast cells, which binds to parietal cells, causing adenyl cyclase to be activated. The adenyl cyclase also converts ATP to c-AMP. HCL secretion increases as a result of this conversion. The experiment is carried out on male guinea pigs. The animal is taken after a 36-hour fast. The histamine corrosive sulphate is then infused intraperitoneally in a dose of 50 mg. In addition, 15 minutes before and 15 minutes after the histamine infusion, a 5mg dose of promethazine hydrochloride is infused intraperitoneally to prevent histamine toxicity. The drug to be tested then gave a histamine infusion for 30 to 45 minutes. The guinea pigs are sacrificed, stomachs are evacuated, and the results are analysed after 4 hours. The goal of the ulcer file is to determine the severity of ulcers[31-33]. This method has also been successfully used to investigate ulcer healing and its methodology is well elaborated in Figure 8.

Ethanol induced gastric ulcer model

Another antiulcer model is ethanol induced mucosal damage, in which we used too much ethanol because too much ethanol causes gastritis, which is marked by sub-epithelial haemorrhages, cellular exfoliation, inflammatory cell infiltration, and mucosal oedema. Various drugs, such as prostaglandins, can at least partially inhibit these lesions. Several researchers have tweaked this method from time to time[34].

In the ethanol-induced ulcer model, the gastric ulcer was induced by injecting 96 percent ethanol (5 mL/kg,) into the stomach. The animals were anaesthetized with intraperitoneal administration of ketamine (50 mg/kg) and xylazine (10 mg/kg) one hour after ethanol instillation. To determine the number and length of

gastric lesions, the stomachs were dissected and opened along the greater curvature. A section of the stomach was dissected and homogenised in a cold potassium phosphate buffer (0.05 M, pH 7.4). The homogenate was centrifuged for 10 minutes at 5000 rpm. The supernatant was kept at 80°C until malondialdehyde and nitric oxide levels were measured[35-36]. This method has also been successfully used to investigate ulcer healing and its methodology is well elaborated in Figure 9.

Acetic Acid-induced Gastric Ulcer

By causing an increase in acidic gastric juice due to gastric obstruction, acetic acid is said to cause ulcers. Phenobarbitone (35 mg/kg, i.p.) was used to anaesthetize the rats. The stomach was visualised after the abdomen was opened. In rats, 50 percent acetic acid (0.06ml/animal) was used to cause gastric ulcers on the anterior serosa surface of the glandular portion of the stomach, 1 cm away from the pyloric end. The test and control drugs were given orally on day 1, 4 hours after the application of acetic acid, and continued for up to 3 or 7 days after ulcer induction. The animals were sacrificed on the 4th or 8th day of the experiment, 18 hours after the last dose of test drug, to assess ulcer size and healing[20]. This method has also been successfully used to investigate ulcer healing and its methodology is well elaborated in Figure 10.

Cysteamine Induced Duodenal Ulcer

Cysteamine causes duodenal ulcers by stimulating gastric acid secretion while inhibiting Brunner's gland secretion of alkaline mucous. Acute and chronic duodenal ulcers are the two types of ulcers. Acute ulcers can be induced by giving a single dose of cysteamine HCL (400mg/kg of body weight). Cysteamine HCL (400mg/ kg of body weight) can be given twice at a 4-hour interval to induce chronic ulcers. The ulcer areas are measured after a cut is made along the antimesenteric side[37-39]. This method has also been successfully used to investigate ulcer healing and its methodology is well elaborated in Figure 11.

Reserpine-induced Duodenal Ulcer

Reserpine was isolated from the root of the Rauwolfia serpentina in 1952 and is used to treat hypertension. However, it has side effects such as gastric mucosal lesions (GMLs), sexual dysfunctions, and depression when taken in excess or for a long period of time. Reserpine causes gastric lesions by lowering sympathetic tone and increasing cholinergic tone, the latter of which causes excessive gastric acid secretion[40]. Solitary chronic gastric ulcers were caused by reserpine. Reserpine causes severe haemorrhagic glandular ulceration of the stomach, which has been linked to gastric mast cell degranulation and subsequent histamine liberation. These events are thought to be mediated by cholinergy. The destructive changes in the mucosa of human gastric ulcers are very similar to the morphological changes in gastric mucosa[41]. The experiment is carried out on female Sprogue - Dawley rats in this model. For 48 hours, the animals are fasted. The test drug is given intraperitoneally. Half an hour later, 15mg/kg of reserpine is administered intraperitoneally. Animals are sacrificed 4 hours later, their stomachs are removed and dissected, and the Ulcer Index is calculated[40,42]. This method has also been successfully used to investigate ulcer healing and its methodology is well elaborated in Figure 12.

