EXPERIMENTAL ANIMAL MODELS FOR GASTROINTESTINAL ULCER DISEASE

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ABSTRACT

Gastric ulcer is one of the most serious gastrointestinal disease. Ulcers are mainly caused by imbalance between the gastroduodenal mucosal defensive factors versus aggressive factors. In gastric ulcer disease, animal models have helped to understand the basic mechanisms responsible for the formation of gastric ulcers and its treatment. The limited number of animal models for the study of gastric ulcer has hindered the process of research in gastrointestinal disorders. Therefore it is important to review the available literature for animal models of gastric ulcer. Available models include primates, rats, mice, rabbits, cats, guinea pigs, ferrets and pigs. The main aim is to provide scientific information about different animal models to induce gastric ulcers as well as for the screening of antiulcer activity. In this review, we summarize different experimental animal models used in clinical research during past few decades to carry out antiulcerative activity of new agents as well as its underlying mechanisms.

KEYWORDS: Gastric ulcer; animal models; NSAIDs; antiulcerative activity; diethyldithiocarbamate; COX.

1.0 INTRODUCTION

Gastric ulcer is a common gastrointestinal disorder, which includes both gastric and duodenal ulcers affecting many people throughout the world.\textsuperscript{[11]} It affects around 3\%–10\% of the global population.\textsuperscript{[2]} About 10\% of the world population is on high risk of developing gastric ulcer at some point in their lifetime.\textsuperscript{[3]} Globally, an estimated 15 mortality was recorded per year out of every 15,000 complications of gastric ulcer.\textsuperscript{[4]} It can be defined as a damage to the
mucosa that ruptures the muscle layer and forms an injury followed by inflammation.\[2\], [5] Generally normal gastric mucosa is exposed to the offensive factors. This may result from an imbalance between the defensive factors and the offensive factors present in the gastric mucosal layer.\[6\] The defensive factors like mucin, adequate blood flow, nitric oxide, prostaglandin secretion, bicarbonate and growth factors and the offensive factors include increased secretion of hydrochloric acid and pepsin, reactive oxygen species, improper dietary habits, administration of non-steroidal anti-inflammatory drugs, consumption of alcohol, stressful conditions and infection with Helicobacter pylori infection.\[7\], [8] So the imbalance between these offensive factors and the defensive factors is the main cause for the pathogenesis of gastric ulcers.\[9\] The gastric acid, reactive oxygen species (ROS), and inflammatory cytokines are continuously in contact with gastric mucosa and can lead to gastric tissue damage.\[10\] Nowadays, the drug therapy for gastric ulcer is mainly based on the reduction in acid secretion and the protection of gastric mucosa.\[11\] The drugs which are commonly used for the treatment of gastric ulcers consist of antacids, anticholinergics, proton pump inhibitors and H2-receptor antagonists.\[12\], [13] However, the current therapy is not completely effective and continuous use of these drugs can produce side effects\[14\] such as hypersensitivity, hematopoietic changes, gynecomastia and arrhythmia.\[15\] The search for a new, effective and affordable ulcer treatment, reducing its side effects, current studies are moving towards natural products.\[16\] Hence for the screening of novel antiulcer agents, suitable animal models are necessary, which can mimic the conditions and show resemblance to that of the human disease state. Therefore it is important to review the available literature for animal models of gastric ulcer to screen antiulcer agents. Researchers have used some technologies to generate transgenic rats\[17\], cats\[18\], dogs\[19\], rabbits, pigs, sheep\[20\], goats, cattle, chickens\[21\], zebrafish\[22\] and non-human primates\[23\] as animal models to study different disease mechanisms.

The main aim is to provide scientific information about different animal models to induce gastric ulcers as well as for the screening of antiulcer activity. Therefore in this review, authors put forth different experimental animal models used in clinical research during past few decades to carry out antiulcer activity of new agents as well as its underlying mechanisms.
2.0 Animal models

To study the actual pathogenesis and mechanisms of gastric ulcer in humans, rodent models are helpful.\textsuperscript{[24]} Many scientists are using different animal models to induce gastric ulcer such as pylorus ligation model, alcohol induced ulcers, NSAIDs induced ulcers, stress ulcers, histamine induced gastric ulcers, cysteamine induced duodenal ulcers. These models could also serve as effective tool for the better understanding of pathophysiological mechanisms, like antisecretory, gastroprotective, antioxidant and healing of ulcers. But the limited number of animal models for the study of gastric ulcer has hindered the process of research in gastrointestinal disorders.

