6.0 Introduction

Peptic ulcers would mean gastric and duodenal ulcers, the 2 major forms of diseases of upper GIT. In both the disease acid pepsin secretions are implicated in their pathogenesis. The incidences of Peptic ulcer are more frequent in middle aged adults, unquestionably been a disease of the twentieth century. Epidemiological data for this disease and its complications has shown striking geographical variations in incidence and prevalence. Ulcers are deep lesions penetrating through the entire thickness of the gastrointestinal tract (g.i.t) mucosa and muscularis mucosa. Broadly ulcers are classified in 2 types of ulcers, peptic ulcer, and gastric ulcer. The etiologic factors for peptic ulcers is due to 1. Damage to the lining of the stomach, 2. Helicobacter pylori 3. Decreased Mucus secretion 4. Life style - Alcohol consumption, smoking etc 5. Hormonal factors- elaboration of gastrin by islet cell tumor in Zollinger Elison syndrome (Harsh Mohan., 2005). Duodenal ulcer, which was associated with excessive acid secretion by the stomach. Various factors are implicated that play a pivotal role in the pathogenesis of ulcerations like, sedentary life style, alcohol intake, spicy food, drugs and various bacterial infections. Moreover, several endogenous substances have been identified and are reported to be involved in the production of gastrointestinal lesions in animals. The more important ones include some of the bacterial infection, various drugs and chemicals, gastric secretion, lipid metabolites, neuropeptides, inflammatory mediators and reactive free radicals. Oxidative stress has emerged as one of the major pathogenic factors in progression of ulcer that directly impaired the cellular functions and promotes cellular organelles damage in the cells, including mitochondria, lysosomes, and nucleus. Also, NO is accepted as vital mediator of GIT mucosal defense as decreased NO generation or synthesis contribute to the pathogenesis of ulceration (Kumar Sunil et al., 2012).

Peptic ulcers are chronic, most often solitary, lesions that occur in any portion of the gastrointestinal tract exposed to the aggressive action of acid/peptic juices. Peptic ulcers are usually solitary lesions less than 4 cm in diameter, located in the following sites, in order of decreasing frequency:
Duodenum, first portion

Stomach, usually antrum

At the gastroesophageal junction, in the setting of gastroesophageal reflux or Barrett esophagus

Within the margins of a gastro jejunostomy

In the duodenum, stomach, and/or jejunum of patients with Zollinger-Ellison syndrome

Within or adjacent to an ileal Meckel diverticulum that contains ectopic gastric mucosa.

Gastric ulcer is a benign lesion of the gastric mucosa, which occurs at a site where the mucosal epithelium is exposed to acid and pepsin. Gastric ulcers arise due to various factors (McGuigan.,1991), stress, smoking, nutritional deficiencies and ingestion of non-steroidal anti-inflammatory drugs can contribute to increase the incidence of gastric ulcer (Belaiche et al.,2002). In addition, the gastric mucosa has agents like mucus, bicarbonate and prostaglandins that protect the stomach against these lesions (Goel and Bhattacharya., 1991). However, when the superficial levels of mucosal defense fail or are overwhelmed by a luminal insult, an inflammatory response is installed with exposure of tissue to a high oxidative stress, characterizing the onset of the ulcer (Luisa Mota da Silva et al., 2013). Even though the etiology of gastric ulcers is still debated, it is accepted that ulcers are caused due to net imbalances in mucosal offensive and defensive factors (Goel and Bhattacharya., 1991).
6.1 Role of Prostaglandins:

The extremely high concentration of H⁺ in the gastric lumen requires robust defense mechanisms to protect the esophagus and the stomach. The primary esophageal defense is the lower esophageal sphincter, which prevents reflux of acidic gastric contents into the esophagus. The stomach protects itself from acid damage by a number of mechanisms that require adequate mucosal blood flow, perhaps because of the high metabolic activity and oxygen requirements of the gastric mucosa. One key defense is the secretion of a mucus layer that protects gastric epithelial cells. Gastric mucus is soluble when secreted but quickly forms an insoluble gel that coats the mucosal surface of the stomach, slows ion diffusion, and prevents mucosal damage by macromolecules such as pepsin. Mucus production is stimulated by prostaglandins E₂ and I₂, which also directly inhibit gastric acid secretion by parietal cells. Thus, alcohol, aspirin, and other drugs that inhibit prostaglandin formation decrease mucus secretion and predispose to the development of acid-peptic disease. (Goodman 11th, 2004)

Numerous studies have indicated that gastroduodenal protection by prostaglandins include both increase in mucosal resistance as well as decrease in aggressive factors mainly acid and pepsin. Prostaglandins E₂ and I, are the predominant prostaglandins synthesized by the gastric mucosa and are known to inhibit the secretion of gastric acid and stimulate the secretion of mucus and bicarbonate. Hydrophobic surfactant like phospholipid secretion in the gastric epithelial cells is also stimulated by Prostaglandins (Sumangala P. Rao et al., 1998). Hawkey and Rampton found that prostaglandins exert their cytoprotective actions by stimulating the mucus and bicarbonate secretion, maintaining mucosal blood flow, and by enhancing the resistance of epithelial cells to injury induced by cytotoxins. Prostaglandins found to be inhibits the leukocyte recruitment which could contribute to the beneficial effects of these substances in situations in which the GI mucosa is inflamed. Prostaglandin E2 (PGE2) has been shown to be a potent suppressor of release of PAF, histamine and of TNF-α from peritoneal and intestinal mucosal mast cells (Kumar Sunil et al., 2012.)