Serotonin induced ulcer model

A disruption of gastric mucosal microcirculation is thought to cause serotonin-induced gastric ulceration. It takes about 18 hours for serotonin and reserpine to cause ulcers[43]. Four groups of rats (fasted for 24 hours) received subcutaneous injections of serotonin creatinine sulphate (Sigma USA) (20 mg/kg). 30 minutes before the serotonin injection, the test drug or control vehicle (Distilled water) was administered intraperitoneally. After 18 hours, the animals were sacrificed, their stomachs were removed, and the ulcer index was calculated as described previously[44].

Methylene Blue Induced Ulcer

Methyl blue is a synthetic drug used to cause gastric mucosal lesions. Antiulcer drug screenings typically use methylene blue. Methyl blue activates H+/K+-ATPase, causing an increase in hydrochloric acid secretion in the stomach and gastric lesions. Methyl blue also produces free radicals, such as superoxide dismutase, which cause oxidative stress and ulcers in the stomach. Methyl blue also causes acidity by interfering with the blood supply. Methyl blue binds to (M receptors) muscarinic or acetylcholine receptors and inhibits cholinesterase activity. In most cases, rats are used in this experiment. Albino rats (weight 150-250 g) select and divide themselves into groups as adults. The animals were given a test dose and a standard drug dose (such as ranitidine 50 mg/kg and omeprazole 200 microgram/ml). The animals are fasted for 24 hours before receiving methyl blue (125 mg/kg) via oral administration. After 4 hours of methyl blue administration, the animals are sacrificed. Dissect the stomach and wash it with saline solution, then look for ulcers and calculate the ulcer index. The contents of the stomach are used to calculate acidity and ph. Prepare the slide and observe pathophysiology after that[45-46].

Ischemia-reperfusion- (I-R-) induced ulcers

The ischemia-reperfusion model is commonly used to induce gastric ulcers. Ischemia affects the mucosa of the gastrointestinal tract. Ischemia-reperfusion causes the production of free radicals, which leads to ulceration and erosion of the gastric mucosa. To begin, experimental animals are divided into groups and selected for experiments. Before the experiment, the animals should fast for 20 hours. Xylazine and ketamine (15+60 mg/kg) were used to anaesthetize the animals. Bull god clips are used to bind the oesophageal and pyloric ends of the stomach during laparotomy. The celiac artery carefully separates itself from the surrounding tissues. The celiac artery is ligated for 30 minutes to induce ischemia, and then the ligature is removed to allow for 3 hours of reperfusion. Dissect the stomach and wash it with saline solution, then look for ulcers and calculate the ulcer index. The contents of the stomach are used to calculate acidity and ph. Prepare the slide and observe pathophysiology after that[43, 47-50].

***In-vitro* Models**

Acidity is one of the most common gastrointestinal issues, causing functional disorders such as peptic ulcers and eventually affecting the mucosal layer of the stomach. We use various types of antacids, either allopathic antacids or herbal antacids, to neutralise this type of acidity. These antacids neutralise gastric acids by lowering the gastric pH, and these antacids are easily available in your nearest shop nowadays. Following in vitro methods have been developed to assess antiulcer drugs in the laboratory, which are useful in determining the capacity and effect of the drug in peptic ulcer, gastric ulcer, or other diseases.

There are basically 4 in-Vitro models which can be used in the analysis of peptic ulcer. They are:-

- Using a Titration Method of Fordtran's Model for the Determination of Neutralizing Capacity In-vitro.
- H+ /K+ -ATPase Inhibition Assay

- Determination of the Duration of Neutralization Capacity of Prepared Preparation on Artificial Gastric Acid
- Neutralization Effects of Prepared Preparation on Artificial Gastric Acid [17]

However further research and studies are required to establish the role of in-vitro models in the study of peptic ulcers.

Parameters to be Calculated

The ulcer index, percent protection ratio, and percent curative ratio are three parameters calculated using Takagi and Okabe method for evaluating anti-ulcer activity of drugs in in-vivo models[51-52]. Table 1 can be considered while validating ulcer models.

Relative Area/mm^2	Ulcer Index
No ulcer Found	0
91-100	0.1
81-90	0.2
71-80	0.3
61-70	0.4
51-60	0.5
41-50	0.6
31-40	0.7
21-30	0.8
11-20	0.9
1-10	1.0
Perforation	1.0

a. Calculation of Ulcer Index (UI) based on ulcer score

By using the ulcer score as described above, the ulcer index can be calculated as follows:

Ulcer Index (UI) = Total ulcer score /Number of animals ulcerated.

b. Calculation of % protection ratio and % curative ratio by using the Ulcer Index

The following formula may be used for the calculation of percentage protection and percentage curative ratio:

% protection ration = UI of ulcerogen treated group /UI of ulcerogen treated.

% Curative Ratio = UI of ulcerogen treated group/ UI of ulcerogen treated[53-55]

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