1.1 Introduction

1.1.1 Anatomy and Physiology of Gastrointestinal Tract

The gastrointestinal (GI) tract, or alimentary canal (*alimentary*-nourishment), is a continual pipe that lengthens from the mouth to the anus within the thoracic and abdomino-pelvic cavities. Parts of the gastrointestinal tract encompass the mouth, large portion of the pharynx, esophagus, stomach, small intestine (duodenum, jejunum and ileum) and large intestine. The associated digestive organs include the teeth, tongue, salivary glands, liver, gallbladder and pancreas (Waugh and Grant, 2014).

The GI tract has food since the time it is taken until it is digested and absorbed or excreted. Contractions of muscular wall in the GI path physically/mechanically smash down the food by churning it. Secreted enzymes by accessory organs of digestive tract and cells that stripe the tract chemically break down the food.

After mechanical and chemical digestion (to some extent) in mouth the solid food becomes soft and flexible called as bolus and can be easily degutted. This semisolid bolus then reaches into stomach via the pharynx and esophagus. Stomach serves as reservoir organ where mechanical and chemical digestion takes place and food is mixed with acidic gastric juice. From here, acidified chyme (churned liquefied food), is pushed into duodenum (the first part of small intestine) by a force driven by stomach. In duodenum acidic chyme become alkaline after mixing with bile and pancreatic juice. Most digestion and absorption of material happen in small intestine. The undigested and unabsorbed food material passed to large intestine is removed by defecation process (Tortora and Derrickson, 2012).
1.1.2. Gastric Secretion

About 2.5 litres of gastric juice is secreted by the stomach daily. The major exocrine constituents are proenzymes such as prorennin and pepsinogen secreted from the chief or peptic cells, and hydrochloric acid (HCl) and intrinsic factor elaborated by the oxyntic or parietal cells. The presence of acid is needed for supporting the proteolytic break down of food materials, iron absorption and eradicating pathogens. Mucus-emitting cells are also present amid the gastric mucosa of surface cells. Secreted bicarbonate ions are trapped by the mucus, generating a gel-like protective barrier that sustains the mucosal surface on a pH of 6–7 in front of a very much acidic atmosphere (pH 1–2) of the lumen. Bile and alcohol can interrupt this mucus layer. Locally formed ‘cytoprotective’ prostaglandins kindle the secretion of both mucus as well as bicarbonate. Disturbance either in the secretory (aggressive) or protective mechanisms are believed to be incorporated in the pathogenesis of peptic ulcer, and definitely in many other forms of gastric damage including gastro-oesophageal reflux disease (GERD) and damages due to non-steroidal anti-inflammatory drugs (NSAIDs) (Rang et al, 2013).

1.1.3. Etiology of peptic ulcer disease

Apart from above secretory and protective mechanisms, other aggressive factors such as Helicobacter pylori infection, drugs (NSAIDs and corticosteroids), stress, spicy food, lifestyle characteristics, smoking, reflux of bile, formation of free radicals, 5-hydroxytryptamine, platelet activating factor and cytoprotective factors including the surface active phospholipids, mucosal blood flow, cell renewal and migration, nutritional supplements, enzymatic and non-enzymatic antioxidants and some growth factors contribute in etiology of peptic ulcer disease (Khushtar et al, 2016). Helicobacter pylori, NSAIDs, emotional stress,
alcohol abuse, and smoking are the principal etiological factors associated with peptic ulcer (Vimala and Shoba, 2014).

1.1.4. Epidemiology

Peptic ulcer is the most common clinical problem of gastrointestinal disorders affecting 10% people globally with annual prevalence of 0.1-0.19%. Its occurrence in India is with 4-10 per thousand populations. The disease results in chronic suffering, loss of weight, appetite and working hours and occasional fatality. The disease may lead to upper gastrointestinal haemorrhage and perforation which have high mortality and morbidity rate (Zaghlool et al, 2015, Khushtar et al, 2016). Among the gastrointestinal diseases its share is 40% in developed countries and 80% in developing countries (Adinortey et al, 2013). An expected 3 per 1000 peoples are affected with peptic ulcer and 15000 died every year in India as a consequence of peptic ulcer (Gulia and Choudhary, 2011). Yearly episode approximation of peptic ulcer hemorrhage and perforation were 19–57 and 4–14 per 100,000 individuals, correspondingly (Lau et al, 2011). It is a new epidemy of 21st century because it affects 4 million people in the world annually (Pinto et al 2014).

1.1.5. Market Share of Anti-ulcer Drugs

The contribution of antiulcer and antacids drugs in pharmaceutical trade of India is 6.2 billion rupees and capture 4.3% of the total market share (Vimala and Shoba, 2014). As per literature, the total expenditure of PUD in USA (both direct and indirect due to loss of work output) has been projected to reach annually 6.46 billion USD (Barazandeh et al, 2012). A study in the Netherlands evaluated the per individual costs of hemorrhage, perforation, or a combination of both to be EUR 12,000, EUR 19,000 and EUR 26,000 correspondingly (Lau et al, 2011).
1.1.6. Anti-Ulcer Drugs and their Side Effects

Inhibitors of proton pump (PPI), antagonists of histamine (H₂) receptors, antacids cytoprotectants (sucralfate and colloidal bismuth subcitrate), anti- cholinergics, demulcents, and prostaglandin analogues are being employed to cure the ulcer but numerous side effects are produced by them.

However, the main problem is that despite a healing rate, ulcers treated with H₂-antagonists and proton pump inhibitors can present recurrence within one year after the end of treatment. However, recurrence is the key problem even though these drugs have a high healing rate. Recurrences occur in one year subsequent to the end of treatment.