The continuous generation of prostaglandins by cyclooxygenase isoenzymes in the gastric mucosa helps to maintain an adequate mucosal blood flow and also stimulates the generation of mucus (Ishihara et al., 1988). The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with the occurrence of de novo adverse digestive events, including gastric mucosal erosions, ulcers, bleeding and perforation, as well as an increased risk of
severe complications from pre-existing chronic ulcers. The pathophysiology of NSAID induced gastric injury depends, at least in part, on their ability to decrease prostaglandin production through cyclooxygenase (COX) inhibition, and partly on COX-independent mechanisms. The combination of COX-dependent and COX-independent mechanisms leads to oxidative tissue injury, which seems to play a major role in the pathogenesis of NSAID induced gastric damage. Consistently with this view, gastric mucosal levels of malondialdehyde (MDA), a product arising from tissue oxidation, have been found to increase following NSAID administration. Moreover, gastric ulcer repair is highly regulated by growth factors. Among these, vascular endothelial growth factor (VEGF) promotes ulcer healing via stimulation of new microvessel formation, and indomethacin has been shown to interfere with this process through a down regulation of VEGF expression (Matteo Fornai et al., 2012)

Ulcer therapy is now mainly focused on limiting the deleterious effects of offensive acid secretion, but the search for new safer alternative drugs have rekindled the interest in cytoprotective drugs, which protect the gastric mucosa from damaging agents without influencing acid secretion or neutralising intragastric acidity (Robert.,1979). Although few drugs like sucralfate and prostaglandin analogs, i.e. misoprostol are recognised as cytoprotective agents (Vergin and Kori-Lindner., 1990), many natural drugs have been reported to possess this activity (Goel et al.1985; Rao et al.2000; Sairam et al., 2001).

Gastric ulcers arise due to various factors (McGuigan.,1991). Even though the etiology of gastric ulcers is still debated, it is accepted that ulcers are caused due to net imbalances in mucosal offensive and defensive factors (Goel and Bhattacharya., 1991). Ulcer therapy is now mainly focused on limiting the deleterious effects of offensive acid secretion, but the search for new safer alternative drugs have rekindled the interest in cytoprotective drugs, which protect the gastric mucosa from damaging agents without influencing acid secretion or neutralising intragastric acidity (Robert.,1979). Although few drugs like sucralfate and prostaglandin analogs, i.e. misoprostol are recognised as cytoprotective agents (Vergin and Kori-Lindner., 1990), many natural drugs have been reported to possess this activity (Goel et al., 1985; Rao et al., 2000; Sairam et al., 2001).
(K. Sairam S and Priyambada., 2003)
Decreased prostaglandin level impairs almost all aspects of gastroprotection and increases acid secretions which in turn, aggravate the ulcer (Miller., 1983).
6.2 PHARMACOLOGICAL REVIEW OF PLANTS HAVING ANTI ULCER ACTIVITY
Peptic ulcer disease (PUD) is one of the major gastrointestinal disorders which occur due to an imbalance between offensive (acid, pepsin and Helicobacter pylori) and defensive (mucin, prostates gland in and bicarbonate) factors. Consequently reduction of gastric acid production as well as reinforcement of gastric mucosal protection has been the major therapeutic approaches of peptic ulcer disease (Hoogerwerf and Pasricha, 2006). A number of anti-ulcer drugs including proton pump inhibitors (PPI) and H2 receptor antagonists are available for the treatment of PUD, but clinical evaluation of these drugs has shown incidence of relapse, side effects and drug interactions. This has been the rationale for the development of new anti-ulcer drugs and thus these arch for novel molecules has been extended to medicinal plants that can offer better protection and decrease relapses (V. Lakshmi 2010)

**Ocimum sanctum Linn. (Tulsi)**. P Dharmani et al., 2006.

Ocimum sanctum (OS), popularly known as Tulsi in Hindi contains a number of chemical constituents that interact in a complex way to elicit their pharmacodynamics responses. OS is highly effective in a wide spectrum of diseases and reported to possess anticarcinogenic, anthelmintic, antiseptic, antirheumatic, antistress, and antibacterial properties. Clinical trials have reported the usefulness of OS in heart diseases and diabetes. OS also possess anti-inflammatory and immunomodulatory properties, attributed to its potential to inhibit cyclooxygenase and lymphokines results fortify the ethno pharmacological importance of OS as an antiulcer and ulcer healing agent. Furthermore, OS and its active constituents may emerge as potent therapeutic agents against PUD.


Allophyllus serratus Kurz (Synonym Allophyllus cobbe Raeuschel, Allophyllus edulis Radlk), is one of the largest genus of family Sapindaceae and carries a strong ethno pharmacological background. The plant is used in Ayurveda, to treat problems like inflammation, elephantiasis, edema, and fractures of bones. It is also used in several gastrointestinal disorders including dyspepsia, anorexia, and Pharmacognostic studies and phytochemical screening of Allophyllus serratus (AS) showed the presence of various chemical compounds in different parts of AS plant. Leaves of the plant...
CHAPTER 6 PEPTIC ULCER

contain β-sitosterol. They also contain *Aedulis* has also been reported to contain two flavonoid glycosides that are effective against ulcer PUD.