Certain conditions should be fulfilled while selecting the proper experimental animal model for the screening of antiulcer agents.

- It should be simple and reproducible.
- It should be easy for the quantification of the results.
- It should induce a proper ulceration at targeted site.
- It should involve different mechanisms by which ulcers are produced.

Gastric ulcer can be induced by various methods and can be classified as (A) Physical methods, (B) Chemical methods and (C) Surgical methods. These models are listed in Table 1.

Table 1. List of Animal models.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Animal models</th>
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<tbody>
<tr>
<td>Physical methods</td>
<td>Stress induced ulcers</td>
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<td></td>
<td>Water immersion stress induced ulcers</td>
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<td></td>
<td>Cold restraint stress induced ulcers</td>
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<td>Chemical methods</td>
<td>NSAIDs induced gastric ulcers</td>
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<td>Ethanol induced gastric ulcers</td>
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<td>HCl/ethanol induced gastric ulcers</td>
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<td>Acetic acid induced gastric ulcer</td>
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<td></td>
<td>Serotonin induced gastric ulcer</td>
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<td></td>
<td>Reserpine induced gastric ulcers</td>
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<td></td>
<td>Diethyldithiocarbamate induced gastric ulcers</td>
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<td></td>
<td>Histamine induced duodenal ulcers</td>
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<td></td>
<td>Cysteamine HCl induced duodenal ulcers</td>
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<tr>
<td>Surgical methods</td>
<td>Pylorus ligation induced gastric ulcers</td>
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<td></td>
<td>Ischemic reperfusion induced gastric ulcers</td>
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<td></td>
<td>Mucosectomy induced gastric ulcers</td>
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</table>
The principle along with their underlying mechanism of action is described below and a brief procedure for the same is given in table 2.

2.1 Physical methods
Certain physical methods are used to induce gastric ulcers in experimental animals. Generally physical methods are responsible for the production of oxidative stress and increases reactive oxygen species in the stomach.

2.1.1 Water-immersion stress or cold-resistant stress induced gastric ulcers
Physical stress and psychological stress can cause gastric ulcers in humans. Hence various stressors are responsible for the production of gastric ulcers in animal models.[25] This model involves the restraint technique developed by Brodie and Hanson[26] employed with coupling of new method developed by Levine i.e. cold water immersion method which induces gastric ulcers in a synergistic manner. Gastric ulcers induced by water-immersion stress or cold water-restraint stress or cold-restraint stress in animals are completely resemble to human ulcer condition by histopathologically.[27] This model is widely used to study the gastroprotective and healing effect of test agents, especially those with mucus enhancing and cytoprotective properties, for gastric ulcers in rats. The pathophysiology behind stress-induced gastric ulcers is complex and difficult to understand. Generally these ulcers are produced due to the release of histamine, which resulting into increased acid secretion and reduced mucus production[22] and poor gastric blood flow.[28] Excessive production of reactive oxygen species and inhibition of prostaglandin synthesis also promote stress induced ulcer formation.[29] [30] Increased gastrointestinal motility produced by stress results into formation of folds in the stomach[31] which are more susceptible to damage gastric mucosa when they come in contact with gastric acid. Increased vagal activity is also one of the factor responsible for the production of stress-induced ulcers.[26] As mucus plays a crucial role in the protection of stomach wall and enhances healing of gastric ulcers, this model is suggested for evaluating mucus enhancing and cytoprotective agents.
Table 2. Animal models of gastric and duodenal mucosal lesions and ulcers.