The main cause of this is neutrophil deposition and ROS generation, ensuing in an imperfect healing progression. Moreover, adverse effects such as hypergastrinemia, osteoporosis and hyperplasia of enterochromaffin-like cells (ECL) are profound in the prolonged treatment by anti-secretory drugs (Da Silva et al 2013, Tygat 2011). Enhanced risk of enteric and respiratory infections is reported by use of proton pump inhibitors (Katzung et al, 2012). The aim of treating peptic ulcer disease are to diminish the pain, cure the ulcer and prevent ulcer recurrence. Presently there is no economic treatment that fulfills all these aims. Thus, attempts are on to discover a appropriate treatment from herbal products heritage (Mohua et al, 2013).

Herbal medicines are believed to be harmless for the management of ulcers and have minor adverse effects, are cost-effective, competent and comparatively less toxic. Widespread research has been done to discover potent antiulcer agents of plant origin (Mohua et al, 2013; Sajid 2015).
Many natural drugs and herbal products have exhibited good effect in vitro or in animal studies (http://www.rayssaheline).

Widely used therapeutic plants such as Garlic (*Allium sativum*), Tulsi (*Ocimum sanctum*), Brahmi (*Bacopa monniera*), Babul (*Acacia Arabica*) and Satavari (*Asparagus racemosus*) (Chauhan et al, 2015) and many common herbs such as Adrak (*Zingiber officinales*), Haldi (*curcuma longa Linn*.), Heel kalan or Bari Ilaichi (*Amomum subulatum Roxb*), Kalonji (*Nigella sativa Linn*), Karela (*Momordica charanta*), Kela (*Musa paradisiaca Linn*.), has been studied for their anti-ulcer effect (Jamal et al, 2006).

1.2. Hypothesis

1.2.1. Basis of Models Selection

There are several experimental models available for the evaluation of anti-ulcer drugs in animals like rats, mice, guinea pigs and dogs. The methods include pylorus ligation (Shay et al, 1945), stress ulcers, histamine-induced gastric ulcers, acetic acid-induced ulcers, gastric mucosal damage induced by non-steroidal anti-inflammatory drugs, single chronic gastric ulcers produced by reserpine, gastric mucosal lesions caused by serotonin, gastric ulcers stimulated by dimaprit and gastric mucosal injury induced by endotoxin (Parmar and Desai, 1993).

In humans multiple etiologies has been reported for peptic ulcer disease, and among them *H.pylori* infection and NSAIDs use are main contributing factors (Jones, 2006; Levenstein 1999; Kanno et al, 2013). Stress is an unavoidable factor in modern day life style whereas acid hypersecretion is a well known threat for ulcer induction in humans (Katzung et al, 2012; Levenstein, 1999).
Therefore in our study the NSAIDs (Indomethacin), stress and pylorus ligation (to observe the effect of test drug on gastric acid secretion) induced gastric ulcers models were selected. The study was further conducted in rats following two approaches –preventive (pre-treatment) and curative (post-treatment). In preventive model approach the animals were administered the test compounds and their protective effect was observed through inducing the disease. The curative model approach is treatment of disease by the test compounds after inducing the disease. These approaches were employed so as to differentiate the test compounds that may have a

a) Protective action only

b) Curative action only

c) Both protective and curative

Furthermore in animal studies, the pre-treatment model is preferred as in post-treatment model survival after disease induction is a matter while the post-treatment model resembles more to human model of disease.

In preventive (pre-treatment) approach the gastric ulcer was induced by NSAIDs (Indomethacin), stress and pylorus ligation method whereas in curative (post-treatment) approach the gastric ulcer was induced by NSAIDs (Indomethacin) and stress only. Further, before conducting the study on curative model the survival and self healing days was observed after inducing the disease in rats provided only with vehicle. And dose (survival dose) at which animal survived after disease induction and treatment duration was determined.

In curative approach pylorus ligation was not included because after abdominal incision and stitching (as done in this model) to keep the animals alive is a difficult task.
1.2.1.1. Indomethacin Induced Gastric Ulcer Model

1.2.1.1.1. Basis of Indomethacin Induced Gastric Ulcer Model Selection

Despite effective eradication of *H. pylori* by triple and quadruple drugs regimens peptic ulcer disease and related complication remains a substantial problem due to wide spread use of acetyl salicylic acid (aspirin) and other NSAIDs (Lau et al, 2011). NSAIDs have been reported to be the second most common cause of peptic ulcer after *H.pylori* (Adinortey et al, 2013; Barazandeh et al, 2012; Gulia and Choudhary, 2011). Chronic administrations of NSAIDs cause gastro-duodenal mucosal erosions in approximately 35- 60% of patients, gastric or duodenal ulceration in 10-25% of patients and severe complications such as gastrointestinal hemorrhage or perforation in 1% of patients (Shakeerabanu et al, 2011).

1.2.1.1.2. Mechanism of Ulcer Induction by NSAIDs

The pathogenic basis of gastric ulceration induced by NSAIDs includes the blocking of action of the cyclooxygenase isoenzymes (COX-1 and COX-2) produced decreased mucus and bicarbonate synthesis, depressed mucosal blood circulation, impairement of platelet aggregation, changing of microvascular organizations leads to damage of epithelium, angiogenesis reduction and increased leukocyte attachment. Increased formation of reactive oxygen species (ROS), increment of lipid peroxidation, and infiltration of neutrophil also take part in oxidative damage of mucosal layer by NSAIDs. Gastric peroxidases are restrained by NSAIDs also and mucosal hydrogen peroxide and hydroxyl ion levels might increase that will direct oxidative damage of mucosa (Adinortey et al, 2013).

1.2.1.2. Stress Induced Gastric Ulcer

1.2.1.2.1. Basis of Stress Induced Gastric Ulcer Model Selection
Many studies however indicated that many (16-30%) people developed peptic ulcer disease without having \textit{H. pylori} infection and NSAIDs history or any other recognized factors (Levenstein, 2014; Jones, 2006). These types of ulcers are idiopathic and a lot unmanageable to therapy (Levenstein, 1999). Development of PUD without \textit{H. pylori} is emphasised by fact that many \textit{H. pylori} positive people never developed peptic ulcer (Jones, 2006). There are clear evidences that psychological stress contribute in etiology of these type of ulcer and association of PUD with stress is strong enough to be ignored. A study indicated that stress plays a role in 30-65\% of cases (Jones 2006, Levenstein, 2000). The significant increased (from 13\% in 2010 to 24\% in 2011) in the proportion of non-\textit{H. pylori} and non-NSAID ulcers after the earthquake in 2011 in Japan also suggests that psychological distress alone induced peptic ulcers in humans.

