1 INTRODUCTION

1.1 PREMABLE:

1.1.1 Introduction to Research Work:

The stomach is a pouch like muscular organ. Upper side of the stomach, esophagus is present and the lower side duodenum is present. The stomach is dividing into 3 part, fundus, body and pyloric end. The fundus is grayish in color. The body areas help in churning movement with the greater curvature and lower curvature. Distal area is known as pyloric end. It having pyloric sphincter which control the passes of food into the small intestine. Cardiac end means the end of the stomach which is followed by esophagus. The pyloric sphincter open in first part of small intestine -duodenum.

The stomach divide into two curvature

I. lesser and

II. greater.

The stomach has four coats;

I. serous (peritoneal),

II. muscular

III. sub-mucosa, and

IV. mucous coat.

The thick muscular has three layers;

I. outer longitudinal,
II. inner circular,

III. oblique layer is visible in cardiac end it extends into the lesser curvature. Obviously, gastric muscles are smooth muscles. The circular layer of the gastric muscles is particularly thick in pyloric area. The gastric mucosa is bulky, at the time of empty stomach and make longitudinal fold known as rugae. But at the time of food filled stomach, the rugae disappear. Normally, over the mucousa of the stomach, lies thick viscid mucus.

The gastric mucosa, according to modern research is divided into three areas:

I. cardiac glandular area

II. oxyntic glandular areas and

III. pyloric glandular areas.

They are also called

I. fundus

II. body and

III. pyloric areas respectively.

Stomach contains various glands like gastric glands and oxyntic glands which having major roll in the gastric juice secretion. Gastric juice includes 99% of gastric juice and 1% of solid materials which contains:

I. Inorganic-HCl, HCO₃ and

II. Organic- pepsinogen, mucus, intrinsic factor.
Major function of gastric juice include:

I. digestive
II. antimicrobial
III. protective and
IV. absorption vit-B12 that due to intrinsic factor.

Three chemicals
I. gastrin,
II. histamine, and
III. acetylcholine released from vagal parasympathetic fibers acting as neurotransmitter, stimulate HCl secretion from parietal cells. The parietal cells containing receptors of gastrin, histamine and acetylcholine. Gastrin and acetylcholine combine with their respective receptors leads to rise of Ca^{++} ion concentration within the cell, abbreviated [Ca^{++}]. This causes increased H^{+}, K^{+} ATPase activity; more HCl secretion. Combination of H with its receptor causes rise of intracellular cAMP causes rise in HCl emission.

Inhibition of HCl secretion is done by the somatostatine which secreted by the D-cells in pyloric glands. Somatostatine inhibits the parietal cells, G cells, ECL cells responsible for the HCl stimulations. Other gastric inhibitory hormones are secretin, cholecystokinn, gastrin inhibitory peptide. Majority of the community gets suffered by the peptic ulcer. At the stomach on lesser curvature and first part of the duodenum are common sites for peptic ulcers. Aggressive factor, consisting of acid pepsin mixture which, if left unopposed and allowed to act will digest the gastric mucosa, and mucosal barrier described earlier, that can defend gastric mucosa contrary to harsh deed of acid pepsin mixture. If
aggressive factor become more powerful or mucosal barrier become weak, gastric mucosa will be damaged.

There are two most important causes of development of peptic ulcer:

I. Helicobacter pylori infection and,

II. mucosal damage by NSAIDs.

Gastric ulcer form by the secretion of gastric acid and against it decreases in the secretion of bicarbonate in gastric mucosa. Because of gastric ulcer sharp burning pain is occur in epigastrin. In the cephalic phase of acid secretion excess amount of acid get secret and it will damage the epithelial layer of stomach.

Gastric ulcer may cause the nausea, vomiting where as its pain produce weight loss and anorexia. One forth percentage of people is suffering from gastric ulcer which causes hemorrhage some time. There is significantly rising in the complication and death because of gastric ulcers. Gastric ulcer is very usual disease; lots of people are affected by that in throughout the world. Because of that there is arising in the mortality rate. In United state four million people have peptic ulcer and each year 3,50,000 new cases reported. Allopathic treatment is base on the observation and etiology of disease is base on manifestation of an abnormal physiology. However it has not been able to adequately helpful in the drug development discovery program to provide new molecules base on synthetic chemistry. Disillusioned by the non availability of drug to cure in chronic disease and failure of drugs in current use to give long term relief, that is why people are look after for alternative drug therapies as hope of a permanent cure. Unconfirmed and wrong claim of cure provided by traditional drugs leading
to lots of misuse. Therefore it is a major area of interest to work on such claims and claims in literature of traditional drugs for exacts scientific search before they are give to humans.

It is fascinating to know that there is advance synthetic chemistry but we are fail to synthesize new molecule which having high therapeutic value and less adverse action than existing molecule. By searching in an ancient literature, identification of natural drug molecule used in local and tribal medicine pursue investigation into the phytochemical profile are emerging as new trend in drug discovery. Isolation of active molecule, finding of their chemical structure and testing of biochemical activity is also advance fame of work. On a basis of ancient literature and tribal medicine very less work has been done and in India there is rich biodiversity so world researcher are eager to study on a dug use in India with hope that they may be potential source for the discovery of newer medicine.

In a treatment of gastric ulcer majority of patients are taking long term therapy ex; H2 blockers, proton pump inhibitors which having less chances of permanent cure. (Akram 2010) With the use of such a drugs help in healing, relieve pain and complications. Therapy includes following drugs like ranitidine, cimetidine, famotidine, prostaglandins, antacids, anticholinergics, omeprazole, etc. These all drugs are synthetic which is having many side effects; sometimes effects are unbearable for the patients. (Pharmaguide 2006) All above drugs are give successful effect in treating and controlling peptic ulcer but still treatment is unsatisfactory due to lack of complete information about etiology and pathophysiology of disease. Drugs use in peptic ulcer having less of morbidity and mortality but may create many unlikeable reactions like gynecomastia, sterility, haemopoietic variations along with that higher chances of recurrence. It
was observed that reactive oxygen species are main participants in many gastrointestinal diseases including peptic ulcer in recent studies.

In the last decade rise in awareness to growing biological concept result an increase interest in herbal formulation throughout world because it has been proved that herbal formulation is more advantageous than the synthetic drugs.(Narayan 2004, Dhuley 1999) The polyherbal formulation may carries various effects like inhibition of acid secretion, decrease formation of free radical and erosion of mucosa etc. by its individual substance or may be by its synergistic effects.

In this research work, anti-ulcer and anti-secretory action of polyherbal formulation was carried out and evaluated. In this study Dalbergia sissoo, Carissa carandas and Gymnema sylverstre drugs are extracted and using different solvent. After getting these solvent the anti ulcer study was performed. Select the one extract from each drug who having great anti ulcer activity and formulated different formulation using different possible probability. These formulations were evaluated for stability study and again for anti ulcer, anti secretory action.

The present research work was involved in different ulcer models get used like acetic acid induced ulcer model, pylorus ulcer model and stress induce ulcer models. Among this models, acetic acid induced ulcer model was found chronic and in that ulcer get produced by the acetic acid and drug was given for 10 days. On the 11th day rats get euthanized and ulcer index get counted and compared it with the standard and control. Another model is pylorus ligation in which ret get ligated on pyloric end of the stomach and gastric juice get collected. This pyloric juice used for different secretory action and compared it
with standard. In the cold stress model the animals were placed in low temperature for estimated time. Due to this stress get developed and ulcer get formed in the stomach. Produced ulcer get compared with the standard using ulcer index.

