ABSTRACT
Peptic ulcer disease is an imbalance between offensive and defensive gastric factors. This is a major cause of mortality in developing countries. This has attracted several scientists for their research contributions to this area. Pharmacological interventions like proton pump inhibitors, H2-blockers, anti-H.pylori drugs, antacids etc. have their potential roles in management of various gastrointestinal disorders and also at the same time, they are liable for adverse effects. Good scientific confirmation of traditional knowledge of drugs for management of various disorders has made herbal approach, a scientific budding area of interest today. This review includes physiological, pathophysiological aspects related to peptic ulcer disease and list of herbal drugs for treatment of gastrointestinal ulcers. This review concludes that traditional use of plant drugs should be validated using scientific parameters.

Keywords: Herbal Drugs, Peptic ulcer

1. INTRODUCTION
Peptic ulcer disease is an imbalance of aggressive gastric luminal factors like acid and pepsin and defensive mucosal barrier function may be environmental and host factors contribute to ulcer formation by increasing gastric acid secretion or weakening the mucosal barrier1-3. Elaborately, peptic ulcer disease is characterized by the imbalance between gastric offensive factors like acid, pepsin secretion, lipid per-oxidation, nitric oxide and defensive mucosal factors like mucin secretion, mucosal cell shedding, glycoproteins, proliferation & antioxidant enzymes like catalase, superoxide dismutase & glutathione levels4. Peptic ulcers include both gastric and duodenal ulcers5. A bacterium called Helicobacter pylori has been considered a major causative agent for gastric and duodenal ulcers6.

2. STOMACH AND CONTENTS OF GASTRIC JUICE
Stomach is a J-shaped organ7. Mohan H. has said in his book that it is also known as “gland with cavity” extending from its junction with lower end of the oesophagus (cardia) to its junction with duodenum (pylorus). Histologically, the wall of the stomach consists of four layers viz.

a) Serosa
b) Muscularis (outer longitudinal, the middle circular and the inner oblique)
c) Submucosa (loose fibroconnective tissue)
d) Mucosa
   (i) superficial: cardiac mucosa, oxyntic mucosa antral mucosa
   (ii) Deep layer consists of glands of the crypts - cardia, body-fundus and pylorus

Glands of body-fundus mucosa is further subdivided into parietal (oxyntic), chief (peptic/zymogenic), mucin-secreting neck and endocrine (Kulchitsky/enterochromaffin) cells.

Gastric juice consists of hydrochloric acid (HCl), pepsin, mucin and electrolytes like Na+, K+, HCO3-. Cl-. HCl is produced by the parietal (oxyntic) cells by the interaction of Cl- ions of the arterial blood
with water and carbon dioxide in the presence of the enzyme, carbonic anhydrase. The degree of the gastric activity is correlated with the ‘total parietal cell mass’.

3. PHYSIOLOGY OF GASTRIC ACID SECRETION AND PATHOPHYSIOLOGY OF PEPTIC ULCERS

I. HCl is secreted into stomach by parietal cells (oxyntic glands) of fundus and body of the stomach. The parietal cell actively transports H⁺ across apical canalicular membranes via H⁺/K⁺-ATPases, called as proton pumps that exchange intracellular H⁺ for extracellular K⁺. Three neurohormonal secretagogues regulate this process:

a) Histamine
b) Gastrin
c) Acetylcholine (ACh).

Each of these secretagogues binds to and activates specific receptors on the basolateral membrane of the parietal cell, thereby initiating the biochemical events which are necessary for active transport of H⁺ out of the cell.

Histamine released by enterochromaffin-like (ECL) cells located in and adjacent to the oxyntic glands and by mast cells in the lamina propria, binds to histamine H₂ receptors on the parietal cell. H₂ receptor activation stimulates adenyl cyclase (AC) and increases intracellular cyclic adenosine monophosphate (cAMP). In turn, cAMP activates cAMP-dependent protein kinase, which phosphorylates H⁺/K⁺-ATPase in the apical membrane of the cell. Phosphorylation of the exchanger activates extrusion of H⁺ from the parietal cell into the gastric lumen.

Gastrin is secreted by G cells in the gastric antrum and ACh is released from postganglionic nerves with cell bodies located in the submucosa (Meissner’s plexus), bind to their respective receptors on the parietal cell which in turn increase intracellular calcium levels (Ca²⁺). Ca²⁺ binds to calmodulin and stimulates adenylyl cyclase. Ca²⁺ also activates protein kinase C, which phosphorylates and activates H⁺/K⁺-ATPase to increase H⁺ secretion.

Somatostatin-secreting D cells and prostaglandins inhibit the extent of gastric acid secretion. Somatostatin decreases acid secretion via three mechanisms-

1. Inhibition of gastrin release from G cells by a paracrine mechanism
2. Inhibition of histamine release from ECL cells and mast cells
3. Direct inhibition of parietal cell acid secretion.

Prostaglandin E₂ (PGE₂) enhances mucosal resistance to tissue injury by

1. Reducing basal and stimulated gastric acid secretion
2. Enhancing epithelial cell bicarbonate secretion, mucus production, cell turnover, and local blood flow.

