INRODUCTION

Now a day’s most of the peoples are suffering from various digestive disorders. The common digestive problems includes diarrhea, Ulcerative colitis Gastro-esophageal reflux disease (GERD), Irritable Bowel Syndrome many people are suffering from various kinds of ulcer. Some of them are life-threatening which include gastroduodenal ulcer one of the common digestive disorders (Garg, et al., 2014). Peptic ulcer is prevalent, common condition that affects most people all over the world.

Peptic ulcer causes lesions in the mucosal lining of the stomach as well as duodenum which results to form gastric ulcer or duodenal ulcer. Peptic ulcers are arises due the disturbed or imbalanced level of offensive and defensive mechanism of the intestinal mucosa. Peptic ulcers may be acute or chronic (Jorgensen, and Vergara, 2006).Imbalanced secretion of gastrointestinal tract causes erosion, cellular necrotic changes when tract is continuously exposed to the gastric acid, pepsin and digestive enzymes (Bovenberg, 1997).

Both type of ulcer primarily arises by Helicobacter pylori infection (Hua and Kong, 2000; Bigheti, et al., 2005) and longer, continuous use of pain relieving drugs (NSAID) induced stress, unhealthy diets, modern lifestyle (Ostenson and Gudmudson, 2003), dietary modification such as spicy foods, fast food additives, alcohol drinking, cigarettes smoking (Moshowitz, 2000; Ostenson and Gudmudson, 2003), tobacco smoking (Rosenstock, et al., 2003) caffeine. The unusual cause of ulcer is an imbalance occurred in the secretion of mucosal lining protective factors includes bicarbonate, mucus, prostaglandins, nitric oxide, mucosal blood flow, growth factors, surface epithelial cells while, aggressive factors especially acid and pepsin (Marhuenda, et al., 1993), all these interact in complex ways to cause an ulcer. The duodenal mucosal deterioration occurred by multiple causes such as bacteria (Lykoudes,1958; Marshall and Warren, 1983) chewing gum, smoking, steroids, food allergies, poor nutrition, prolonged stress condition (Kim, et al.,2007) and sex differences (Anders, et al.,2008).
Gastro duodenal cells mucosal erosion also occurred by stomach secretion gastric juice, imbalance between the gastric pepsin and acid and the bicarbonate secretion, glycoprotein secretion (Falcao, et al., 2008) and harmful noxious byproducts in the gastric mucosa (Jainu and Devi, 2006; Wallace, 2011).

Peptic ulcers and their sensitivity increases with age (Bonnevie, 1975. Ostensen, et al., 1985 and Christensen, et al., 2006). Duodenal ulcer arises in the areas where high content of acid and pepsin released. The most common location is the duodenal bulb, i.e., within 2-3 cms from the pyloric region and especially near the junction of antral (pyloric) and duodenal mucosa. Ulcers occur in junction of stomach and duodenum because the mucosa in these areas is less resistant to acid, pepsin or other damaging factors. Chronic duodenal ulcers are usually round or oval, some time it is elliptical or elongated in shape. Such type of ulcer showed high erosion, deep and penetrate the muscularis mucosa. The floor of ulcer showed intact epithelium with eosinophilic necrosis inflamed region and tissue fibrosis (Isenberg, et al., 1978).

The ulcer of duodenum is artificially induced by injection of cysteamine or propionitrile and it acts as excellent model of duodenal ulcer (Selye and Szabo, 1973; Adler, et al., 1983). The morphological, histological changes and imbalanced biochemical secretary activity of mucosal lining of duodenum leads to erosion during development of cysteamine induced duodenal ulcer (Poulsen, et al., 1981; Hirscowitz, 1989). Cysteamine-HCl induced ulcer alters the structure and secretary function of Brunners glands via cellular exfoliation and erosion in the mice (Ashokan, et al., 2010).

i) **CAUSES OF PEPTIC ULCER:**

- **Smoking :**

  Arthur and John, 2000 reported that smoking is risk factor for ulcer formation. the main component nicotine present in cigarettes stimulates hyperacid secretion in the stomach and also they studied that ulcer healing mechanism collapsed in smokers they unable to recover early (Steven, 1996). Spincter muscles of pyloric stomach relaxed due to smoking which causes back
flow of bile into stomach they produces harmful effects on gastrintestinal mucosa (McGuigan, 1991).

- **Helicobacter pylori infection:**
  
  Most ulcers prominently formed by the bacterial infection of *Helicobacter pylori* (*H.pylori*). *H. pylori's* are gram negative bactreia, they able to survive in highly acidic envioronment. They are deeply penetrating mucosal lining of stomach or duodenum. They have ability to produce urease enzyme that produces ammonia and neutralizes the hyperacidic environment and survive mean while their secretions affects the mucosal lning of stomach (Simon,2008). Hence, mucosal liining easily susceptible to pepsin as well as gastric acid results into gatric erosion and causes ulcer.

![Diagrammatic representation of causes of peptic ulcer](image)

Fig. Diagrammatic representation of causes of peptic ulcer

- **Alcohol:**
  
  Stomach and intestinal mucosal lining of alcoholic person re aseasily susceptible to acute and chronic heemorrhagic gastric damages in man (Debashis, *et al.*, 2002).Severity of ulcer formation are more common seen in
the alcoholic and liver cirrhosis person. Nonprotein sulphydryls concentration decreased in ethanol induced ulceration (Szabo, et al., 1981). Lowered nonprotein sulphydryls concentration leading to cause of ulcer ultimately enhanced the level of free radical formation results into stress (Baiery, et al., 2002).

- **Stress and free radicals:**

  Stress has major contribution in the pathogenesis of both type of ulcer formation (Cho, et al., 1992; Allen, et al., 1993). Physical and emotional stress implicated in the ulcer formation stressful environment alter the physical function of muocosal cells also alters the physical properties and concentration of mucus secreteted by gastrointestinal tract (Allen, et al., 1993). Increased amount of reactive oxygen species (ROS) during stress condition exhibits ulcerogenic effect (Pihan, et al., 1987). Salim, et al., 1990 investigated that development gastric mucosal lesion proliferated by the saturation of free radicals during ethanol induced ulceration. The gastric mucosal damages caused by NSAIDs, ethanol mediated through the involvement of free radicals (Davies, et al., 1994; Yoshikawa, et al., 1996).

- **Food and drinking habit:**

  The spicy food material and caffeine stimulates the acid secretary activity results into hypeesecretion. High content of acid affects the gastric mucosal cells frequent exposure to acidic environment reduces the mucus secretion may responsible for ulcer formation such diet recurrence of ulcer (Steven, 1996)

- **Acid, pepsin and Diminished mucosal resistance:**

  The stomach has ability to produce mucus which acts as lubricant that covers the lining of stomach and protect the gastric cells from acid, pepsin. The chemical material as bicarbonate involved in the neutralization of digestive enzymes and converts it into simpler harmless products (Gillson, 2008).

- **Non steroidal anti-inflammatory drugs (NSAIDs):**

  The continuous use of pain relieving drugs such as Diclofenac and Naproxen side effect they enhance the acid secretion in stomach (Ivey,
The cyclooxygenase formation activity diminished by mucosal damage results in lower prostaglandin secretion. Prostaglandins played a significant role in the conservation of mucosal cell structural integrity (Malagelada, 1986; Mizuno, 1997). Lowered level of cyclooxygenase impairs blood flow, bicarbonate and mucus secretion (Langman, et al., 1991).

ii) METHODS OF ULCER INDUCTION:

Various models have been adopted to induce gastroduodenal ulcers to study their pathogenesis and antiulcerogenic effects of some medicines. They are:

- Stress induced gastric ulcer (Parmar and Jagruthi, 1993).
- Acetic acid caused gastric ulcer (Asad, et al., 2001).
- Indomethacin induced gastro-duodenal ulcer (Prabha, et al., 2003).

iii) PATHOGENESIS OF PEPTIC ULCER:

Pathogenesis of peptic ulcers leads to decreased mucosal resistance due to erosion of gastric mucosal lining affecting the goblet cells as well as their secretion (Bart and Rex, 2001). It is well established that a duodenal ulcer tends to develop when there is an unfavorable balance between acid pepsin secretion and mucosal resistance (Sturdevant, and Walsh, 1978).

- Pathogenesis of duodenal ulcer:

The development of Cysteamine-HCl induced duodenum ulceration widely investigated by various researchers. Many previous work done on drugs suggested that the drug-induced duodenal ulceration is concern mainly to major amount of gastric acid secretion (Black, 1972, Wilkes, 1991; Prinz, 1993; Hersey and Sachs, 1995) delay in gastric emptying (Lichtenberger, 1976 and Szabo, 1976) elevation in serum gastrin levels (Lichtenberger, 1977) and depletion of tissue somatostatin (Szabo and Reichalsion, 1981). Cys-HCl induced ulcer showed pronounced changes in the histological structure of duodenal gland. The secretary cells of duodenum flattened in shape and acini of lumen becomes dilated, the cells unable to synthesize mucosal
glycoprotein’s (Poulsen, et al., 1981). The administration of or subcutaneous injection of Cys-HCl induced ulcer at specific site nearer to the sphincter, invades the wall of duodenum (Krantis and Nicholson.,1989). The possible and perfect mechanism of Cysteamine-HCl caused duodenal ulcer is unknown but model exhibit possible mechanisms such as erosion of gastric mucosa lead to deterioration in mucosal resistance, promoting gastric emptying and high amount of acid secretion (Lichtenberger, et al., 1977 and Briden, et al., 1985). Other factors responsible are heredity, stress, drugs, and cigarettes take part in the development of duodenal ulcer. The process of ulcer by cysteamine-HCl include formation of ROS, loss in the bicarbonate secretion, reduction in the mucosal blood flow leads to hypoxia, imbalanced redox state of cell and reduced mucosal resistance (Choi, et al., 2012). Stress caused by oxidation reaction in body generates abundant amount of free radical as compared to the endogenous cellular antioxidants (Halliwell, 2011 and Christijanti, et al., 2017). Free radicals of oxygen atoms may alters the cellular structural integrity of the tissues. The harmful effect of such radicals brings the lipid peroxidation, that cause damage in the plasma membranes of cells via releasing the intracellular secretary components, includes lysosomal enzymes enhance the cell destruction s and alters the secretary mechanism. The radicals also enhance mucus cell deterioration of tissue cell layer via the impairment of cellular structural and functional of the basement cytoplasmic membrane cell components that exhibits total functional loss of cell assembly and loss of functions of genetic material. The mechanism of Lipid peroxidation changes the viscosity of plasma membrane that is lipid bilayer, responsible for altered ion transport and disturbs the cytoplasmic membrane integrity leading to formation of gastric erosion (Demir, et al., 2003 and Dokmeci, et al., 2005). Numbers intracellular antioxidants produced by the cells against the ROS. Antioxidants are those substances which are involved in the delay or inhibit oxidization of free radicals (Antolovich, et al., 2002). The formation of reactive oxygen species causes gastric cells mucosal damage via the metabolic
reactions of arachidonic acid, blood cells, helper and killer cells (Kwiecien, et al., 2002 and Nasuti, et al., 2006).

- **Acid, pepsin hypersecretion** –

  The peoples suffering from the duodenal ulcer secretes higher amount of acid content than normal person (Davenport, 1977). In response to a meal, the rate of acid secretion by normal subjects compared to those with duodenal ulcers showed a significant increase in the latter case. Although fasting serum gastrin hormone content are normal in duodenal ulcer susceptible person, gastrin secretion responsible for hypersecretion of acid which is seen in the peptic ulcerated peoples.

