INTRODUCTION TO PEPTIC ULCER

Introduction

The Stomach

The stomach, once called the seat of the soul and still a recognized source of ecstasy and grief is one of the most metabolically active organ of the body. The stomach contributes in many ways to the complex adaptatics of the human being, from its decisive acceptance or rejection of food to its indispensable contribution to the production of red blood cells.¹

Physiology of Stomach

The stomach is a ‘J’ shaped organ which lies between the oesophagus and the duodenum. It has two curvatures namely, the lesser curvature and the greater curvature.

It is composed of two units:
1. Fundus and Body.
2. Pyloric region.

There are three different types of gastric glands viz.

a. The cardiac glands.
b. Fundus and Body glands.
c. Pyloric glands.

The peptic cells, mucoid cells and parietal or oxyntic cells belong to the fundus and body glands. The peptic or chief cells secrete pepsinogen which is converted to pepsin at pH 1.8 in the gastric lumen. The mucoid cells secrete mucin which is a high molecular weight glycoprotein. These mucoid secretions have properties of adhesion, cohesion and high viscosity. The parietal cells secrete hydrochloric acid.

Introduction to Peptic Ulcer

Composition of gastric juice

The gastric juice is composed of solid (0.56%) and water (99.44%). The solids include many organic substances like mucin, intrinsic factor, enzymes like pepsin, rennin and lipase. The inorganic constituents like Na+, Cl⁻, KCl, CaCl₂ and HCl (0.4-0.5%) are present in the water portion.
Peptic Ulcer
Up until fairly recently it was usual for a lecturer of gastroenterology to say, “we know little more than we did one hundred years ago about the cause and treatment of peptic ulcer disease.” Actually there have been notable and significant advances with regard to etiology, pathogenesis, pathophysiology, and biochemistry of this disease, as well as what might prove to be dramatic advances in medical management. Modern therapy is extraordinarily effective in the management of gastric and duodenal ulcers, like Black’s Nobel Prize for creating H2 blockers. Such success, however, make doctors assume that every ulcer is caused by excess acid. But the bismuth compounds and antibiotics also speed the healing of ulcers; some remain unconvinced that every peptic ulcer is caused by Helicobacter pylori because of the very ubiquity of that alien invader. However, it may be equally simple to deem all ulcers the product of excess acid.
Indeed, different comments were on “heterogeneity” of peptic ulcer, to suggest that craters have different causes. Some, like those of the Zollinger-Ellison syndrome, was clearly erosions from a torrent of hydrochloric acid. In some patients with arthritis, the defense less mucosa deprived of its protective prostaglandins inhibited by an excess of anti-inflammatory agents; the growing incidence of peptic ulcer in older women attest to hat. The gastric ulcers turning up in young “crack” smokers tell of the ischemic origin of yet other ulcer. Some ulcer may even be the result of “stress”. In any event, growing agreement that “peptic ulcers” are multifactorial in origin means that there is no more reason to think that an ulcer crater signifies a specific disease.

Epidemiology
Gastric and duodenal ulcers have overlapping epidemiologic and pathophysiologic features, but they have significant differences. Duodenal ulcer patients have a younger age of onset and on average have increased parietal cell mass and acid secretion. Gastric ulcer patients have normal or decreased acid secretion, which is often associated with decreased mucosal defense. In the USA, about 10% of adults have peptic ulcer disease. Although incidence information in the elderly is limited, hospitalization, morbidity, and mortality rates from peptic ulcer disease are higher for the elderly than for the general population. High gastric ulcers tend to be large, tend to heal slowly and may be more prone to recur. Duodenal ulcers are more common than...
gastric ulcers. According to study in Australia up to 10% of the population will develop peptic ulcer disease at sometime in their lives.

**Pathophysiology**

Peptic ulcer disease is an excoriated segment of the gastrointestinal mucosa, typically in the stomach (gastric ulcer) or first few centimeters of the duodenum (duodenal ulcer), which penetrates through the muscularis mucosae. The pathophysiology of peptic ulcer is best viewed as an imbalance between mucosal defense factors (bicarbonate, mucin, prostaglandin, nitric oxide, other peptides and growth factors) and injurious factors (acid and pepsin). On average, patients with duodenal ulcers produce more acid than do control subjects particularly at night (basal secretion). Although patients with gastric ulcer have normal or even diminished acid production, ulcers are rare if ever occur in the complete absence of acid. Presumably, a weakened mucosal defense and reduced bicarbonate production on rebate to the injury from the relatively lower levels of acid in these patients. *H. pylori* and exogenous agents such as non-steroidal anti-inflammatory drugs (NSAIDs) interact in complex ways to cause an ulcer.