*Dalbergia* genus having 300 species all over world and about 25 species available in the India. In view of brightening and frequently fragrant wood, rich in aromatics show in timber trees Dalbergia are foreign. *Fabaceae* is a family of *Dalbergia sissoo* (*D. Sissoo*) also identified as Shisham local to Indian Subcontinent. Other than it is known as Indian rosewood, sheesham, tahli, sisu. Dalbergia sissoo is an expansive tree having stature of 25 meter and width of 2-3 meter. It has 15cm long rugged takes off. Leaves are engraved having flyers are 3-5, substitute, 2.5cm-3.6 cm in width. They are wide praise taper, glabrescent, petiolules 3-5mm long. Blossoms are whites pink in shading, 5-8mm long, pale white to dull yellow shading. Racemes 2.7-3.7cm long in short axillaries panicles. Its crown is fit as a fiddle; natural products are chestnut and case like shape which is 5-7.5cm × 8-13mm and having 1-4 seeds. Seeds are kidney fit as a fiddle having width of 6-8 × 4-5mm. Organic product is dry and hard. sapwood is white to pale cocoa in shading where as heartwood is brilliant to dim chestnut in colour. (Orwa et al 2009)

It is a huge deciduous tree found all through India, has been accounted for in people drug and is utilize basically as sexual enhancer, abortifacient, expectorant, anthelmintic and antipyretic. It is additionally use in conditions like emesis, ulcers, leucoderma, loose bowels, stomach inconveniences and skin ailments, diabetes,(Singh N. and Jain K. 2010) abrasions, gonorrhea, pain relieving and antipyretic activities. Dried leave of Dalbergia sissoo is accounted for have antibacterial, hostile to protozoal, mitigating movement. Plant having
soflavones irisolidone, biochanin-A, Municode, tectorigenin, prunetin, genestein, 
sissotrin and prunetin-4-0-galactoside. (Taha and Abdul 1999),

Carissa Carandas has family Apocynaceae.(Khare 2007) It is otherwise called 
karamarda, karinkaara. It is local plant normally find in India, Malaysia, Shri-
Lanka, Myanmar and Pakistan. The plant contain different cardiovascular 
glycosides, a triterpenoidal constituent carisson and β-sitosterol were accounted 
for from root separate. Alongside this it contain carissic corrosive, ascorbic 
corrosive, lupeol, glucose, serine, glutamine, alanine, valine, phenylalanine and 
glycine.(Gupta and Sharma 2005) In conventional arrangement of solution, 
plant is utilized as an anthelmintics, astringents, starter, antipyretics, in biliary & 
stomach issue, ailment and infection of brain (Kirtikar 2005) furthermore 
indicates action against acidity.(Khare 2007) Earlier studies have demonstrated 
that concentrate of plant has cardiotonic, antipyretic and hostile to viral 
carandas additionally indicate antibacterial, foragers of free radicals and 
inhibitors of xanthine oxidase, cell reinforcement, circulatory strain, 
hepatoprotective, pain relieving and calming movement and it likewise valuable 
in hypoglycemic conditions.(Hasnain 1990, Bhashar 2009)

Gymnema sylvestre belongs to family Asclepiadaceace(Khare 2007) it is also 
known as Madhunashini, Gudmar. It is native to India. This Plant leaves are 
being utilized as a part of India for more than 2000 years for treatment of 
madhumeha. Gudmar or sugar destroyer name is given depend on its function, 
eating leaves it destroy ability to destroy sweet test. Plant contains resins, 
saponins, stigmasterol, gymnemic acid, quercitol, betaine, choline and 
trimethylamine.
Gymnema sylvestre is utilized in diuretic, stomachic, refrigerant, tonic (Kapoor D. 1990), along with that it is used in heart disorder, leucoderma, inflammation, piles, curing burning sensation, bronchitis, asthma, biliousness and ulcer.

Gymnema sylvestre possessed anti-diabetic activity by increasing secretion of insulin from β-cell of pancreas. Along with that it increases enzyme activity those who increase glucose uptake and utilization and inhibits secondary consumption of glucose by somatotrophin and corticotrophin. Plant extract have also reported to inhibit epinephrine-induced hyperglycemia.

1.1.2 Introduction to Stomach:

1.1.2.1 Stomach:

It is a J-shaped organ lying in abdomen under the diaphragm. The stomach connects to the esophagus at upper and duodenum at the lower part. It has 1-2 liter capacity. It stores the food and partially digests it by gastric juice that it secretes. Its mechanical digestion is by gastric contractions, with cardiac and pyloric sphincters closed.
1.1.2.2 Internal structure of stomach:

It has main four main parts.

- Cardiac: Surround the upper aperture of the stomach.
- Fundus: The rounded upper left part of the stomach.
- Body: Inferior to the fundus.
- Pylorus: Connection with stomach and duodenum.
  - Pyloric sphincter: Association with stomach and duodenum of small digestive system when upper GI is unfilled, mucosa lies in expansive folds, known as rugue.
1.1.2.3 Histology:

Stomach contains four different basic layers like serosa, sub mucosa, muscularies mucosa and mucosa.

![Figure 2 Histology of stomach](image)

1.1.2.3.1 Serosa:

It is comprised of straightforward squamaous epithelium and areolar connective tissue which is covering of stomach and is piece of instinctive petritoneum.

1.1.2.3.2 Sub mucosa:

It composed of the areoler connective tissue, blood vessels and nerve fibers.

1.1.2.3.3 Muscularis externa:

It consist of 3 layers of muscles fibers. External longitudinal layer, center round layer and inward diagonal layer. They are in charge of strong compressions which agitate nourishment.
1.1.2.3.4 *Muscularis interna*:

It is a characteristic of stomach and consists of 2-3 layers of muscles running longitudinally and circularly.

1.1.2.3.5 *Mucosa*:

Mucosa layer is made out of straightforward columnar epithelial cell.

Stomach is consists of three type of the tubular glands

I. Peptic glands : Secretes pepsin, found in body of stomach

II. Oxynatic glands : Secretes HCL, found in fundus

III. Mucus glands : Secretes alkaline mucus, found in pylorus portion.

The stomach is well supplied with the gastric vessels both by sympathetic and parasympathetic supply inhibit the secretomotor activity of the stomach and the parasympathetic nerve stimulates the glands.

1.1.2.4 *Mechanism of Gastric secretion*:

Gastric corrosive is a discharge framed in stomach. It is one of principle arrangement which discharged together various proteins and components in charge of numerous response. Artificially it is a corrosive arrangement having a pH of 1 to 2 in stomach lumen, comprising chiefly of HCl, KCl and NaCl.

Gastric corrosive is created by parietal cell (oxyntic cell) in stomach. Parietal cells contain canaliculi, a broad secretory system from which gastric corrosive is emitted into lumen of stomach. Human GI lumen pH is 2-3 in acidity maintained
by H+/K+ ATPase. Parietal cell discharge bicarbonates in circulatory system simultaneously, which causes a makeshift ascent of pH in blood, known as antacid tide. Furthermore, numerous M.O. have development repressed in acidic situation which is useful to forestall disease.

### 1.1.2.5 Mechanism of gastric acid secretion:

Hydrogen particle focus in parietal cell emissions is about 3 million fold higher than in blood, and chloride is discharged against both a fixation and electrical slope. Therefore, capacity of parietal cell to emit corrosive is subject to dynamic transport. key player in corrosive emission is a H+/K+ ATPase or "proton pump" spotted in cannalicular film. This ATPase is magnesium-subordinate, and not restraining by ouabain.

![Figure 3 Mechanism of gastric acid secretion](image)
- Hydrogen particles are produced inside parietal cell from separation of water. Hydroxyl particles shaped in this procedure quickly consolidate with carbon dioxide to structure bicarbonate particle, a response catalyzed via carbonic anhydrase.

- Bicarbonate is transported out of basolateral film in return for chloride. Outpouring of bicarbonate into blood brings about a slight rise of blood pH known as "soluble tide". This procedure serves to keep up intracellular pH in parietal cell.

- Chloride and potassium particles are transported into lumen of canaliculus by conductance channels, and such is fundamental for discharge of corrosive.

- Hydrogen particle is pumped out of cell, into lumen, in return for potassium through activity of proton pump; potassium is in this manner adequately reused.