<table>
<thead>
<tr>
<th>Assay</th>
<th>Types of animals</th>
<th>Method of induction</th>
<th>Types of lesions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress induced gastric ulcers</td>
<td>Rat</td>
<td>Animals are placed in a stress cage and immerse it vertically in water bath (15–20°C) upto the level of the xiphoid for 17 hours to induce stress ulcer.</td>
<td>Gastric, Acute, Chronic</td>
<td>[32], [33]</td>
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<tr>
<td>Water immersion stress</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cold restraint stress</td>
<td>Rat</td>
<td>Animals are restrained in plastic cages in a ventilated refrigerator at 2-3°C for 2-4 hours and then sacrificed.</td>
<td>Gastric, Acute, Chronic</td>
<td>[34]</td>
</tr>
<tr>
<td>NSAIDs induced ulcers</td>
<td>Rat or Mouse</td>
<td>24-36 hrs fasted animals receive a single dose of aspirin (125-150 mg/kg) administered by oral route and after 4 hrs animals are sacrificed for ulcer examination.</td>
<td>Gastric, Acute</td>
<td>[28], [35]-[38]</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
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</tr>
<tr>
<td>Indomethacin</td>
<td>Rat or Hamster</td>
<td>Animals receive a single dose of indomethacin in the range of 40-100 mg/kg subcutaneously and sacrificed after 5 hrs.</td>
<td>Gastric, Acute, Chronic</td>
<td>[28], [37], [39]-[42]</td>
</tr>
<tr>
<td>Ethanol induced ulcers (Absolute ethanol)</td>
<td>Rat</td>
<td>After 24-36 hrs of fasting, animals receive ethanol (1ml/rat) orally and sacrificed after 1 hr to check gastric lesions.</td>
<td>Gastric, Acute</td>
<td>[41], [43]-[46]</td>
</tr>
<tr>
<td>HCl/ethanol induced Ulcers</td>
<td>Rat</td>
<td>Animals receive a mixture of 1.0 mL EtOH/HCl (60 mL ethanol, 1.7 mL hydrochloric acid, 38.3 mL distilled</td>
<td>Gastric, Acute</td>
<td>[47]</td>
</tr>
<tr>
<td>Condition</td>
<td>Animal(s)</td>
<td>Procedure Description</td>
<td>Location(s)</td>
<td>References</td>
</tr>
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</tr>
<tr>
<td>Acetic acid induced gastric ulcers</td>
<td>Rat, Cat</td>
<td>After an acute laparotomy, stomach is exposed and 20% acetic acid (0.03 mL) is injected into the sub-serosal layer of the antrum at multiple sites. After 24 hrs animals are sacrificed.</td>
<td>Gastric, Chronic</td>
<td>[48]-[50]</td>
</tr>
<tr>
<td>Serotonin induced ulcers</td>
<td>Rat</td>
<td>After 30 min of drug treatment, Serotonin Creatinine Sulphate (20-50 mg/kg) is administered subcutaneously and after 6 hours animals are sacrificed.</td>
<td>Gastric, Acute</td>
<td>[51], [52]</td>
</tr>
<tr>
<td>Reserpine induced ulcers</td>
<td>Rat</td>
<td>After 36 hrs of fasting, reserpine (5–8mg/kg) is administered intraperitoneally and after 24 hrs animals are sacrificed.</td>
<td>Gastric, Acute</td>
<td>[53]</td>
</tr>
<tr>
<td>Diethylthiocarbamate induced ulcers</td>
<td>Rat</td>
<td>In this model, acute glandular lesions are induced by subcutaneous injection of 1 mL of diethylthiocarbamate (800mg/kg) in saline followed by oral dose of 1 mL of 0.1N HCl.</td>
<td>Gastric, Acute</td>
<td>[54], [55]</td>
</tr>
<tr>
<td>Histamine induced ulcers</td>
<td>Rat</td>
<td>Histamine phosphate (40–100mg/kg) is administered subcutaneously and after 2 hours animals are sacrificed.</td>
<td>Gastric, Duodenal, Acute</td>
<td>[56], [57]</td>
</tr>
<tr>
<td>Cysteamine HCl induced ulcers</td>
<td>Guinea pig, Rat, Mouse</td>
<td>A single dose of cysteamine hydrochloride (400mg/kg p.o.) is sufficient to induce acute duodenal ulcers in experimental rats.</td>
<td>Duodenal, Acute</td>
<td>[35], [36], [40]</td>
</tr>
</tbody>
</table>
### Pylorus ligation induced ulcers

<table>
<thead>
<tr>
<th>Animal</th>
<th>Procedure</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>After an acute laparotomy, pyloric end of animals stomach is ligated for 4 hrs. Then animals are sacrificed for ulcerative lesions examination.</td>
<td>Gastric, Acute</td>
<td>[38]</td>
</tr>
</tbody>
</table>

