IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON PEPTIC ULCER DISEASE: DIAGNOSIS AND MANAGEMENT APPROACH

[1]Mrs. Tulsi Tilva, [2]Ms. Akshita Dholakiya

[1]Associate Professor, [2]B. Pharm Scholar

[1]Department of Quality Assurance

[1 & 2]Smt. R. D. Gardi B. Pharmacy College, Rajkot, Gujarat, India.

Abstract:

Peptic ulcer is a chronic disease affecting up to 10% of the world's population. The formation of peptic ulcers depends on the presence of gastric juice pH and the decrease in mucosal defences. Peptic ulcer disease occurs mainly due to consumption of NSAIDs, infection by H. pylori, stress, or due to a pathological condition such as Zollinger –Ellison Syndrome are the two major factors disrupting the mucosal resistance to injury. Conventional treatments of peptic ulcers, such as proton pump inhibitors (PPIs) and histamine-2 (H2) receptor antagonists, have demonstrated adverse effects, relapses, and various drug interactions.

Keywords: Peptic ulcer disease; Helicobacter pylori infection; Zollinger –Ellison Syndrome.

1. INTRODUCTION

Peptic ulcer is one of the most common, chronic gastrointestinal disorder in modern era. Now it has become a common global health problem affecting a large number of people worldwide and also still a major cause of morbidity and mortality.[1] Peptic ulcer disease can be characterized by inflamed lesions or excavations of the mucosa and tissue that protect the gastrointestinal tract. Damage of mucus membrane which normally protects the oesophagus, stomach and duodenum from gastric acid and pepsin causes peptic ulcer.[6] The pathophysiology of this gastro-intestinal disorder is viewed as an imbalance between mucosal defensive factors such as bicarbonate, prostaglandin, nitric oxide, peptides, growth factors and injurious factors like acid, pepsin.[2,3]

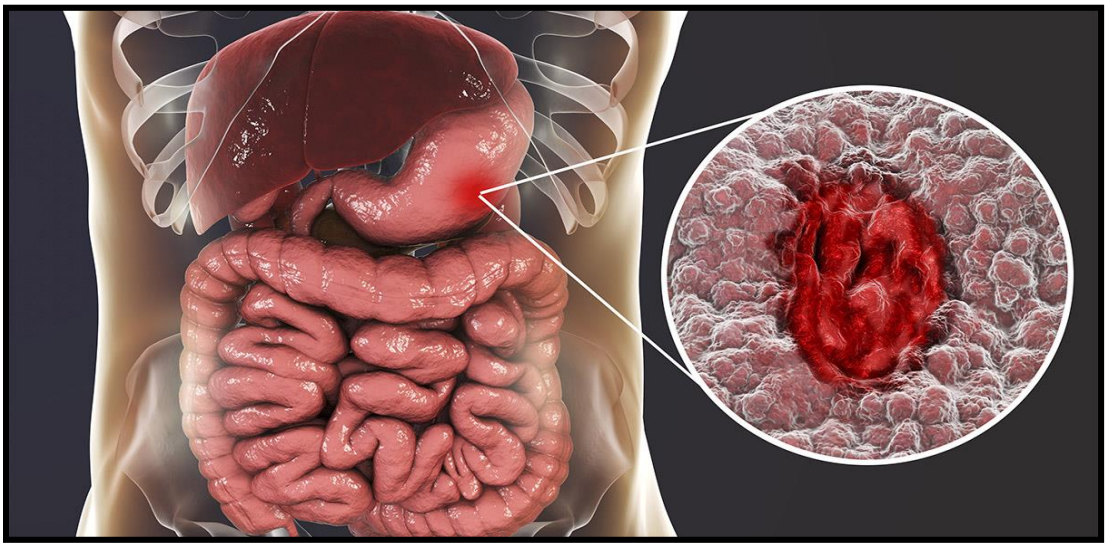

Figure 1. Peptic ulcer

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. Prevalence of peptic ulcer has reduced from past few years mainly due to an effective treatment of H. pylori infection eradication, however widespread use of NSAIDs and aspirin (acetylsalicylic acid) causes certain gastrointestinal complications.[4] NSAIDs and aspirin may lead towards gastrointestinal mucosal injury, and hence the complications.[5]