- Pepsinogen converts to pepsin which is then aids in processing connecting amino acids, a process called proteolysis.

1.1.2.5.1 Protective mechanism:

- Mucus creates by cells of gastric mucous organs, which structure a slight defensive layer on gastric mucosa.
• Bicarbonate emitted by surface of epithelial cells, which shield gastric mucosa from impact of very corrosive gastric luminal substance.

• Mucosal blood stream which is rich and which evacuate corrosive that may diffuse through mucosa.

• Prostaglandin's which upgrade all typical gastroduodenal defensive system.

• Normal cells replenishment and a skillful pyloric sphincter, which keeps regulation of forceful element bile corrosive and pancreatic proteins into GIT.

1.1.2.5.2 Phase of Gastric Acid Secretion:

Gastric acid secretion procedure contains three phases:

1.1.2.5.2.1 Cephalic phase:

This stage happens before sustenance get enters stomach and includes arrangement of body for eating and absorption. Sight and thought empower cerebral cortex. Taste and smell jolt is sent to hypothalamus and medulla oblongata. After this, it is directed through vagus nerve and arrival of acetylcholine. Gastric discharge at this stage climb to 40% of most extreme rate. Acridity in stomach is not cradled by nourishment right now and in this way demonstrations to repress parietal (secretes corrosive) and G cells (emit gastrin) action by means of D cell discharge of somatostatin.
1.1.2.5.2 Gastric phase:

This stage takes 3 to 4 hours. It is invigorated by extension of stomach, vicinity of sustenance in stomach and lessening in pH. Expansion exercises long and myentric reflexes. This initiates arrival of acetylcholine, which invigorates arrival of more gastric juice. As protein enters stomach, it ties to hydrogen particles, which lower pH of stomach to around pH1-3. Restraint of gastrin and HCL emission is lifted. This triggers G cells to discharge gastrin, which thus fortifies parietal cells to emit HCL. HCL discharge is likewise activated by acetylcholine and histamine.

1.1.2.5.2.3 Intestinal phase:

This has mainly two sections, excitatory and inhibitory. In part processed sustenance fills duodenum. This triggers intestinal gastrin to be discharged. Enterogastric reflex restrains vagal cores, initiating thoughtful filaments bringing about pyloric sphincter to fix to keep more nourishment from entering, and restrain neighborhood reflexes.

1.1.2.6 Regulation of secretion:

- GI secretion is controlled by ANS and a few hormones. Vasoactive intestinal peptide, cholecystokinin, and secretin all restrain creation. generation of gastric corrosive in stomach is hard directed by positive controllers and negative criticism instrument. Four sorts of cells are included in this methodology: parietal cells, G cells, D cells and enterochromaffine like cells. arrival of histamine is imperative positive
regulation instrument of emission of gastric corrosive in GI. Histamine discharge is fortified by gastrin and Ach and repressed by somatostatin.

- Somatostatin is discharged from D cells and its decline gastric corrosive discharge by three systems:
  - Inhibite G cell and hinder gastrin discharge,
  - Inhibit histamine discharge,
  - Directly hinder parietal cell discharge.

1.1.2.7 Composition of gastric juice

1.1.2.7.1 Gastric juice

Bodily fluid cover of stomach secretes gastric juice. Clear and dreary liquid containing 0.4% HCL. It contains gastric rennin, pepsin and gastric lipase. Gastric juice having pH 0.9-1.5. Body and fundus of stomach insider facts an acidic juice while pyloric part privileged insights a soluble juice. Fasting stomach secretes 10-60ml gastric juice/ hour while 500ml gastric juice is discharged after feast. It has been concentrated on in creatures.

<table>
<thead>
<tr>
<th>Arrangement</th>
<th>Function</th>
<th>As Result</th>
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<tr>
<td>MUCOSA</td>
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<tr>
<td><strong>Chief cells</strong></td>
<td>Secrete pepsinogen</td>
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<td>Pepsin, initiated structure.</td>
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<td>Conceal lipase</td>
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<td>Part triglycerides to monoglycerides and free acid.</td>
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<td><strong>Parietal cells</strong></td>
<td>Secrete HCL</td>
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<td></td>
<td>Kills M.O. in nourishment, denature protein, change over pepsinogen into pepsin.</td>
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<td>Secrete intrinsic factor</td>
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<td></td>
<td>Required for assimilation of methycobalamine, which is utilized as a part of red platelet development.</td>
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<td><strong>Surface mucous cells and mucous neck cells</strong></td>
<td>Secrete mucus</td>
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<td></td>
<td>From a defensive hindrance that counteracts processing of stomach divider.</td>
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<tr>
<td></td>
<td>Absorption</td>
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<td></td>
<td>Little amount of water, particles, short-chain unsaturated fats, and some medication enter circulation system.</td>
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<tr>
<td><strong>G cells</strong></td>
<td>Secrete Gastrin</td>
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<td></td>
<td>Empower parietal cell to emit HCL and boss cells to discharge pepsinogen, contracts lower esophageal sphincter, expand motility of stomach, and unwinds pyloric sphincter.</td>
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<tr>
<td><strong>Muscularis</strong></td>
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</tbody>
</table>
Muscularis | Mixing waves | Macerate nourishment and blend it with gastric juice, structuring ring.
---|---|---
Peristalsis | | Strengths ring to go through pyloric sphincter.

### Pyloric sphincter

| Pyloric sphincter | Open to permit passage of chime into duodenum | Manages entry of ring from stomach to duodenum, keeps reverse of toll from duodenum to stomach.

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**1.1.2.7.2 Function of gastric juice**

- Protein

  \[
  \text{Pepsin} \quad \text{HCL} \quad \text{Peptones + proteases}
  \]

- Renin converts caseinogens to casein which is further digested by pepsin.

- HCL act as an antiseptic and carry out hydrolysis of food.

- Gastric juice excretes toxins, heavy metals and certain drug like opium.

- Normal gastric squeeze likewise contains blood structuring component known as characteristic variable/ manor. It is essential for assimilation of vit. B12 which is new perceived outward nourishment variable. It will empower fresh recruits development by coming to bone marro
1.1.2.8 Function of stomach

1.1.2.8.1 Mechanical
Reservoir of food, mixing of food with digestive juice, liquefaction and propagation of food further into duodenum.

1.1.2.8.2 Secretion
Secretes gastric juice which converts food into chime and helps in digestion.

1.1.2.8.3 Antiseptic
Anti-bacterial/ bacteriolytic effect. Antiseptic to prevent infection.

1.1.2.8.4 Digestion
Protein and fats.

1.1.2.8.5 Absorption
Water, alcohol, glucose and some other drugs are absorbed from stomach with help of extrinsic factor.

1.1.2.8.6 Excretion
Toxin and drugs.

1.1.2.8.7 Reflex function
gastro salivary reflex cause stimulation of salivary juice. Gastro-iliac reflex which stars after entry of food cause starting of peristalsis in lower part of ileum. Mass peristalsis when foods in stomach, pancreatic and biliary secretions are also stimulated.

1.1.2.9 Control of HCL secretion:
Three chemicals

I. gastrin,

II. histamine, and

III. acetylcholine released from vagal parasympathetic fibers acting as neurotransmitter, stimulate HCl secretion from parietal cells.

1.1.2.9.1 Stimulators of HCl secretion:

The parietal cells containing receptors of gastrin, histamine and acetylcholine. Gastrin and acetylcholine combine with their respective receptors leads to rise of Ca$^{++}$ ion concentration within cell, abbreviated [Ca$^{++}$]. This causes increased H$^+$, K$^+$ ATPase activity; more HCl secretion. Combination of H with its receptor causes rise of intracellular cAMP causes rise in HCl emission.

1.1.2.9.1.1 Gastrin

Gastrin is gastrointestinal hormone, produced by G-cells of pyloric glands and first part of duodenum. Effect of gastrin of pyloric gland and those of duodenum are almost same but their amino acid compositions differ from each other.