### Ischemia reperfusion induced ulcers

<table>
<thead>
<tr>
<th>Animal</th>
<th>Procedure</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>A laparotomy is carried out under anesthesia, and the superior mesenteric artery (SMA) is clamped with a bulldog clip for 30 min (The ischemic stage). After that, bulldog clip is removed to permit reoxygenation of the gastric tissue for 15 minutes (the reperfusion stage). Then animals are sacrificed for ulcerative lesions examination.</td>
<td>Gastric, Intestinal Acute</td>
<td>[58], [59]</td>
</tr>
</tbody>
</table>

### Mucosectomy induced ulcers

<table>
<thead>
<tr>
<th>Animal</th>
<th>Procedure</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbits, Guinea pigs</td>
<td>After a median laparotomy, 0.2 mL of isotonic saline is injected into the submucosal layer of the upper corpus. A diameter of 7-10 mm of the swollen mucosal layer is resected with scissors. After the procedure, animals are placed to individual cages for recovery.</td>
<td>Gastric, Acute</td>
<td>[60]–[62]</td>
</tr>
</tbody>
</table>

### 2.2 Chemical methods

Various chemicals are used to induce ulcers because they directly ruptures the gastric mucosa (Ethanol, Acetic acid) or some other mechanisms are also involved in it.
2.2.1 NSAID’s induced gastric ulcers
Gastric ulcers are known to be induced by excessive use of several Non-Steroidal Anti-Inflammatory Drugs (NSAID’s) like aspirin, indomethacin, and ibuprofen. This is the most common model used for inducing gastric ulcer. NSAID’s are responsible for the production of gastric ulcers by inhibiting prostaglandin synthesis via cyclooxygenase (COX) pathway. Prostaglandins play an important and protective role in the production of mucus and secretion of bicarbonate, which maintains mucosal blood flow and regulates mucosal cell integrity. Thus the suppression of production of prostaglandins by NSAIDs leads to the gastric mucosal damage and gastric ulcers. The mechanism behind NSAIDs-induced gastric ulceration includes blocking activity of the cyclooxygenase enzymes (COX-1 and COX-2), by NSAIDs, which further leads to the decreased mucus and bicarbonate secretion, impaired platelet aggregation, decreased mucosal blood flow, changes in microvascular structures leading to epithelia damage. Increased reactive oxygen species (ROS) and lipid peroxidation (LPO) are also responsible for gastric mucosal damage. NSAID’s specially those are having chemically acidic nature, can exert direct cytotoxic effects on epithelial cells, which disrupt surface active phospholipids on the mucosal surface thus making the mucosa more susceptible to damage by luminal acid. Thus this model is commonly used for the evaluation of antisecretory and cytoprotective agents. Specially, most commonly used ulcerogen used for the induction of gastric ulcers are aspirin and indomethacin. A correct route and an appropriate vehicle (e.g. water, 1% carboxymethyl cellulose) is selected for administration of ulcerogen.

2.2.2 Ethanol induce gastric ulcers
Ethanol has been commonly used as a damaging agent to gastric mucosa for the induction of gastric ulcers. Administration of absolute ethanol (>99%) has been used as a reproducible method to induce gastric mucosal damage in experimental animals. The pathology behind ethanol-induced gastric ulcer generally involves three main parameters: inflammatory response, oxidative stress and apoptosis.

In the gastrointestinal tract, the motility of the esophagus, stomach, and gut as well as the capacity of gut absorption can be severely affected by alcohol exposure. It can cause severe mucosal damage and even carcinogenesis specially gastric cancer. Ethanol causes severe gastric damage by producing several instabilities in the gastric mucosal layer such as a...
decreased bicarbonate secretion, gastric blood flow and mucus production. Ethanol can stimulate gastric acid secretion, resulting in microvascular injuries which facilitate vascular permeability, through release of gastrin and histamine from sensitive nerve terminals present in the gastric mucosa.\textsuperscript{[72]} Ethanol ruptures gastric mucosal integrity through exfoliation of cells, which leads to increase in mucosal permeability and in somehow causes bleeding.\textsuperscript{[73], [74]} Intra-gastric administration of absolute ethanol results in severe gastric mucosal injury characterized by disturbances in microcirculation, mast cell secretory products, inhibition of prostaglandin synthesis, reduction in mucus production and reactive oxygen species.\textsuperscript{[75]} Neutrophil infiltration in the gastric mucosa is also responsible for the production of lesions induced by absolute ethanol.\textsuperscript{[76]}