Various drug regimens available include proton pump inhibitors (PPIs), H2 receptor antagonist, antacids, antibiotics and mucosal protective agents. The diagnostic tests include blood tests, urea breadth test, stool antigen test and endoscopy.[6]

2. EPIDERMIOLOGY

The lifetime risk for developing a peptic ulcer is approximately 5% to 10%[7] with the rate of 0.1% to 0.3% per year.[8] Peptic ulcers resulted in 301,000 deaths in 2013, down from 327,000 in 1990.[9]

In Western countries, the percentage of people with H. pylori infections roughly matches age (i.e., 20% at age 20, 30% at age 30, 80% at age 80, etc.). Prevalence is higher in third world countries, where it is estimated at 70% of the population, whereas developed countries show a maximum of a 40% ratio. Overall, H. pylori infections show a worldwide decrease, more so in developed countries. Transmission occurs via food, contaminated groundwater, or human saliva (such as from kissing or sharing food utensils).[10]

Peptic ulcer disease had a tremendous effect on morbidity and mortality until the last decades of the 20th century when epidemiological trends started to point to an impressive fall in its incidence. The reason that the rates of peptic ulcer disease decreased is thought to be the development of new effective medication and acid suppressants and the rational use of nonsteroidal anti-inflammatory drugs (NSAIDs).

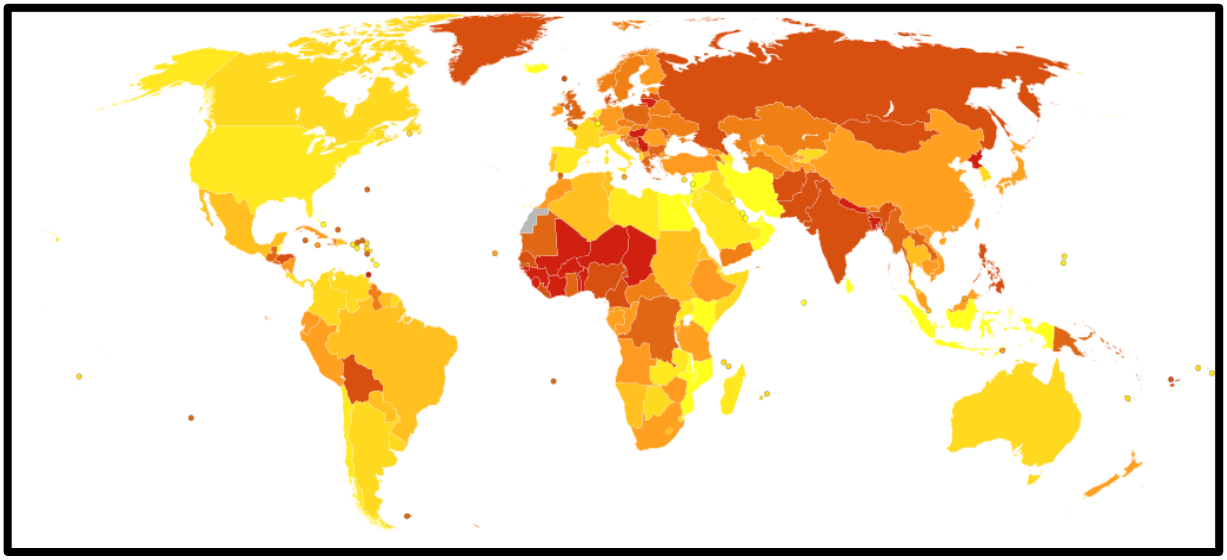

Figure 2. World map shows the area of spread peptic ulcer.