After G cell secret gastrin, gastrin is absorb by venous blood and it reached to right atrium after that it goes to pulmonary circulation and return back to left atrium to ventricle and reach to aorta and through it reach to parietal cell and stimulate HCl production. Gastrin combined with its receptor in membrane of parietal cell and produce its effect.

Gastrin production is stimulated by:

I. peptides and amino acid produced by digestion of food protein by pepsin,

II. alcohol and
III. to some extent by vagal stimulation.

Gastrin combines with its receptors in parietal cell and stimulates HCl secretion. It also stimulates ECL cells so that more histamine is release. Histamine stimulates HCl secretion powerfully this is a major mechanism of action of gastrin.

1.1.2.9.1.2 Acetylcholine:

It will stimulated, vagal parasympathetic fibers release ACh as neurotransmitter in their ending. ACh receptors are available at cell membrane of parietal-cells and are of muscarinic, rather M₃ type. When vagal fibers are stimulated, they not only stimulated M₃ receptors of parietal cells directly but also stimulated ECL cells to release histamine. Histamine get activated by parietal-cell.

1.1.2.9.1.3 Histamine:

Enterochromaffin like (ECL) cells is produced and stored histamine in gastric gland, which is situated close to parietal cell. released H diffuses locally to parietal cell. Elsewhere in body, histamine combines with H₁ receptors and produce effects on fine blood vessels and finer bronchial tubes. But here, in parietal cell, receptors of histamine are of H₂ type. Combination of histamine with H₂ receptor in parietal-cells produces large quantities of HCl. The ECL-cells are stimulated by gastrin and ACh. On ECL-cells, receptors of ACh and gastrin are present.

1.1.2.10 Inhibitions of HCl secretion

Somatostatin is produce by D cells situated in pyloric glands. It has three major actions:
a. Inhibition of parietal cells,

b. Inhibition of G cells,

c. Inhibition of ECL cells.

Also when gastrin secretion is excessive, so that pH of gastric juice is very low, there gastrin stimulates D cells release somatostatin which reduces HCl production. This is auto regulatory mechanism which protects gastric mucosal damage due to excessive acidity.

Other GI hormones that can inhibit HCl secretion are

a. secretin

b. cholicystokinin (CCK)

c. Gastrin inhibitory peptide (GIP)

When acid gastric chyme enters duodenum, or fatty acid are produce in small intestine, these GI hormones are secreted. They have various functions one of which is to suppress HCl secretion.

1.1.3 Introduction to Peptic ulcers

In modern life, Peptic ulcer affect about 10% of entire population. Commonest sites of peptic ulcer are: i) Stomach, particularly in lesser curvature, when it is called gastric ulcer and ii) where in chief portion of duodenum known duodenal ulcer.

Peptic ulcers produce various symptoms, e.g. abdominal pain. But in addition it can also produce life threatening complications like perforation or hemorrhage.
There are two opposite factors which determine development of peptic ulcer:

I. Aggressive factor, consisting of acid pepsin mixture which, if left unopposed and allowed to act will digest gastric mucosa, and

II. Mucosal barrier described earlier that defends gastric mucosa contrary to corrosive exploit of acid pepsin mixture. If aggressive factor become more powerful or mucosal barrier become weak, gastric mucosa will be damaged.

There are two most important causes of development of peptic ulcer:

a) Helicobacter pylori infection and,

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Gastric ulcer is very usual disease; lots of people are affected by that in throughout world. Because of that there is arising in mortality rate. In United state four million people have peptic ulcer and each year 3,50,000 new cases reported.

Allopathic treatment is base on observation and etiology of disease is base on manifestation of an abnormal physiology. However it has not been able to adequately helpful in drug development discovery program to provide new molecules base on synthetic chemistry. Disillusioned by non availability of drug to cure in chronic disease and failure of drugs in current use to give long term relief, that is why people are look after for alternative drug therapies as hope of a permanent cure. Unconfirmed and wrong claim of cure provided by traditional drugs leading to lots of misuse. Therefore it is a major area of interest to work on such claims and claims in literature of traditional drugs for exacts scientific search before they are give to humans.

It is fascinating to know that there is advance synthetic chemistry but we are fail to synthesize new molecule which having high therapeutic value and less adverse action than existing molecule. By searching in an ancient literature, identification of natural drug molecule used in local and tribal medicine pursue investigation into phytochemical profile are emerging as new trend in drug discovery. Isolation of active molecule, finding of their chemical structure and testing of biochemical activity is also advance fame of work. On a basis of ancient literature and tribal medicine very less work has been done and in India there is rich biodiversity so world researcher are eager to study on a dug use in
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All above drugs are give successful effect in treating and controlling peptic ulcer but still treatment is unsatisfactory due to lack of complete information about etiology and pathophysiology of disease. Drugs use in peptic ulcer having less of morbidity and mortality but may create many unlikeable reactions like gynecomastia, sterility, haemopoietic variations along with that higher chances of recurrence. Recently finding suggests that responsive oxygen species can be main participants for many gastrointestinal diseases including peptic ulcer. (Tandon R et al., 2004)

In last decade rise in awareness to growing biological concept result an increase interest in herbal formulation throughout world. In search of traditional medicinal plants always they care hope of new and safe medicines. WHO has also taken steps to search a new medicine from plants. With use of valid phytopharmaceutical techniques effectiveness of lots of herbal preparation has been checked.
Recent trend now shifted towards polyherbal formulation for treatment of peptic ulcer, because it has been proved that herbal formulation is more advantageous than synthetic drugs. (Narayan S, 2004 and Dhuley, 1999) polyherbal formulation carries various effects like inhibition of acid secretion, decrease formation of free radical and erosion of mucosa etc. by its individual substance or may be by its synergistic effects.

Because of acid peptic secretion in gastric mucosa get degenerate and necrosis is forming which causes peptic ulcer. Generally it can take place at any area of alimentary canal but normally it can take place in duodenum and stomach due to exposure of HCL and pepsin. Peptic ulcer having two types Acute and another is chronic.

1.1.3.1 Etiology

Following stress may cause peptic ulcer:

- Psychological stress
- Physiological stress which may be
- Shock
- Sever trauma
- Septicaemia
- Extensive burn
- Intracranial lesion
Drug intake

Local irritant

Gastric ulcer caused by damaging of normal mucosal barrier by acid-pepsin resulting digestion of gastric mucosa. In case of gastric ulcers etiology not a single factor get involves but is multi factorial. These factors are as follows:

1.1.3.1.1 *Helicobacter pylori gastritis:*

The infection of H. pylori in gastric is asymptomatic sometime. presence of H. pylori can be identified by histopathological examination of gastric mucosa.

1.1.3.1.2 *Acid-pepsin secretion:*

There is evidence that acid and pepsin secretion in some level get cause gastric ulcer. But in gastric ulcer with pernicious anaemia is not co-related because acid - pepsin secretion by parietal and chief cells are absent.

1.1.3.1.3 *Mucus secretion:*

The development of gastric ulcer by decreasing quantity and quality of protecting layer of mucus. Which is a major factor of gastric ulceration.

1.1.3.1.4 *Gastritis:***
Some level of gastritis is present in surrounding of gastric ulcer. It is not clear that it is a cause or effect of gastric ulcer.

1.1.3.1.5 **Local irritants:**

Local irritant majorly affect pyloric antrum and slighter warp of stomach so called side of occurrence of gastric ulcer. Examples of irritants are alcohol, cigarette smoking, spice food, non-steroidal anti-inflammatory drugs etc.

1.1.3.1.6 **Dietary factor:**

Gastric ulcer may cause by nutrition deficiency which is common in South Insia but not seen in European countries and U.S.

1.1.3.1.7 **Psychological factor:**

Psychological factors like stress, anxiety, fatigue and ulcer type personality may cause gastric ulcer.

1.1.3.1.8 **Genetic factor:**

Gastric ulcer seen more common in blood group O than other blood groups. Genetic influence is more in duodenal ulcers.