Oxidative stress plays a significant role in alcohol-induced gastric mucosal damage.\textsuperscript{[77]} Ethanol is also known to increase cellular oxidative stress\textsuperscript{[78]} and produce changes in gastric cell calcium levels\textsuperscript{[79]} which may lead to the pathogenesis of gastric mucosal injury. However, it is not a suitable animal model to evaluate antisecretory activity and ulceration dependent on acid secretion, because this model is independent of gastric acid secretion. Ethanol directly increases the levels of free radicals that can alter the cell structure and function\textsuperscript{[75]} and can also gives its direct toxic effects on the gastric mucosa resulting in reduced bicarbonate secretion and gastric mucus production.\textsuperscript{[80]} Hence this model is more preferable for evaluating the gastroprotective potential of test materials which has cytoprotective as well as antioxidant activities.

2.2.3 HCl/ethanol induced gastric lesions

This model is considered to be an advanced model of an absolute ethanol induced ulcer model. Instead of ethanol only, a mixture of HCl and ethanol is used to induce ulceration. Direct necrotizing action of HCl/ethanol is the pathogenesis for gastric lesions on the gastric mucosa. Hence the combination of ethanol with HCl leads to induction and progression of gastric injury.\textsuperscript{[81]}

2.2.4 Acetic acid-induced gastric ulcers

Chronicity of the gastric ulcer disease is one of the least understood aspects for researchers. Takagi et al.,\textsuperscript{[82]} developed an animal model to induce chronic gastric ulcers by sub-mucosal injection of acetic acid and he also reported healing process of ulcers for extended time intervals after the ulcer formation. The experimental gastric ulcers induced by acetic acid are
considered as chronic ulcers due to its prolonged steadiness in gastric mucosa and resemblance to human chronic ulcer both physiologically and histologically.

To overcome certain problems like adherence of ulcer to the adjacent organs such as the liver, method given by Takagi, was modified and the one that is currently most commonly used is developed by Okabe and Pfeiffer.\cite{83} This method consists of intraluminal application of acetic acid solution. Thus acetic acid induced gastric ulcer model is most suitable for evaluating antisecretory and cytoprotective activity of various test agents against chronic gastric ulcers.\cite{82,84} This model is easy and reliable to produce round and deep ulcers in the stomach and duodenum of mice, rats, Mongolian gerbils, guinea pigs, cats, dogs, miniature pigs, and monkeys.\cite{49,85}

### 2.2.5 Serotonin-induced gastric ulcers

Serotonin is a vasoconstrictor. It causes disturbance in gastric mucosal microcirculation and reduces blood flow to gastric mucosa resulting in acute gastric mucosal damage which causes gastric ulcers.\cite{86}

### 2.2.6 Reserpine-Induced Peptic Ulcer

Reserpine is also used for induction of gastric ulcers by scientist. Reserpine causes degranulation of mast cells resulting into release of histamine, mediated by cholinergic system\cite{87} and this histamine is responsible for formation of gastric ulcer. Although this model is dependent on gastric acid secretion, gastric hypermotility also plays an important role in the induction of gastric mucosal lesions.\cite{53}

### 2.2.7 Diethyldithiocarbamate induced gastric ulcers

This model is useful to assess the antioxidant activity of test drug which is mediates gastroprotection by preventing gastric damage\cite{54} and also to evaluate the cytoprotective potential of test agents. It is reported that antral lesions are induced by diethyldithiocarbamate through the mobilization of superoxide and hydroxyl radicals. Superoxide radical and hydroxyl radicals play a pathogenic role in the induction of this ulcer.\cite{55}

### 2.2.8 Histamine-induced gastric ulcers

Release of histamine in stomach also causes gastric ulcers and hence histamine can be used for inducing gastric ulcers in animals. On this basis histamine induced gastric ulcer model is developed.\cite{57} Mast cells secretes histamine, which gets bind with receptors which are present
on the surface of parietal cells, resulting into activation of adenylate cyclase, which is responsible for the conversion of ATP into c-AMP. This process of conversion of AMP to c-AMP enhances gastric acid secretion from parietal cells. Histamine produces disturbances in gastric mucosal layer subsequently cause severe damage in gastric mucosa.\[88\]

The mechanism by which histamine produces gastric ulcers is its potent acid stimulating and vasodilatory effect in animals. Vasodilating capability of histamine causes increase in vascular permeability.\[89\] This model is commonly used for evaluation of antisecretory effect of test drug which acts as H2 receptor antagonists.