  The acid hypersecretion and duodenal ulcer formation in response to cysteamine administration is based on an intact vagus nerve (Lichtenberger, et al., 1976). The severity of ulcer formation and development is lowered in the vagoctomised patients, sympathectomy, lowered histamine concentrated people and H$_2$-receptor antagonist administered patients (Szabo, et al., 1979). Moreover, hypophysectomy, thyroidectomy or adrenalectomy and the H$_2$-receptor antagonist exerted a dose dependent anti-ulcer effect. Similar mechanism observation seen in the anticholinergic methscopolamine bromide helps to recover cysteamine or propionitrile caused duodenal ulcers (Robert, et al., 1974 and Robert, et al., 1975) eye muscle relaxant such as atropine or surgical operation of vagus nerves that is vagotomy lowers the gastric acid output enhanced by cysteamine (Ishii, et al., 1976). In opposite to the findings that acid secretion of stomach is significantly increased in cysteamine induced ulceration (Robert, et al., 1974). The chemical ulcerogens inhibited gastric secretions although their ulcerogenic action could be stopped by the treatment of either antacids or antisecretory factors (Robert, et al., 1975). It has been also established that chemically-induced duodenal ulceration is associated with a decrease in acid neutralization after injection of cysteamine. In other words, a mechanism of action of cysteamine acts via the impairment of duodenal mucosa ultimately unable to neutralizes acid and thus, altered protective mechanisms. Such disturbed defensive system causes the back diffusion of
hydrogen ions present in between the lumen of the mucosa (Adler, et al., 1983.). However, other investigators reported that experimental duodenal ulcerogenesis seems to occur in the presence of large amounts of gastric acid without corresponding increase in the buffering power of duodenal bicarbonate (Ohe, et al.1982).

- **Delay in gastric emptying** - In addition to increased gastric acid secretion and duodenal ulcer formation, an intact vagus is required for other cysteamine-HCl induced responses, including mainly delayed gastric emptying (Cannon, 1982, Abrahamsson, 1973). The gastric stasis is the primary action of ulcerogens and that the resultant gastric distention in turn mechanically stimulates both hyper acid and gastrin secretion, thus mediating duodenal ulcer formation (Szabo, et al., 1979).

- **Elevation in serum gastrin level** - The elevation of serum gastrin level this is further enhanced by peptone and food intake and its association with duodenal ulcer (Szabo, et al., 1979). He proposed the idea that ulcerogens may stimulate gastrin release in the rat, thus mediating the functional pathological changes induced by these drugs. Hypophysectomised experimental animals exhibits decreased susceptibility towards duodenal ulcer formation via reducing their serum gastrin level concentration (Enochs and Johnson, 1976.). Lichtenberger (1977) reported that elevated serum gastrin level helps to prevent cysteamine or propionitrile induced ulcer.

- **Action of Somatostatin** - Treatment of somatostatin completely prevents the duodenal ulcer formation and reduces the mortality produced by cysteamine (Schwedes, et al., 1977). It was further reported that somatostatin infusion in a patient with a bleeding duodenal ulcer apparently stopped the bleeding (Mattes, et al., 1975). Cysteamine is a relatively specific depletor of tissue somatostatin through acting on the cellular level by reducing its synthesis, or by breaking preformed somatostatin (Szabo and Reichlin, 1981).
All these pathomorphological investigations converge to reveal the major aspects and importance of chemically-induced duodenal ulceration.

Mucosal defensive system helps to prevent ulcer formation and protect the stomach and duodenum from different toxic chemicals and noxious agents.

iv) **ANATOMY AND HISTOLOGY OF DUODENUM:**

The gastrointestinal system is a continuous, muscular digestive tube with mucosal surface area via essential nutrients and fluids enter inside the animal body. The small intestine is an important anatomical structure in the digestion of food and its size varies from one animal species to another (Lahey, 2009).

The small intestine is the largest part of digestive system and the major site of digestion, absorption and assimilation. The small intestine is consists of mainly three parts – duodenum, jejunum and ileum. Histologically duodenum consists of mainly four layers such as serosa, muscularis mucosa, submucosa and mucosa.

- **Serosa:** The serosa is the outer most visceral outer most layer of the peritoneum, covers the duodenum of small intestine. It is outer thin delicate smooth layer of connective tissue helps to involved in the secretion of serous fluid. Fluid secreted by this layer acts as lubricant decreases the friction between the serosal layer and the muscular layer.

- **Muscularis mucosa:** The muscularis is the layer of muscle nearer to the submucosal layer. Small intestinal function or peristalsis mechanism which is caused by muscularis mucosal cell layer. It’s composed of two different smooth muscle layer - Outer thinner longitudinal and inner thicker circular layer.

- **Submucosa:** It is the dense layer made up of connective tissue or loose connective tissue that gives support to the mucosa, mucosal layer joined with the smooth muscle due to submucosa. The submucosa region consists of loose connective tissue, blood vessels and the Meissner’s plexus. In the submucosal region tubular gland is observed known as Brunners gland (duodenal gland). Such compound Brunners gland only present in the
duodenum. Brunner’s gland involved in the secretion of mucus which is alkaline in nature contains abundant bicarbonate. Secretion of these gland neutralize the amount of acid present in the chyme added from the gastric cells of stomach and responsible to maintain the alkaline condition which required for normal functioning for intestinal enzyme activity, leads to help in the absorption function and lubricate the intestinal walls.

- **Mucosa:** It is the innermost layer of the duodenum and this layer prominently involved in the secretion of digestive enzymes and hormones. It consist of epithelial cells, lamina propria and muscularis mucosae. The intestinal villi are most important part of the mucosa. At the base villi simple tubular structures are present called as crypts of Lieberkuhn. Crypts of Lieberkhun lie between the villi. It is an extension of lamina propria. This innermost layer which is made up of simple columnar epithelial cells, lamina propria (it is a connective tissue layer) and lamina muscularis (smooth muscle layer). The enterocytes of intestine that is epithelial cells are responsible for secretion of glycoproteins and mucin. Paneth cells are present in the spaces present in between or lumen of crypts, play role in then antimicrobial defense. Villi contain 3 types of cells:
  - **Simple columnar cells**- They perform absorptive function due to the presence of brush border consisting of large no. of microvilli.
  - **Goblet cells**- Such cells continuously associated secretion of mucus and they are interspersed between the columnar cells.
  - **Endocrine cells**.

In the small intestine, proximal duodenum mucosa formed by single layer of surface epithelium overlying a delicate connective tissue layer the lamina propria, which in turn rests upon a fine band of smooth muscle; the muscularis mucosa. Morphologically, the mucosal surface area is dramatically increased by fingerlike lumenal villi, which consist of epithelial cells overlying a central lamina propria core. Between villi the epithelium dips down to form the crypts of Lieberkuhn (Banks, 1986). The epithelium consist of two kinds of cells namely the tall columnar enterocyte and the goblet cell. The apical surface
of these absorptive cells is covered with short slender microvilli, each limited by plasma membrane in the rat (Palay and Karlin, 1959; Shiner, 1983). A surface coat or glycocalyx, consisting of numerous vital glycoprotein enzymes, receptors and carriers, projects into the lumen from the microvilli. Rubin, 1991 reported glycocalyx is necessary for digestion, intercellular absorption, and active transport of various nutrients such as sodium, glucose and chloride ions (Barrett and Dhamsathaphom, 1991). Goblet cells of proximal duodenum secrete mucus glycoproteins important in the epithelial surface of the duodenum (Porter and Bonneville, 1968). They are embedded in the plasma membrane of gastrointestinal wall and they played important role in protection of mucosal surface against the acid and different proteases (Tauber, R. and Gerok, 1987). The gastrointestinal mucosa is concealed by a viscoelastic, gel-like watery, transparent secretion predominantly formed by mucin glycoproteins (Spiro, 1973). They have water soluble properties such as high molecular weight glycoprotein that involved in the gel forming properties of mucin. In simple terms the glycoprotein’s are organic compounds made up of proteins that contains carbohydrate moiety (such as hexosamine, fucose, hexose and sialic acid) which covalently attached to polypeptide chain (Nandave, et al., 2005). Each glycoprotein subunit has core part of protein bristling with short side chains of carbohydrates. Several types of glycoproteins are synthesized in mammalian body but in human two main kinds of glycoproteins such as plasma globulins or plasma proteins and second mucus glycoproteins. The protein core of mucus glycoprotein somewhat different from that of plasma glycoproteins. The protein core of mucus glycoproteins consists of high amount of different amino acids such as serine, threonine, aspartic acid, proline and glutamic acid and very less amount of aromatic and sulphur-containing amino acids. While, carbohydrate side chains consists of different types of sugars includes sialic acid, fucose, N- acetylgalactosamine, N- acetyl glucosamine and galactose (Johansson, et al., 2011).
Difference between Plasma glycoproteins and Mucus glycoproteins depicted in following table (Dennis, *et al.*, 1977):

<table>
<thead>
<tr>
<th></th>
<th>Plasma glycoproteins</th>
<th>Mucus glycoproteins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amino acid</strong></td>
<td>High amount of serine, threonine, aspartic acid, proline, glutamic acid</td>
<td>Typical protein</td>
</tr>
<tr>
<td></td>
<td>Less amount of aromatic and sulphur-containing amino acids</td>
<td></td>
</tr>
<tr>
<td><strong>Amount of Carbohydrates</strong></td>
<td>More than 50% carbohydrates</td>
<td>Less than 25% carbohydrates</td>
</tr>
<tr>
<td><strong>Linkage</strong></td>
<td>O-glycosidic N-acetylgalactosamine to serine or threonine</td>
<td>O-glycosidic, N-acetylglicosamine to aspargine</td>
</tr>
<tr>
<td><strong>Mannose content</strong></td>
<td>Very less amount or some time absent</td>
<td>Present</td>
</tr>
<tr>
<td><strong>N-acetylgalactosamine</strong></td>
<td>Present</td>
<td>Very less amount or some time absent</td>
</tr>
</tbody>
</table>

The carbohydrate components are thought to stabilize the glycoprotein molecule and to protect the protein core from digestion by proteolytic enzymes within the digestive tract. The both outer and inner carbohydrates moieties of gastrointestinal tract are played essential role in cell-cell communication, as well as functions of tissues. Such mucus showed antioxidant activities in the gastrointestinal tract as well as they easily pass low molecular weight compounds easily essential in the absorption of various nutrient (Forstner, 1978).

Glycoproteins are the most significant component of plasmamembrane and cell organelles. The sialic acid and neutral substances such hexose, fucose and hexoamine all these components are readily involved in the formation of gel and viscoelastic properties of mucus. Nature of mucus helps in the determination of thickness and turnover rate of mucus secretion (Lukie and Frostner, 1972).
L-fucose (6-deoxy-L-galactose) is a deoxyhexose sugar. The pathogenesis of several diseases like atherosclerosis, ulcer and cancer showed that altered expression of fucosylated oligosaccharides. They are involved in the cell–cell communication process.

Sialic acid is important constituent of most mucosubstances such as glycoprotein and glycolipids. Sialic acid has central importance in the gastrointestinal tract because it protects the mucosal intrinsic factors from proteolytic degradation. Mucilagenous nature of glycoprotein results due to abundant amount of water content. This pronounced binding ability to water due to content of neuraminic acid (Clamp, 1978) in sialic acid.