Gastric ulcers induced by cold-water-restraint stress (CWRS) or cold-restraint stress (CRS) or water-immersion stress (WIS) in rats or mice are known to resemble human peptic ulcers, both grossly and histopathologically (Adinortey et al, 2013).

\textbf{1.2.1.2. Mechanism of Ulcer Induction by Stress}

Stress activates both the sympathetic as well as parasympathetic drive of the stomach, which incites an amplified gastric motility with muscular tightening directing to vascular compression which produces mucosal ischemia. Stimulation of sympathetic pathway also causes arteriolar vasoconstriction directly and, so, greatly diminishes stomach blood flow which lead to local hypoxia along with near or real “ischemia.” The condition of ischemia raises the seepage of \textit{O}_2^- from the mitochondrial electron transport chain and directs to increase in level of \textit{H}_2\textit{O}_2, which on conjugation with \textit{O}_2^- produces \textit{OH}^\mathit{-} via the metal-catalyzed Haber-Weiss reaction. \textit{OH}^\mathit{-} oxidizes vital cellular components such as functional
and structural membrane lipids, proteins, and glutathione like cellular antioxidants are depleted. Lipid peroxidation brings about membrane fluidity loss, ion transport impairment and membrane integrity, and ultimately loss of cellular performance (Das et al, 1997). Histamine mediated increase secretion of acid owing to stress has been demonstrated by many researchers both clinically and pre-clinically (Konturek et al, 2011; Adinortey et al, 2013). Role of histamine in stress induced acid secretion has also been reported (Cho and Ogle, 1979; Adinortey et al, 2013).

Furthermore stress has also been shown to cause decrement in quality and quantity of protective mucus layer (Adinortey et al, 2013). Evidences of alteration in gut microbiota due to stress have also been reported (Konturek et al, 2011).

1.2.1.3. Pyloric Ligation Induced Gastric Ulcer

1.2.1.3.1. Basis of Pyloric Ligation Induced Gastric Ulcer Model Selection

Gastric hypersecretion is a classic and well-established threat for peptic ulcer production (Levenstein, 1999). Despite the multifactorial etiology of peptic ulcer the suppression of acid secretion is main approach for preventing peptic ulcer disease, related symptoms and complications (Golbabapour et al, 2013; Katzung et al, 2012). The pyloric ligation model was therefore used for observing the acid suppression aspect of Triphala.

1.2.1.3.2. Mechanism of Ulcer Induction by Pyloric Ligation Technique

The basis of gastric ulcer pyloric ligation are believed to be due to stress induced increase in gastric hydrochloric acid secretion and/or stasis of acid and the volume of secretion is also an significant cause in the formation of ulcer due to contact of the unprotected lumen of the stomach with the accumulated gastric juice. Induction of ulcer with pylorus ligation is due to auto digestion of the gastric mucosa and breakdown of the gastric mucosal barrier (Dashputre

1.2.2. Basis of Drug Selection

Triphala formulation is an antioxidant enriched herbal remedy and has diverse valuable properties. Triphala is used in Ayurvedic practice for gastric disorders such as digestion problems, poor food absorption, constipation, cleansing of colon, and strengthen the gastrointestinal tract and colon (Baliga, 2010). Triphala is also effective in maintaining levels of serum cholesterol, improve circulation, bile duct relaxation and as a protective agent of hepatocytes. Regular use of Triphala is believed to promote usual appetite, proper digestion, slowing senescence and increasing hemoglobin, red blood cells and immunity. Triphala is supposed to maintain proper release of the endocrinal system accountable for maintaining the proper homeostasis in the human body and assisting the vital physiological processes. Daily consumption of Triphala is also thought to perk up the skin complexion and to offer cosmetic benefit. Triphala, on external use as a hair tonic/rinse or on oral consumption, ensures radiant growth of mane and to avoid greying of hair. Triphala is used for vision improvement and beneficial in treating conjunctivitis and cataracts. It has been described to possess antioxidant, free radical scavenging, , anti-inflammatory, antipyretic, analgesic, antimicrobial, anticataract, antiobesity, antihypercholestrimic, antimutagenic, anticariogenic, wound healing, antistress, hypoglycaemic, adaptogenic, anticancer, chemoprotective, radioprotective and chemopreventive effects (Baliga, 2012). In gastrointestinal tract Triphala has been found effective in diarrhea (Biradar et al, 2008), colitis (Rayudu and Raju, 2014) and prevents intestinal damage (Yoon et al, 2012; Nariya, 2009) in rats. Clinical studies have
also shown that it has sound laxative property, improve appetite and lessen gastric hyperacidity (Mukherjee et al, 2006). It is effective equal to that of chlorhexidine in preventing dental caries and gingivitis (Chainani et al, 2014).

In Unani system of medicine Triphala is known as itrifal and many Unani formulations are available in combinations with Triphala for different purposes other than gastrointestinal (National formulary of Unani medicine, 2006).

1.3. Aim and Objectives

The proposed study was carried out with the following aims and objectives:

Aim:

- Evaluation of gastroprotective and curative potential of hydroacoholic extract of Triphala in experimental gastric ulcer models in rats.

Objectives:

- To prepare the 70% ethanolic extract of Triphala.

- To evaluate the gastroprotective and curative potential of hydroalcoholic extract of Triphala in gastric ulcer models induced by Indomethacin and to compare with ranitidine, a standard anti-ulcer drug.