![Diagram showing balanced aggressive factors and defensive processes.](image)

Fig. Aggressive factors balanced by defensive and reparative processes. It is possible to divide peptic ulcers into three etiologic groups: those due to massive acid peptic hypersecretion in the Zollinger-Ellison syndrome; those due to nonsteroidal anti-inflammatory drugs (NSAIDs); and ulcers associated with *Helicobacter pylori* infection. *H. pylori* related ulcers forms the largest and least well understood subset of ulcer disease.
Normal control of acid secretion depends on endocrine (gastrin), neural (vagal cholinergic nerves), and paracrine (histamine) limbs. Ingestion of meal causes increased acid and pepsin secretion due to an increase in gastrin release and vagally mediated Acid, Pepsin, NSAID, H.Pylori, Bicarbonate, Blood flow, Mucus, Cell junctions, apical resistance Restitution, Mucoid cap, Proliferation growth factor cephalic stimulus to the parietal cell. After gastric and duodenal pH has been lowered, gastrin release is inhibited and acid secretion returns to baseline. Pepsinogen is secreted from the chief cell in response to gastrine and histamine. In the presence of acid, pepsinogen is elevated to pepsin, which is active at pH less than 4. It has been shown that acid is much more damaging to intestinal mucosa in the presence of pepsinogens.

**Mechanism of gastric secretion:**

It is classified into:

1. Vagal-Antral Phase.
2. Intestinal Phase.

1. Vagal Antral Phase:

The sight, thought, smell or taste of food provokes a secretory response. An appetizing meal, result in secretion of large amounts of acid. Secretion occurs either by direct stimulation of the cells via cholinergic stimulation or by direct stimulation of the acid secreting cells which is mediated by a hormone called gastrin. Stomach secretes small amount of pepsinogen. However, the output of pepsin is enhanced with stimuli like histamine.

2. Intestinal phase:

Secretory activity reaches a peak during each meal and then wanes. The continuous interdigestive acid secretion is under the influence of the intestinal phase of gastric secretion.

**The regulation of acid secretion by parietal cells**

The regulation of acid secretion by parietal cells is especially important in peptic ulcer and constitutes a particular target for drug action. The secretion of the parietal cells is an isotonic solution of HCl (150 mmol/l) with a pH less than 1, the concentration of H⁺ being more than a million times higher than that of plasma. The Cl⁻ is actively transported into canaliculi in the cells which communicate with lumen of the stomach.
This Cl$^{-}$ secretion is accompanied by K+, which is then exchanged for H+ from within cell by a K+/H+-ATPase. Carbonic anhydrase catalyses the combination of carbon dioxide and water to give carbonic acid which dissociates into H+ and bicarbonate ion$^{8}$. HCO$_3$ diffuses into nearby blood capillaries. This “alkaline tide” of bicarbonate ions entering the blood stream after a meal may be large enough to elevate blood pH highly and make urine more alkaline$^{9}$. Three main stimuli act on the parietal cells
1. Gastrin (a hormone)
2. Acetyl choline (a neurotransmitter)
3. Histamine (a local hormone).

Out of the three physiological secretagogues, histamine, acting through H2 receptors plays the dominant role because the other two, gastrin and Ach act partly directly and partly indirectly by releasing histamine from paracrine enterochromaffin like cells called “histominocytes” located in the oxyntic glands$^{59}$. Prostaglandins have been ascribed a “cytoprotective” role in the gastric mucosa by increase mucus & bicarbonate secretion, as well as other actions. PGE2, produced by gastric mucosa, inhibits acid secretion by opposing cAMP generation (in parietal cells) & gastrin release (from antral cells)$^{9}$.

**Factors producing ulceration in the stomach:**$^{11,12}$

Factors producing ulceration are divided into three groups viz.
1. General factors.
2. Constitutional & environmental factors.
3. Local factors in the stomach.

**1. General Factors:** Vagal effects, hormonal effects (Histamine & Epinephrine), insufficient circulation, shock and general ischaemia etc.

**2. Constitutional & environmental factors:** Sex, age, family history, social class, geographical difference, occupation.

**3. Local factors in the stomach:**


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Pharmacognostic, phytochemical and pharmacological investigation on *Pterospermum acerifolium* WILLD. (Sterculiaceae)
Factors involved in the development of chronic peptic ulcer which alter the balance between aggressive factors and defensive factors are as follows:

1. **Gastric hypersecretion & mucus and cellular turnover:**

   Increased amount of acid and pepsin in higher concentration is supposed to be the basic cause of ulcer. The usual cause of peptic ulceration is too much secretion of gastric juice in relation to the degree of protection afforded to the mucosa by the mucus. Pure gastric juice is capable of destroying and digesting all living tissues including stomach. In the absence of extraneous stimuli, the human stomach secretes acid at a low rate. The parietal and chief cells secrete hydrochloric acid and pepsin which is a proteolytic enzyme. This proteolytic activity of pepsin in an acid medium carries the risk for the mucus membrane of gastrointestinal tract.62

   The gastric mucosal barrier is broken down by many compounds like acids in high concentration, aliphatic acids, detergents, ethanol in high concentration 10%, salicylic acid and aspirin. Mucosal permeability is increased with high concentration of the above compounds which causes free access of acid to the gastric mucosa which causes ulceration.