**Desmodium gagentoicum.** Dharmani *et al.*, 2006.

While studying the ethanolic extract of DG for its antiulcerogenic potential in four induction models, namely CRU, ASP, PL and AL we observed that a dose of 200mg/kg was most effective in all the models. Efficacy of DG in the CRU model maybe due to its antioxidant activity. This is in agreement with some earlier reports about the antioxidant activity of DG, which suggests the free radical scavenging effect of DG. Such activities may also be responsible for the antiulcer effect of DG. The reduced acid output measured after pyloric ligation, indicates the effect of the extract’s protective mechanism on gastric mucosa, causing an inhibition of gastric secretion. The cytoprotective ability was depicted by increased mucin secretion in the AL and the ASP induced ulcer models.

**Azadirachta indica.** Dharmani *et al.*, 2006

*Azadirachta indica* A.Juss commonly known as “Neem,” has been extensively used in India as an ayurvedic medicine for the treatment of various diseases, such as, leprosy intestinal helminthiasis, and respiratory disorders in children. Bandypadhyay *et al.* have reported the gastro protective property of dried bark extract of *Azadirachta indica* (AI) in the mercapto methyl imidazole, PL, CRU, indomethacin, AL, and HST induced ulcer models. It acts mainly by inhibiting acid secretion and blocking oxidative damage of the gastric mucosa. Inhibition of acid secretion was confirmed by inhibition of H⁺K⁺ATPase activity, while blockade of oxidative damage of gastric mucosa was evident from blocking of lipid peroxidation and scavenging of endogenous hydroxyl radical (OH·). Furthermore, they compared the bark extract with known antiulcer drugs, ranitidine and omeprazole in the PL and the stress ulcer models and found that the extract was almost equipotent to the standard drugs. The bark extract exhibited more antioxidant activity than a variety of known antioxidants. Garg *et al.*, have also reported an antiulcer effect of neem leaf extract and the prevention of mucus depletion and mast cell degranulation as possible mechanism.
Arctium lappa L, Luisa Motada Silva., 2013

Oral administration of EET (1, 3, 10 and 30mg/kg) reduced the gastric lesion area in 29.2%, 41.4%, 59.3% and 38.5%, respectively, and at 10mg/kg promoted significant regeneration of the gastric mucosa, which was confirmed by proliferating cell nuclear antigen immuno histo chemistry. EET(10 mg/kg)treatment did not increase the gastric mucus content but restored the superoxide dismutase activity, prevented the reduction of glutathione levels, reduced lipid hydroperoxides levels, inhibited the myeloperoxidase activity and reduced the microvascular permeability. In addition, EET reduced the free radical generation and increased scavenging of 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals in vitro. Furthermore, intra duodenal EET(10 and 30mg/kg) decreased volume and acidity of gastric secretion.

Smithia conferta. Rajiv Agrawal et al., 2010.

Smithia conferta Sm. (Leguminasae), is a commonly used plant in Indian traditional medicine. In the current study anti-ulcer activity of its petroleum ether, alcohol and aqueous extracts of leaves were investigated using different animal models. All extracts were also subjected to phytochemical analysis and their toxic potential. Petroleum ether extract was found to contain steroids; alcohol extract revealed the presence of isoflavonoids, alkaloids and carbohydrates; while aqueous extract was found to contain amino acids, carbohydrates and flavonoids. S.conferta aqueous and alcoholic extracts were found to be non-toxic up to 5000mg/kg dose level while petroleum ether extract was safe only up to a dose of 2000mg/kg after single dose administration of the extracts.

During confirmation of the claimed anti-ulcer activity, treatment with aqueous and alcoholic extracts showed significant reduction in ulcer index, free acidity as well as total acidity in pylorus ligated rats. However, petroleum ether extract showed relatively less profound reduction in all these indices. The anti-ulcer activity observed in aqueous extract treatment group was nearly equivalent to the standard group.
**Toonaciliata Roemer** *(heartwood)*. P.Malairajan *et al.*, 2007

The ethanol extract of *Toonaciliata Roemer* *(heartwood)* was evaluated for its anti-ulcer activity against aspirin plus pylorlous ligation induced gastric ulcer (antisecretory), HCl–ethanol induced ulcer (cytoprotective) and water immersion stress induced ulcer in rats. We found that *Toonaciliata* extract at a dose of 300mg/kg p.o. markedly decrease the incidence of ulcers in all the three models. Ethanol extract of *Toonaciliata* showed significant reduction in gastric volume, free acidity, total acidity and ulcer index. The plant extract also showed gastroprotective activity (52.94%), where as standard drug sucralfate showed 94.85%. *Toonaciliata* extract showed protection index 43.0% in water immersion stress induced ulcer, whereas standard drug omeprazole showed protection index100%.

**Voacanga Africana.** Paul V.Tan., 2000

The antiulcerogenic effects of the bark methanol extract of *Voacanga Africana* were studied using various experimental ulcer models in rats. The effects of the extract on the volume of gastric juice, gastric pH, acid output, mucus production and peptic activity were recorded, as well as the preventive action against lesions caused by HCl/ethanol and indomethacin. Oral administration of the extract (500–750mg/kg) inhibited the formation of gastric lesions induced by HCl/ethanol (40–63% inhibition). The inhibitory effect against HCl/ethanol was significantly *(P<0.01)* suppressed by pretreatment of the rats with indomethacin (30 mg/kg, i.p.). The extract significantly reduced gastric lesion formation in pylorus ligated rats, but this was not associated with an increasing mucus production or with a reduction in acid content, volume of gastric secretion or pepsin activity of the gastric juice.