Gastric secretions increase considerably during a meal. There are three phases of gastric acid secretion. The cephalic phase includes responses to sight, taste, smell, and thought of food. “Sham feedings,” experiments in which food is chewed but not swallowed, trigger an increase in acid secretion mediated by vagal stimulation and increased gastrin secretion. Mechanical distension of the stomach and ingestion of amino acids and peptides stimulate the gastric phase. Distension activates stretch receptors in the wall of the stomach that are linked to short intramural nerves and vagal fibers. Luminal nutrients, such as amino acids, are strong stimulants for gastrin release. Gastrin travels via the blood to the oxyntic mucosa and stimulates ECL cells to release from antral G cells. Acid secretion is also inhibited by release of somatostatin from antral D cells. The intestinal phase
involves stimulation of gastric acid secretion by digested protein in the intestine. Gastrin plays a major role in mediating this phase as well.

Factors that protect the gastric mucosa include gastric mucus, gastric and duodenal bicarbonate, prostaglandins, restitution (repair), and blood flow. The epithelial cells of the stomach secrete mucus, which acts as a lubricant that protects the mucosal cells from abrasions. Composed of hydrophilic glycoproteins that are viscous and have gel-forming properties, the mucus layer enables formation of an uninterrupted layer of water at the luminal surface of the epithelium. Together, the mucus and water layers attenuate potential damage due to the acidic environment of the gastric lumen. Prostaglandins stimulate mucus secretion, whereas NSAIDs and anticholinergic medications inhibit mucus production. In addition, H. pylori disrupts the mucus layer.

Bicarbonate, like mucus, protects the gastric epithelium by neutralizing gastric acid. Bicarbonate is secreted by epithelial cells at the luminal surface of the duodenal mucosa. Bicarbonate secretion in the duodenum serves to neutralize acid entering the intestine from the stomach. Restitution refers to the ability of the gastric mucosa to undergo repair. Damage is repaired through migration of undamaged epithelial cells along the basement membrane to fill defects created by the sloughing of injured cells. The final protective factor is blood flow. Blood flow to the gastric mucosa removes acid that has diffused across a damaged mucus layer.

II. Pathophysiology
A peptic ulcer is a break in the lining of the stomach or duodenum. The break can involve the mucosa, muscularis mucosa, submucosa, and in some cases, the deeper layers of the muscle wall. This compromise of mucosal integrity can cause pain, bleeding, obstruction, perforation, and even death. Peptic ulcers are caused by an imbalance between protective factors and damaging factors in the gastrointestinal mucosa.

a. H. pylori
H. pylori, a gram-negative, spiral-shaped bacterium, is most common cause of non-NSAID-associated peptic ulcer disease. H. pylori has been found mostly in the gastric antrum. H. pylori lives in the acidic environment of the stomach and is acid resistant because of its production of the enzyme urease, which converts urea to ammonia. The ammonia buffers the H+ and forms ammonium hydroxide, creating an alkaline cloud around the bacterium and protecting it from the acidic environment of the stomach. Urease is one of these damaging factors because it is an antigen that causes a strong immune response. In addition, the ammonium hydroxide produced by urease causes gastric epithelial cell injury. Other virulence factors include lipopolysaccharides (endotoxins), as well as a lipase and a protease that are secreted by the bacteria and degrade the gastric mucosa. Acid secretion is increased in patients with H. pylori-associated duodenal ulcers. This is thought to result from increased levels of circulating gastrin, causing parietal cell proliferation and increased acid production. Gastrin secretion is elevated by two mechanisms: (1) the ammonia generated by H. pylori produces an alkaline environment near the G cells and thereby stimulates gastrin release; and (2) the number of antral D cells is lower than normal in H. pylori-infected patients, resulting in decreased somatostatin production and increased gastrin release. H. pylori also decreases
duodenal bicarbonate secretion and thereby weakens the protective mechanism of the duodenal mucosa. The presence of H. pylori infection can be detected using the $^{13}$C urea breath test, which is based on the organism’s production of urease. In this test, urease converts ingested $^{13}$C-urea to $^{13}$CO$_2$ if H. pylori is present in the stomach, and the $^{13}$CO$_2$ is detection include histologic examination of a gastric mucosal biopsy, serologic testing for H. pylori antibodies, and a stool antigen test.

b. NSAIDS
Adverse effects of NSAID use, is well reported for gastrointestinal system. NSAID-associated gastrointestinal damage is liable to produce topical injury as well as systemic effects of NSAIDs. Local effects: Most of the NSAIDs are weak organic acids. These drugs are neutral compounds in acidic environment of stomach, cross the plasma membrane and enter gastric epithelial cells. In the neutral intracellular environment, the drugs are re-ionized and trapped, resulting in intracellular damage representing local gastrointestinal injury associated with NSAID use.