   Alkaline mucus is the first line defense for gastric mucosa and it acts as a protective barrier. Mucus is a mixture of glycoprotein, water, serum and cellular macromolecules. Its capacity to protect the gastric mucosa is due to the presence of glycoprotein mucin which is secreted by mucus cells. The protection afforded by this layer is partly mechanical by preventing the access of acid and pepsin to the epithelial cells and partly chemical because it can neutralize the acid14,15. When the gastric epithelium is damaged, the mucus secretion is reduced. The mucosa then gets inflamed. The slightest injury brings about haemorrhagic spots and erosions. Mucus secretion is stimulated by mechanical contact with food. On contact with drugs, there is vigorous mucus secretion, followed by de-squamation of the surface cells. Repeated insult exhausts the ability to secrete mucus. The superficial layer of gastric mucosa renews itself every 2-3 days, so that any minor breaks in the mucosa are rapidly healed under normal circumstances. Alteration in the rate of cell renewal in upper elementary mucosa may account for progression of ulcer from acute to chronic.
In addition to mucous protection, the duodenum is protected by the alkalinity of small intestinal secretions. Especially important is pancreatic secretions which contain large quantity of sodium bicarbonate which neutralises the hydrochloric acid of gastric juice thus inactivating the pepsin to prevent the digestion of the mucosa.

2. Inflammatory Change:
Gastritis precedes the development of the ulcer. Inflammation causes the development of ulcer by altering the resistance of mucosa to digestion.

3. Bile Reflux:
The increased concentration of bile salts in stomach interferes with the integrity of gastric mucosa thus, predisposing to the development of ulceration.

4. Blood Supply:
Resistance of mucosa to digestion is reduced as a result of impaired blood supply. Such impairment could occur as a result of venous or arterial thrombosis or because of ‘shunting’ of blood within the mucosa.

5. Heredity:
A strong family history is frequently found in patients who develop ulcer in childhood or adolescence. There is an association between duodenal ulcer and blood group ‘O’.

6. Sex Incidence:
Duodenal ulcers occur 5-10 times more often in men than in women and the perforation is 20 times more often in men. Although, these effects may be due to differences in life pattern of men and women, there are grounds for supposing that female sex hormones are in some way protective against peptic ulcer\textsuperscript{16}.

7. Stress:
There is undoubted association between development of acute ulcers in stomach or duodenum and physical or mental trauma or surgical operations.

8. Diet:
Absence of protective factors like fibres in the diet causes peptic ulcer. Janz & Beuting (1983) suggested that accumulation of Histamine and Tyramine in food by microbial action and their concentration in various food, wine, beer, fermented products also cause hyperacidity and ulceration.

9. Drugs:
Drugs like Phenylbutazone, Aspirin, Indomethacin, Cortisone and Reserpine are reported to cause ulcers.

10. Habit:
The incidence of ulceration is more in persons that are habituated to drink alcoholic beverages and tobacco smoking.

11. Constitutional factors:
There is sexual difference in occurrence of peptic ulcer. Peptic ulcer occurs at all ages in men. The incidence is very high (80%) in men compared to women. Ulcers are rare in women during the reproductivity age and particularly during pregnancy. Ulcers may occur in women after menopause.

12. Occupation:
Duodenal ulcers are found to be more common among the physicians and business executives than among other professionals. The incidence is low in agricultural labourers. Other factors responsible for ulceration are chronic lung diseases, chronic liver diseases and hyperparathyroidism. Number of parietal cells present in stomach and hydrochloric acid secretion plays important/significant role in ulcer formation. Latest information suggests the role of bacterial organism, *Helicobacter pylori* which colonize the gastric mucosa, particularly the antral region in the development of chronic ulceration.