**Caesalpinia pulcherrima** Linn. Vivek Sharma., 2011.

Anti-inflammatory action of the ethanolic and aqueous extracts of *C. pulcherrima* (100 and 200 mg/kg b.w.) (CPE and CPA) were evaluated by cotton pellet granuloma models. Pylorus ligation and aspirin induced ulcer models were employed for evaluating antiulcer activity for both the extracts. Ulcerogenic potential of CP was also evaluated. The ethanolic and aqueous extracts of *C. pulcherrima* significantly decreased *(P<0.01)* the granuloma tissue development. CPE and CPA at both the doses exhibited significant *(P<0.01)* antiulcer activity by decreasing the ulcer score in both the ulcer models and it was not ulcerogenic.
The ethanolic and aqueous extracts of aerial parts of *C. pulcherrima* (CPE and CPA) possess significant anti-inflammatory and antiulcer activities

*Andrographis paniculata*. Geeta Arumugam *et al.*, 2011

Rats were pretreated with HAEAP (100,200,500mg/kg b. wt for 30 days) and then gastric ulcers were induced by ethanol, aspirin, pylorus ligation and cold restraint stress models. Ulcer score was determined in all the ulcer models. pH, gastric volume, titrable acidity, pepsin, mucin, myeloperoxidase, H⁺K⁺ATPase, thiobarbituric acid reacting substances (TBARS) and antioxidant enzyme activities were assayed in ethanol-administered rats. The ulcer score was found to be low in HAEAP-pretreated rats. Among the doses studied, 200 mg/kg b.wt was found to be optimum for significant ulcer reduction. The test drug significantly reduced the acidity, pepsin concentration, myeloperoxidase and H K ATPase activities in ethanol-administered rats. The elevated TBARS and decreased glutathione (GSH) and mucin levels observed during ulcerogenesis were found to be altered in HAEAP-received animals. The ulcer preventing effect of HAEAP may partly be due to its regulating effect on H⁺K⁺ATPase activity and/or mucin preserving effects. The flavonoids present in the HAEAP might be responsible for the gastroprotective action probably by maintaining the antioxidants and thiol status in the gastrointestinal tract.

*Samanea saman* (Jacq.) merr.  
Suresh Arumugam,2011.

Gastric lesions were induced in rats by oral administration of absolute ethanol (5 ml/kg) and stress induced by water immersion. The antiulcer activity of methanolic extract of *Samanea saman* (Jacq) Merr bark (100 mg/kg, 200 mg/kg, 400 mg/kg) was compared with standard drugs. The parameters studied were ulcer index, gastric juice volume, pH, free acidity and total acidity. Result: *Samanea saman* (Jacq) Merr showed a dose dependent curative ratio compared to ulcer control groups. The extract at 400 mg/kg showed significant anti ulcer activity which is almost equal to that of the standard drug in both models. The volume of acid secretion, total and free acidity was decreased and pH of the gastric juice was increased compared to ulcer control group.
**Benincasa hispida** fruit extract  Manish. A Rachchh et al., 2008.

Petroleum ether and methanol extracts were administrated orally at the dose of 300 mg/kg, and omeprazole (reference standard) at the dose of 20 mg/kg. Ulcer index was common parameter studied in all the models. Further, vascular permeability was evaluated in ethanol model, and effect on lipid peroxidation, viz. melondialdehyde (MDA) content, superoxide dismutase (SOD), and catalase (CAT) levels were studied in CRS model. Results: Both the extracts produced significant reduction in ulcer index (\(P < 0.05\)) in all the models and the results were comparable with that of omeprazole-treated group. Further, significant reduction in vascular permeability (\(P < 0.05\)) was observed. In CRS model, MDA content was significantly reduced along with increase in CAT levels compared to control group. Petroleum ether and methanol extracts of *B. hispida* possess significant antiulcer as well as antioxidant property.

**Pterocarpus marsupium** M.C.Joshi et al., 2004.

NIDDM was produced in 5-day-old rat pups by administering streptozotocin (70 mg/kg, i.p). The animals showing blood glucose level > 140 mg/dl after 12 weeks of STZ administration were considered as NIDDM positive rats. The effective hypoglycemic dose of PMS (750 mg/kg/day, p.o.) for 6 days was studied for its gastric ulcer (GU) protective effects against cold restraint stress (CRS), aspirin (ASP), ethanol (EtOH) and pylorus ligation (PL)-induced GU both in normal (NR) and NIDDM rats. To ascertain the mechanism of action, the effects of NIDDM and that of PMS treatment in NIDDM rats on mucosal offensive acid-pepsin, free-radicals (LPO,NO) and defensive mucin secretion, cell shedding, cell proliferation, glycoproteins and antioxidant enzymes (SOD and CAT) were studied. NIDDM increased the propensity to GU by affecting both offensive (increased) and defensive (decreased) mucosal factors. Though PMS, a hypoglycemic agent, did not show any protection against ulceration induced by CRS, ASP, EtOH and PL in normal rats, it protected the mucosa against the same in NIDDM rats by affecting the above mucosal offensive and defensive factors.
**Tephrosia purpurea.** S.S.Deshpande., 2003.

Antiulcer activity of AETP was studied in rats in which gastric ulcers were induced by oral administration of ethanol or 0.6 M HCl or indomethacin or by pyloric ligation and duodenal ulcers were induced by oral administration of cysteamine HCl. AETP was administered in the dose of 1 to 20 mg/kg orally 30 min prior to ulcer induction. The antiulcer activity was assessed by determining and comparing the ulcer index in the test drug group with that of the vehicle control group. Gastric total acid output and pepsin activity were estimated in the pylorus ligated rats. Omeprazole was used as a reference drug. The ulcer index in the AETP treated animals was found to be significantly less in all the models compared to vehicle control animals. This antiulcer property was more prominent in animals in whom ulcers were induced by HCl, indomethacin and pyloric ligation. Omeprazole (8 mg/kg) produced a significant gastric and duodenal ulcer protection when compared with the control group. The anti-ulcer activity of AETP was however, less than that of omeprazole.