3. SYMPTOMS

The most common peptic ulcer symptom is burning stomach pain. Stomach acid makes the pain worse, as does having an empty stomach. The pain can often be relieved by eating certain foods that buffer stomach acid or by taking an acid-reducing medication, but then it may come back. The pain may be worse between meals and at night. Many people with peptic ulcers don't even have symptoms. Less often, ulcers may cause severe signs or symptoms such as:

- Vomiting or vomiting blood
- Unexplained weight loss
- Feeling faint
- Dark blood in stools, or stools that are black or tarry[11]
- Nausea or vomiting
- Appetite changes
- Trouble breathing

Figure 3. Peptic ulcer symptoms

If symptoms remain untreated, it may lead to complications like gastrointestinal bleeding, perforations, penetration, narrowing and obstruction.

4. PATHOGENESIS OF PEPTIC ULCER

- Almost half of the world's population is colonized by H. pylori, which remains one of the most common causes of peptic ulcer disease.[12] The prevalence of H. pylori is higher in developing countries, especially in Africa, Central America, Central Asia, and Eastern Europe.[13]
- The organism is usually acquired in childhood in an environment of unsanitary conditions and crowding, mostly in countries with lower socioeconomic status. H. pylori causes epithelial cell degeneration and injury, which is usually more severe in the antrum, by the inflammatory response with neutrophils, lymphocytes, plasma cells, and macrophages. The mechanism by which H. pylori induces the development of different types of lesions in the gastroduodenal mucosa is not fully explained.
- H. pylori infection can result in either hypochlorhydria or hyperchlorhydria, thus determining the type of peptic ulcer. The main mediators of H. pylori infection are cytokines that inhibit parietal cell secretion, but H. pylori can directly affect the H+/K+ ATPase α-subunit, activate calcitonin gene-related peptide (CGRP) sensory neurons linked to somatostatin, or inhibit the production of gastrin.[14] Although the formation of gastric ulcers is associated with hyposecretion, 10–15% of patients with H. pylori infection have increased gastric secretion caused by hypergastrinemia and reduced antral somatostatin content.[15]
- This leads to increased histamine secretion, and subsequently the increased secretion of acid or pepsin from parietal and gastric cells. Additionally, the eradication of H. pylori leads to a decrease in gastrin mRNA expression and an increase in somatostatin mRNA expression.[16] In the remaining majority of patients, gastric ulcers are associated with hypochlorhydria and mucosal atrophy. The main mechanism of NSAID-associated damage of the gastroduodenal mucosa is the systemic inhibition of constitutively expressed cyclooxygenase-1 (COX-1), which is responsible for prostaglandin synthesis, and is associated with decreased mucosal blood flow, low mucus and bicarbonate secretion, and the inhibition of cell proliferation.
- NSAIDs inhibit the enzyme reversibly in a concentration-dependent manner. The co-administration of exogenous prostaglandins and cyclooxygenase-2 (COX-2)-selective NSAIDs use reduces mucosal damage and the risk of ulcers.[17] However, the different physicochemical properties of NSAIDs cause differences in their toxicity.[18] NSAIDs disrupt mucus phospholipids and lead to the uncoupling of mitochondrial oxidative phosphorylation, thus initiating mucosal damage.
- When exposed to acidic gastric juice (pH 2), NSAIDs become protonated and cross lipid membranes to enter epithelial cells (pH 7.4), where they ionize and release H+. In that form, NSAIDs cannot cross the lipid membrane, and are trapped in epithelial cells, leading to the uncoupling of oxidative phosphorylation, decreased mitochondria energy production, increased cellular permeability, and reduced cellular integrity. Patients who have a history of peptic ulcers or haemorrhage, are over the age of 65, also use steroids or anticoagulants, and take high doses or combinations of NSAIDs are at the highest risk for acquiring NSAID-induced ulcers.