- To evaluate the gastroprotective and antisecretory potential of hydroalcoholic extract of Triphala in gastric ulcer models induced by pyloric ligation and to compare with ranitidine, a standard anti-ulcer drug.

- To evaluate the gastroprotective and curative potential of hydroalcoholic extract of Triphala in gastric ulcer models induced by stress and to compare with ranitidine, a standard anti-ulcer drug.
1.4. Significance

In Unani and Ayurvedic medicine herbs, animals and mineral origin remedies are being used clinically for the management of peptic ulcer disease without any harmful effects. These are centuries old, time tested, risk-free for use and economic. However it is needed to maintain their quality, purity and safety by subjecting to scientific authentication (Jamal et al, 2006).

As Triphala is very useful traditional medicine for gastric and intestinal ailments in Unani and Ayurvedic medicine the present work was carried out to study the effect of Triphala in experimentally- induced gastric ulcers in rats and their possible mechanisms of action by studying their effects on several mucosal offensive and defensive factors on modern parameters to find out a scientific rationale for its use in traditional medicine.

1.5. Literature Review

1.5.1 Peptic ulcer disease

An ulcer is described as a break in the mucosal layer of the alimentary tract, which may extends through the muscularis mucosa upto the submucosa or much deeper. While ulcers may occur anyplace in the gastrointestinal tract, none are so common as the peptic ulcers that arise in the duodenum and stomach. Severe systemic stress may also produce acute gastric ulcers.

1.5.1.1 Peptic ulcers

Peptic ulcers are chronic and usually solitary lesions that arise in any segment of the gastrointestinal tract come in contact to the aggressive action of acid-peptic juices. Peptic ulcers are most often solitary abrasions less than 4 cm in diameter, situated in the following location, in order of declining frequency:

- Duodenum, initial portion
• Stomach, frequently antrum part
• At the gastroesophageal joint, in the case of gastroesophageal reflux
• Within the borders of a gastrojejunostomy
• In the stomach, duodenum or jejunum of patients of Zollinger-Ellison syndrome
• Within or nearby to Meckel diverticulum that have ectopic gastric mucosa (Cotran et al, 1999).

1.5.1.2 History of Peptic Ulcer

The presence of gastric ulceration was described by Diocles of Carystos (350 B.C.), Celsus, and Galen (131–201 A.D.). Schwartz (1910) first given the dictum “No Acid, No Ulcer” (Gulia and Chaudhary, 2011). Marshall and Warren (1982) described the first revealed about important pathogenic aspect in disease of peptic ulcer with the finding of *Helicobacter pylori* (*H. pylori*). The pathophysiology of peptic ulcer has moved from Schwartz’s adage “No acid-No ulcer” to “No mucosal disruption-No ulcer” and presently to “No *Helicobacter pylori*-No ulcer”. John Lykoudis, a general physician in Greece, treated patients of peptic ulcer disease by antibiotics, starting in 1958, long ago it was actually documented that bacterias were a main cause of the disease (Gulia and Chaudhary, 2011).

Lieber and Lefevre (1959) demonstrated that antibiotics inhibit the transformation of urea to ammonia in stomach of the human.

Susser and Stein (1962) established that stress is also a causative factor for peptic ulcer disease. The innovation of the molecule cimetidine at the UK laboratories by researchers of Smith Kline and French in the 1970s changed the lives of millions of sufferer. It was the first successful anti-ulcer medicine that brought a revolutionary impact on ulcer treatment (Smith and Scharschmidt, 1979).
Marshall and Warren (1982) confirmed that there is a correlation between Peptic Ulcer Disease (PUD) and *H. pylori*. In June, 1984 their paper was publicized. Many reviewers did not like the paper. In an attempt to reply his critics, he experienced on himself and engulfed *H. pylori* and became sick. After that he took antibiotics and got cured. In 2005, Marshall and Warren were rewarded with the Nobel Prize in physiology or medicine for their discovery on *H. pylori* and PUD.

Rauws and Tytgat (1990) depicted the treatment of duodenal ulcer by eradication of *H. pylori* by a triple-therapy regimen having 2 antibiotics and bismuth. Triple drug therapy, simplified to a PPI and 2 antibiotics quickly became first line remedy for eradication.


Chan et al (2001) demonstrated in a randomized control trial that suppression of *H. pylori* even inhibits hemorrhage from ulcers that are aroused by aspirin and other Non-steroidal anti-inflammatory drugs (NSAID).

1.5.1.3 Epidemiology

Peptic ulcer is a world-wide problem and its prevalence in India is quite high. Several field studies from different parts of our country suggest its occurrence in 4 to 10 in per thousands population. Tamil Nadu, Andhra Pradesh, and Jammu and Kashmir are considered to be very high risk areas. The just right cause of peptic ulcer is not known, the disease outcomes in chronic suffering, loss of working hours and occasional fatality. Smoking, alcoholism, and spices help to chronocity of the disease and often precipitate serious complication of ulcer (Tandan, 2003; Khushtar et al, 2009).
India is a country of diverse cultural and food habits, which may create regional variations in occupancy and the usual course of peptic ulcer (Dogra, 1941; Malhotra, 1964). A relatively high occupancy of peptic ulcer in South India was accredited to the sloppy diet which needed modest mastication. It was revealed that saliva had a buffering power and protective effect on the creation of peptic ulcer (Malhotra et al, 1965).

In the United States, about 40 lakhs people are patient of peptic ulcers (duodenal and gastric), and 3.5 lakhs new sufferer with peptic ulcer disease are detected every year. The lifetime probability of having a peptic ulcer for a American men is 10% and for American women is 4% approximately.

Peptic ulcers are remitting and relapsing abrasions that are most frequently detected in middle –aged to older persons, but it may possibly first become apparent in adolescent life. It often appears without known precipitating factors and may appear after duration of week to months of active sickness, restore to health with or without any remedy. Even after healing, yet, the susceptibility to redevelop peptic ulcers remnants, in part since of the susceptibility for recurring infectivity with *H. pylori*. Duodenal ulcers ratio for male to female is approximately 3:1 and it is 1.5 to 2:1 for gastric ulcers (Cotran et al,1999).