**Role of H. pylori in Infection:**

*H. pylori* is a major etiological factor in peptic ulcer disease. About 95% of patients with duodenal ulcers and perhaps 80% of patients with gastric ulcers are infected with this bacterium and its eradication greatly diminishes the recurrence of these ulcers. *Helicobacter pylori* is a gram negative spiral bacterium that is found in apatchy distribution overlying the gastric epithelium. It was formerly named as *Campylobacter pylori* organism. *H. pylori* is a gram negative bacterium with the presence of sheathed flagella which gives motility, an external glycocalyx, major isoprenoid quinone being menaquinone-6 and a G+C content of chromosomal DNA of 35-44 mole %. *H. pylori* organisms have strong capability of urease production. The bacteria then splits urease into urea and the NH3 thus released may become cause of increased acidity and hence enabling organism to survive. The released ammonia may be etotoxic.
Treatment Aspect for Peptic Ulcer:
The treatments mentioned in various sources for Peptic Ulcer includes the following list. But one should always seek professional medical advice about any treatment or change in treatment plans.

Principles of peptic ulcer therapy:
As the exact cause of ulcer is not known, therapy is still empirical. It consists of:

- Controlling gastric acidity, hypermotility and spasm and thus relieving the associated pain.
- Promoting ulcer healing.
- Prevention of complication and recurrence.

Gastric and duodenal ulcer, or peptic ulcer disease (PUD), Zollinger-Ellison’s syndrome (ZES) and gastroesophageal reflex disease (GRD) are upper gastrointestinal disorders sharing a common abnormality: too much acid and pepsin activity for the degree of local tissue resistance. Therapy for these disorders is directed at correction of an apparent imbalance between acid and pepsin activity and mucosal resistance. Success of therapy is measured in terms of symptom control, ulcer healing, relapse rate and the prevention of complications secondary to the disease and its treatment.

The development of agents for the therapy of peptic ulceration has been a major pharmaceutical success story. The exciting era of the development of specific anti-ulcer therapy began with the observations of the workers in the laboratories of...
Smithkline and French and Welwyn-Garden city outside London and culminated in the development of new series of drugs termed H2-receptor antagonists, representing classical and rational pharmacological approach. Thus, Cimetidine and later Ranitidine revolutionized the treatment of peptic ulcers, with H2-receptor antagonists being the most widely used and effective novel drugs over the past decade. However, relapse ulceration following cessation of treatment with such agents is a frequent clinical observation. It is against this background that we have to deal with the current status and future advances in drug developments for the therapy of gastrointestinal ulceration. The stomach is constantly exposed to a variety of irritating and damaging factors, including its own acid pepsin secretion, bile, spicy foods, micro-organisms, alcohol and drugs. Inspite of this hostile environment, the gastric mucosa is usually capable of maintaining its integrity due to several protective mechanisms which include (1) mucus/alkaline secretion that adheres to the surface of the epithelium and exhibits a pH gradient within the unstirred water layer; (2) the gastric mucosal barrier preventing the penetration of acid into the mucosa; (3) rapid epithelial cell renewal allowing for a quick recovery from the mucosal insults; (4) rich mucosal blood flow providing oxygen and necessary nutrients to increased cellular resistance; and (5) the presence of natural humoral factors, particularly certain prostaglandins whose action may explain various aspects of mucosal protection. It is interesting to see how some of these natural protective mechanisms have been replicated or activated by exogenous means to treat the underlying peptic ulcer disease. Currently drugs are available that may neutralise gastric acid, reduce gastric acid secretion, or enhance mucosal defences through “cytoprotective” or possible antimicrobial activities.

**Antisecretory Agents:**
The usual therapeutic approach towards the treatment of peptic ulcer disease is to reduce gastric acid by antacids and antisecretory drugs (anticholinergics, H2 blockers) or even acid reducing gastric surgery. Hydrochloric acid is secreted by the parietal cells under strict hormonal control. There are at least three major routes of parietal cell activation: vagal, histaminergic and gastrinergic. The earliest drugs that partially inhibited secretion depended on their ability to block the muscarinic receptor. The major problem with these type of drugs (e.g. atropine) was relative lack of efficacy...
and uncomfortable side effects. The currently used drug from this class, Pirenzepine, has selective anti-muscarinic actions and it inhibits gastric acidity to a similar extent to conventional anticholinergics, but largely without affecting smooth muscle. It increases the healing rate of duodenal and probably also gastric ulcer. A major advance into anti-ulcer therapy was made with the development of H2–receptor antagonists. Cimetidine was the first followed by Ranitidine and these drugs are being followed by others.