5. STAGES OF PEPTIC ULCER

1. Acute Stage

Characteristic signs of acute peptic ulcer disease are symptoms that often appear suddenly, manifest clearly and progress in a short time. At this stage, if detected and treated properly, the disease can be completely cured. However, most patients often ignore the symptoms, subjectively do not go to the doctor, making the disease more complicated.[19]

2. Chronic Stage

Acute peptic ulcer disease, when left untreated, will cause inflammation and swelling for a long time, and after a while, it may turn into a chronic form.[20] In the chronic stage, the lesions spread, the disease is more difficult to treat, and can even lead to dangerous complications such as atrophic inflammation, intestinal metaplasia,[21] pyloric stenosis, hemorrhage, perforation, and gastric cancer.[22]

6. CAUSES OF PEPTIC ULCER

1. Helicobacter pylori infection.

H.Pylori infection is the leading cause of stomach ulcers. After entering the stomach, this bacterium will get into the mucous layer of the gastric mucosa, secreting toxins that damage the gastric mucosa, inhibit the production of protective factors of the stomach lining, forming scars. ulcer.[23]

2. Long-term use of non-steroidal anti-inflammatory drugs (NSAIDs)

The long-term use of NSAID drugs such as ibuprofen, naproxen, diclofenac, etc. will cause stomach damage. These drugs inhibit the synthesis of prostaglandins, reducing the protective effect of the gastric mucosa, making the stomach susceptible to ulcers.[24]

3. Other causative agents

Increased acid secretion in the stomach, this can happen for a variety of reasons, including genetic factors, smoking, stress, or the consumption of certain foods.[25]

Peptic ulcer disease can also occur if you have a rare condition called Zollinger-Ellison syndrome. This condition forms a tumor of acid-producing cells in the digestive tract. These tumors can be cancerous or noncancerous. The cells produce excessive amounts of acid that damages stomach tissue.

7. DIAGNOSTIC TEST FOR PEPTIC ULCER

- **Blood test**

Doctors may use blood tests to check for signs of H. pylori infection or complications of peptic ulcers. For a blood test NIH, a health care professional will take a blood sample from you and send the sample to a lab.

- **Urea breath test**

  Doctors may use a urea breath test to check for H. pylori infection. For the test, you will swallow a capsule, liquid, or pudding that contains urea “labelled” with a special carbon atom. If H. pylori is present, the bacteria will convert the urea into carbon dioxide. After a few minutes, you will breathe into a container, exhaling carbon dioxide.

A health care professional will test your exhaled breath. If the test detects the labelled carbon atoms, the health care professional will confirm an H. pylori infection in your digestive tract.

- **Stool test**

  Doctors may use stool tests to check for H. pylori infection. Your doctor will give you a container for catching and holding a stool sample. You will receive instructions on where to send or take the kit for testing.[25]

- **Upper gastrointestinal (GI) endoscopy and biopsy**

For an upper GI endoscopy, a doctor uses an endoscope a flexible tube with a camera to see the lining of your upper GI tract, including your esophagus, stomach, and duodenum. During upper GI endoscopy, a doctor obtains biopsies by passing an instrument through the endoscope to take small pieces of tissue from your stomach lining. A pathologist will examine the tissue under a microscope.[25]