In addition to goblet cells and enterocyte precursors, the crypts of Lieberkuhn also contain intestinal endocrine cells and Paneth cells. Paneth cells are confined entirely to the crypts and contain dense PAS-positive secretory granules and lysosomes within their cytoplasm (Cheng, 1984; Satoh, 1984). Paneth cells plays important role in mucosal immunity and antimicrobial defense (Ouilette and Selsted, 1996). The endocrine cells for example, enterochmmaffin cells are also confined primarily to the crypts. They secrete both peptide hormones and biogenic amines eg. Vasoactive intestinal peptide, serotonin and somatostatin, substances which are important in gut regulation (Shiner, 1983). The epithelium are separated from the lamina propria by a filamentous matrix called the basal lamina. The lamina propria contains a central lacteal, fenestrated capillary.

- **Functions of Duodenum:** The secretion of the duodenal glands made up of only low amounts of digestive enzymes which is viscous due to the glycoprotein with less alkaline in nature than pancreatic secretion. The secretion has less digestive ability. Alkaline secretion of duodenum involved in the acidic gastric juice neutralization process. The duodenal secretion carried processing of incompletely digested food. It also involved in the digestion of chyme, meanwhile bile from associated gland, pancreatic enzymes mixed with chyme and much of the absorption of water, they shows higher affinity towards electrolytes and nutrients absorption.
v) GASTRIC MUCOSAL DEFENSE MECHANISM:

The gastric mucosal layer provided by the epithelial cells is postulated to act as the ‘First line of defense’ against mucosal injury. This layer of mucous together with the ‘Second line of defense’ a healthy epithelial cells themselves, have been thought to play significant role in defense of the mucosa against injury and ulceration (Lipkin, 1971). Healthy status of gastric mucosa and duodenal mucosa depends on the balanced secretion of gastric juice as well as mucosal resistance factor of stomach and duodenum. The stomach secrets different substances, certain substances primarily secreted into the direct circulation or into the gastric lumen. Such substances include electrolytes (mainly hydrogen), water, intrinsic factor, pepsinogens, and mucus. Among that various factors and components are involved to resist again mucosal injury such processes termed as mucosal defense. The protective action of the mucosal resistance is attributed to neutralizing acid absorption power; inhibit pepsin action (Heatley, 1959) and barrier to the passage of acid or pepsin (Davenport, 1977). Mucosal defense it is a dynamic process it increased when harmful substances implicated in the gastrointestinal tract.

The balance between defensive and offensive factors maintains structural integrity of upper gastrointestinal tract. Several mechanism are involves for maintenance include mucosal blood flow, epidermal growth factors (EGF) cell restitution and renewal, mucous bicarbonate barrier, neural mechanisms and mucosal immune system.

Defensive factors included gastric mucus, pepsin, bicarbonate and prostaglandins.

- **Gastric mucus** – The entire gastrointestinal mucosal lining covered by mucus glycoprotein’s. Mucus glycoproteins (Hiruma-Lima, et al., 2012) is formed by water and glycoproteins which is secreted by mucosal lining of epithelial cells, the mucosal neck cells and submucosal Brunner’s gland. Glycosylated glycoproteins (5%) and water (95%) has major contribution in viscoelastic mucus covering epithelial cells and found in the lumen. Mucus gel formed by the mechanical shearing during digestion and proteolytic
degradation. Mucus or mucosal gel is a first factor of mucosa involved in gastric mucosal defense mechanism. Mucosal gel secreted by the epithelial cells gives protection against various chemical agents (Bora, et al., 2011). They also avoid the risk of epithelial cells from exposure of gastric acid of the stomach and protects the internal lining from various harmful foreign substances such as chemicals (Sturm and Dignass, 2002). Mucus barrier inhibits the gastric acid activity, cytotoxicity of bacteria and different macromolecules and chemical agents (Allen, 1978 and Atuma, 2001). Mucus has capable of acting as antioxidants thus it can decreases the severity of mucosal damage caused by formation of oxygen free radical (Reptto and Llseuy, 2002).

Several functions are carried out by the mucus which significantly involves the cytoprotection, lubrication and mechanical protection to the mucosal cells from the gastric acid escretion from the stomach such as acid, pepsin and other chemical agents. Protective selective barrier of mucous prevents the small quantity of bicarbonate ions from mixing with the bulk of hydrogen ion in the lumen. It controls unidirectional flow of hydrogen ions from the stomach into the duodenal lumen. It played important role in prevention of back diffusion of pepsin and pepsinogen activation. It engaged in the repair and mechanism of superficial mucosal deterioration and also showed antibacterial activity.

- **Pepsin (Pepsinogen)** – Pepsinogen is an inert precursor of the pepsin which is synthesized by chief cells of the stomach. When pepsinogen contacts with hydrochloric, it activate to form active pepsin. Gastrin hormone and vagus nerve starts the release of both pepsinogen and HCl when food is administered.

- **Bicarbonate** – Bicarbonate is secreted by superficial epithelial cell to neutralize the acid present in the of mucosal cells. They raise pH and prevent acid produced damages.

- **Prostaglandins** – Prostaglandins are synthesized by gastric mucosa and play role in gastric epithelial defense mechanism. They helps to recover
gastric injury by its cytoprotective activity via stimulation of bicarbonate and mucus secretion helps in inhibition of hyper acid secretion by parietal cells and enhancement of mucosal blood flow and epithelial cell restitution.

vi) GASTRIC MUCOSAL OFFENSIVE FACTORS:

- Parietal cells of the stomach secrete HCl in response to the acetycholine, gastrin and histamine hormones. Parietal cells of stomach contains specific receptors for binding of acetycholine, gastrin and histamine molecules. The HCl produced by the parietal cells of stomach isotonic in nature. The secretary activity parietal cells associated with these hormones which is important in both gastric and duodenal ulcer.

- Enterochromaffin like (ECL) cells of stomach only involved in the secretion of Histamine. The rate of formation and secretion of HCl by parietal cells is directly related to the amount of Histamine secreted by acetylcholine released from vagus nerve and hormonal gastrin.

- Endocrine cells of the mucosa of gastric antrum and duodenum are takes part in synthesis of gastrin hormone. The main function of gastrin is stimulation of the parietal cell for synthesis of acid.

- Prostaglandins the use of NSAID’S inhibits the mucosal prostaglandins synthesis. Prostaglandins played prominent role in the maintenance of cells structural integrity of both stomach and duodenum they are also involved in the repair mechanism (Johansson and Bergstrom, 1982). It acts as an important gastroprotective factor. It suppresses the parietal cells secretary activity and protects the muocosal cell lining leading to enhance mucus secretion. Increased level of mucus content causes vasodilation of blood vessel network in sub mucosal region.

- Acid produced by NSAID’S induces ulcer formation by following way:
  - Different growth factors are played prominent role in the development, maintenance and control normal mucosal cells integrity.
  - The functions of growth factors are impaired during acidic environment, leads to enhance the rate of mucosal cells necrosis in than superficial damages (Szabo, et al., 2000).
Hyper acidic condition inactivates the mechanism of growth factors, hence they are acid labile.

vii) CONTROL OF GASTRIC ACID SECRETION:

The rate at which parietal cells secrete acid is regulated by hormonal and neural factors that could inhibit or induce the process. The inhibitors include enkephalins, somatostatin, prostaglandins, catecholamines, magnesium and other peptides such as secretin, glucagon, GIP and VIP, whereas the inducers act through gastrin, histamine and acetylcholine. It is thought that the plasma membrane of parietal cells contains receptors for these substances (Feldman, et al., 1983.) Besides the endogenous substances, calcium ions also have a role in regulating gastric acid secretion. Intragastric administration of calcium stimulates gastric acid secretion (Fordtran, 1968) by the parietal cells results into increased gastrin level (Reeder, et al. 1978).The major two aspects that characterize duodenal ulceration include increased rate of acid formation in parietal cells of and normal level of secretion of gastrin and their regulation disturbed (Grossman, 1975).Duodenal ulceration also occur in association with hyperparathyroidism (Frame, and Haubrich,1960) and continuous infusion of histamine secretions (Robert, et al., 1970) all are these factors leads to duodenal ulcer (Szabo, et al., 1985).

Aging is a universal, natural biological process which changes in molecular and cellular structures that disrupt organism’s homeostasis mechanism over the passage of time. As a result, aging leads to progressive decline in metabolic activity and all physiological functions of tissue and impaired regeneration, which cause functional limitations, (Kirkwood and Austad 2000; Hamet and Treblay 2003; Vellai, 2009) imbalanced homeostasis mechanism, increased susceptibility, vulnerability for chronic diseases, disability and mortality (Seals, 2016). Age-associated physiological dysfunctions are a major obstacle for maintaining quality of life in old age (Hanna, 2015).

It is a simple process which is identified by the degeneration of required functions occurs in cell metabolic reactions in all multicellular organisms
The cellular deterioration is the primary effect of aging process (Vellai, 2009). It is influenced by several environmental and epigenetic factors so that, which is thought to be called as dynamic and malleable process (Hamet and Tremblay, 2003). Severity of disorder and diseases are higher at the progression of age. During aging the molecular, biochemical, physiological and structural alterations occurred in the organism resulted into the retardation of growth also, the homeostatic balance of various organs of animal body collapsed (Holiday, 1995). Many evidences reported that various structural and functional changes occurred at the onset of aging such as saturation of high amount of free radicals, increased lipid peroxidation and physiological deterioration seen at molecular and cellular level caused damages in nucleic acids and other macromolecules (Harman, 1972 and Rattan, 1996), decreased number of mature cells, neuronal cells loaded with aged pigment (Ivy, et al., 1984), normal secretary activity of hormones decreased (Rosner and Cristafalo, 1981) protein synthesis and enzyme activity also declined (Ksheerasagar, et al., 2011) the fluidity and permeability of cell membranes has been decreased (McNeil and Steinhardt, 1997): or impaired immunity (Ferguson, et al., 1995). Animal body tissue looses their normal form and functions during aging.

During the aging a decline in tissue regeneration after damage especially observed in the case of skeletal muscle, which loses the ability to repair itself later in life (Grounds, 1998). During aging normal metabolic process of cells generates byproduct that are harmful to genetic material, proteins, lipids results into formation of damages in structural integrity of cell components, also they disrupts mitochondrial oxidative phosphorylation via formation of additional metabolic by-products (Harman, 1972). By the cellular damages and stress, aged cells readily undergo senescence and exhibits age-associated pathological changes through its morphologically appearances and secretory activities (Baker, 2011).

Aging or senescence involves deterioration of the cell morphology and results into alteration or loss of functions of body tissue over time. Aging
disturb the structural, functional organization of distinct organs correlated with
the alteration of oxidative stress of an organism (Rosa, et al., 2005). Oxidative
stress leads to destruction of cells of different tissues and cell components
leading to aging process (Rosa, et al., 2005) such damaged cells and aged cells
replaced by regeneration process. Free radical theory (Harman, 1972) of aging
stated that oxygen derived free radicals are responsible for production of
oxidative stress causes cellular and tissue damages.

viii) MECHANISM OF AGING:

   Many theories has been proposed by the various researchers related to
the mechanism of aging, these are free radical theory aging (Harman, 1972)
free radicals are harmful to cellular components (Semsei, et al., 1991)
generates oxidative stress and alters the cellular defense mechanism it is first
cause of aging (Sohal and Weindruch 1996) leads to forms degenerative effect
during aging (Vertechy, et al., 1989). All theories it has been reported that
aging is multifactorial process (Semsei, 2000) because both extracellular,
intracellular factors and all cellular components equally takes part in aging
process (Sanocka and Kurpisz, 2004). The disease susceptibility is higher in
aging. Different ways changes are occurred at the onset of aging during normal
healthy status. Some common diseases are specific and they are associated at
progression of aging such disorders or diseases are supposed to be age related
diseases.