**H2 antagonists:**

H2 antagonists are capable of over 90% reduction in basal, food stimulated, and nocturnal secretion of gastric acid after a single dose. These drugs also block the acid secretion stimulated by histamine, gastrin, cholinomimetic drugs and vagal stimulation. Histamine antagonists prevent occurrence of stress induced ulcers. However their use in combination with antacids may be preferred. In addition, they are important in the medical management of ZES and gastric hypersecretory states seen in systemic mastocytosis. These drugs include mainly Cimetidine, Ranitidine, Famotidine and Nizatidine, Zaltidine, Mifentidine, TZU-0460, CM-57755 etc. are also under investigation and have shown better antiulcer activity. H+/K+ - ATPase as target for antisecretory drugs:

Omeprazole represents this new class of gastric acid secretion inhibitors whose action can be described to the highly specific inhibitory action on gastric proton pump. Blockade of this pump constitutes a more direct mechanism for acid secretion inhibition compared to blockade of histamine and cholinergic receptors. Omeprazole is not the active inhibitor of H+/K+ ATPase enzyme but is reversible transformed in acidic media to the Sulfonamide, which can react with thiols to form disulfides, thus representing a model for the covalently linked enzyme-drug complex. The drug appears to require activation in the acid environment of the secretory canaliculus of the parietal cell i.e. it is a prodrug and probably acts from the external side of the membrane. NC-1300, RO 18-5362, B831-56 are series of fluorinated benzimidazoles and are potent and long lasting inhibitors of acid secretion in animals and have shown mechanism similar to that of Omeprazole.

**Cytoprotective Agents:**
In 1968 Robert recognized that prostaglandins (PGs) inhibit gastric acid secretion and protect against experimental ulcers. According to Robert et al., cytoprotection refers to protection against chemically (e.g. concentrated ethanol, acid or base) or physically (e.g. heat) induced hemorrhagic acute gastric erosions and ulcer by prostaglandins in doses much smaller than those needed to reduce gastric secretion in the rat. Histological investigations revealed that only the deep hemorrhagic necrosis is prevented whereas the surface cell injury is not decreased by so-called protective compounds. The mechanism for such gastroprotection by prostaglandins has not been clearly defined but some theories have been proposed:

a) Prevention of gastric barrier disruption:
Prostaglandins prevent disruption of the gastric mucosa from barrier breakers like Aspirin, Indomethacin, Ethanol and Bile salts etc. Disruption of the barrier allows hydrogen ions to diffuse from the gastric lumen back into the mucosa and sodium and potassium ions to diffuse from the mucosa into the gastric lumen. Barrier disruption can cause gastric mucosal damage and bleeding into the gastric lumen.

b) Stimulation of gastric protectors:
Prostaglandins stimulate the formation of gastric mucus and nonparietal cell alkaline secretion rich in sodium and chloride ions and in bicarbonate. These effects can impede the back diffusion of the hydrogen ion, enhance its neutralization and contribute to the prevention of mucosal damage and ulcers.

c) Other proposed mechanisms for prostaglandin cytoprotection include:
Enhancement of gastric mucosal blood flow, stimulation of DNA, RNA and protein synthesis (a doubtful mechanism for protection against acute gastric injury but it may encourage healing), stimulation of gastric mucosal cyclic AMP levels; stabilization of tissue lysosomal membranes, dissolution of gastric mucosal folds otherwise associated with hydrochloric acid and ethanol-induced gastric injury, maintenance of gastric mucosal folds otherwise associated with hydrochloric acid and other noxious water soluble agents. It seems doubtful that a single mechanism will explain the cytoprotective effects of all prostaglandins. Different types probably exhibit anti-ulcer activity by different mechanisms. The four synthetic prostaglandins currently undergoing clinical trials include Misoprostel (Searle), Arbaprostil (Upjohn), Trimoprostil (Roche) and Enprostil (Syntex). They share a number of advantages,
differences in comparison to the histamine H2 antagonists, antisecretory and cytoprotective actions, greater potency and relative lack of adverse effects and serious toxicity. Recently, a new prostaglandin Ro-22-6923, developed by Hoffman La Roche Inc. has been shown to possess highly significant anti-ulcer, antisecretory and cytoprotective properties. Further studies on this compound are under progress.

**Mucosal Protective Agents:**
The dictum 'no acid- no ulcer' fostered the concept that effective reduction in gastric acid secretion was the rational basis of peptic ulcer therapy. However, it soon became apparent that increased acid secretion was seen in not more than 30-40% of duodenal ulcer patients and rarely in patients of gastric ulcer. The proposition that peptic ulcer disease was induced by relative deficiency in the mucosal defense system, rather than increase in the offensive acid-pepsin factor, has led to a sustained quest for drugs which could restore or augment mucosal defense.

**Essential fatty acids:**
Arachidonic acid, the PG precursor, exerts mucosal protection and this forms the basis of putative use of essential fatty acids in ulcer therapy. Long term exposure to ethanol in rats and man, results in decreased arachidonic acid and linoleic acid levels in membrane lipids in several tissues and may contribute to gastroduodenal mucosal injury induced by it.