Systemic effects: NSAIDs may also cause systemic injury to the gastrointestinal lining, largely because of decreased mucosal prostaglandin synthesis. Two cyclooxygenase (COX) enzymes catalyze the formation of prostaglandins from arachidonic acid. COX-1 is constitutive in nature and produces the gastric prostaglandins responsible for mucosal integrity, whereas COX-2 is inducible as it is induced by inflammatory stimuli. COX-1 inhibition by NSAIDs can lead to mucosal ulceration because inhibition of PGE$_2$ synthesis removes one of the protective mechanisms maintaining the integrity of the gastric mucosa. COX-2 selective NSAIDs (coxibs) have lower risk of ulcer formation than nonselective NSAIDs but other adverse effects like increase in myocardial infarction and stroke occur. Withdrawal of COX-2 selective NSAIDs have been reported. NSAIDs increase expression of intercellular adhesion molecules in the vascular endothelium of the gastric mucosa, thereby increasing adherence of neutrophils to the vascular endothelium, causes release of free radicals and proteases that lead to gastric mucosal damage.

c. Acid hypersecretion
Another causative factor in patients of peptic ulcer disease is acid hypersecretion, characterized in Zollinger-Ellison syndrome and Cushing’s syndrome in which hyperacidity leads to peptic ulcer disease. In Zollinger-Ellison syndrome, a gastrin-secreting tumor of the non-beta cells of the endocrine pancreas leads to increased acid secretion. In Cushing’s ulcers, seen in patients with severe head injuries, heightened vagal (cholinergic) tone causes gastric hyperacidity.

d. Other factors
Pepsin, digestive enzyme secreted by gastric chief cells as the inactive precursor pepsinogen, has role in ulcer disease because of its impairment of mucosal blood flow and healing and its inhibition of pancreatic bicarbonate production. Caffeine ingestion (increased acid secretion), alcoholic cirrhosis, glucocorticoid use, and genetic influences are also associated with peptic ulcer disease. Finally, chronic psychological stress (stress induced ulcers) may occasionally be an important cause of peptic ulcer disease.

e. Inhibition of gastric secretion by post-stomach intestinal factors
Intestinal chime stimulates gastric secretion during the intestinal phase of secretion and paradoxically, it often
inhibits gastric secretion during the gastric phase. This inhibition results from at least two influences: (1) The presence of food in the small intestine initiates a reverse enterogastric reflex. Transmitted through the myenteric and vagus nerves, that inhibits stomach secretion. The reflex can be initiated by distention of the small bowel, the presence of acid in the intestine, the presence of protein breakdown products, or irritation of the mucosa. This complex mechanism explains slowing down of stomach emptying when the intestines are already filled. (2) The presence of acid, fat, protein breakdown products, hyperosmotic or hypo-osmotic fluids, or any irritating factor in the upper small intestine causes the release of several intestinal hormones. One of these is secretin, which is especially important for control of pancreatic secretion. However, paradoxically, secretin opposes stomach secretion. Three other hormones–gastric inhibitory peptide, vasoactive intestinal polypeptide, and somatostatin – also have slight to moderate effects in inhibiting gastric secretion. Stomach secretes a few milliliters of gastric juice each hour during the “interdigestive period” when little or no digestion is occurring anywhere in the gut, nonoxynctic type composed mainly of mucus that contains little pepsin and almost no acid. Emotional stimuli frequently increase interdigestive gastric secretion to 50 milliliters or more (and highly peptic and acidic) per hour. This increase of acid secretion may also be responsible for peptic ulcer disease.

4. MANAGEMENT OF GI DISORDERS - A HERBAL APPROACH

Various pharmacological interventions like antacids, anticholinergics, H₂-receptor antagonists, PPIs, K⁺ therapy, cholecystokinin-2 receptor antagonists (CCK₂R; Proglumide), prostaglandin analogues, sucralfate, carmexololone, rebamipide, ecabet, bismuth compounds, antimicrobial agents, alone or in combination have proved benefits in treatment of peptic ulcer disease in several studies but not free from their adverse effects¹¹. Now a days, various approaches have been made to study herbal drugs for treatment of various gastrointestinal disorders. Today, we have a bunch of herbal drugs that have very good potential to treat peptic ulcer and other gastrointestinal disorders both from traditional knowledge and scientific data. Following herbal drugs are found to be scientifically beneficial for gastroprotection and treatment of GI disorders in various animal models:

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<th>S.No.</th>
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<td>Ananassa nosacon</td>
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<td>Quisqualis amara</td>
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<td>Berberis vulgaris</td>
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<td>Saururus chinensis</td>
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<td>Scrophularia nigra</td>
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<td>20</td>
<td>Mucuna pruriens</td>
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The herbal drug approach is providing much satisfactory effects in many diseases or pathological conditions. This review reveals that herbal drugs have good potential for management of peptic ulcers and also enlisted plant drugs having scientific confirmation for use. In future, more herbal drugs need to scientifically prove their biological effects in different experimental and clinical studies. Therefore, it can be concluded that traditional medicinal plants should be validated.

5. ACKNOWLEDGEMENT
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6. REFERENCES