   In animal body various metabolic processes regulated by different
physiological chemical reactions. Such physiological reactions involves the
losing and gaining of one or more pair of electrons, this process said to be
oxidation or reduction reactions essential for normal metabolism. Different by
products are formed at the time of cellular reactions one of them is release of
free radical (Sanocka and Kurpisz, 2004). Free radical contain more than one
unpaired electron in their outermost shell, such radical does not depends on
other atom their existence is free from all sorts of reaction (Floyd, 1990). Free
radicals are also exogenous environmental contaminants disturbed the cellular
functions and forms free radical. They are involved in the chain reaction for
stability either losing or gaining an electron (Harman, 1972). It played prominent, significant role in healthy status of human and defensive role in several diseases. The aerobic processes and metabolic pathways required more amount of oxygen, carbon and hydrogen substrates to generate energy required for life. During normal aerobic metabolism list amount of electrons are leaked and they directly act on the oxygen atom, the reduction of oxygen molecule forms reactive oxygen species or free radicals (Harman, 1994). Various animal model studies reported that progression of aging caused due to increased cellular oxidative damages leads to high oxidative stress, imbalanced or decreased antioxidant enzyme activity (Rana, et al., 2014).

In aerobic organism metabolism and regulation of cells diminished due to stressful situation leading to generates high amount of free radicals formation. Such reactive oxygen species interfere with the intracellular molecules resulted into peroxidation of lipid molecules.

**Lipid peroxidation (LPO):** Lipid peroxidation is a self-catalytic, boundless and continuous general process responsible for usual death of cells of tissue (Bandhyopadhyay, et al., 1999). It is one of the most important outcome and key indicative of oxidative stress induced by aging. Lipids easily disposed and degraded by the exposure of free radicals results into formation of peroxidation of lipid molecules of bilayer and causes detrimental side effects on cell membrane (Lekyo and Bartosz, 1986). Such changes produced by the action of hydroxyl radical with plasma membrane develops into lipid conjugated radicals include peroxides and hydrocarbon moieties with double bond of carbon. Such highly reactive products that cause oxidative damage (Yoshikawa, et al., 1996). It is a deteriorative reaction that is involved in aging process, cancer and atherosclerosis.

Lipid peroxidation is a chain reaction started by different radicals such as alkoxy, hydroxyl and peroxyl ions. The hydrogen peroxides and superoxide ions both are not involved in this process. The OH (carboxyl) group containing radicals reacts with phospholipids of cell membrane such as polyunsaturated fatty acid moieties (PUFA) results into formation of lipid derived
hydroperoxides (LH). Such product further degraded into two radicals one is peroxyl which acts as reaction starter produce endoperoxides by the cyclic reaction other one is aloxy radical. The endoperoxides acts as precursor of malondialdehyde (MDA) (Draper and Hadley, 1990). Overall reaction end product of lipid peroxidation include harmful substance that is 4- hydroxy-2-nonenal (HNE) and malondialdehyde (MDA). Such end products readily involved in number of diseases (Nordmann, 1992).

Malondialdehyde (MDA) is the prominent aldehyde, toxic end product of lipid peroxidation. Lipid peroxidation process losses membrane fluidity, transport mechanism of ions and cell membrane structural integrity impaired. So that all cellular membrane functions and altered functions of proteins results to denature enzyme catalyzed reactions (Goel, et al., 2004).

On the basis of origin free radicals are of two types one is reactive oxygen species (ROS) and second is reactive nitrogen species (RNS). Reactive oxygen species (ROS) which is further divided into two radicals such as oxygen-centered radicals which include (superoxide anion radical (O$_2^-$), hydroxyl (OH$^-$), peroxyl (ROO$^-$) and alkoxyl (RO$^-$) radicals) and another is oxygen centered non radicals (singlet oxygen (1O$_2$), hydrogen peroxide (H$_2$O$_2$), ozone (O$_3$) and hypochlorous acid (HOCl)). All free radicals are by-products of aerobic metabolism.

- **Superoxide radical (O$_2^-$)**-

Superoxide radical (O$_2^-$) is a reduced form of diatomic oxygen. Superoxide anion radical (O$_2^-$) are generated during aerobic energy transduction process due to oxygen reduction mechanism of electron transport system (ETS) in mitochondria. Superoxide anion formed by one electron added into an oxygen molecule of metabolic processes sometimes oxygen molecule activated due to physical irradiation which is supposed as ‘primary reactive oxygen species’ they react with another molecules via either metal or enzyme catalysed reaction (Valko, et al., 2005) to form ‘secondary reactive oxygen species’ (Miller, et al., 1990). It is the primary product formed by the reduction of oxygen molecule during metabolic processes and which converts into
hydrogen peroxide (H₂O₂) and molecular oxygen (O₂) by dismutation reaction. Superoxide dismutase (SOD) acts as catalyst for Superoxide anion radical (O₂⁻) formation or it may be formed spontaneously (Fridovich, 1986; Halliwell, et al., 1992; Cadenas, 1998). Oxidative enzymes, such as NADPH/NADH oxidase and xanthine oxidase are acts as important source for Superoxide anion radical (O₂⁻) formation.

- **Hydroxyl Radical (−OH⁻)** –

  It is the easily responsive ion, powerful radical neutral form of the hydroxide ion produced during reaction of H₂O₂ and O₂⁻ in the existence of ferrous ions (Fe²⁺). Hydroxyl Radical (.OH⁻) possesses strong reactivity, due to this property it suddenly react with biological molecule. It can attack on biological membranes and cause damages in fatty acids (lipids) initiate lipid peroxidation (LPO) leads to oxidative stress. Such radical are formed in the body by the action of hydrogen peroxide and superoxide anion when there is trace amount of transition metal ions such as copper and iron (Liochev, et al., 2002). The structural bonding of lipid, amino acids and nucleic acids (Harman, 1956; Davies, et al., 2003; Beckman and Ames, 1998) which is breaked by hydroxyl radical (Valko, et al., 2005) results into disturbed activity.

- **Peroxyl and alkoxy radicals:**

  Peroxyl and alkoxy radicals are good oxidizing agents and intermediate of hydroperoxide. These are the reactive derivatives of oxygen molecule involved in metabolic processes of all living cells (De Grey, 2002). They are generated during when the oxygen direct reaction with alkyl radicals, dissociation of peroxides when there is trace amounts of transition metal ions such as copper and iron present, irradiation of UV light, degradation of alkyl peroxides (-ROOH).

- **Hydrogen peroxide (H₂O₂):**

  Hydrogen peroxide is oxygen centered non-reactive oxygen species which are more stable. H₂O₂ which is produced from the superoxide anion by the continuous reduction an oxidation reaction process catalysed by superoxide dismutase enzyme. Other enzymes also have ability to produce H₂O₂ these are
peroxisomal oxidase, glucose oxidase, L-hydroxy acid oxidase xanthine oxidase, as well as NADPH oxidase, fatty acyl oxidase and D-amino acid oxidase (Lin, 1998; Halliwell, et al., 1992). Hydrogen peroxide (H₂O₂) survives under neutral range of body pH and body temperature even though lacking of metal ions due to its most stable property. It has weak oxidizing and reducing property hence which is considered as least reactive molecule as compared to remaining ROS (Mc Cord, 2000). It is harmful by product of cellular metabolic reaction, highly diffusible easily passing through plasma membrane and dissociates into water and oxygen hence it shows limited toxicity (Barbouti, et al., 2002). It also acts as intermediate for most reactive hydroxyl radicals formation due to presence of oxidation of transition metals and super oxide dismutase (Leonard, et al., 2004). It is acts as mediator of aging via the production singlet oxygen (O₂⁻) results into cellular oxidative stress.

- **Singlet oxygen (1O₂):**
  
  Singlet oxygen is a non-radical reactive oxygen species. It is highly reactive for electrons or low ionization energy organic compound. Singlet oxygen originates from hydrogen peroxide (Davies, 2003). It is take part in the process of oxidation and cholesterol degradation of such as LDL and which is fight against malignant cells and they produce resistance to microorganisms (Stief, 2003). It has milder oxidant property among other reactive oxygen species (ROS).

- **Reactive Nitrogen Species (RNS):** Reactive Nitrogen species (RNS) generates nitro oxidative stressed that changes the structure of proteins results into impairment of cellular function (Bergendi, et al., 1999).

- **Nitric oxide (NO):** Nitric oxide is the important signalling molecule containing one unpaired electron involved in the sequential chain reactions include substitution, redox, addition and chain terminating reactions) of the cell. They take place in the presence of enzymes such as nitric oxide synthases (Ghafoourifar and Cadenas, 2005). It plays dual role in both health and disease (Bredt, 1999). Nitric oxide when reacts with water molecule and oxygen leads to produce nitrite ions and nitrate. It plays vital role in many physiological
processes include blood pressure regulation, relaxation of smooth muscles, immune system regulatory mechanism, acting as intracellular signalling molecule by stimulating protein kinases and guanylycyclases. Higher amount of NO’ is thought to involved in gastrointestinal abnormalities, ischemia, stroke, achalasia and congenital hypertrophic pyloric stenosis, etc. disorders (Umamaheshwari, et al., 2015).

- **Nitric dioxide (NO₂)**: The peroxyl radical and NO reacts with each other to forms Nitric oxide. It is responsible for lipid peroxidation reaction by changing the mobile hydrogen atoms to from double bond leading to generates harmful free radicals (Ridnour, et al., 2004).

- **Peroxynitrite (ONOO-)**: Peroxynitrite is a powerful oxidizing agent. It has a same property like hydroxyl radical. It is easily pass through cell membrane hence; it is most harmful to the cells. Onset of inflammation cells produces superoxide and nitric oxide radicals that react together to form tissue toxic peroxynitrite. It also generated at the time of neurological and kidney disorders. Peroxynitrite can cause oxidation of proteins, damages in nucleic acids metabolism and involved in lipid peroxidation resulting in oxidative stress observed in age-related disorders like joint diseases and aging process (Valko, et al., 2005). It also responsible for destruction of tissue results into death of the cells, which further leading to cause various disorder include cardiac disorders, stroke, arthritis, gastrointestinal abnormalities such as inflammatory bowel disease, ischemia-reperfusion injury (Virag, et al., 2003) and neurological disorders.

The levels of free radicals are elevated than antioxidants then oxidative stress arises. The balance between both types free radicals disturbed the antioxidants defense mechanism of cell is lost leads to accumulation of free radicals (Droge, 2002) generates oxidative stress (Thomas and Kalyanaraman, 1997). Reactive oxygen species are constantly produced during energy transduction processes of cell and they are safely trapped by a body antioxidant system (Oslen, et al., 1986).
ix) ROLE OF ANTIOXIDANTS IN AGING:

Antioxidants are substance that decreases the oxidative damage of target molecule or inhibiting the oxidation of other molecule. They are easily reacts with the wondering free radicals. Antioxidants donates own one electrons to them neutralize free radical and stop the carbon-stealing reaction. They are involved in the trapping cellular radicals and prevent cell and tissue damages. Cell produces resistance towards accumulated free radicals via the cellular repair mechanisms, and their antioxidant defense system.

In living cell two intracellular or endogenous enzymatic and extracellular or exogenous non-enzymatic antioxidant defense systems are present. Antioxidants mechanism activated by the development of reactive oxygen species (ROS). Antioxidants exhibits its protective action by stealing catalytic transitions metals, trapping oxygen or lowering the oxygen concentrations, scavenging the hydrogen peroxide and superoxide ions. They also interrupt the chain reaction via free radicals and removing the single oxygen (John and Gutteridge, 1995).