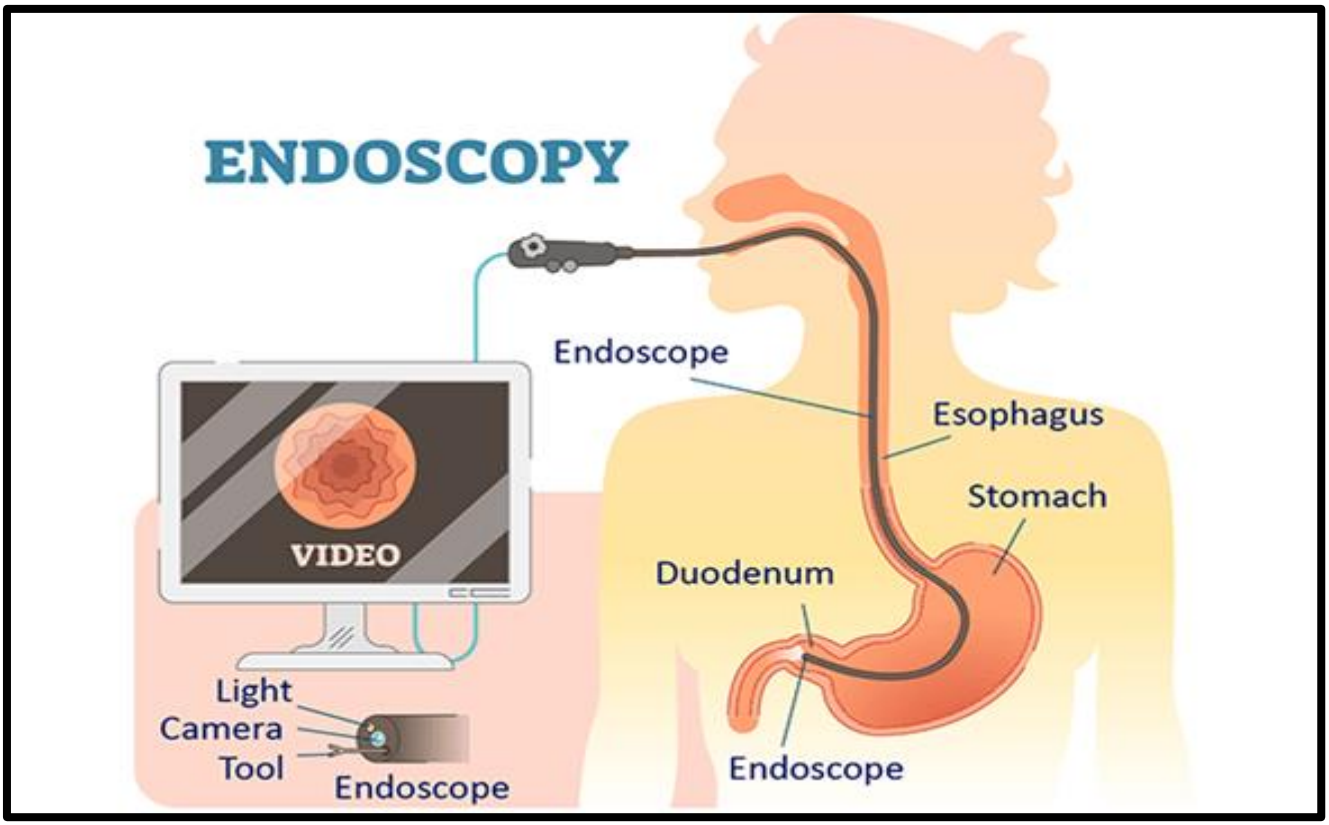

Figure 4. Upper GI endoscopy

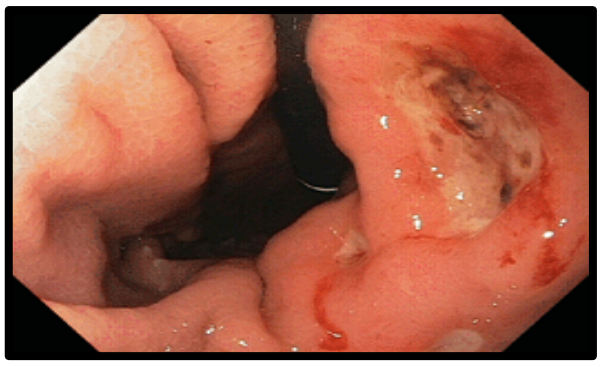

Figure.5 Photograph of a peptic ulcer taken during an upper endoscopy.

6. CASE STUDY

A 23 years old male visited clinic with complains of an upper abdominal pain, heartburn, nausea and sometimes vomiting. He was in usual state of health 5 days back when he started having epigastric pain. Pain aggravated at night after taking large meal. He was fond of fried and spicy food. He had a family history of peptic ulcer disease. He denied cigarette smoking.