2.2.9 Cysteamine-Induced Duodenal Ulcers

Selye and Szabo\[32\] depicted the technique for acceptance of duodenal ulcers in rodents by utilizing cysteamine HCl. Duodenal ulcers incited by cysteamine in rodents has been generally utilized as a model of duodenal ulcer. Cysteamine prompted ulcer looks like duodenal ulcer in human as for its area, histopathology and a few parts of pathophysiology too. The genuine component associated with generation of ulcer by cysteamine has not been completely known. But it is reported that Cysteamine is responsible for the excessive secretion of gastric acid and inhibits the alkaline mucus secretion from Brunner’s glands in the proximal duodenum resulting in the formation of duodenal ulcer. Cysteamine is also responsible for excessive pepsin secretion in the gastric mucosa\[90\] and consequently causes decrease in the production in defensive factors like bicarbonate and mucus.\[91\] From different studies, it was reported that cysteamine also reduces somatostatin bioavailability and elevates serum gastrin levels, which is associated with an increase in gastric acid secretion.\[92\] Additionally certain transcription factors like early growth response factor-1, hypoxia-inducible factor-1 and their target genes assumes a vital role in the pathogenesis of cysteamine-induced duodenal ulcers.\[57\]

2.3 Surgical methods

By performing a surgical method we can induce gastric ulcers in experimental animals.

2.3.1 Pylorus-ligation induced peptic ulcer

Shay (1945) developed an animal model for the investigation of gastric secretory activity of a drug by ligating the pylorus end of the stomach which causes accumulation of gastric acid in the stomach and produces ulcers. This excessive gastric acid is responsible for auto digestion of gastric mucosal layer which cause breakdown of the gastric mucosa. So obstruction in
pylorus causes mucosal digestion by an increase in acid pepsin pool. This model is commonly used for the evaluation of cytoprotective and antisecretory effect of a drug which increases secretion of mucus and reduce secretion of gastric acid, respectively.\textsuperscript{[57],[93]}

2.3.2 Ischemia-Reperfusion induced gastric ulcer
Gastric mucosa is highly sensitive to ischemia or ischemic shock. Hence reperfusion followed by ischemia causes formation of free radicals which is responsible for gastric mucosal injury.\textsuperscript{[57]} This involves damage to the muscularis mucosac which is developed by clamping the celiac artery. Intestinal injury is generally induced by 60 min clamping of the superior mesenteric artery followed by 60 min reperfusion.\textsuperscript{[59]}

2.3.3 Mucosectomy induced gastric ulcer
This is also called as mucosal resection method where gastric mucosa is exposed by median laparotomy. Normal saline is injected into the submucosal layer of stomach and swollen mucosal area is resected with scissors.\textsuperscript{[61]} Endoscopic resections have certain advantages over conventional methods. They are more economical and less invasive.\textsuperscript{[62]}

3.0 CONCLUSION
Actually it is not possible to understand the actual mechanism of any disease in human. No one can predict which is the actual factor or mediator responsible for disease progression. Without knowing this basic information, it is difficult to design treatment strategies for any disease. In this review, we tried to cover several animal models of gastrointestinal ulcers that are widely used in clinical research. Here we also reviewed available experimental animal models of gastrointestinal ulcers for the evaluation new medicinal compounds having potential antiulcerative as well as gastroprotective activity. In each model, we have discussed the underlying mechanism behind the production of gastric ulcer. This will definitely help scientists and investigators to select a suitable animal model of gastric ulcer for the evaluation of antiulcerative activity of the test compound. Animal models also plays an important role in pre-clinical research, specially for the identification of drug targets.

4.0 Abbreviations
ROS- Reactive Oxygen Species
NSAIDs- Non-Steroidal Anti Inflammatory Drugs
HCl- Hydrochloric Acid; SMA- Superior Mesenteric Artery
COX- cyclooxygenase
COX 1- Cyclooxygenase 1
COX 2- Cyclooxygenase 2
ATP- Adenosine triphosphate
c-AMP- Cyclic Adenosine monophosphate.

5.0 Conflict of interest
Authors have no conflict of interest.

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