- **Enzymatic / Endogenous Antioxidants:** Several enzymes are important in the antioxidant defense system, because they metabolize reactive oxygen species products and intermediate products. Endogenous antioxidant defenses balance the ROS production by catalytically remove oxidants. Significant endogenous antioxidants include SOD, Catalasae, Reduced glutathione (GSH) and glutathione peroxidase (GPx). All these antioxidants play significant role suppressing the activity of oxidants leading to suppress the oxidative damage (Vile, et al., 1994) and protect the living organisms from oxidants harmful effects.

**Superoxide dismutase (SOD):** SOD is a foremost internally derived antioxidative enzyme present in cytoplasm and mitochondria of all aerobic cells (Johnson and Giulin, 2005). It act as the prime component of defense system acts against reactive oxygen species (ROS) which helps to trap superoxide radicals to $\text{H}_2\text{O}_2$ (Marklund, 1974). SOD are family of metalloproteins. Superoxide dismutase (SOD) safe the organism body against
the deleterious effects of harmful substances such as radicals. In our body system there are 3 kinds of SODs are present: cytosolic Cu-Zn SOD, Cu-Zn SOD in the extracellular space an mitochondrial Mn-SOD

\[
2\text{O}_2^{-} + 2\text{H} \rightarrow \text{H}_2\text{O}_2 + \text{O}_2
\]

SOD plays important role in neutralization of reactive oxygen species (Tamura, et al., 2013). SOD prevents the accumulation of potentially toxic \( \text{O}_2 \) and it transform the most reactive superoxide anion into the reduced form of \( \text{H}_2\text{O}_2 \) (Yoshikawa and Naito, 2002).

**Catalase (CAT):**

Catalase is a prevalent enzyme found in animal body. CAT is a haemoprotein, tetrameric enzyme found especially in peroxisomes of eukaryotic cell (Ighodaroab and Akinloyeb, 2018). That is mainly involved in the transformation of harmful to less reactive harm less substance via acceleration of reaction of hydrogen peroxide into the molecular oxygen as well as water as compared to the other enzyme. The single catalase molecule has highest turnover rate. They have ability to turn millions of hydrogen peroxide molecules converts into water and oxygen molecule per second. It uses \( \text{H}_2\text{O}_2 \) as a substrate for its reaction. In the presence of cytoplasmic hydrogen peroxide activity of catalase enzyme enhanced (Shull, et al, 1991).

**Reduced glutathione (GSH):**

It is a strong, sturdy and tripeptide antioxidant found in the cytoplasmic space of cells. It is present in the form of significant nonprotein thiol compound (NPSH). Thiol (SH) groups present in GSH which is react with hydroxyl radical and hydrogen peroxide and involved in the repair mechanism of tissue damage. With the help of GPx, GSH traps the reactive oxygen species. It interfered in polyunsaturated fatty acids peroxidation reaction and inhibits the peroxidation either acting as coenzyme in tissues (Chatterjee, et al., 1992).

**Non-Enzymatic / Exogenous Antioxidants:**

They are unable to synthesized in our body such antioxidants are phytoantioxidants, vitamin and trace elements. Natural antioxidants such as
vitamin A (retinoids), selenium and carotenoids they shows positive effect against cancer as well as stress related diseases (Demir, et al., 2003). The phytoconstituents such as phenolic and polyphenolic compound such as coumarins, tocopherols, flavonoids, cinnamic acid derivatives and polyfunctional acids also acts as antioxidants. These are found in more or less amount vegetables, fruits, grains, cereals, eggs, meat, legumes and nuts (Donald, 2009).

**Vitamin E (α-tocopherol):**

It is soluble in fat (Malafa, et al., 2002; Songthaveesin, et al., 2004). It played important role in the protect cell membrane from harmful byproducts of metabolic reactions of cell. (Rietjens, et al., 2002; Albanes, et al., 1996; Papas, 1999). Vitamin E and selenium both antioxidants exhibit a positive effect against stress induced gastric ulceration as well as chemically formed erosions (Tariq, et al., 1988).

**Vitamin C:**

Vitamin C is common natural extracellular antioxidant involved in the removal of ROS (Kim and Lee, 2004). It is present in tissue in the form of ascorbic acid associated with GSH in plasma. Vitamin C showed ant carcinogenic properties (Park, 2013).

Body gives response to remove free radicals via endogenous antioxidants. Antioxidants inhibit the production of ROS via free radicals are trapped by breaking the chain reaction or can reduce the concentration of free radicals by giving or loosing hydrogen and an electron leads to decreases lipid peroxidation process and free radical conducted metabolic processes (Repetto and Llesuy, 2002) and protect the human body from several diseases which alters cell function to generates free radical (Dokmeci, et al., 2005) decrease the amount of oxidants associated with whole cell, also prevents ROS activity (Halliwell and Gutteridge, 2007; Erenel, et al., 1993; Chaudiere and Ferrari-Iliou, 1999). Oxidation damages induced by free radicals is ameliorated by the termination or neutralization of free radicals (Halliwell, 1996) via the enzymatic and non enzymatic antioxidants systems.
x) GASTROINTESTINAL TRACT AND AGING:

The gastrointestinal tract is more complex system; it contains different types of cells which performs variety of functions which are needed for normal life processes. Such intestinal cells not only takes part in the process of digestion of food, secretion, assimilation and absorption of essential nutrients, process of removal of nitrogenous waste material via the excretory mechanism of excretion but they are played potent role in the defence system.

Aging alters the structure and function of gastrointestinal tract and digestive glands, such type of changes have positive relationship with the altered homeostatic mechanisms and susceptibility to certain diseases with aging (Geokas, et al., 1985). Diseases are expressed in higher incidence with advancing age, gastrointestinal tract have high rate of cell turnover and continual renewal. Because of its high rate of cell turnover and continual renewal, the mucosa of the gastrointestinal tract (GIT) susceptible to age related disruptions in the normal cell proliferative process leads to altered function that may result in the induction of malnutrition or malabsorption of particular nutrients or greater incidence of gastrointestinal diseases (Majumdar, et al., 1997). Age-related physiological, cellular and molecular alteration in the tract are variable, such changes are accelerated by the extrinsic as well as internal factors in the cells are passed through aging mechanism. The functional activity of gastrointestinal tract changes continuously throughout the life of an animal especially effect of the aging mainly associated with the structural, morphological and secretary alterations in gastrointestinal tract. The morphology and mucosal mass of small intestine of rat changed with advancing age (Raul, et al., 1988 and Holt, et al., 1984).

During normal body state of an organism the oxidants, antioxidants and biomolecules involved all cellular metabolic processes exist in stable and balanced form. Increased production of free radicals disturbs the natural antioxidant defense mechanism results into oxidation and generates cellular impairment (Fucso, et al., 2007). More or fewer changes occurred with aging in oropharyngeal and oesophageal functional activity of gastrointestinal tract
Major changes occur with respect to anatomical point of view, the significant alteration are seen in peristaltic mechanism of oesophagous (Hazzard, et al., 1999) and other changes includes decreased contractile activity, impaired lower esophageal sphincter (Khan, et al., 1997), dilation of esophageal tract. At normal or healthy state of the body the mucosal surface of gastro intestinal tract (GIT) represent as potent largest immunological organ as compared to other system. The gastric mucosal immune response is collapsed with aging (Solana, et al., 2006; Gomez, et al., 2011) may leads to increased susceptibility to various diseases, gut infections and intestinal inflammation (Ogra, 2010) because, much more infections enters into body via gastro-intestinal tract (GIT). Gomez-Pinilla, et al., 2011 studied at progression of aging the meshwork and number interstitial cells of Cajal declined in stomach and colon. The secretary activity of gastric mucosa altered with aging. The gastric mucosal secretary cytoprotective factors or luminal factors such as mucosal prostaglandin level lowered, gastric mucosal bicarbonate output and pH of the lumen decreased while increased rate of parietal cells secretion (Saltzman, et al., 1995 and Khalli, et al., 1998), secretary rate of growth factors (TGF - α and enzyme) leads to altered mucosal repair mechanism.

Among the other parts of gastrointestinal tract (GIT) the small intestine has large surface area it is helpful in digestion, absorption and secretion. Various animals studies states that aging affect the mucosal nutrient uptake capacity and showed region specific changes in small intestine such as proliferation rate of crypts cell enhanced (Saltzman, et al., 1995), atrophy in mucosa of duodenum and jejunum not in the ileum. In prior to aging various diverse effects are seen in large intestine (Ryhammer, et al., 1997; Kagay, et al., 1997 and Khalil, et al., 1998). Previous reports suggested that the height and cell number of duodenal villi not changed but the depth and number of Crypt of Liberkhun increased in old rats (Goodlad and Wright, 1990). Some of the reports concluded that the height of duodenal villi and internal surface area in duodenum of rat were decreased (Drozdowski and Thomson, 2006) but in the duodenum of mice, height of villi gets increased at the onset of aging decreased.
villi height and number of crypts (Martin, *et al.*, 1998). In aged animal the level of the villus surface area and brush border membrane components of intestine decreased but the absorption of some nutrients such as glucose, vitamins continues to increased, whereas absorption of cholesterol and fatty acids decreased (Thomson and Keelan, 1997). Absorption capacity of the intestine changed some time it will decreased prior to enzyme secretion of the enterocyte brush border of mucosal cells. The sub cellular enzyme distribution and enzyme activity impaired with senescence such alterations may control under the hormones (Balogh and Boland, 2000). The secretion of mucus as well as bicarbonates decreased with aging (Salles, 2009). Specific enzymes activity of mucosal tissues such as alkaline phosphatase, sucrase and maltase are higher at the progression of age (Jang, *et al.*, 2000). In rat early age stage 1-35 days the number of villi are less while other intestinal parameters increased but after 35 days rate becomes vice-versa (Vigueras, *et al.*, 1999). Glucose absorption in young and old aged people increased at progression of ageing (Drozdowski and Thomson 2006; Thomson, 2009). Alteration occurred in the large intestine with respect to impaired growth rate of mucosal cells, decreased metabolism and reduced immune response. The several common disorders and diseases such as diverticulitis, irritable bowel syndrome and colon cancer observed in colon in the normal aging. During normal aging process colonic mucosal crypts cell proliferation rate is higher, it becomes two folds because colonic tissue easily susceptible to carcinogens leads higher rate of tumor formation in colon.

During the aging body system exhibited different pattern of alterations with respect to reduced physiological activity, structural and functional characteristic changes in cell, tissue and organ. The primary target molecules damaged by the free radicals are deoxyribose nucleic acid, proteins and lipids. Free radicals attacked over DNA disturb the cellular repair mechanism results into impaired cellular metabolism, cell division process promote cells to form malignancy (Floyd, 1990). Impaired cellular metabolism provokes decreased
protein synthesis (Rattan, 1996) in the neural cells with aging. Certain reports stated that the enzyme synthesis decreases with age.

xi) GASTRIC MUCOSAL AND OXIDATIVE STRESS:

Gastric mucosa is an essential significant cell protective substance secreted by the gastric mucosal cells. It consists of a viscoelastic, sticky and watery gel which is composed by 5 % glycoproteins and 95 % water content cover the complete gastrointestinal mucosal layer. Mucosa has ability to act as an antioxidant and helps to suppress mucosal erosion caused by oxygen free radicals (Penissi and Piezzi, 1999). A decreased mucus secretion in the mucosal cells that cells easily susceptible to toxic effects produced by hyperacidic environment (Szabo, et al., 1981), cold restraint and drugs stress (Parmar and Jagruthi, 1993). Stress induced free radicals acts on surface of epithelial cells at same time luminal intracellular mucus prevent and protect the mucosal cells (Seno, et al., 1995). The reactive oxygen species are formed intracellularly in gastric mucosa by auto oxidation, enzymatic reactions (enzymes involved in the generation of ROS are cytochrome p450, oxides, peroxides, lipoxygenases and dehydrogenases) also from both endogenous compounds and xenobiotics.

xii) DRUGS USED TO CURE GASTRO-DUODENAL ULCER:

Peptic ulcer disaease caused by various factors depends on those causative agents different synthetic drugs are widely used to cure both types of peptic ulcers. Which includes antibiotics , various cytoprotective agents, Histamine (H₂) receptor antagonist , antisecretary, Proton Pump Inhibitors and acid neutralizing components such as antacids.