**Synclisia scabrida.** Orisalve OE et al., 1996.

The ethanol extract of *S. scabrida* was subjected to a column and preparative thin layer chromatography to obtain partially pure fractions of A and B which were subjected to antiulcerogenic screening and effects on alkaline phosphatase activity using aspirin and 0.6N NaOH ulcer models. The results showed that fractions A and B significantly (P<0.05) reduced both the ulcer index and alkaline phosphatase activity when compared with aspirin or 0.6N NaOH only.

**Tea root extract.** S.Maity., 2003

Tea root extract (TRE) was administered intraperitoneally to rats for 10 days at a dose of 10 mg/kg/day. Ulceration was induced in rats by administering 50% ethanol intragastrically. On day 11, the stomach was examined for ulcer by the severity of hemorrhagic erosions in acid secreting glandular mucosa. Total acid and peptic activity were determined in gastric juice using hemoglobin as substrate. Reduce glutathione (GSH) and glutathione peroxidase (GPX) were also estimated from gastric mucosa. Pretreatment with TRE for 10 days significantly reduced the incidence and severity of gastric erosions induced by ethanol. TRE treatment also favorably altered changes in volume and peptic activity of gastric juice in ethanol-treated animals. Single administration of succimer (60 mg/kg, i.g.), the standard sulfhydryl containing anti-ulcer
agent used as a reference drug, was also effective. Reduction of gastric erosions caused by TRE was reversed by 25 mg/kg, i.p. of N-omega-monomethyl-L-arginine methyl ester (L-NMMA). Furthermore, the levels of GSH and GPX were significantly decreased after treatment with ethanol, and this decrease was prevented by TRE pretreatment.

*Samanea saman (Jacq) merr.* Suresh Arumugam., 2011.

Gastric lesions were induced in rats by oral administration of absolute ethanol (5 ml/kg) and stress induced by water immersion. The antiulcer activity of methanolic extract of *Samanea saman* (Jacq) Merr bark (100 mg/kg, 200 mg/kg, 400 mg/kg) was compared with standard drugs. The parameters studied were ulcer index, gastric juice volume, pH, free acidity and total acidity. *Samanea Saman* (Jacq) Merr showed a dose dependent curative ratio compared to ulcer control groups. The extract at 400 mg/kg showed significant anti ulcer activity which is almost equal to that of the standard drug in both models. The volume of acid secretion, total and free acidity was decreased and pH of the gastric juice was increased compared to ulcer control group.


The ethanol extract of *Polyalthia longifolia* was investigated for its anti-ulcer activity against aspirin plus pyloroscopic ligation induced gastric ulcer in rats, HCl-Ethanol induced ulcer in mice and water immersion stress induced ulcer in rats at 300 mg/kg body weight.p.o. A significant (*P*<0.01, *P*<0.001) anti ulcer activity was observed in all the models. Pyloroscopic ligation showed significant (*P*<0.01) reduction in gastric volume, free acidity and ulcer index as compared to control. It also showed 89.71% ulcer inhibition in HCl-Ethanol induced ulcer and 95.3% ulcer protection index in stress induced ulcer.


NIDDM was produced in 5-day-old rat pups by administering streptozotocin (70 mg/kg, i.p). The animals showing blood glucose level > 140 mg/dl after 12 weeks of STZ administration were considered as NIDDM positive rats. The effective hypoglycemic dose of PMS (750 mg/kg/day, p.o.) for 6 days was studied for its gastric ulcer (GU) protective effects against cold restraint stress (CRS), aspirin (ASP), ethanol (EtOH) and pylorus ligation (PL)-induced GU both in normal (NR) and NIDDM rats. To ascertain the mechanism of action, the effects of NIDDM and that of PMS treatment in
NIDDM rats on mucosal offensive acid-pepsin, free-radicals (LPO,NO) and defensive mucin secretion, cell shedding, cell proliferation, glycoproteins and antioxidant enzymes (SOD and CAT) were studied. PMS (750 mg/kg) decreased the blood sugar level both in NR and NIDDM rats. NIDDM rats exhibited an increased propensity to GU, induced by CRS, ASP, EtOH and PL. Though, PMS did not protect the NR rats against GU induced by the above methods it reversed their increased propensity in NIDDM rats. NIDDM PL rats showed an increase in acid-pepsin secretion, cell shedding and decrease in mucin secretion and mucosal glycoproteins with little effect on cell proliferation. PMS treatment in NIDDM rats reversed the acid-pepsin secretion, enhanced mucin and mucosal glycoproteins and decreased cell shedding without any effect on cell proliferation. NIDDM-CRS rats showed a significant increase in LPO and NO and a decrease in SOD and CAT levels, which were, reversed by PMS treatment.

The anti-ulcer effect of aqueous extract *Murraya Koenigii* was studied in Pylorus ligation and NSAIDs induced ulcer model in albino rats. The extract at dose of 200,400 mg/kg produced significant inhibition of gastric lesion induced by NSAIDs and Pylorus ligation induced ulcer. The extract reduced ulcerative lesion, gastric volume, free and total acidity but raised the $p^H$ of gastric juice in Pylorus ligation model. The result obtained suggesting that extract possesses significant anti-ulcer activity.