1.1.3.1.9 **Hormonal factor:**

Discharge of some hormones by tumor cell is also associated with gastric ulcer. Examples are: In Zollinger-Ellision syndrome, islet cell tumor get secret gastrin.

1.1.3.1.10 **Miscellaneous:**

Alcoholic serosis, chronic pancreatitis, renal failure, Hyperparathyroidism may associated with gastric ulceration.

1.1.3.2 **Pathogenesis:**

There are two major factors causing gastric ulceration:

1. Gastric mucosa directly exposed to acid-pepsin secretion.
2. H. pylori infection is major etiologic association.

There is more acid-pepsin secretion against impaired mucosal defense lead to gastric ulcer. Some other pathogenetic factors are as follows:

- Due to increase in serum level of gastrin in response to ingested food hypersensitivity may occur.

- In some patients of gastric ulcer with normal or low acid-pepsin secretion; may influence of gastritis, bile reflux, cigarette smoke, etc in occurrence of ulcer.

- In gastric ulcer normal protective gastric mucus barrier is deranged. quality or quantity of gastric mucosa is depleted. rezone behind of depletion is colonization of gastric mucosa by H. pylori present in 75-80% patients of gastric ulcer.

1.1.3.3 Pathological changes in peptic ulcers:

Peptic ulcers may be round to oval shape having 1-2.5 in diameter and 80% solitary. Gastric mucosa meets towards ulcerated part and very in superficial to deep layer of mucosa. There may be chances of chronic gastric ulcer convert to malignant which is larger, bowl shaped with elevated gastric mucosa. (Szasz S, 1949)

1.1.3.4 Macroscopical appearance:

Generally, GI ulcer observed in slighter warp of GI tract within round and oval shape damage having 2-4 cm diameter. border of gastric mucosa is not elevated or irregular in normal case but in ulcer it elevated and inflammation is present. In chronic ulcer gastric mucosa seen might be in radial folds in response of parietal damaging.

1.1.3.5 Microscopical appearance:
Acid-pepsin aggression leads to mucosal damage which penetrates muscularis mucosa and causes gastric ulcer. Ulcer may cause chronic gastritis. Gastric ulcer having four histological zones, from outside to inside which is as follow:

I. **Necrotic zone**- It lies in surface of ulcer and it composed of fibrous exudates, containing necrotic debris and few leucocytes.

II. **Superficial exudative zone**- It lies in below necrotic zone. tissue elements contain aggregating necrosis giving eosinophilic, blur appearance with nuclear debris.

III. **Granulation tissue zone**- It is merging into necrotic zone, having non specific inflammatory infiltrate and proliferating capillaries.

IV. **Zone of cicatrisation**- It is merging into thick layer of granulation tissue, composed of dense fibro-collagenic scar tissue over which granulation tissue rest. Ulcer crosses thrombosis or sclerotic arteries which causes erosion result in hemorrhage. (Tripathi D, 2003)

### Table 2 Feature of gastric ulcer

<table>
<thead>
<tr>
<th>Feature</th>
<th>Gastric Ulcer</th>
</tr>
</thead>
</table>
| 1. **Incidence** | Less normal than duodenal ulcer  
Normal past sixth decade  
More normal in male than female |
| 2. **Etiology** | Gastric mucosa get tainted H. pylori  
Annihilation of mucosal hindrance which is exceedingly harming element  
Additionally connected with gastritis, liquor, tobacco, bile reflux, drugs. |
3. Pathogenesis
Most normal along lesser curve and pyloric antrum
Reflexive like duodenal ulcer

4. Pathological changes
Most normal along lesser curve and pyloric antrum
Reflexive like duodenal ulcer
Histologically, made out of 4 layers-necrotic, shallow, exudative, granulation tissue and cicatrisation

5. Complications
Discharge, holes and now and again block, dangerous change

6. Clinical features
Nourishment torment design
No night torment
Heaving regular
Hematemesis
Noteworthy loss of weight
Profound delicacy in midline in epigastrium
No occasional variety
All the more frequently in laboring gatherings

1.1.3.6 Complications:
Acute and sub-acute gastric ulcers get heal without leaving any visible scar. But in case of chronic gastric ulcer produces major complications which are as follows:

- Obstruction: Pyloric stenosis is present sue to development of fibrous scar ant pyloric end. Due to fibrosis and contraction may produce hour glass at lesser curvature of healed ulcer.
• Hemorrhage: In gastric ulcer minor bleeding can observe in stool due to erosion in minor blood capillaries of deep ulcer layer. Iron deficiency may present in chronic blood loss. Coffee ground vomitus or melaena also occur in severe bleeding. Major arteries also may erode in penetrating chronic ulcer may cause severe hematemesis and some time death.

• Perforation: A perforated gastric ulcer is an acute abdominal emergency. Perforation occurs more common in chronic gastric ulceration. It may lead to:
  
  I. Acute peritonitis may occur due to perforation content get come out and accumulate in lesion or peritoneal cavity.

  II. Imaging advent of air underneath diaphragm existing because of air drips from liver and denigrations amid liver and diaphragm.

  III. Due to infection subphrenic absesa seen between hepatic and diaphragm.

  IV. Malignant transformation: observation says that cancers ulcerate but ulcer produce cancer in very rear chances. proportion of ulcer convert in carcinoma is very less.

1.1.3.7 Clinical features:

Gastric ulcer are remitting and producing lesions. chronic behavior and recurrence of peptic ulcer must saying of patients that; Once gastric ulcer patient, always patient of gastric ulcer. chronic gastric ulcer shows variation in clinical features which are as follows:

• Age: Majority of gastric ulcer occurs in old age patients but due to changes in lifestyle it may seen in all age.
• **People at risk:** Gastric ulcer may seen in people suffering with higher stress and strain of life and also seen in laboring groups.

• **Periodicity:** Gastric ulcer may present last from 2-6 week, with interval of 6 month.

• **Vomiting:** Patients with gastric ulcer vomiting may produce relives in pain.

• **Pain:** Gastric ulcer produce pain in epigastric pain immediately or within 2 hours after food but is absent in night time.

• **Haematemesis and melaena:** In gastric ulcer it may produce in proportion of 60-40 ratio.

• **Appetite:** In patient with gastric ulcer having good appetite but they are afraid of eat.

• **Diet:** The patient with gastric ulcer may advisable to take milk, egg, or normal food. They are restricted to take spicy food or fry foods.

• **Weight:** Loss of body weight is very common in patient of gastric ulcer.

• **Deep tenderness:** It can see in mid line of epigastrium in gastric ulcer.

### 1.1.4 Treatment of Ulcer:

#### Table 3 Classification of anti ulcer drugs with examples:

<table>
<thead>
<tr>
<th>Sr No.</th>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduction of gastric acid secretion</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>H2 receptor blockers</td>
<td>Famotidine and Ranitidine</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>2</td>
<td>PPI</td>
<td>Omeprazole and Rabeprazole</td>
</tr>
<tr>
<td>3</td>
<td>Anticholinergics</td>
<td>Pirenzepine</td>
</tr>
<tr>
<td>4</td>
<td>Prostaglandins analogs</td>
<td>Mesoprostol</td>
</tr>
</tbody>
</table>

<p>| |</p>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutralizing of gastric acid</td>
</tr>
</tbody>
</table>

|   | Systemic antacid               | Sodium bicarbonate, Sodium citrate   |
|   | Non systemic antacid           | Alluminium Hydroxide, Magnesium hydroxide, Magaldrate, Calcium carbonate |
| Ulcer shielding                      | Sucralfate                           |
| Anti- H.pylori                       | Clarithromycin and Tinidazole        |

1.1.4.1 Reduction of gastric acid secretion:

1.1.4.1.1 H₂ receptor antagonist:

**Mechanism of action:** Many drugs come into this category like cimetidine, ranitidine etc which block H₂ receptor thereby inhibit acid discharge.