**Sucralfate:**
Sucralfate, a basic aluminium salt of sucrose octasulphate was initially proposed to enhance the mucus gel component of the mucus-bicarbonate barrier, provides an ideal physical barrier which can protect the ulcer site from offensive intraluminal factors. Furthermore, it can also attenuate peptic activity by adsorption of the enzyme and its substrates.

**Carbenoxolone:**
The first drug in this series was shown to be an effective antiulcer agent though it had no effect on gastric acid secretion. It was postulated that it augmented the mucosal defense and was termed a "cytoprotective agent".

**Liquorice products:**
Glycyrrhiza glabra has been used for many years for the treatment of peptic ulcer with the assumption that it exerts a demulcent effect over the ulcer crater and facilitates healing\textsuperscript{21}.

**Antacids:**

Aluminium containing antacids are known to stimulate mucosal PG synthesis in low doses not likely to exert significant antacid effect. Long term use of these antacids, in subantacid doses, have been shown to induce significant mucosal protection.

**Sulphydryl compounds:**

Intragastric administration of cysteamine or dimethylmaleate induces significant mucosal protection, which appears to be PG mediated, initial clinical studies are encouraging. **Bismuth salts:**

Tripotassium dicitrate bismuthate, a colloidal bismuth preparation, was initially introduced as an improved version of bismuth subnitrate, a demulcent used to aid ulcer healing. Bismuth also inhibits the growth of H-pylori and may be of benefit in ulcer relapse\textsuperscript{22}.

**Natural products:**

Vegetable banana (\textit{Musa paradisiaca}), narikelkhand (Coconut) and Tamrabhasma (Copper preparation)\textsuperscript{23} Abhra rasayana, Araucaria bidwillii, Vernonia lasiopus, Vernonia galamensis, Black Tea, Asparagus racemosus, Glycyrrhiza glabra, Centella asiatica, Nux vomica, Pongamia pinnata, Aegle marmelos, Emblica officanalis, Cauvery-100-Polyherbal formulation, UL-409, PHF, Rhinax- PHF, Shankha Bhasma.\textsuperscript{24, 25}

**Ulcerogenic Drugs**

Aspirin, Indomethacin, Digitoxin, Ibuprofen, Reserpine, Cinchophen, Diamprit, Endothelin, Acetylcholine, Cryteamine HCl, Acetic acid, Dulcerozine, Ethanol, Histamine, Vasopressin, Hypertonic HCl/NaOH.
MATERIALS AND METHODS

Animal used

Albino Wistar rats of either sex weighing between 150-250g were used. Animals were housed under standard conditions of temperature (24 ± 2°C) and relative humidity (30-70%) with a 12:12 light: dark cycle. The animals were given standard diet and water ad libitum. All procedures involving animals were carried out under the institute ethics committee approval.

Antiulcer activity

Aspirin induced ulcer

Animals were divided in groups of six animals each. Group I served as negative control received distilled water, Group II served as positive controls and received omeprazole at the dose of 20 mg/kg, and animals of group III, IV and V received TMPAW, TMPAB and TMPAL at the dose of 200 mg/kg, orally daily, respectively, for five days for ulcer protective studies. Aspirin in dose of 20 mg/kg was administration to the animals on the day of the experiment and ulcers were scored after 4 h. The animals were sacrificed and the stomach was then excised and cut along the greater curvature, washed carefully with 5.0 ml of 0.9 % NaCl and ulcers were scored by a person unaware of the experimental protocol in the glandular portion of the stomach. Ulcer index was then calculated by adding the total number of ulcers per stomach and the total severity of ulcers per stomach

A score for the ulcer was made as: 0.5-Hemorrhage, 1-Streaks, 2-Spot ulcer, 3-Sever ulcer or Sever steaks, 4-Erosions, 5-Perforation.

Mean ulcer score for each animal was expressed as ulcer index. The percentage of ulcer protection was determined as follows:

\[
\text{% Protective} = \frac{\text{Control mean ulcer index} - \text{test mean ulcer index}}{\text{Control mean ulcer index}} \times 100
\]

Ethanol induced ulcer

The gastric ulcers were induced in rats of either sex weighing between 130-150 g by administrating absolute ethanol (8 ml/kg). They were kept in specially constructed cages to prevent coprophagia during and after the experiment. The rats were divided into groups each containing six animals and fasted for 24 h and allowed free access to
water. The first group received control vehicle only and the second group received standard ranitidine in the dose of 20 mg/kg, group III, IV and V received TMPAW, TMPAB and TMPAL at the dose of 200 mg/kg, orally daily respectively, for five days for ulcer protective studies. On the sixth day of experiment the drugs were administered orally 30 min prior to the oral administration of absolute ethanol. The animals were anaesthetized 6 h latter with ether and stomach was incised along the greater curvature and ulceration was scored. The number of ulcers and the length of each ulcer were measured. A score for the ulcer was made as mentioned above.