Historically, duodenal ulcer to gastric ulcer ratio is greater in developing nations but as incidence of *H. Pylori* infectivity turn down with developments in hygiene and frequency of gastric ulcer enhance by use of ulcerogenic medicines, the duodenal to gastric ulcer ratio is declining. The incidence of *H. pylori* still tends to be elevated in the Asian adult population in whom a lesser parietal cell mass has been found. In the developed countries, cases of reinfection are low, about 0.3-1.0% per year, whereas in the developing world reinfection rates are higher, around 20-30% (Walker and Whittlesea, 2012).
1.5.1.4 Types of Peptic Ulcers

Though they can appear at any level of the alimentary pathway that comes into the contact of hydrochloric acid and pepsin, they arise most frequently (98-99%) either in the duodenal region or in the stomach by the ratio of 4:1. both of the types may exist in acute form or chronic form. In description below concise account of both acute peptic ulcer (stress ulcers) and chronic peptic ulcers has been discussed.

1.5.1.4.1 Acute Peptic (Stress) Ulcers

Acute peptic ulcers or stress ulcers are numerous, minute mucosal disruption, noticed most usually in the stomach but rarely in the duodenum region.

Etiology

These ulcers produce subsequent to severe stress. The reasons are:

1. Psychological stress
2. Physiological stress as in
   - Shock
   - Severe trauma
   - Septicaemia
   - Extensive burns (Curling’s ulcers in the posterior aspects of initial portion of the duodenum)
   - Intracranial lesions (Cushing’s ulcers developing from hyper acidity following excessive vagal stimulation).
   - Drug intake e.g. aspirin, butazolidine, steroids, indomethacin).
   - Local irritants (e.g. smoking, alcohol, coffee etc.)
**Pathogenesis**

It is not known clearly how the mucosal eruptions take place in stress ulcers because genuine oversecretion of gastric acid is presentable in Cushing’s ulcers only happening from intracranial situation such as owing to brain trauma, brain tumours and intracranial surgery. In other pathologic aspects, gastric acid release is normal or under normal. In these circumstances, the probable hypothesis for origin of stress ulcers is:

1. Damage to the mucosal cells due to ischemic hypoxia.
2. Diminution of the gastric mucus ‘barrier’ making the mucosa prone to hit by acid –pepsin.

**Pathologic changes**

Acute stress ulcers grossly are multiple (more than 3 ulcers in 75% cases). They are mostly present in the stomach, followed by decreasing frequency of incidence in the first portion of duodenum. There shape may be circular or oval, usually smaller having diameter less than in 1 cm.

*On Microscopic view*, the stress ulcers are superficial and do not occupy the muscular layer. The boundaries and the bottom may illustrate some inflammatory response according to duration of the particular ulcers.

**1.5.1.4.2 Chronic Peptic Ulcers (Gastric and Duodenal Ulcers)**

It is not mention; peptic ulcers would mean duodenal and gastric ulcers. The two main kind of ‘peptic ulcer disease’ of the upper GIT in which the acid, pepsin secretions are mixed up in their pathogenesis. Peptic ulcers are frequent in the modern day life of the civilized and industrialized world.

Gastric and duodenal ulcers correspond to two dissimilar diseases as far as their clinical features, pathogenesis and etiology are seen. However, pathological reportings in both are
parallel and quite diagnostics. The distinct appearances of both these cases are demonstrated together below.

**Incidence**

Peptic ulcers are found more frequently in middle-aged persons. The peak occurrence for duodenal ulcer is 5\textsuperscript{th} decade, whereas for gastric ulcer it is 6\textsuperscript{th} decade. Duodenal and gastric ulcers are more familiar in males than in females. Duodenal ulcer is about four times more frequent than gastric ulcers, while the overall occurrence of gastroduodenal ulcers being around 10\% of the male gender.

**Etiology**

The instant foundation of peptic ulcer disease is interruption in usual defensive mucosal barrier through acid-pepsin, resulting in damage of the mucosa. However in distinction to duodenal ulcers the patients of gastric ulcer have low-to-normal gastric acid secretions. Also 10-20\% of patients of gastric ulcers may comprise co-existents duodenal ulcers as well. Therefore the etiology of peptic ulcers possibly cannot be justified on the basis of single factor but is multifactorial. These factors are:

i. **Helicobacter pylori gastritis:** Approximate 15-20\% cases infected with *H. pylori* developed duodenal ulcers in their life time, while colonization of *H. pylori* in stomach never develops ulcerations and stayed asymptomatic.

ii. **Acid-pepsin secretions:** There is definite evidence that some amount of acid pepsin release is necessary for the formation of both duodenal and gastric ulcers. Peptic ulcers never arise in link with pernicious anemia into which there is lack of pepsin acid secreting chief and parietal cells respectively.
iii. **Mucus secretion:** Any situation that decreases the amount or quality of usual protective mucus barrier inclines to the development of peptic ulcer.

iv. **Gastritis:** Some extent of gastritis is forever present in the area of gastric ulcer. Chronic gastritis and gastric ulcer are similar in their distribution pattern.

v. **Local irritants:** Pyloric antrum as well as lesser curvature of the stomach is the locations most exposed longer time-interval to local irritants. A few of local irritating substances concerned in the etiolopathology of peptic ulcers are alcohol, heavily spiced foods, cigarette smoking. Non-steroidal anti-inflammatory drugs, unbuffered aspirin etc.

vi. **Dietary factors:** Nutritional deficiencies have observed as etiologic factors in peptic ulcers.

vii. **Psychological factors:** Psychological stress, ulcer-type personality, anxiety, and fatigue may aggravate as well as influence to peptic ulcer disease.