H₂ receptor having a major roll on gastric acid secretion when agonist bind on it than it activate cyclic AMP which is major substance for initiation of gastric acid. But blocking of this lead to no activation of cyclic AMP and no further gastric secretion.
Pharmacokinetic-

**Cimetidine** – Cimetidine is given orally which has bioavailability is only 60-80% because it has first pass metabolism. Majority of drug is excreted unchanged via urine and bile, it has elimination t½ is 2-3h.

**Ranitidine** – It is 5 to 10 times more potent to cimetidine and having very less side effect.

**Adverse effects** – Majorly this kind of drugs having muscle pain, CNS problems like dizziness, headache, confusion, hallucination etc. Along with diarrhea, reduce sperm count and reduce metabolism of various drugs because it activate cytochrom P-450.

### 1.1.4.1.2 Proton pump inhibitors:

**Mechanism of action** – Variety of drugs present in this class like pantoprazole, lansoprazole, omeprazole, rabeprazole these drugs are act on proton pump present on parietal cells helps to prevent entry of hydrogen ions into gastric lumen.

**Pharmacokinetic** – One to two hours is plasma t½ and metabolite substance excreted in urine.

**Adverse effect** – Such a kind of drugs having common side effect like abdominal pain, loose stool, vomiting, nausea, dizziness.

### 1.1.4.1.3 Anticholinergic drugs

Cholinergic nerve pathway having a roll on gastric acid secretion by activation of muscarinic receptor. Pirenzepine is cholinergic antagonists which blocks activation of muscarinic receptor and ultimately reduce gastric acid secretion.
1.1.4.1.4 Prostaglandin analogues

Prostaglandin produce by gastric mucosa, which is give protection against HCL secreted by stomach. In absence of prostaglandin HCL may damage gastric mucosa leads to gastric ulcer.

Mesoprostol is an analogue of prostaglandin E which helps in making of layer in stomach and prevents ulcer formation.

Adverse effect- Common adverse effects are diarrhea, abdominal discomfort, uterine bleeding and not suitable in pregnancy.

1.1.4.2 Neutralizing of gastric acid:

1.1.4.2.1 Antacids

Antacids work on simple mechanisms on neutralizing acid. It reacts with acid and diminished acidity. Antacids having two types,

- Systemic antacids
- Non systemic antacids –
  - i) Buffer type
  - ii) Non buffer type

1.1.4.2.1.1 Systemic antacids

Systemic antacids act rapidly and increase pH up to 7.4. Systemic antacids may produce alkalosis because it will produce NaCl and CO₂. This NaCl remain unchanged and not able to neutralize bicarbonate which get absorbed and causes alkalosis.

1.1.4.2.1.2 Non systemic antacids-
**Buffer type**- Aluminium hydroxide and Magnesium trisilicate is an example of buffer type of antacids. They have slow onset of action and long duration of action.

Adverse effect: Constipation and diarrhea is a major side effect.

**iNon buffer type**- Potent antacids having fast onset of action which rise pH>7. These types of antacids having common adverse effect like constipation. Example: Calcium carbonate, Magnesium hydroxide.

Calcium carbonate causes hypercalcaemia when it given with milk. Another example of non buffer type of antacid is magnesium hydroxide having mild cathartic action and if it absorbed by blood than it produce toxicity and also causes renal dysfunction.

1.1.4.3 Ulcer protective drug:

1.1.4.3.1 Sucralfate

Octa- alluminium sulfate of sucrose is nothing but sucralfate. Sucralfate having ability to produce sticky layer at lower pH along with this it having a characteristics to bind with pepsin and bile and at result of these it helps in ulcer as well as in acidity.

1.1.4.4 Anti- H. Pylori drugs:

Major antibiotics have been used to cure H. pylori infection i.e. amoxicillin, clarithromycin. H. pylori are gram –ve bacteria present in stomach, which having ability to bind with surface of mucosal layer and produce infection. Presence of H. Pylori may causes chronic gastritis, dyspepsia and peptic ulcer. Metronidazole and tinidazole may also use in H. Pylori infection. (Tripathi D, 2003; Kalyanakrishnan R, 2007)
1.2 ORGANIZATION:

The work was done in Smt. B.N.B. Swaminarayan pharmacy college, principle object of college to added to functional and modern situated abilities in every understudy. Trust was secured in 1983 with nobal to teach populace of area. seed of training was sown by honorable Pujya Keshavpurani Swaminji joined by Pujya Swami Kapiljivandasji shastri, Managing trustee Swaminarayan Shikshan Seva Kendra, Salvav, now it has been turn into tree offering natural products, bloom and haven to penniless people.

The vicinity of this association in this geological domain is capable current procedures, writing contemplations business to humanity. It is consequently felt important to advance higher and specialized instruction which will be underlying driver of social and budgetary upliftment of general public on loose.

Since most recent eighty years college is running. College is resolved to give phenomenal instructive and social environment suitable to development and all round improvement of understudies, rationally and cannily. college having learned showing and non- showing staff part with all late offices.

The college offered the course of B. pharmacy and M. pharmacy, four year and two year course respectively. The college has highly qualified and experienced faculty from academia and industry. Along with industry experts from various field to help elaborate the real world experience so as to equip students, with practical experience and knowledge.
Besides their pivotal role in academic our faculty members contributed by publishing number of pharmacy book published by various national and international publishers.

The college offered pre-campus placement training cell to develop confidence and communication skills.

Smt B.N.B. Swaminarayn Pharmacy college has superb contract in pharma-world, to give temporary position and situation aid in lucky professions.

Also college has a magnificent reputation for situations with understudies set in prominent carrers in national and multinational organizations and Government associations. Taking after are a percentage of organizations; college appreciates a vital organization together with rumored pharma businesses like: INdchemie Health Specialty, Sun Pharma, Zydus Biochem and S Kant Health Care Pvt. Ltd.

The college belived that sports and recreation is just as significant for a student’s development as education, hence college have best of sport training facilities with other recreation option such as: Volly Ball, Basket Ball, Table tennis, cricket, shuttlecock etc.

Swaminarayan Pharmacy College has performed consistently in pharmaceutical field over years, achieving top spot in university. According to Gujarat Technological University result analysis, college ranked among first top colleges in Gujarat state from year 2008.
The college have Thin Client computer Laboratory which offer ideal combination of individual working with great flexibility and next generation computer network system for substantial understanding with round and clock high speed broadband internet facility.

Consistently college sorted out Industrial visit for understudies which is considered as a standout amongst most strategic strategies for instructing. Fundamental explanation for this – it tells understudies to things essentially through collaboration, working routines and work hones. In addition, it gives introduction from scholastic perspective.

The college connected with, enlivened and worked together with longest-enduring and most flexible classroom innovation for encouraging and safe learning environment to keep inquisitive personality keen on intelligent lesson content.

Library is sanctum sanctorum of any instructive establishment and at Smt. B.N.B. Swaminarayan Pharmacy College very nearly significance has been given to development and upkeep of a decently loaded library indulging needs of employees and understudies of all. library has an extensive and open perusing room. spacious library brags of more than 5000 books and a few national and universal diaries, online diary like Bentham Sciences and Science Direct, Elsevier and so forth.

Decently outfitted research centers with ultra advanced instruments and types of gear, which are continually updated and kept up. Uniquely intended to give best reasonable guidelines to understudies.
The machine room has a well assembled zone of machines for most part experienced in Pharmaceutical Industry. This research facility gives a window to youthful and yearning drug specialist to be knowledgeable with flow Pharmaceutical Scenario.

The course lobby is furnished with cutting edge varying media gear like Slide and film projectors, CC TV cams, inherent sound feature frameworks, draw down screens and open location frameworks with cordless mouthpieces.