- **Past medication history**

He was using Synflex (naproxen) to relieve pain from past 2 days, but no significant effect. Then he decided to consult doctor. Past medical history: Past medical history reveals the absence of any disease in the patient.

- **Family history:** Patient's father had a history of peptic ulcer disease.

- **General examination**

Weight: 58kg

Height: 5feet 8inches

BMI: 19.44kg/m2

Temperature: 98°F

BP: 120/70mmHg

- **Diagnosis of peptic ulcer**

According to the provided information, patient's laboratory tests were done. There were no signs of bleeding as Hb values were normal (13.5g/dl) and absence of blood in stools and vomiting. Serological and Urea breadth test confirmed H. pylori positive infection in the patient.

- **Medication therapy:**

- **Pharmacist Interventions**

Pharmacist made three types of interventions after reviewing the patient history and physician prescription. These include drug related interventions, dietary modifications and lifestyle modifications (Table 1)

- **Drug related interventions**
  - Take Omeprazole before meal.
  - There is no need of ranitidine (H2 receptor antagonist) at this stage of patient. Triple drug therapy is followed in the patient. As, PPIs and Mucaine syrup is already added in medication to relieve burning sensation so, Glamet is skipped from therapy.

Table: Medication therapy

Brand	Generic	Strength	Frequency
Amoxil	Amoxicillin	1g	BID
Clarithro	Clarithromycin	250mg	BID
Risek	Omeprazole	40mg	OD
Glamet	Ranitidine	150mg	BID
Mucaine suspension	Aluminium hydroxide, magnesium hydroxide, oxethazaine	120ml	1 Tablespoon TID

➢ **Dietary modifications**

a. Omega-3 polyunsaturated fatty acids should be added as they have an anti-inflammatory effect and protect stomach from ulcers.

b. Avoid spicy food.

c. Avoid late night meals.

d. Take healthy balanced diet having low cholesterol.

e. Take plenty of water and fresh juices.

➢ **Lifestyle modifications**

a. Avoid lying down in bed immediately after meal.

b. Elevate head of bed.

c. Avoid stress Outcomes Patient used the medicine regularly, routine tests and monitoring was done and patient was improved on follow-up. He was advised to visit in case of any complication.

Figure 6. Diet and lifestyle modification for peptic ulcer

7. Treatment

The goal of therapy for peptic ulcer disease is to relieve symptoms, heal craters, prevent recurrences, and prevent complications. Medical therapy should include treatment with drugs, and attempt to accomplish the following:

1) Reduce gastric acidity by mechanisms that inhibit or neutralize acid secretion,

2) Coat ulcer craters to prevent acid and pepsin from penetrating to the ulcer base,

3) provide a prostaglandin analog,

4) Remove environmental factors such as NSAIDs and smoking, and

5) reduce emotional stress (in a subset of patients).[26-28]

8. Allopathic medicines

Category	Medication	Mechanism action	Adverse effects	Reference
Proton Pump Inhibitors (PPIs)	Omeprazole, Lansorazole, Rabeprazole, Esomeprazole, Pantoprazole	Inhibition of the gastric H+/K+- ATPase (proton pump) enzyme system	Headache Abdominal pain, Diarrhoea Nausea Vomiting Constipation Flatulence Vitamin B12 deficiency Osteoporosis	29
H2 Receptor Blockers	Cimetidine	Blocking the action of histamine at the	Headache, Anxiety Depression Dizziness, Cardiovascular	30

Antacids	Aluminium hydroxide Magnesium hydroxide	Increases gastric pH to Causes osmotic retention of fluid Causes osmotic retention of fluid	Frequency not defined: Nausea Vomiting Hypophosphatemia Chalky Taste Constipation Abdominal Cramping Diarrhoea, Electrolyte imbalance	31
Potassium Competitive Acid Blocker	Vonoprazan	Inhibits H+, K+- ATPase in gastric parietal cells at the final stage of the acid secretory pathway	Nasopharyngitis Fall Contusion Diarrhoea Upper respiratory tract inflammation Eczema Constipation Back Pain Diarrhoea.	32
Cytoprotective Agent	Misoprostol Sucralfate	Stimulate mucus production and enhance blood flow throughout the lining of the gastrointestinal tract	Abdominal pain Headache Constipation	34

Fig.7 Rabeprazole sodium & domperidone tablet

Fig. 8 Dried aluminium gel, magnesium hydroxide gel & activated dimethicone susp.