The plant extract of *Excoecaria agallocha* bark herbal preparation that has been suggested as useful in the treatment of varies diseases (anti tumor, anti microbial, anti wound killing agents and anti oxidant). In this, study to determine the gastro protective effect of *E. agallocha* in a model of NSAID induced ulcer rat. The lyophilized extract was given by oral gavages (125 and 62.5mg/kg) three times at 12 h intervals before administering diclofenac 100mg/kg. Pretreatment with the extract resulted in a significant decreased of the ulcerated area. The volume and acidity of the gastric juice decreased in the pretreated rats. The plant extract was elevated in the gastric juice of untreated rats, showed hear normal levels in the pretreated rats. The *E. agallocha* was able to decrease the acidity and increase the mucosal defense in the gastric areas, there by justifying its use as an antiulcerogenic agent.
The flowers of *Ixora pavetta* have been extracted by ethanol and evaluated for the antiulcer activity by Aspirin induced and pylorus ligation of rats. The extract significantly decreased the gastric secretion, free acidity as well as gastric ulcers in the aspirin induced and pylorus ligated rats and the effects were compared with Omeprazole.

*Morinda Citrifolia* Linn Fruit Extract. P. Muralidharan., 2009
The study was designed to investigate the antiulcer activity of ethyl acetate extract of the fruits of *Morinda citrifolia* Linn (Rubiaceae) using different models of gastric and duodenal ulceration in rats. Gastric ulcers were induced by oral administration of ethanol, aspirin and by pyloric ligation and duodenal ulcers were induced by oral administration of cysteamine HCl. The extract was administered at a dose of 200 and 400 mg/kg orally 30 min prior to ulcer induction. Ranitidine (50 mg/kg) was used as a reference standard. The antiulcer activity was accessed by determining and comparing the ulcer index in the test group with that of the standard drug treated group. Gastric volume, total acid and free acid were estimated in the pylorus ligated rats. *M. citrifolia* (400mg/kg) showed maximum inhibition of gastric acid, free acid and total acid to 53.54%, 52.55% and 30.30%, respectively. The ulcer index in the *M. citrifolia* treated animals was found to be significantly less in all the models compared to standard drug treated cases. The antiulcer activity of *M. citrifolia* was, however, less than that of ranitidine. The results suggest that *M. citrifolia* possesses significant antiulcer property which could be due to cytoprotective action of the drug or strengthening of gastric and duodenal mucosa with the enhancement of mucosal defence.

Momordica Charantia. N venkat rao et al., 2011.
*Momordica charantia* (Cucurbitaceae) is a plant, reported for its variety of ethnic medicinal uses. Hence we have planned to screen antiulcer activity of fruit of the plant with the alcoholic and aqueous extracts. Fruit powder successively extracted with alcohol and water were subjected for phytochemical screening to identify different phytoconstituents. LD 50 studies for both (alcoholic and aqueous) extracts were conducted upto the dose level of 2 g/kg by following OECD up and down method of guidelines No.425. Anti ulcer activity was evaluated in various animal models like Pylorus ligation, aspirin, Stress induced ulcer models in rats. Preliminary
phytochemical studies revealed the presence of saponins, sterols, mucilage, glycosides, alkaloids, steroidal saponins in both the alcoholic and aqueous extracts of *M. charantia*. No mortality was observed with any of the 2 extracts up to the maximum dose level of 2 g/kg. Further alcoholic and aqueous extracts at 200 and 400 mg/kg, p.o but not with 100 mg/kg p.o doses significantly (P < 0.01) reduced the ulcer score, ulcer number, ulcer index, free acidity and total acidity in Pylorus ligation, aspirin, Stress induced ulcer models in rats. The present study revealed the antiulcer activity of fruit extracts of *M. charantia* and the activities are due to the presence of phytochemical constituents1,2,3 such as saponins, sterols, mucilage, glycoside, alkaloids, steroidal saponins as these phytochemical constituents were already reported for the above mentioned effects.
6.3

RESEARCH DESIGN
AND METHOD
PURPOSE AND RATIONAL

Intragastric application of absolute ethanol is a reproducible method to produce gastric lesions in experimental animals (Robert et al., 1979; Szabo et al., 1981). These lesions can be at least partially inhibited by various drugs, such as some prostaglandins. The protective effect against various irritants has been called cytoprotective activity (Robert et al., 1979). The method has been modified, the high picture quality picture with proper light arrangement were taken, and later this pictures were converted to Bitmaps and measured ulcerated area with the help of software. Parkinsonia acculeata is reported to be used as an abortifacient and in the present study evaluated for anti ulcer activity.

6.4 MATERIALS METHODS

All the chemicals used in the study were procured from Standard manufacturers and were of Analytical grade.

6.5 Animals

Sprague Dawley rats (weighing 150–180 g) were fed with standard pellet diet and water ad libitum and housed under standard environmental conditions. The animals were deprived of food for 24 h prior to ulcer Induction.

Table 6.5 - 8  Experimental groups and treatment given.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment (dose/kg, p.o.)</th>
</tr>
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<tbody>
<tr>
<td>Group I</td>
<td>Normal control</td>
</tr>
<tr>
<td>Group II</td>
<td>Control ulcer Ethanol(1 ml body wt)</td>
</tr>
<tr>
<td>Group III</td>
<td>Misoprostol 50ug (Standard drug)</td>
</tr>
<tr>
<td>Group IV</td>
<td>Parkinsonia aculeata ether extract (500 mg/kg)</td>
</tr>
<tr>
<td>Group V</td>
<td>Parkinsonia aculeata aqueous extract (500 mg/kg p)</td>
</tr>
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</table>

Ethanol induced ulceration in Rats.