The Pharmaceutical Garden is a presentation of herbs and flavors which yield restorative mixes of demonstrated esteem in present therapeutic practice and are in overall utilize today. utilization of creatures for examination has come about extraordinary disclosures have profited all people. A multi compartment creature house is decently outfitted and intended to give fitting abilities from rearing to lodging for experimentation. creature house is affirmed via CPCSEA, New Delhi.
1.3 PROBLEMS IN HAND & NEED OF STUDY:

Gastric ulcer form by the secretion of gastric acid and against it decreases in the secretion of bicarbonate in gastric mucosa. Because of gastric ulcer sharp burning pain is occur in epigastrin. In the cephalic phase of acid secretion excess amount of acid get secret and it will damage the epithelial layer of stomach.

Nowadays peoples change their lifestyle and they are get adapted for junk-food which can only fill the stomach without any nutrient supply. It can majorly damage the gastric intestinal track and form the gastric ulcer. Gastric ulcer can easily seen in the major population.

Gastric ulcer may cause the nausea, vomiting where as its pain produce weight loss and anorexia. One forth percentage of people is suffering from gastric ulcer which causes hemorrhage some time. There is significantly rising in the complication and death because of gastric ulcers.

Gastric ulcer is very usual disease; lots of people are affected by that in throughout the world. Because of that there is arising in the mortality rate. In United state four million people have peptic ulcer and each year 3,50,000 new cases reported.

In market there are lots of medicines have been used to treat GI ulcer like H₂ receptor antagonists frequently used for the gastric ulcer. But it having some adverse effect like pain, skin rash, weakness, arrhythmia. Another drug use for the gastric ulcer is proton pump inhibitors it may cause hyper gastinemia and atrophic gastritis.
Another kind of drugs like antacids and anticholinergic drugs may causes the stomach disturbances, belching, constipation and there is risk of ulcer perforation, urinary retention, constipation, xerostomia, dry mouth, blurred vision, fluctuation in intra ocular presser.

Postaglandin analogues is another category of drug used in gastric ulcer. But when it can be used there may be a chances of abortion in pregnant woman, abdominal disturbances, uterine bleeding, dizziness, diarrhea, hypophosphatemia.

So there is always need for safer drug to treat gastric ulcer and herbal medicine is always good option to treat gastric ulcer because of drugs are more safe, freely available, less toxic and more important that they are more compatible with human body.

Drugs like Cimetidine, Famotidine, Ranitidine, Sucralfate, Prostaglandins, Omeprazole, Anticholinergics but many case studies shows that they having many major side effects likes; PPIs having higher risk of fracture (Yang X, 2006), alter iron absorption and causes iron deficiency anaemia (Sharma R, 2004; Hutchinson C, 2007), risk of vitamine B12 deficiency.

When acid suppressive therapy is given that time higher chance of community acquired pneumonia is present. Both H2 receptor antagonist and PPIs have major effect on cardiac system. It’s prolong atrioventricular conducting time, sinus arrest, sinus bradycardia, and higher risk of community acquired pneumonia. (Laheij R, 2004; Gulmez E, 2007; Eom CS, 2011)
New drugs Famotidine and Nizatidine shown decrease stroke volume (Halabi AV & Kirch W, 1992; Hinrichsen H et al., 1992; Kirch W et al., 1989) and also shows negative chronotropic effect. (Halabi AV& Kirch W, 1991)

People can used many marketed for gastric ulcer like Cimetidine, Famotidine, Ranitidine, Sucralfate, Prostaglandins, Omeprazole, Anticholinergics but many case studies shows that they having many major side effects likes;

PPIs having higher risk of fracture, alter iron absorption and causes iron deficiency anaemia (Sharma R, 2004), risk of vitamine B12 deficiency (Lodato F, 2010)

When acid suppressive therapy is given that time higher chance of community acquired pneumonia is present.

Both H2 receptor antagonist and PPIs have major effect on cardiac system it’s prolong atrioventricular conducting time, sinus arrest, sinus bradycardia. (Hinriachsen, 1992) and higher risk of community acquired pneumonia. (Gulmez, 2007)

New drugs Famotidine and Nizatidine shown decrease stroke volume (Hinriachsen, 1992; Kirch W, 1989) and also shows negative chronotropic effect.

The drugs used in gastric ulcer and acidity have major drug-drug interaction. few examples are given in below.
The clopidigrel drug used in platelet aggregation to inhibit aggregation having contraindication when it used with proton pump inhibitors. It reduce its anti-platelet activity. (Halabi A, 1991; Gilard M, 2006)

Clopidigrel (Anti-platelet) + Proton pump inhibitors → Decrease Anti platelet activity

When ranitidine is used with tolazaine (drug having α adrenergic receptor blocking action) it alter action. (Gilard M, 2008)

Tolazoline (Alfa adrenergic receptor blocker) + Ranitidine → Alter effect of Tolazoline

When proton pump inhibitors used with ketoconazole and atazanavir it reduce bioavailability of drugs.

Ketoconazole & Atazanavir + Proton pump inhibitors → Reduce bioavailability

Drug used in CNS problems like diazepam and phenytoin given with proton pump inhibitors it reduce drug clearance.

Diazepam & Phenytoin + Proton pump inhibitors → Reduce clearance
Drugs use in peptic ulcer having less of morbidity and mortality but may create many unlikeable reactions like gynecomastia, sterility, haemopoietic variations along with that higher chances of recurrence.(Ogawa R, 2010)

1.4 OBJECTIVE OF RESEARCH WORK:

I. To study acute toxicity of different extracts of each selected drugs.

II. To study anti-ulcer activity of extracts by using following models

   Acetic acid induced chronic gastric ulcer

   Pylorus ligation induced gastric ulcer

   Stress induced gastric ulcer

III. To evaluate stability of formulations.

IV. To study anti ulcer activity of prepared formulations.
1.5 PLAN OF RESEARCH WORK:

1.5.1 Survey:
Communicated with tribal people who are practicing with traditional medicines and from Pubmed, Science Direct, Medline, website, drug information center, standard books, physicochemical database, Pharmacopeia, Internet facilities, literature search.

1.5.2 Methodology and procedure of proposed work:
Collection and authentication of plants: All three plant materials, viz Dalbergia sissoo, Carissa carandas and Gymnema sylverstre were collected from forest of Dharampur, Dist- Valsad, Gujarat and authenticated by Dr. S.B. Narkhede, Asso. Prof Department of Pharmacognosy. Specimens of above plants were placed in herbarium of Smt. BNB Swaminryan Pharmacy College, Salvav (PCOG.H-221).

1.5.3 Preparation of extracts: Extract preparation was done by maceration process.
The powdered material was subjected to solvent extraction using polar and non-polar solvents. Three different kind of solvent were used; petroleum ether, chloroform, alcohol, aqueous for each selected plants.

1.5.4 Phytochemical investigation of extracts
These above extracts have been exposed to Phytochemical investigations to recognize phytoconstituent present. Alcoholic bark extract of Dalbergia sissoo containing carbohydrates, amino acid, proteins, phenolic compounds and flavonoids. Alcoholic bark extract of Gymnema sylverstre contain tannin, flavonoids, triterpenoids, saponins, and alkaloids. Alcoholic root extract
contains carbohydrates, tannin, steroids, phytosterol, flavonoids, triterpenoids, saponins.

1.5.5 Acute toxicity study of extracts

It has been carried out as per OECD guidelines and LD$_{50}$ was determined and as per CPCSEA guideline therapeutic dose was calculated for different experimental animal models. In case of *Dalbergia sissoo* extract and *Carissa carandas* extract 500mg/kg and for *Gymnema sylverstre* extract 200 mg/kg dose get fixed.

1.5.6 Anti-ulcer activity

This activity was assessed by using following model;

- Acetic acid induces chronic gastric ulcer.
- Pylorus ligated rats.
- Stress induced gastric ulcer.

Out of all extracts alcoholic extract of each selected drugs were showed more potent anti ulcer activity and after that using selected particular extract we make formulation of them.