viii. **Genetic factors:** Persons with blood group ‘O’ shown to be more chances of developing peptic ulcers than other blood groups. Genetic predispositions seem to have larger role in duodenal ulcers as substantiated by their incidence in monozygotic twins, families and relationship with HL A-B5 antigen.

ix. **Hormonal factors:** Secretion of definite hormone by tumours is linked with peptic ulceration e.g. in Zollinger-Ellison syndrome release of gastrin from islet-cell tumour, endocrine releases in adenomas and hyperplasia of parathyroid glands, anterior pituitary and adrenal cortex.

x. **Miscellaneous:** Duodenal ulcers have been showed to occur in alliance with various other settings such as alcoholic cirrhosis, chronic renal failure, hyperparathyroidism, chronic obstructive pulmonary disease, and chronic pancreatitis.
Pathogenesis of Chronic Peptic Ulcer

Though the role of a variety of etiologic factors just expressed is well known in ulcer formation, two most very important features in peptic ulcer are:

- contact of mucosa to stomach acid and pepsin release
- Strong etiologic association with *H. pylori* infection. There are discrete differences involved in the pathogenetic mechanisms of gastric and duodenal ulcers are as below:

(i) **Duodenal ulcer:** There is definite evidence to sustain the role of elevated acid-pepsin discharge in the development of duodenal ulcers. In addition to this, a small number of other noteworthy aspects in the etiology of duodenal ulcers are as below:

a) There is usually hypersecretion of acid into the empty stomach at night which is due the effect of vagal stimulus. There is elevated basal as well as maximal acid output (BAO and MAO) in reaction to different stimuli.

b) Duodenal ulcer Patients have quick emptying of the stomach thus the food which in general buffers and neutralizes the stomach acid, delivered into the small intestine and the duodenal mucosa rendered to the aggressive action of stomach acid.

c) *Helicobacter* gastritis affected by *H. pylori* is noticed in 95-100% incidences of duodenal ulcers. The mucosal regions colonized by this bacterium are worn-out of the defensive mucus ‘barrier’, so that underlying epithelial cells become exposed to the damaging influences of acid pepsin release.

(ii) **Gastric ulcer:** The etiopathogenesis of gastric ulcer is mostly described on the basis of weaken gastric mucosal protections against acid-pepsin elaborations. Some other aspects in the etiopathogenesis of gastric ulcer are as below:
a) Hyperacidity may arise in gastric ulcer due to augmented *serum gastrin* levels in reaction to eaten foodstuff in an atonic stomach.

b) However a lot of patients of stomach ulcer have low to normal stomach acid levels. Ulcer formation in such type of patients is described on the basis of injurious influence of other aspects such as cigarette smoke, bile reflux and gastritis etc.

c) The usually defensive *gastric mucus ‘barrier’* adjacent to acid-pepsin is depleted in gastric ulcer. There is derangement in the both quantity and quality of mucus of stomach. One of the reasons for its diminution is colonisation of the mucosa of stomach by *H. Pylori* found in 75-80% gastric ulcer patients.

**Pathological Changes**

Gross and microscopic alterations in duodenal and gastric ulcers are comparable and quite distinctive. *Gastric ulcers* are originated predominantly alongside of the lesser curvature in the area of pyloric antrum, more frequently at the posterior than the anterior side wall. Most *duodenal ulcers* are originated in the first portion of the duodenum, usually just post-pyloric, more generally on the anterior than the posterior side wall.

Grossly, typical peptic ulcers are usually small (1-2.5 cm in diameter), solitary (80%), round to oval and typically ‘punched out’. Benign ulcers generally have smooth margins in level with the neighboring mucosa. The folds of mucosa converge towards the ulcer margin. The ulcers may differ in deepness from being shallow (restricted to mucosa) to deep ulcers (piercing into the muscular layer). In about 10-20% of incidences, duodenal and gastric ulcers are co-existing, mostly peptic ulcers are benign.

*Microscopically*, 4 histological zones are found in chronic peptic ulcers. From inside to outside, these are:
1. Necrotic zone
2. Superficial exudates zone
3. Granulation tissue zone
4. Zone of cicatrisation

1.5.1.5 Complications

Acute and sub-acute peptic ulcers usually heal without leaving any visible scar. However, healing of chronic, larger and deeper ulcers may result in complication. These are as follows:
1. Obstruction
2. Haemorrhage
3. Perforation
4. Malignant transformation

1.5.1.6 Clinical Features

Lesions of peptic ulcers are remitting and relapsing. Their persistent and recurring behavior is concised by proverb: ‘once a peptic ulcer patient forever a peptic ulcer patient’ the two major types of chronic peptic ulcers exhibit variations in clinical appearance which are as presented in the table 1.1 (Mohan H, 2005).
Table 1.1: Distinctive Features of Two Major types of Peptic Ulcers