**Pyloric ligation method**

In this method albino rats were fasted in individual cages for 24 h. Group I served as negative control received distilled water, Group II served as positive controls received ranitidine (20 μg/kg, p.o), and animals of group III, IV and V received TMPAW, TMPAB and TMPAL at the dose of 200 mg/kg, orally daily respectively, 1 h before pylorus ligation. Under light ether anesthesia, the abdomen was opened and the pylorus was ligated. The abdomen was then sutured. At the end of 4 h after ligation, the animals were sacrificed with excess of anesthetic ether, and the stomach was dissected out. Gastric juice was collected and its volume was measured. The glandular portion was then exposed and examined for ulceration. Ulcer index was determined.

**Estimation of total acid output**

Total acid output of the gastric juice was estimated by titration of 0.1 ml of gastric juice with 0.01 N sodium hydroxide using phenolphthalein as indicator. Total acid output was expressed as mEq/L per 100 gm of body weight.

**2.6. Statistical analysis**

Mean values ± S. E. M. were calculated for each parameter. For the determination of significant intergroup differences, each parameter was analyzed separately and one-way analysis of variance (ANOVA) was carried out. p<0.05 was consider significant.
RESULTS AND DISCUSSION

Ulcer index parameter was used for the evaluation of anti-ulcer activity since ulcer formation is directly related to factors such as reduction in gastric volume, decrease in free and total acidity. TMPAW, TMPAB and TMPAL at the dose of 200 mg/kg have decreased the intensity of gastric mucosal damage induced by ulcerogenic agents.

TMPAW, TMPAB and TMPAL at the dose of 200 mg/kg and omeprazole at 20mg/kg produced a significant (p < 0.001) reduction in the ulcer index (figure 6.4.1) and has protection index of 65.94 %, 73.18, 51.78 and 86.54 % respectively as shown in table 6.4.1. Aspirin has been reported to produce ulcers by both local and systemic effects. Aspirin causes direct irritant effect and mucosal damage by interfering with prostaglandin synthesis, increasing acid secretion by increasing the H⁺ ion transport/back diffusion of H⁺ ions, resulting overproduction of leukotrienes and other products of 5-lipoxygenase pathway. It decreases mucin, surface active phospholipids bicarbonate secretion, mucosal proliferation and also produces damage by formation of free radicals. The possible protective effect of TMPAW, TMPAB and TMPAL against aspirin-induced gastric lesions could be due to prevention of direct irritation and due to its 5-lipoxygenase inhibitory effect.

TMPAW, TMPAB and TMPAL showed the ability to reduce significantly (p < 0.001) the severity of ulceration of stomach induced by absolute ethanol. Among all the extracts TMPAB at dose of 200 mg/kg and ranitidine at 20mg/kg has shown significant (p< 0.001) reduction in ulcer index upto 52.67 and 36.66 with protection index of 60.55% and 72.53% respectively as shown in table 6.4.1. The results of histopathological investigation revealed that the pretreatment with TMPAB and ranitidine absolutely prevented the ethanol-induced congestion, hemorrhage, edema, necrosis, inflammatory and erosions and ulceration in the gastric mucosa of rats. The stomach appearance was normal. The incidence of ethanol-induced ulcers predominant in the glandular part of stomach was reported to stimulate the formation of leukotriene C4 (LTC4), mast cell secretory products, and reactive oxygen species resulting in the damage of rat gastric mucosa. In ethanol model, ulcers are caused due to perturbations of superficial epithelial cells, notably the mucosal mast cells leading to the release of the vasoactive mediators including histamine, thus causing
damage to gastric mucosa. Mucosal blood flow has been attributed to be an important factor in the damage caused by alcohol and is modulated by prostaglandin. Ethanol causes direct chemical damage, independent of acid secretion, to the surface epithelium as well to the microvascular apparatus, leading to increased vascular permeability and decrease in mucosal blood flow which is followed by hypoxia and hemorrhagic ulcer. Ethanol also lowers cellular glutathione level which by decreasing prostaglandin biosynthesis affects the natural gastroprotection. Ethanol also causes gastric damage by increasing the formation of leukotrienes and by generating ROS. Ethanol also induces gastric epithelial cell apoptosis triggered by the enhancement of mucosal TNF-α. It appears that TMPAB blocks ethanol induced gastric damage by modulating these phenomena. The results are presented in table 6.4.1.