- **Non-Specific control Measures**: This nonspecific control measures plays significant role in the healing and treatment of Peptic Ulcer Disease (PUD). Following are the non specific measures in the Peptic Ulcer Disease (PUD) such as -

- **Avoidance of Smoking**: Smoking increases the susceptibility to various acute and chronic diseases. Smoking delays the ulcer healing capacity in patients (Palmer and Penman, 1999). It increases the incidence and risk of ulcer via impairing the ulcer healing mechanism.
• **Stress and anxiety Management:** Stress is the high risk factor in many acute and chronic diseases. Stress accelerates the ulcer severity it acts as barrier in ulcer healing process (Cho, *et al.*, 1992). Exercise plays vital role to relieve stress via relasing hormones and chemicals such as endorphins and deacreasing the corticosteroid hormone level (Walsh, 1992) by stimulating the anti-anxiety effects. Exercise decreases the body weight, promotes the muscle gain and improves the physical fitness to maintain good health.

• **Avoidance of Alcohol Consumption:** Drinking of alcohol causes gastritis, heartburn and ulcer by increasing the acidic level in the stomach. The Alcohollowers the immune system and affects the healing mechanism during ulcer (Palmer and Penman, 1999).

• **Specific control Measures:** Various factors are involved in the specific control measures but they exhibited more or less its side effects (Barrowwan and Pfeiffer, 1992). Hence, no single agent exhibits complete healing activity without its side effects (David, 1998). Hence many agents are involved in the Specific control Measures they are -

  • **Antacids:** Antacids are widely used from many yeas to get relief from ulcer. They neutralize the gastric acid secretion by their alkaline nature via lowering the corrosive action of acid and relieving the pain (Mc Quaid, 2004). Neutralization of acid decreases the peptic activity and maintain the pH level near to the alkaline condition (Arthur and John, 2000). Antacids strenthen the mucosal defensive mechanism by increasing prostaglandin secretion of the mucoal cells (David, 1998 and Mc Quaid, 2004).

  • **Cytoprotective agents:**

    A variety of cytoprotective agents are used for lowers the severity and recurrence of peptic ulcer. These are involved in the protection of mucosal cells of the stomach and intestine and they gives protection against corrosive effect of gastric acid. They helps to strengthen the gastric and duodenal defenses mechanism (Venkatanganna, *et al.*, 1998). They maintain natural mucous barrier by reducing damage and reduces the pain from the ulcer.
Cytoprotective agents are mainly the prostaglandins analogs, which suppresses the gastiric acid production by directly acts on parietal cells of stomach and helps to protect stomach and duodenum from ulcer. Its available in the tablet and suspension form include Misoprostol, Sucralfate, bismuth subcitrate. They are available in both chelate and complex form. They coat the mucous lining of ulcerated surface results into formation complex with proteins of wall lining and promotes ulcer healing. The PGE1 and PGE2 PGI are mostly secreted by the gastric mucosal cells. Misoprostol is a PGE1 analog, which is used against NSAIDs, induced ulcer (Collins, 1990) while PGE2 protects the stomach corrosive action of gastric acids, pepsin, NSAIDs and alcohol (Pennington, 1985).

Sucralfate undergoes polymerization at acidic pH and forms the viscous and demulcent (McCarthy, 1999) gel like coating over the ulcer area. Sucralfate stimulates prostaglndins secretion and epidermal growth factor production also involved in the pepsin adsorption (McCarthy, 1999). Such analogs suppresses the acid secretion results to stimulates bicorbominate and mucus secretion and improves the blood flow (Ibu, et al., 1994).

- Antibiotics / Eradication of Helicobacter pylori:

  The small spindle spiral shaped gram negative bacteria that is H. pylori are prevalently responsible for ulcer production. The ulcer caused by H. pylori controlled by here drugs with 2-3 antibiotics combined with Proton pump inhibitors (PPIs) that drugs kill the bacteria (William, et al., 2017) and reduce the infection by suppressing acid secretion and protect the stomach (Walsh and Peterson, 1995). Most common antibiotics used in the treatment of H. pylori amoxicillin, metronidazole, Claritromycin, and tetracycline. (Romano and Cuomo, 2004).

- Proton Pump Inhibitors (PPIs):

  Proton Pump Inhibitors (PPIs) directly reduces the gastirc acid secretion by blocking the H⁺K⁺ATP-ase proton pump these are present in the of the parietal cells which is responsible for acid secretion (Lindberg, et al., 1990). Such H⁺K⁺ATP-ase enzyme inhibitors suppresses the acid secretion and
promotes ulcer healing in peptic ulcer (Mc Tavish et al., 1991). They showed specific activity due to their selective effect on \( H^+K^+ATP \)-ase, also form active metabollite in acidic envioronment include Lansoprazole and Omeprazole (Barradell, et al., 1992). They are available in capsule, tablets and injection form such as esomeprazole, pantoprazole lansoprazole, rabeprazole, and aripiprazole. PPIs showed direct antimicrobial effects in vitro on \( H \) pylori infection.

- **Histamine H\(_2\)-Receptor Antagonists:**

  \( H_2 \) block receptors stop the action of hisatmine of parietal cells \( H_2 \) receptors of the stomach \( H_2 \) block receptors lowers the parietal cell stimulation for acid secretion ultimately results into decrease in the acid production. They are cimetidine, ranitidine and Famotidine.

  In spite of all these treatments yet ulcers are not cure successfully with these drugs. Several medicines showed adverse effects hence, the treatment of ulcer has been a challenge to the researchers. Now there is trend and there is trial to use plant drugs to cure peptic ulcer.

**xiii) HERBAL PRODUCTS USED TO CURE GASTRO-DUODENAL ULCER:**

Now days, concentration on medicinal plant research enhanced all over the world. Number of researchers has collected evidences regarding the medicinal plants are primarily and regularly used in the ancient traditional herbal products system. In all culture especially tribal peoples many plants and their products directly used as remedy for various injuries, disorder and diseases. Pharmaceutical plants played a significant role to cure peoples from acute and chronic diseases many years ago. Many plants possess different medicinal properties frequently used in developing countries for curing chronic diseases. Herbal plant extract contains various compounds which unable to react with molecular targets. They are easily absorbable by human body Kanniappan, et al., 2018). For centuries; numerous plants used as key ingredients for dietary supplements. The large number of drugs is originated from the medicinal plants (Tripathy and Afrin, 2016).
Various researchers have been reported that several plants showed various medicinal properties such as antiulcer and antioxidant.

**Patola churna: Trichosanthes cucumerina** linn. is constantly applied to cure several alimentary canal and liver disorder. The **Patola churna** is renounced ayurvedic formulation of *Trichosanthes cucumerina*. The 50% ethanolic extract of *Trichosanthes cucumerina* formulation exhibited significant anti-ulcer activity against Cys HCl induced duodenal ulcer as well as ethanol, aspirin and pyrolus ligion induced gastric ulcer in rat (Galani, *et al.*, 2011).

**Curcuma longa L.** is a traditionally used medicinal plant product. Turmeric is widely used as homemade or herbal home made remedy against various disorders, wounds, acute and chronic diseases. The plant exhibited different pharmacological activities such as significant anti-ulcer activity (Savaringal and Sanalkumar, 2018) antibacterial, antioxidant, antifungal, anti-inflammatory and rheumatism (Tuorkey and Karolin 2009). Methanolic extract of Turmeric possesses potent antioxidant activity also showed antiulcer activity against experimentally induced ulcer by its cell protective action (Rafatollah and Tariq, 1990).

Sevamathy, *et al.*, (2010) proved that hydro alcoholic extract of *Swertia chirayita* possess antiulcer activity by its herbal formulation used in drugs which bears cytoprotective and antisecretary agents by accessing enzymatic antioxidant status.

**Phyllanthus amarus** extract showed prominent effect on secretory activity of gastric mucosa and it maintains balance between them. Plants cure gastric lesions induced by ethanol (Shokunbi and Odetola, 2008).

**Heliotropicum(linn)** its deciduous medicinal plant. The plant contains important compounds such as alkaloids, flavonoids, phenolics, polyesters and tannins all are used against number of gastrointestinal disorders. The ethanolic extract (Shenoy, *et al.*,2011) and herbal extract showed ulcer healing activity by balancing secretion, reducing lesions and decreasing stress in both experimental and drug induced ulcer model (Nethaji, *et al.*,2013).
Sweet potato (*Ipomoea batatas*) contains reliable ulcer healing effect correlated with trapping free radical and suppresses the lipid peroxidation (LPO) process via phytoconstituent against stress induced and drug induced ulcer in rat (Panda, and Sonkamble, 2012).

*Ocimum sanctum* (*Holi basil or Tulasi*) belonging to the family *Labiatae*. It is traditionally used to cure everyday ailments skin disorders, also possesses anti-inflammatory and antiulcer activity (Sanjivekumar, 2018). The sanctum fixed oil is an naturally originated drugs which having valuable antiulcer activity (Singh, *et al.*, 1999) aqueous extract gives protection against ethanol induced gastric ulceration by protecting gastric mucosal damages.

*Glycyrrhiza glabra* L. belong to family *Fabaceae*. Plant has ancient medicinal use in Ayurveda. It showed antibacterial as well as ulcer healing activity against *H. pylori* induced peptic ulcer (Rahnama, *et al.*, 2013).

Though several drugs have been used since long to cure gastroduodenal ulcer yet not satisfactory results for this to cure severe ulcers. The treatment of ulcer primarily concentrated on lowers the adverse effects of increased concentration of acid content. The phytoconstituent of *Aloe vera* contains potent cytoprotective agents for all aspects of disorders.

Phyto-constituents of plants acts as precursor for the synthesis curative effect of herbal drugs (Abolaji., *et al.*, 2007). Recently the use of herbal plants increased for extraction and development of several drugs, as the basis for maintenance of good health and life expectancy (UNESCO, 1998). *Aloe vera* is most significant plant used in modern traditional system and it has many therapeutic properties (Grindlay, *et al.*, 1986). From the ancient times *Aloe vera* are continuously used to cure the several diseases such as ulcers (Surjushe, *et al.*, 2008).

*Aloe vera* (*Aloe barbadensis*): The *Aloe vera* with origins in the eastern and southern regions of Africa is also known as *Aloe barbadensis* and *Aloe vera ferox* (Cheney, 1970).
Classification:

Kingdom – Plantae
Order- Asparagales
Family- Liliaceae (Xanthorrhoeaceae)
Genus- Aloe
Species – Aloe vera (A.barbdensis)

The scientific name of Aloe vera plant is Aloe barbadensis. It belongs to Asphodelaceae (Liliaceae) family but recently it included into Xanthorrhoeaceae family and it a shrubby or arboescent, perennial, xerophytic, succulent, pea-green colour plant. The plant aloe vera with origins in the eastern and southern regions of Africa is also known as Aloe barbadensis and Aloe vera ferox (Chenny, 1970). It was originally classified in the family lilliaceae, but according to Reynolds, 1950 it has now been designated its own family, known as aloaceae (Wallander and Albert, 2000). Aloe vera well adapted to arid and semi-arid environment for their growth and development. The flowers appears bright red orange and are arranged in an erect position with terminal spikes in candle-shaped while the capsules contain numerous angular seeds. Aloe vera does not like crowded roots and the use of standard potting soil mixed with sharp sand will help the plant growth (Johnson, 1999 and Leffers, et al., 2003).When grown under low light intensity, the pale green. Aloe vera tolerable to dry air and requires 21°C temp.during day time and night.
xiv) BOTANICAL DISTRIBUTION:

The yet origin of Aloe vera is not firm but its native to North Africa, the mediterranean regions of southern Europe (Carter, 2011). Now days it is found to be cultivated throughout the West Indies, tropical America and in the tropics in general (Ross, 1999). The Aloe vera plant is short stemmed or entirely stems less succulent plant (Ross, 1999). The leaves fleshy, grayish-green and thick with a brownish tinge when they are young and can grow to be 20-60 cm long and 6-7 cm wide at the base.