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>DUODENAL ULCER</th>
<th>GASTRIC ULCER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Four times more frequent than stomach ulcers</td>
<td>Less common than duodenal ulcers</td>
</tr>
<tr>
<td></td>
<td>Usual age 25-50 years</td>
<td>Usually beyond the 6\textsuperscript{th} decade</td>
</tr>
<tr>
<td></td>
<td>Mostly found in males than in females (4:1)</td>
<td>More frequent in males than in females (3.5:1)</td>
</tr>
<tr>
<td>Etiology</td>
<td>Most frequently as a result of \textit{H. pylori} infection.</td>
<td>Stomach colonization by \textit{H. pylori} asymptomatic however greater chances of formation of duodenal ulcer. interruption of mucus barrier most significant aspect. connection with bile reflux, drugs, gastritis, tobacco, alcohol</td>
</tr>
<tr>
<td></td>
<td>Other factors-overproduction of acid-pepsin, relationship with alcoholic cirrhosis, hyperparathyroidism, tobacco, blood group O, chronic pancreatitis, genetic factors</td>
<td></td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Mucosal digestion from hyperacidity most important factor</td>
<td>Usually normal-to-low levels; hyperacidity if present is due to high serum gastrin</td>
</tr>
<tr>
<td>Pathologic changes</td>
<td>Mostly present in the first portion of duodenum</td>
<td>Mostly present at pyloric antrum and along the lesser curvature</td>
</tr>
<tr>
<td></td>
<td>Often single, size-1-2.5 cm, oval to round, punched out</td>
<td>Grossly similar to duodenal ulcer</td>
</tr>
<tr>
<td></td>
<td>Histologically, consisted of 4 layers – necrotic, superficial exudative, granulation tissue and cicatrisation</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td>Commonly haemorrhage, perforation,</td>
<td>Perforation, haemorrhage and at</td>
</tr>
<tr>
<td>Clinical features</td>
<td>sometimes obstruction; malignant transformation never occurs</td>
<td>times obstruction; malignant transformation in less than 1% cases</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Pain-food-relief pattern</td>
<td>Food-pain pattern</td>
<td></td>
</tr>
<tr>
<td>Pain at night common</td>
<td>Night pain not present</td>
<td></td>
</tr>
<tr>
<td>Vomiting not found</td>
<td>Vomiting frequent</td>
<td></td>
</tr>
<tr>
<td>Melaena more common than haematemesis</td>
<td>Haematemesis more common</td>
<td></td>
</tr>
<tr>
<td>No weight loss</td>
<td>Loss of weight noteworthy</td>
<td></td>
</tr>
<tr>
<td>No specific choice of diet</td>
<td>Patients prefer plain diet without fried foods, chilies etc.</td>
<td></td>
</tr>
<tr>
<td>Profound tenderness in the right hypochondrium</td>
<td>Profound tenderness in the middle epigastrium</td>
<td></td>
</tr>
<tr>
<td>Affected by seasonal variation</td>
<td>Not affected by seasonal Variation</td>
<td></td>
</tr>
<tr>
<td>Arise more frequently in the persons at greater stress</td>
<td>More frequently in labouring people</td>
<td></td>
</tr>
</tbody>
</table>
1.5.1.7 Diagnosis

The common procedure includes for the diagnosis of peptic ulcer:

(i) Barium meal X-ray

Peptic ulcer in distortion of the duodenal cap or in the lesser curvature is detected by Barium meal X-ray.

(ii) Endoscopy

Techniques of Fiber optic were firstly used mainly for diagnosis, but now they have been used for treatment also. Tip control and optical resolution Excellence let direct visualization of mucosal deformities, with desired photographic record. End-viewing tools are adopted to see esophagus, stomach and duodenum mucosal surfaces.

(iii) Gastric function tests

Stomach secretions are accumulated via a nasogastric tube prior to (basal secretion) and subsequent stimulation by pentagastrin injection. The acid status is not valuable for the routine case of peptic ulcer because of the match with normal values. The main application of this test is in the Zollinger –Ellison syndrome (Haslett et al, 2002)

(iv) H.Pylori detection

(a) Endoscopic Tests

The significant role of endoscopy for the identification of H.pylori is to find gastric mucosal biopsies which are employed for both indirect tests (urease testing) and direct tests (culture and histology). The biopsy based examinations are reliant on the actual bacterial load and identify patients only with infection of active H.pylori. Medicines that affect the mass or viability of H.pylori bacterias within the stomach lessen the sensitivity of these examinations by rising the chance of sampling error. Hence, antibiotics and bismuth compounds should be
withdrawn for 4 weeks, and PPIs should be withdrawn for 1 to 2 weeks prior to testing of 
*H. pylori* by endoscopy.

**Culture:** Culture has the benefit of allowing for the antibiotic sensitivity determination. Detection of *H. pylori* is done on the base of colony morphology that include curved rods gram-negative, that give positive test for urease, oxidase and catalase.

**Histological assessment:** This is performed using a range of histological stains. Though *H. pylori* is easily seen on slides of biopsy specimens stained by hematoxylin and eosin (HE), for improved detection of the organism, particular staining techniques have been employed also.

**Rapid urease tests:** *H. pylori* urease breakdown the urea presented in the test packet of agar gel and starts to formation of ammonia, pH increases and color of the phenol red indicator changes. When urease is present, ammonia is formed from urea infused into a reaction strip.

**Polymerase chain reaction (PCR):** Assays by PCR, which have been known to be sensitive and precise, have been used for the identification of many *H. pylori* strains in gastric mucosal biopsies. Though, the varied genetic organization of *H. pylori* may influence the assay sensitivity.

**(b) Nonendoscopic Tests**

**Antibody test:** Antibody identifies both under diagnose (false negative results) as well as over diagnose (false positive results) *H. pylori* infection. Ingested bismuth compounds, PPIs, or antibiotics do not cause false negative serologic test results.

**Urea breath test:** Patients swallow $^{13}$C or $^{14}$C-labelled urea. If *H. pylori* is found in the stomach, labelled urea hydrolyzes urease and labelled $\text{HCO}_3^-$ is released, which is carried to the lungs by the bloodstream and is exhaled in the form of labelled carbon dioxide. Blood or
breath is collected, and the radioactive $^{14}$C isotope either is detected by a scintillation counter or infrared spectroscopy or mass spectroscopy is utilized to identify nonradioactive $^{13}$C. False negative results may arise in patients taking drugs, such as PPIs, that reduce the population of *H.pylori* organisms or its enzymatic activity.

**Stool antigen test:** The stool antigen examination is measured as a valuable non-invasive option for diagnosis of *H.pylori* when UBT is not accessible. Diluted stool and a peroxidase conjugated polyclonal antibody are mixed, then substrate 1 hour later. In patients infected with *H.pylori*, enzyme-substrate binding shows a color change, which can be identified spectrophotometrically or visually.