Fig.9 Vonoprazon

Fig.10 Lansoprazole gastro-resistant capsule

Fig.11 Omeprazol capsule

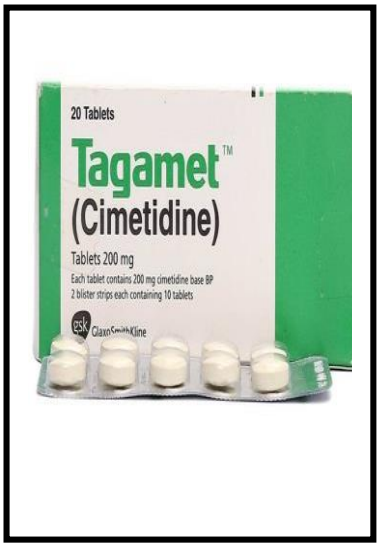

Fig.12 Cimetidine tablet

9. ANTI-ULCER ACTIVITY OF SOME MEDICINAL PLANTS

9.1 ASPARAGUS RACEMOSUS

Figure 13. Asparagus Racemosus

- **Family:** Asparagaceae
- **Chemical constituent:** Shatavari roots contain 4 steroid saponin, shatavarin I-IV (0.2%). Shatavarin I is the major glycoside with 3 glucose and rhamnose moieties attached to sarsapogenin ,whereas in shatavarin IV 2 glucose and 1 rhamnose moieties are attached.[35]
- **Uses:** Asparagus racemosus (Shatavari) is recommended in Ayurvedic texts for prevention and treatment of gastric ulcers, dyspepsia and as a galactogogue.

  root is employed in diarrhoea as well as in chronic colic and dysentery problems.

Root boiled with some bland oil, is applied in various skin diseases Juice of this drug taken with milk is useful in gonorrhea.[36]

9.2 ERUCA SATIVA

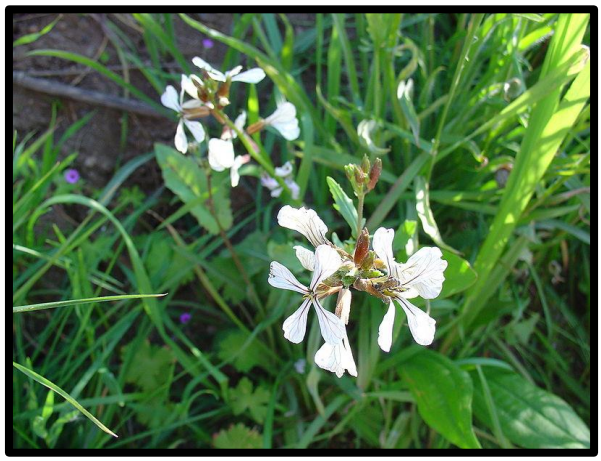

Figure 14. Eruca Sativa

- **Synonyms:** Rocket(roquette) or Arugula

- **Family:** Brassicaceae

- **Chemical constituent:** Phytochemical investigations of the aqueous extract of Eruca sativa fresh leaves, afforded the presence of nine natural flavonoid compounds which were isolated and identified as kaempferol 3-O-(2"-O-malonyl-β-D-glucopyranoside)-4'-O-β-D-glucopy-ranoside , kaempferol 3,4'-O-diglucopyranoside, rhamnocitrin 3-O-(2"- O-methylmalonyl-β-D-glucopyranoside)-4'-O-β-Dglucopyranoside, 3-O-glucopyranoside, 4'-Oglucopyranoside, rhamnocitrin 3-Oglucopyranoside, 4'-O-glucopyranoside, kaempferol and rhamnocitrin.[37]

- **Uses:** Rocket extract possesses anti-secretary, cytoprotective, and anti-ulcer activities against experimentally-induced gastric lesions.