Taking following ratio of each drugs different formulation were made and LD$_{50}$ was calculated.
**Table 4 Drugs Different Formulation**

<table>
<thead>
<tr>
<th>Extract</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; cut off mg/kg b.w.</th>
<th>Healing Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Dalbergia sissoo, Carissa carandas, Gymnema sylverstre</em> (1:1:0.4) (A)</td>
<td>2000mg/kg</td>
<td>200mg/kg</td>
</tr>
<tr>
<td><em>Dalbergia sissoo, Gymnema sylverstre</em> (1:0.4) (B)</td>
<td>3000mg/kg</td>
<td>300mg/kg</td>
</tr>
<tr>
<td><em>Dalbergia sissoo, Carissa carandas</em> (1:1) (C)</td>
<td>5000mg/kg</td>
<td>500mg/kg</td>
</tr>
<tr>
<td><em>Carissa carandas, Gymnema sylverstre</em> (1:0.4) (D)</td>
<td>2000mg/kg</td>
<td>200mg/kg</td>
</tr>
</tbody>
</table>

Evaluation and stability studies of formulations were carried out. Hyphenated analytical techniques were used for analysis of complex mixtures of natural origin. After completing experiments results was obtained.

**1.5.7 Statistical analysis**

The factual importance was evaluated utilizing restricted investigation of fluctuation (ANOVA) test for Stastical analysis. For looking at nonparametric ulcer scores, ANOVA took after by Tukey-Kramer test will utilize. qualities will be express as mean + S.E.M and level of importance will be figured.
1.6 SCOPE OF RESEARCH WORK:

In last few decades global visions of medicines get changed. Worldwide researchers look forward to herbal medicine. They are believed that traditional herbal medicine may carry potency and safe. (Tandon R. and Goel R, 2004)

The globally medical herbology get accepted. The term medical herbology is study of plants or herbs for medicinal purpose. In broadly it is said to be cultivation, collection and dispensing of herb used in medical purpose. Medical herbology also be known as a herbal medicine, botanical medicine, phytotherapy. (Ameh J, 2010)

It was more noted that plants formed secondary metabolite in metabolic activity with respond to ecophysiological stimuli. These secondary metabolites like alkaloids, terpenes, steroids ect. are called phytochemicals which are used to treat many disease in humans. World Health Organization also shows their interest in phytochemicals by giving place in their regulations. (WHO, 1998a) The guideline on quality control of tredicinal drug, had been framed for worldwide regulation of herbal medicine.

The traditional medicine having following criteria (Ameh J, 2010)

✓ Plants having heavy metal, toxins, microbial contamination under limit of WHO

✓ The phytochemicals present in plants are easily separated by TLC and HPLC technique.

✓ The plants come in medicine having constant and repeatedly give values of loss on dryingwater extractability and ash vaue of herbal molecules.

✓ The plants having no threat of their active molecules or any adverse effects.

✓ The phytochemicals obtain from plants are safe in animals.

✓ Herbal drugs globally with their Regulatory status:To fulfil primary healthcare need majority of population depends on traditional medicine, its about 80%and 90% which is not regulated by government. In 1999 people of developing
countries are depend on traditional medicine was 80% but they contributed only 7.2% to trade. But people of developed countries relies less and contribute 55.2%. Asian countries contribute 37.6%. (Ameh J, 2010) This happened because of developed nation formulate traditional medicine with GMP and used it with GCP.

- Not in India but in china and Korea also kept traditional medicine into national health scheme. Traditional medicine having same as it given to synthetic medicine. In china 1249 traditional medicine took as an essential medicine in 2001 with sales in billion dollars. Herbal remedies also need authority for marketing as per state drug administration law comes under 1985 in china.

- In India most commanding approaches towards herbal medicine. All approaches about herbal drugs for all diseases given in Ayurveda. Vedas and Samhitas also had given ideas about same. Ayurvedic medicine is recognised by Indian Medicine Council Act 1970. WHO also took interest and give funds to encourage research in herbal medicine and in Ayurvedic medicine. Many plants having variety of therapeutic action so it can use in various diseases. Majorly we can find anti oxidant action in plants. Phenol, aromatic amines are majorly found as a phytochemical in plants. Phytochemicals can act differently at different stages generally it having ability to reduce oxygen concentration, reduce superoxide formation, lipid peroxidation, etc. Plants acquired large variety of therapeutic action but in very less amount of thorough study took place on it. Clinical study proved that many plants having ability to treat gastric disorders. Research on it may un-covered mechanism behind it. (Gurbuz C, 2000)

- Herbal medicine, a good and alternative therapy of Ulcer:

- Stephen Defelice gave term NUTRACEUTICAL in 1989 which was used as nutrition and pharmaceutical which describe as a food or any nutrient rich substance used in inhibition, identification and cure of diseases. (Toniolo L, 2001) Recently many research were carried out on nutrition reached plants and their phytochemicals. They concluded that near about 90% of disease can
avoidable if we change in our dietary habits. (Swanson, 1998; Brower, 1998) Because of such a powerful result of herbal component and phytochemicals it increase consumer awareness and potential benefits of substance get by plants in health related problems.

So more research has been done on herbal medicine for different diseases. (Block G, 1992; Trichopoulos D, 1996) Where as many herbal plants get used in preparation of nontoxic, less expensive and easily available drugs for treatment of many disorders including gastric ulcer.

1.6.1 Phytochemicals has been investigated for anti-ulcerogenic activities. Many of them discuss below:

1.6.1.1 Flavonoids:

Out of 4000 natural substances one of substances is flavonoid having wide variety of therapeutic effect including anti-ulcer action. Flavonoid is a major constituent of human diet which is used in traditional and folk medicine globally. By many mechanisms they are possess anti-ulcer activity it includes increase in PG mucosal content, by inhibiting histidine decarboxylase enzyme inhibits histamine release from mast-cells, blocking activity of H. Pylori activity. Along with these it having very good free radicals scavenging activity and research proved that with this action gastric ulcer get easily heal.

1.6.1.2 Quercetin:

Quercetin is richest flavonoids found in many plants. It helps to promot amount of natural glycoside in gastric mucosa. stimulate COX and help to rise amount of PG, inhibit proton pump, and inhibit lipoxygenase pathways, inhibits proton pump, activate platelet activation factor.
1.6.1.3 Naringin:

Naringin is a potent flavonoids glycoside which show anti ulcer activity against chronic ulcer produced by restraint stress, pyloric ligation and ethanol induce ulcer. It showed by increase amount of PG with increase glycoprotein content and viscosity of gastric mucosa. Along with this action it has anti-oxidant activity which can also contribute in anti-ulcer activity.

All over world included in India over counter drugs are easily used for many diseases like hypertension, pain sensation, inflammation, gastritis, etc. But these synthetic medicines having many gastro-duodenal risks for long term uses so, there is an increasing demand for naturally synthesized plant base medicine which having lack of adverse and side effect to treat such a kind of diseases.

The healing property of plants due to ability of plants to generate aromatic substances like phenol and flavonoids which having anti-oxidant activity. Such a kind of phytochemicals get diminished free radical scavenging ability by which it helps to give gastroprotective activities. These free radicals get generated by use of NSAIDs. These NSAIDs inhibits COX activity and decrease release of PG which can affect lining of gastric mucosa and initiate gastric ulceration. (Wallace L, 1997)

Natural polyherbal formulation may showed antiulcer activity because of it involved in angiogenesis and also involved in cell proliferation processes. These processes help in wound healing activity and reepithelization of tissues. Reepithelization can initiated by activation of proangiogenic factor and inhibits or regulate antiangiogenic factors.
Even I visited interior villages of Dharampur, town place come in Valsad district in Gujarat where I found that local people called vaid is used such a kind of herbal to treat numerous diseases and also to cure.

![Figure 4 Vaid serving tribal medicine to local people](image)

So, uses of polyherbal formulation instead of synthetic medicine is alternate therapy to protect from different disorders by preventing oxidative stress and increase stores of critical elements such as antioxidants, vitamins, etc.