### 1.5.1.8 Therapy for Peptic Ulcer

In general treatment is targeted at reducing ulcer pain, curing the ulcer, ulcer recurrence prevention, and reducing complications related to ulcer. The aim of treatment in ulcer patients with *H.pylori* is eradication of this bacterium. Ulcers are healed by successful eradication and risk of recurrence is reduced to less than 10% for 1 year. The target of medication in a patient with NSAID stimulated ulcer is to heal the ulcer as quickly as possible. H$_2$RAs, PPIs and sucralfate are employed to heal *H.pylori* negative and NSAID-induced ulcer patients. PPI or misoprostol is coadministered as a Prophylaxis to reduce the threat of ulcer induction and complications of upper GI in patients who are on nonselective NSAID therapy.

#### 1.5.1.8.1 Non Pharmacological Treatment of PUD

- Patients are instructed to identify and avoid foods that secrete excess HCl; some individuals improve symptoms after doing so.
• Patients are educated that avoidance of caffeine and alcohol make symptoms better and pre-existing ulcer is healed faster.
• Fiber enriched diet can lessen the risk of budding an ulcer and can also pace the healing if it already presents.
• Foods enriched with flavonoid like apples, onions, celery, garlic, tea and cranberries may slow down the *H. pylori* growth.
• Cease, decrease NSAID intake or move to selective COX-2 inhibitor treatment; this a lot relieves problems in mild cases.
• Strongly recommend the patients who smoke to give up because tobacco irritates the gut as well as delays healing.
  Stress relaxation therapy such as sedatives or yoga should be used to mitigate psychological effects.

1.5.1.8.2 Pharmacological Treatment of PUD

Approaches for the treatment of peptic ulcer are:

(i) Reduction of gastric acid secretion

(a) H₂ antihistamines: Cimetidine, Famotidine, Ranitidine, Roxatidine

(b) Proton pump inhibitors: Pantoprazole, Omeprazole, Esomeprazole, Lansoprazole, Rabeprazole

(c) Anticholinergics: Oxyphenonium, Propantheline, Pirenzepine

(d) Prostaglandin analogue: Misoprostol

(ii) Neutralization of gastric acid (Antacids)

(a) Systemic: Sodium bicarbonate,citrate
(b) Nonsystemic: Magnesium hydroxide, Aluminium hydroxide, Calcium carbonate, Mag.trisilicate, Magaldrate.

(iii) Ulcer protectives: Sucralfate, bismuth subcitrate (CBS)

(iv) Anti-\textit{H. pylori} drugs: Clarithromycin, Amoxicillin, Tinidazole, Metronidazole, Tetracycline

1.5.1.8.3 Adverse effect of commonly used anti-ulcer drugs

Table – 1.2 The adverse effect of commonly used antiulcer drugs are illustrated below;

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antacids</strong></td>
<td></td>
</tr>
<tr>
<td>Aluminium hydroxide</td>
<td>Weakness, rebound acidity, hypophosphatemia, osteomalacia, (on regular use).</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>Discomfort, rebound acidity (marked), constipation, absorbed calcium may be hazardous if renal excretion is not proper.</td>
</tr>
<tr>
<td>Magnesium hydroxide</td>
<td>Diarrhea.</td>
</tr>
<tr>
<td><strong>Histamine-2 blockers</strong></td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Bowel upset, dry mouth, convulsions (elderly) confusion, bradycardia has been shown by bolus i.v. injection, antiandrogenic action, cardiac arrest, elevates plasma prolactin and restrains catabolism of estradiol by liver rising risk of gynaecomastia, elevation of plasma aminotransferases, impotence</td>
</tr>
</tbody>
</table>
and loss of libido, it suppresses many cytochrome P-450 isoenzymes and slows down metabolism of several drugs which can show their toxicity.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Famotidine</td>
<td>Dizziness, headache, bowel upset.</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Bowel upset, dizziness, headache, constipation or diarrhoea</td>
</tr>
</tbody>
</table>

**Proton pump inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lansoprazole</td>
<td>Headache, constipation and diarrhea other side effects are same as omeprazole.</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Nausea, headache, dizziness, abdominal pain, loose stools, joint and muscle pain, some report rashes, hepatic malfunction and leucopenia, use on long term in recent times has shown gynaecomastia, quicken osteoporosis and erectile dysfunction, it shows interaction with cytochrome P-450 isoenzymes of many drugs.</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>It has lesser affinity for cytochrome P-450 isoenzymes than omeprazole.</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>Drug interaction and adverse effects profile same as omeprazole.</td>
</tr>
</tbody>
</table>

**Antibiotics**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>Diarrhea.</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Fever and Rashes are rare, only some incidences of pseudomembranous enterocolitis, dysfunction of</td>
</tr>
</tbody>
</table>
liver are known, safeness in lactation and pregnancy not documented, hepatic oxidation of several drugs has been inhibited.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>Anorexia, abdominal cramps, metallic taste are familiar, less commonly dizziness and temporary neutropenia, however neuropathy of peripheral organ and CNS effects produced on long term usage, contraindicated in chronic alcoholism and first three months of pregnancy.</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Epigastric pain, diarrhea, nausea and vomiting. Thrombophlebitis of injected vein, kidney and liver injury, discoloration of teeth, impermanent bone growth inhibition, hypersensitivity, phototoxicity and supra-infections (most common).</td>
</tr>
</tbody>
</table>

### Miscellaneous

<table>
<thead>
<tr>
<th>Medication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colloidal Bismuth</td>
<td>Blackening of the stool and tongue, Diarrhea or constipation, on prolonged use encephalopathy and osteodystrophy.</td>
</tr>
<tr>
<td>Subcitrate (CBS)</td>
<td></td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Abdominal cramps, diarrhea, uterine bleed and abortion.</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Constipation, as it adsorbs several drugs thus may decrease efficacy of other drugs, hypophosphatemia on prolonged use.</td>
</tr>
</tbody>
</table>

(Katzung et al, 2012; Gulia and Choudhary, 2011; Tripathi, 2013).