• **Structural Composition of Aloe vera leaf:**

The leaf of Aloe vera plant consist of two parts- an outer most green colored rind having vascular bundle sheath and inner it contains colorless parenchymal cells bearing pale yellow aloe gel (Hamman, 2008). The plant Aloe vera being a cactus plant contains up to 80% water having pH near about 4.5. The Aloe vera gel contains upto 99.5% water with an average pH 4.5 and 0.5-1% solid material present (Hamman, 2008). The two types secretions by aloe leaves- one is a bitter reddish yellow juice present in the pericyclic cells located under the strongly cutinized epidermis of the leaves while other exudates in the inner central zone (Parenchyma) of the leaf which is watery, mucilaginous or gel produced by the thin walled tubular cells which also called pulp or gel or mucilaginous substance that is viscous clear watery transparent liquid (Capasso and Ganginella, 1997; Naveen, et al., 2013). The remaining 0.5 to 1% solid material consists of a polysaccharides, water soluble or fat soluble vitamins, phenolic compounds minerals, enzymes and organic acids (Mahattanadul, 1995).

• **Chemical constituents of Aloe vera:**

Aloe vera predominantly rich in 75 active potent phyconstituents (Shelton, 1991). The Aloe vera is miracle plant which is a rich source supplementary substances required for body building to maintain healthy normal status of body (Olariu, 2009). The many health benefits of Aloe vera have been attributed to its bioactive constituents found in the gel of the leaves (Hamman, 2008). Aloe barbadensis Miller, commonly identified as Aloe vera,
it has near about 420 species. *Aloe barbadensis* (family: Aloaceae or Xanthorrhoeaceae) is a naturally used cosmetics to prepare herbal products. Number of drugs and medicines a derived from the *Aloe vera* plant. From many centuries *Aloe vera* plant applied in many health related problems, other medicinal and skin, beauty enhancing properties because of its tremendous potent bioactive compounds such as amino acids, enzymes, minerals, anthraquinones, vitamins, lignin, saponins, sterols, sugars and polysaccharides (Bozzi, et al., 2007).

The some constituents of *Aloe vera* have similar biological activities to amino acids, Vitamin C, polysaccharides, growth factors (Davis, et al., 1994), calcium, zinc, glucose, lignin, saponins (Atherton, 1998). *Aloe vera* also contains several potentially bioactive compound that is chemical compound such as anthraquinones, salicylates, mangnesium lactate, acemannan, lupeol, campestrol, β-sistosterol, γ-linolenic acid, alectin A, resins and chromederivative (Hamman, 2008). Bioactive compounds have diverse chemical structures and properties obtained from leaves.

![Chemical Constituents of Aloe Vera Plant](image-url)
The aloe parenchyma tissue or pulp contains lipids, enzymes, vitamins, proteins, amino acids, small organic and inorganic compounds with different carbohydrates (Ni and Tizard, 2004; Reynolds, 2004). Many researchers stated that polysaccharides present in the Aloe vera gel have medicinal, health restorative properties includes immune stimulation, anti-inflammatory effects, hemopoietic cells stimulating, wound healing, radiation caused damage repair mechanism, anti-bacterial, anti-viral, anti-fungal, anti-diabetic, anti-malignant and antioxidant activities (Ni and Tizard, 2004; Feily and Namazi, 2009; Jaradat, 2005; Pawar and Pawar, 2011; Reynolds and Dweek, 1999).

Bioactive chemical Components present in Aloe vera leaves (Hamman, 2008; Josephs and Raj, 2010) listed in the table below and described in more detailed below:

<table>
<thead>
<tr>
<th>Bioactive chemical components of Aloe vera</th>
<th>Derivatives of Bioactive chemical components of Aloe vera</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthraquinones</td>
<td>Aloetic-acid, aloe-emodin Aloin both A, B, emodin, chromones</td>
</tr>
<tr>
<td>Enzymes</td>
<td>Alkaline phosphate, amylase, carboxypeptidase, catalase, lipase</td>
</tr>
<tr>
<td>Vitamins</td>
<td>Thiamine, Riboflavin, choline, β-carotene, B6, B12</td>
</tr>
<tr>
<td>Proteins</td>
<td>Lectins, lectin-like substances</td>
</tr>
<tr>
<td>Polysaccharides</td>
<td>Mannan, acetylated mannan, glucomannan, galactan, cellulose, pectic substance</td>
</tr>
<tr>
<td>Monosaccharides</td>
<td>Mannose, aldopentose, glucose, L-rhamnose</td>
</tr>
</tbody>
</table>

- **Anthraquinones**: Aloe vera consists of free anthraquinones and their derivative such as anthranol, aloe emodin, aloin A and B all together called as barbaloin, iosbarbalion, anthron–c-glycosides chromones and esters of cinnamic acid (Sushen, et al., 2017). They all are phenolic compounds found in the sap of the plant traditionally known as laxatives. These compounds
play an important role in absorption from the gut. Aloein and emodin exerts antibacterial and analgesic effects (Chung, et al., 1997; Joseph and Raj, 2010). In large amount anthraquinones exerts a powerful purgative effect, but in the small quantities they do not exerts their purgative effect, they aid in absorptive processes in the gastrointestinal tract are potent antimicrobial agents (Kumar and Yadav, 2014).

- **Enzymes:** *Aloe vera* contains lipases and proteases which help in digestion by breaking down fats and sugars (Fermenia, et al., 1999). It also contains bradykinase and produces amatory and analgesic effect. It also stimulates the immune system. (Reuter, et al., 2008)

- **Vitamins:** It possess vitamin A (i.e. Beta carotene), ascorbic acid and tocopherol which are anti-inflammatory, riboflavin, thiamine, niacin and even traces B₁₂, folate and choline (Yaron, 1991 and Matsuda, et al., 2008).

- **Minerals:** *Aloe vera* contains significant amount of minerals including manganese, copper, calcium and iron. It also contains antioxidant such as selenium (Zang, 2006).

- **Sugars (Monosaccharide and polysaccharides):** The mucilage layers of the *Aloe vera* plant contain sugars. It mainly consists of both mono and polysaccharides such as acetylated glucomannan including the long chain of sugars involving glucose and mannose. (Hart, et al., 2009). The other polysaccharides are such as arabinose rhamnogalactan, galactans, glucogalactomanan, malonyl glucans and glucornic acid.

- **Fatty acids:** It consists of four plant steroids, campesterol, β-sisterol, lupeol and cholesterol. Three of them have anti-inflammatory action but the lupeol has antiseptic and analgesic properties.

- **Hormones:** Gibberellins and Auxins are present it showed wound healing anti-inflammatory response.

- **Polysaccharides:** 0.015% Aloeroid present in the crude of aloe vera.

- **Miscellaneous compounds:** Other substances like 10-12 human required amino acids and also contains 7-8 essential amino acids. Salicylic acid exhibited antibacterial and anti-inflammatory properties. Lignin helps in the
easily penetration of components in to the skin. Saponin occupies 3% part of the gel that has cleansing and antiseptic properties.

xv) REVIEW OF THE LITERATURE:

The review has been compiled on the basis of available research data on Aloe vera plant relevant to our study which aims antiulcer and antioxidant activity in aged mice.

- **Antitumor activity or effects:**

  Polysaccharides of the Aloe vera gel such acemannan have anticancer effects. The chemicals contained in Aloe vera extract such as lectins, arginine, germanium and beta carotene has powerful antitumor and immune regulating response. They are helpful to inhibit the growth of cancerous cell and enhanced the number of lymphocytes through the stimulation of immunological cells such especially macrophages which destroy the cancerous and microbial cells (especially leukemia) (Amusan, et al., 2002). Aloe emodin fight against human cancer cells and exhibits anti malignant properties (Yu, et al., 2012).

- **Wound healing property:**

  Aloe vera shows the very effective and fundamental use in treatment of wound healing. Several studies have shown that Aloe vera is effective in the healing of various kinds of skin wound and burns including the wound incision, repair mechanism after surgery (Heggers, et al., 1996). Aloe gel has the wound healing activity by making the wound moist, via enhancing epithelial cell migration rate and stimulation of connective tissue such as collagen as well as fibroblast synthesis activity in vitro and in vivo leads to anti-inflammatory activity. (Heggers, et al., 1996; Moon, et al., 1999). Aloe vera leaf pulp showed higher and good wound healing effects than synthetic drug. Aloe vera also stimulates the growth of epithelial cell results to induce lectin like similar to skin wound healing mechanism (Arnold, et al., 2002). Choi et al., 2001 studied via the less content of glycoprotein of Aloe vera that boosted wound healing in human keratinocytes monolayer also showed increased rate of cell multiplication in nude mice. Polysaccharides contents from fresh Aloe vera have been found to stimulates the synthesize tumor necrosis factor alpha (TNF-
α) by the immune cells which is helpful in the production of new tissue. *Aloe vera* contains secondary metabolites such as gibberellins and glucomannans both acts with fibroblast receptors leads to enhance their activity and cell growth that helps to elevates collagen synthesis improves wound healing of dermal tissues (Chithra, *et al.*, 1998).

- **Anti-inflammatory effects:**

  Body gives positive response against injury which is represented via the inflammation, which is characterized by swelling, pin, redness, heat and loss function. Some evidences suggested that *Aloe vera* has anti-inflammatory effects when it was used topically (Reuter, *et al.*, 2008). The mannose 6-phosphate has anti-inflammatory activity which is similar to the acetylated mannan in *Aloe vera* gel. The inhibition of the biosynthetic pathways of prostaglandins is through active steroids like compound present in *aloe vera* gel reduces inflammation (Reuter, *et al.*, 2008). *Aloe vera* activates anti-inflammatory activity via the archidonic acid pathways via cyclooxygenase. The Aloe plant anti-inflammatory response in rats with carrageen an induced arthritis (Davis, *et al.*, 1992).

  The *Aloe vera* has cardioprotective activity by increasing coronary blood flow and myocardial force of contraction via secretion leads vasodilation (Sadhana, *et al.*, 2013).

- **Antidiabetic effects:**

  Several studies had suggested that the *Aloe vera* played very important role in treatment of diabetes mellitus. *Aloe vera* gel reduces circulating serum sugar level in an obese mice model (Kim, *et al.*, 2007). It also displayed anti-hyperglycemic response by decreasing the level of fasting blood sugar (Boudreau, 2006; Panda, 2000; Tanaka, *et al.*, 2006). It capable of exhibit antibiotic properties because of presence of bioactive components lectins mannans and anthraquinones (Can, *et al.*, 2004). *Aloe vera* leaf pulp decrease the blood glucose level in Type –II diabetes induced by streptozotocin in neonatal rats (Can, *et al.*, 2004). Similar positive effects also seen in streptozotocin induced type –I diabetic rats by reducing blood glucose, hepatic
transaminase, plasma and tissue cholesterol, lipid level significantly increased (Ghannam, et al., 1986; Hamman, 2008).