Intragastric application of absolute ethanol is a reproducible method to produce gastric lesions in experimental animals (Robert et al. 1979; Szabo et al., 1981). These lesions
can be at least partially inhibited by various drugs, such as some prostaglandins. The protective effect against various irritants has been called cytoprotective activity (Robert 1979; Robert et al., 1979).

Sprague Dawley rats (weighing 150–180 g) were deprived of food 18 h prior to the experiment but are allowed free access to water. During this time they are kept in restraining cages to prevent coprophagy. The rats are administered vehicle and the cytoprotective drug, Misoprostol 0.50 mg/kg (au 6), Ether extract (500 mg/kg p.o), Aquous extract (500 mg/kg p.o)1 hr prior to administration of 1 ml absolute ethanol. Untreated animals are included as controls. One hour after administration of ethanol, the animals were anaesthetized with diethyl ether and sacrificed, the stomachs were excised, cut along the greater curvature, and gently rinsed under tap water. The stomachs are stretched on a piece of black foam core mat.

The number of ulcers (was noted) and their severity (Khandelwal, 2000), were scored using arbitrary scale as follows.
0 = Normal coloured stomach
0.5 = Red colouration
1.0 = Spot ulcer
1.5 = Hæmorrhagic streaks
2.0 = Ulcers

Mean of ulcer score for each group of animals was expressed as ulcer index by the formula given below:

\[
\text{Ulcer index} = \frac{10}{x}
\]

Where \(x\) = Total mucosal surface/Total ulcerated area

Percentage protection was calculated as

Total protected area - total ulcerated area

6.6 Innovative Method for Measurement of Ulcerated area:

The effectiveness of the drug is usually assessed using a parameter like Ulceration Index (UI) and the conclusions so drawn are as reliable as the value of UI is. It is observed that
during the experiments with animal, the region under study is small enough and it is difficult to closely read the details therein. The presence of ulceration spots of size less than a mm and ulceration streaks with thickness of less than a mm are not much uncommon. Also the estimation of ulceration index (UI) makes use of the affected areas and scoring approaches introduced earlier.

The ulceration affected areas are smaller in size and irregular in shape, this poses difficulties in estimating the actual affected area using regular geometry. Such shapes cannot ordinarily be handled precisely by conventional geometry. To this effect, we developed a new approach of more precisely estimating the affected areas for the purpose of determination of the ulceration index based upon the affected area and corresponding scoring. This approach is based on high resolution photography and image processing for the estimation of area of selected patterns in a given photograph.

![Image](Image)

**Photograph showing area measurement by Pixel Method. Ulcerated areas were picked up and pasted above and measured.**

The pattern to be studied is photographed using a reasonably high resolution camera and to keep track of the actual size, a piece of scale is also included in the photograph to find out the actual number of image picture cells (Pixel) per mm which in turn gives the
number of pixels per square mm. The whole object along with a reference scale is photographed during the experiment and care is taken to keep uniform illumination for better clarity, contrast and resolution.

The photograph so obtained is then analyzed for the presence of affected areas like red colouration (RC), ulceration spots (SP) or haemorrhagic streak (S), ulcerations (U) and perforated ulcers (UU) etc. Once the affected areas are identified, a picture editing and processing software like Photoshop was used to pick the selected and identified areas. Using a tool like magic wand and/or lasso the affected identified portion is selected and copied separately and saved as a separate image file with a suitable name to identify the same from other objects under study. One by one all the identified patterns from a given object under study are selected and copied separately in a different file for further processing. The number of picture cells (Pixels) occupying one square mm of area is also noted.

Figure6.5 - 13: Photographs showing the ulcerated area

Photographs showing the ulcerated area selected by using Photoshop & the selected pictures were converted to black images (1a and 2a). Later the software design specially to measure the pixel was used to measure the area.

The different portions of image selected and identified as ulcer affected area are then converted in to a two colour (Black and White) image that requires on bit per pixel. A bit with occupied regions is marked as logic one (or High) and the background dots are
marked as logic zero (or Low). This is the format in which a two colour Windows bit map file is saved. One byte of memory or file space accommodates eight bits (or point or pixel) information.

The two colour bitmap files (BMP format) are then analysed in a computer program written for this purpose. These images can also be analysed using other mathematical software like mat lab etc. This analysis gives the occupied number of points in the given image. All the affected image patterns derived from an experimental object are subjected to such a counting analysis which gives the number of occupied pixels. As the number of pixels per square mm is already known this count can be converted to the ulcer affected area of the extracted image. All the extracted images are labelled and a table is prepared giving the number of occupied pixels and the corresponding area in square mm. For the purpose of estimation of the effective contribution of the ulcerated areas, weightings are assigned as scores and thus with the help of the scores the effective area contributed by each of the selected portion is calculated and tabulated. Addition of all the areas so calculated gives the net contribution of the ulceration and this is used for the calculation of x, which is the ratio of total area (U) of xxxx to the ulceration area contributed (u) as x = U/u. Once the value of x is known the ulceration index is calculated as UI = 10/x.

The effectiveness of the drug is usually assessed using a parameter like Ulceration Index (UI) and the conclusions so drawn are as reliable as the value of UI is. It is observed that during the experiments with animal, the region under study is small enough and it is difficult to closely read the details therein. The presence of ulceration spots of size less than a mm and ulceration streaks with thickness of less than a mm are not much uncommon. Also the estimation of ulceration index (UI) makes use of the affected areas and scoring approaches introduced earlier.