Gastric secretion was evaluated as gastric juice volume and total acidity for 4 h after pylorus ligation. In pylorus-ligated rats, TMPAB produced a significant (p<0.001) decrease of gastric juice volume; and significantly inhibited gastric acid. This inhibition was less than that of ranitidine (20 mg/kg) as shown in table 6.4.2. The reduction in total acidity, measured after pylorus ligation, suggest that the protective mechanism of the extract on gastric mucosa might involve an inhibition of gastric secretion. Pylorus ligation of rats for 6h resulted in accumulation of gastric secretory volume, and increase in titrable acidity and ulceration (Table 6.4.2). TMPAB has also showed significant effectiveness (P < 0.05) in pylorus ligation induced gastric ulcer model. It shows protection index of 71.31% at the dose of 200 mg/kg whereas standard drug ranitidine at 20mg/kg has shown 73.25 % protection. Total acidity of TMPAB treated group was found to be 27 mEq/L, standard ranitidine treated group 22 mEq/L which is less than that of negative control group which showed 56 mEq/L total acidity as shown in table 2. Pylorus ligation induced gastric ulcers occur because of an increase in acid-pepsin accumulation due to pyloric obstruction and subsequent mucosal digestion and breakdown of the gastric mucosal barrier. A copious amount of mucus is secreted during superficial damage and provides favorable microenvironment in repair. Hence estimation of acid secretion, pepsin secretion and mucus secretion is a valuable part of the study to clarify the mechanism of action of the drug under trial.

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Overall, TMPAB has shown a substantial and significant protection against gastric ulcers in all the models. This protective effect might have been mediated by both anti-secretory and cytoprotective mechanisms. Moreover, further insight into the precise mechanism of action is essential to exploit the complete potency of TMPAB and increase its usage in contemporary medicine.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Aspirin induced ulcer</th>
<th>Ethanol induced ulcer</th>
<th>Pylorus ligated ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ulcer index</td>
<td>% protection</td>
<td>Ulcer index</td>
</tr>
<tr>
<td>Vehicle</td>
<td>144.83±</td>
<td>--</td>
<td>133.50 ±</td>
</tr>
<tr>
<td></td>
<td>4.045</td>
<td></td>
<td>7.143</td>
</tr>
<tr>
<td>TMPAW</td>
<td>49.33±</td>
<td>65.94</td>
<td>95.16±</td>
</tr>
<tr>
<td></td>
<td>±3.018***</td>
<td></td>
<td>2.81***</td>
</tr>
<tr>
<td>TMPAB</td>
<td>38.83±</td>
<td>73.18</td>
<td>52.667±</td>
</tr>
<tr>
<td></td>
<td>2.774***</td>
<td></td>
<td>3.997***</td>
</tr>
<tr>
<td>TMPAL</td>
<td>69.83±</td>
<td>51.78</td>
<td>118.83±</td>
</tr>
<tr>
<td></td>
<td>3.301***</td>
<td></td>
<td>4.246</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>§</td>
<td>§</td>
<td>36.667±</td>
</tr>
<tr>
<td>20mg/kg</td>
<td>§</td>
<td>§</td>
<td>1.498***</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>19.5 ±</td>
<td>86.54</td>
<td>§</td>
</tr>
<tr>
<td>20mg/kg</td>
<td>1.118***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± S.E.M. **p<0.01, ***P< 0.001, **** P< 0.0001 compared to control group. One way ANOVA followed by Dunette’s test.
Table 6.4.2: Effect of TMPAW, TMPAB and TMPAL on Gastric volume and total acidity of pylorus ligation induced-ulcer

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Animals used</th>
<th>Gastric Juice Volume (ml) mean ± S.E.M.</th>
<th>Total Acidity mEq (H⁺)/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6</td>
<td>3.9±0.019</td>
<td>56</td>
</tr>
<tr>
<td>Ranitidine 20mg/kg</td>
<td>6</td>
<td>2.01±0.0413*</td>
<td>22</td>
</tr>
<tr>
<td>TMPAW 200mg/kg</td>
<td>6</td>
<td>3.2±0.13*</td>
<td>42</td>
</tr>
<tr>
<td>TMPAB</td>
<td>6</td>
<td>2.9±0.19*</td>
<td>27</td>
</tr>
<tr>
<td>TMPAL</td>
<td>6</td>
<td>3.7±0.38</td>
<td>37</td>
</tr>
</tbody>
</table>

Values are mean ± S.E.M. *p<0.05 significant as compared to control group.
**Figure 6.4.1:** Effect of various extracts of *Pterospermum acerifolium* on aspirin-induced gastric ulcer. Data are expressed as means ± SEM (n=6).

**Figure 6.4.2:** Effect of various extracts of *Pterospermum acerifolium* on ethanol induced gastric ulcer. Data are expressed as means ± SEM (n=6).
Figure 6.4.3: Effect of various extracts of *Pterospermum acerifolium* on pylorus ligated method induced gastric ulcer. Data are expressed as means ± SEM (n=6).
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