- **Antioxidant activity:**

  The leaves and flowers of *Aloe vera* contains important and beneficial compounds which are rich in vitamin A, vitamin E, flavonoids, vitamin C and tannins having antioxidant activity (Botes, et al., 2008) that helps to increases resistance capacity of body against free radicals (Litita and Timothy, 2002; Yazdani, et al., 2006) also involved in the scavenge the nitric oxide and free radicals (Saini, et al, 2011). *Aloe vera* contain high amount of flavonoids and polyphenol content is associated with significant antioxidant activity (Keyhanian and Sthal-Biskup, 2007). Polysaccharides found in the *Aloe vera* exhibits potent antioxidant properties (Kang, et al, 2014) that stimulates the fibroblast cells to synthesize significant amount of collagen and elastin they are responsible for maintain the moisture in the skin, which showed antiaging property of *Aloe vera* (West and Zhu., 2003). Aloin A and B, anthraquionones are associated with the laxative properties. Roberts and Travis.,1995 reported *Aloe vera* protect the skin against injury,it an antioxidant property of *Aloe vera* gel in response to restoration of tissue getting damaged. Glutathione peroxidase activity, Super oxide dismutase enzyme activity and phenolic derived antioxidant of *Aloe vera* gel which is reason for the antioxidant effects. *Aloe vera* contains plethora of phytoconstituents among that glucomannan, flavonoids, minerals and tannic acids have to reduce oxidative stress induced in rat (Anilkumar, et al., 2010).

  Kaur and Kapoor, 2001 formulated that *Aloe vera* possesses natural antioxidant properties by trapping the free radicals and suppresses the progression of various chronic diseases. Similarly, Pengseng, et al., 2010 reported that the organic compounds such as vitamins C.E.,phenolic compounds with some pigments contributed antioxidant activity of *Aloe vera*.

- **ANTIULCER ACTIVITY:**

  *Aloe vera* predominantly employed in the treatment of digestive system disorders (Leffer, et al., 2003). The antiulcer activities of *Aloe vera* has been
contributed by its different mechanisms which are stimulation of mucus anti-inflammatory properties, healing effects and gastric acid regulation (Suviatay, et al., 2004).

*Aloe vera* showed antibacterial activity acting against *H. pyroli* which is causative agent of stomach ulcer (Maharajan, et al, 2010). Narayanan and Prabhu, 2017 also reported in vivo and invitro antibacterial and ulcer protective properties of *Aloe vera* against *H. pyroli*.

Tara, et al., 2016 suggested that washed fresh *Aloe vera* gel reduced the ulcer sensitivity then unwashed gel, the latex of *Aloe vera* showed higher ulcer protective activity in ethanol and indomethacin induced gastric ulcer.

*Aloe vera* extracts inhibits acid secretion via the presence of phytoconstituent lectin (Ni, et al., 2004). Lectin suppresses the aminopyrine uptake by acid producing cells, helps to reduce hyper acid synthesis by directly attacked on parietal cells of stomach. *Aloe vera* had preventive effects and exhibits protective role against stress induced gastritis (Teradaira, et al., 1993; Suviatay, et al., 1997; Wang, et al., 1998; Yusuf, et al., 2004) and aspirin induced ulcer in rat (Maze, et al., 1997).

*Aloe vera* has also been shown to cure gastric ulcers in rats and humans by the mechanism which may include antioxidant and immune suppressive effects. *Aloe vera contains* aloe emodin gives laxative and purgative properties to aloe extract and glycoprotein Aloctin A suppressed the indomethacin induced gastric ulcers in rats (Ali Esmail Al-Snafi., 2015).

The low molecular weight gel fraction of *Aloe vera* (IgfAV) showed gastroprotective effect by regulation of matrix metalloproteinase-9 inhibitory activity in oxidative stress in alcohol induced gastric erosion in tissue (Chul-Hong, et al., 2017). Increased acid and pepsin secretion in gastric tissue pathogenesis include hemorrhagic plaques in eroded area (Park Heo, et al., 2011; Chul-Hong, et al., 2017) restored by *Aloe vera* both in alcohol and histamine induced ulceration. Pharmacological active compounds of *Aloe vera* reduces the oxidative stress generated by NSAIDs in rats (Borra, et al., 2011) also showed cold restraint and ethanol induced ulceration (Koo, 1994). The
crude extract of *Aloe vera* enhances the mucous resistance; stimulate the cell activity to produce gastric mucus results into inhibition of secretion of acid producing cells (Umar and Shehu, 2016). The supplementation of *Aloe vera* gel along with orange carrot nectar against microbes (Mansour, *et al*., 2014) also, GC-MS analyzed lyophilized *aloe gel* and ethanolic gel extract showed antioxidant and antibacterial activity (Barandozi., 2013). Decreased leukocyte attachment and the level of tumor necrotic factor-α (TNF-α) in swelled tissue leads to anti-inflammatory also, enhancing the cytokine-IL10 activity followed antiulcer property (Eamlamnam, *et al*., 2006).

*Aloe vera* showed antisecretory activity against histamine induced hypersecretion in rat. Histamine considered as key component in the formation of gastric and duodenal ulceration. Increased histamine activity leads to hypersecretion of acid, *Aloe vera* blocks the H₂ receptors of histamine and reduced the acid secretion (Suvitayat, *et al*., 2004).

Kallaya, *et al*., (2006) stated *Aloe vera* repaired microcirculatory alteration of gastric lining, level of cytokine and ulcer healing by epithelial cell proliferation, increasing rate of prostaglandin synthesis, increasing angiogenesis. The TNF-α and leukocyte endothelial interaction results into formation of inflammation which is repaired by reducing vasoconstriction and improving gastric mucosal capillaries circulation. Similarly, Keshavarzi, *et al*., 2014 reported gastric acid output inhibitory action of *Aloe vera* against acetic acid induced ulcer.

Reddy, *et al*., (2016) found that significant suppression of hemorrhagic lesions in gastric ulcer restored gastric mucosal normal structure due to formulation of *Aloe vera* and *Liquorice* relevant to std.drug omeprazole in aspirin induced ulcer. *Aloe vera* boosts the mucosal defense mechanism by stimulating prostaglandins synthesis.

Borra, *et al*., 2011; Umar and Shehu, 2016 reported that *Aloe vera* has gastric acid reducing capacity similar to synthetic drug. *Aloe vera* crude extract directly acts on parietal cell to inhibit acid secretion and cytoprotective action via enhanced mucosal integrity.
Saini, *et al.*, 2011 exhibited ethanolic extract gives protection of DNA from radiation induced DNA damages. *Aloe vera* has high amount vitamins, flavonoids; miscellaneous compounds are involved in protective mechanism.

Mahattandul, 1995 stated that *Aloe vera* efficacious as against HCl induced gastric lesion in rat. Similarly, Khuje and Hulke, 2017 studied consumption of *Aloe vera* pulp and *Holy basil* leaves helpful in the reduction of aphthous ulcer by its natural antiulcer properties.

Naveen, *et al.*, 2013 exhibited aloe extract stimulates the microcirculation, repaired altered mucus secretion, inhibited acid secretion mediated by histamine, increased mucosal cell motility enhances mucus content in stress induced, endomethacin and pylorus ligation induced ulcer.

**xvi) CHOICE OF THE PLANT ALOE VERA:**

Numbers of the reasons have been given by the various researchers regarding the increased use of medicinal plants against various disease, disorders and therapies. They are more effective, superior than synthetic products due to the presence of active ingredients support to enhance biological activities. The *Aloe vera* is renowned medicinal plant for its potent curative activities (Radha and Laxmipriya, 2015). Several researches concluded that *Aloe vera* gel is rich in phyto-nutrients, the use of antioxidant rich diet lowers the risk of diseases at old age (Genkinger, *et al.*, 2004), though aloe gel was significant applied for treating ulcer-induced inflammation from ancient time however, no efforts have been made against to curing a gastroduodenal ulcers in old people and animal using *Aloe vera* gel. Progression of aging the natural /inborn antioxidant defense system is collapsed and body gradually weakens (Tsai, 2000). During aging is a decline in tissue regeneration capacity, declined cell renewal mechanism of gastro-intestinal tract (GIT) leads to decreased mucus and bicarbonate secretion. The gastrointestinal immune response is collapsed in aging; may leads to higher susceptibility towards GIT abnormalities, infection and also swelling unable to recover the normal gut functions (Tsai, 2000).
In the present work our interest is to study the possible interaction of aloe gel with gastro-intestinal tract (GIT) of aged mice to enhance the cell regeneration. Hence, to study the effect antiulcer and antioxidant activities on cysteamine HCl induced duodenal ulcer in aged mice we have select Aloe vera plant for the present investigation.

xvii) CHOICE OF DRUG:
Cysteamine-Hydrochloride (2-Mercaptoethylamine hydrochloride, C2H7NS · HCl):

Different types of methods are used for the induction of experimental duodenal ulcer in rat or mice. They are used as an induced ulcer model to study and investigation of the etiology of ulcer as well as evaluation of antiulcer agents. Cysteamine –HCl induced duodenal ulcers (Szabo.,1973) are widely used for experimental duodenal ulcer model because – it is suitable for studying the pathogenesis of duodenal ulceration and reliable model to study the various drugs effective against duodenal ulcers (Szabo, et al.,1977 and Pascaud,1993). It also helps to investigate the ulcerogenetic agents in our diet and the environment (Szabo, et al., 1975).Several studies have been carried out by using Cys-HCl as potent ulcer inducer for testing the antiulcer drugs. The both protective and aggressive components are take part in pathogenesis of duodenal ulcer induced by cys–HCl (Szabo, 1975).Cys-HCl enhances the rate of parietal cells acid synthesis and lowers the alkaline mucus secretary activity of Brunner glands (Nadar and Pillai,1989).The mechanism of ulcer formation also involves formation of reactive oxygen species (ROS) that leads to tissue hypoxia (Jeitner and Lawrence, 2001) the above search made us to choose the above drug for present research work.

xviii) CHOICE OF ANIMAL:

The present study based on aging it was necessary to select experimental animal of short life span (2- 3 year).Laboratory animal such as mice were easy to take care and easy to handle. Mice are used as an animal model in the research because of genetic and physiology (Theresa Lee., 2004)
and behavior characteristics closely resemble to those of humans (Jenny Halski, 1993).

They reproduce quickly and their reproductive cycle very short. They have high rate of reproduction with a high litter size and a short gestation means within a short time they produce large number of young ones.
AIM AND OBJECTIVES:

AIM: To study the antioxidant and ulcer curing effect of Aloe vera gel.

OBJECTIVES:

- Study of anti-ulcer activity of Aloe vera gel in cysteamine-HCl induced duodenal ulcer in mice by accessing the body weight and ulcer index.
- To study the cytoprotective effect of Aloe vera gel on histopathological changes of duodenum in cysteamine-HCl induced duodenal ulcer in mice.
- To study the effect of Aloe vera gel on histochemical changes of duodenum in cysteamine-HCl induced duodenal ulcer in mice.
- To study the effect of Aloe vera gel on biochemical changes in cysteamine induced duodenal ulcer in mice by accessing the protein concentration and glycoprotein (Sialic acid and Fucose) of duodenum.
- To study the antioxidant and anti ulcerogenic activity of Aloe vera gel on antioxidant enzymes like Super oxide dismutase activity (SOD), Catalase (CAT), reduced glutathione (GSH) and estimation of Lipid peroxidation (LPO).