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6.6 Statistical analysis:

The results of the ulcer index are reported as ± SEM of 6 animals in each groups.

The data was subjected to one way analysis of variance (ANOVA). This was followed by Post Hock Tukey test, to determine the statistical significance of difference in ulcer index.

The level of significance was P < 0.001

Figure 6.6 – 14 : A) Ethanol Treated rats shows mucosal damage; B) Aqueous Extract treated rats; C) Pet Ether treated rats; D) Misopristol treated rats
6.7 RESULTS
The ulcer index was calculated in 2 different ways the in conventional way as described by Khandelwal, 2000. In second case the ulcerated area was measured as discussed above.

Table no 6.7 - 9 Effect of pre treatment with Ethanol on the preventive effect of Parkinsonia aculeta on Ethanol induced gastric lesions in rats.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (mg/kg)</th>
<th>Control a</th>
<th>Ethanol b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ulcer index</td>
<td>Inhibition (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(mean ± S.E.M.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.021±0.071</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Extract 500</td>
<td>0.244±0.010</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Extract 500</td>
<td>0.153±0.006</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Misopristol</td>
<td>0.112±0.007</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>

n = 6 rats per treatment
b Rats pre-treated with ethanol treatment
*Statistically significant relative to control, P < 0.01
CHAPTER 6 PEPTIC ULCER

6.8 DISCUSSION

Ulcers are caused due to imbalance between aggressive and defensive factors of the gastric mucosa. Pepsin and gastric acid make up the offensive factors whose proteolytic effect is buffered by mucin secretion, mucosal glycoprotein, cell shedding, cell proliferation and prostaglandins (Goyal and Bhattacharya, 1999). Different therapeutic agents including plant extracts are used to inhibit the gastric acid secretion, or to stimulate the mucosal defense mechanism by increasing the mucus production protecting the surface epithelia.

Ethanol-induced gastric ulcers have been widely used for Ethanol-induced gastric ulcers by the reduction of gastric mucosal blood flow and mucus production in the gastric lumen, a decrease in endogenous glutathione and prostaglandin levels and an increase of ischemia, gastric vascular permeability, acid ‘back diffusion’, histamine release, efflux of sodium and potassium influx of calcium, generation of free radicals and production of leukotrienes (Glavin and Szabo, 1992). It has been found that oxygen-derived free radicals are implicated in the mechanism of acute and chronic ulceration and scavenging these free radicals can play an appreciable role in healing these ulcers. Ethanol-induced generation of free radicals elevate the lipid peroxide level and reduces the cysteine. There many drugs used in the treatment of
such as pump inhibitors, histamine (H2) antagonists, anticholinergic and antacids, used in the
treatment of ulcer (Gregory et al., 2009), their successes were limited by presence of several
adverse effects (e.g. anaphylaxis reactions, gynecomastia, hematopoietic changes,
thrombocytopenia, acute interstitial nephritis, nephrotoxicity and hepatotoxicity) It is well
known that inhibition of prostaglandin synthesis, which is essential for mucosal integrity and
regeneration, will trigger the mucosal lining damage. It is also believed that the extract exert
its antiulcer activity by increasing the synthesis of endogenous prostaglandins, which in turn
promote mucus secretion and enhance the mucosal barrier against the actions of various
damaging agents. It is also plausible to suggest that the observed antiulcer activity is
associated with Parkinsonia acculeata Linn’s ability to exhibit antioxidant and anti-
inflammatory activities as cited above. This indicates that the acid inhibiting and mucus
production effect of prostaglandins is the major mechanism by which P.aculeata extract
promotes ulcer healing. Oxidative stress, resulting from the increase production of oxygen
derived free radicals (e.g. superoxide anion, hydrogen peroxide and hydroxyl radicals), has
been known to take part in the pathogenesis of various diseases including gastric ulcer
(Shetty et al., 2008) and antioxidants help to protect cells. Gastric mucosal erosions have
been decribed in the course of acute liver failure. The occurrence of hemorrhagic gastritis is
the most frequent event event in the pathological event, heavily affecting its outcome (F
Marotta 1995).
Parkinsonia acculeata Linn’s activity to inhibit gastric ulceration by the virtue of its
antioxidant activity, prostaglandin like protective activity overall its Hepatoprotective
activity it can be utilized as a drug in acute liver failure.

Ethanol-induced ulcer
In Table No. 6.2, ulcer inhibition was evident in all treatment of the Pet Ether and Aqueous
extract of Parkinsonia acculeata Linn compared to the ethanol control. However, statistically
significant ulcer inhibition (p<0.05) could be seen only at doses of 500 mg/kg of the extracts.
### Table No 6.8 – 10 Ethanol induced Ulcer.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Type</th>
<th>Area in Pixel</th>
<th>Area in mm2</th>
<th>Score</th>
<th>Effective Ulcerated area in mm2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RC-1</td>
<td>8146</td>
<td>11.26</td>
<td>0.5</td>
<td>5.63</td>
</tr>
<tr>
<td>2</td>
<td>S-1</td>
<td>2274</td>
<td>3.14</td>
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<td>3.14</td>
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<tr>
<td>3</td>
<td>S-2</td>
<td>1243</td>
<td>1.72</td>
<td>1</td>
<td>1.72</td>
</tr>
<tr>
<td>4</td>
<td>S-2</td>
<td>2047</td>
<td>2.83</td>
<td>1</td>
<td>2.83</td>
</tr>
</tbody>
</table>