  Arugula is possibly loaded with vitamins and minerals that in some way bolster the defenses of the body's immune system. It also have antimicrobial and antiulcer properties.[38]

  In the treatment of erectile dysfunction. Arugula has long been used as a medicine for enhancing sexual desires in men.

9.3 OCIMUM SANCTUM LINN

Figure 15. Ocimum Sanctum Linn

- **Synonyms:** holy basil, tulasi (sometimes spelled thulasi) or tulsi.[39]
- **Family:** Lamiaceae.
- **Chemical constituent:** Fresh leaves and stem of Ocimum sanctum extract yielded some phenolic compounds (antioxidants) such as cirsilineol, circimaritin, isothymusin, apigenin and rosameric acid, and appreciable quantities of eugeno. The leaves of Ocimum sanctum contain 0.7% volatile oil comprising about 71% eugenol and 20% methyl eugenol.[40]
- **Uses:** The fixed oil significantly possessed antiulcer activity due to its lipoxygenase inhibitory, histamine antagonistic and antisecretory effects.[41]

  Pharmacological activities of this plant are anti-bacterial,[anti-inflammatory,anti-hypertensive, cardioprotective, central nervous system depressant,anti-oxidant, chemo preventive, immunomodulatory, analgesic, antipyretic, anti-fertility, anti-arthritic, anti-stress, anti-cataract, anticoagulant, hepatoprotective, radioprotective.[42]

9.4 ZINGIBER OFFICINALIS

Figure 16. Zingiber Officinalis

- **Synonyms:** canton ginger, stem ginger, ardraka.
- **Family:** Zingiberaceae
- **Chemical constituent:** Chemical analysis of ginger shows that it contains over 400 different compounds. The major constituents in ginger rhizomes are carbohydrates (50–70%), lipids (3–8%), terpenes, and phenolic compounds.[43] Terpene components of ginger include zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, and α-curcumene, while phenolic compounds include gingerol, paradols, and shogaol.[45]
- **Uses:** anti-ulcer compounds have been isolated from ginger, including 6-gingesulphonic acid,[42] 6- shogaol and ar-curcumene[46] Most notable is 6- gingesulphonic acid, which showed weaker pungency and more potent anti-ulcer activity than 6- gingerol and 6-shogaol.[47-49] The antiulcer activity of ginger may also be due to the potent thromboxane synthetase inhibition.[50] It has also had anti-bacterial, anti-infflamatory, antioxidant and anti-cancer activities.

9.5 AZADIRACHTA INDICA

Figure 13. Azadirachta Indica

- **Synonyms:** margosa, neem, nimtree or Indian lilac
- **Family:** Meliaceae
- **Chemical constituent:** Azadirachta indica L. (neem) shows therapeutics role in health management due to rich source of various types of ingredients.[51] The most important active constituent is azadirachtin and the others are nimbolinin, nimbin, nimbidin, nimbidol, sodium nimbinate, gedunin, salannin, and quercetin. Leaves contain ingredients such as nimbin, nimbanene, 6-desacetylnimbinene,[52] nimbandiol, nimbolide, ascorbic acid, n-hexacosanol and amino acid, 7-desacetyl-7-benzoylazadiradione, 7-desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione, and nimbiol. [53–54] Quercetin and ß-sitosterol, polyphenolic flavonoids, were purified from neem fresh leaves and were known to have antibacterial and antifungal properties.[55]
- **Uses:** The antiulcer activity of Azadirachta indica has been reported by Chattopadhyay et al. [56] where the aqueous leaf extract was used to prevent gastric ulcers, oxidative damage, acid secretion, and apoptosis.

  The reported pharmacological activities on the leaves of Azadirachta indica are comprised of antiulcer, antifungal, anti-inflammatory, antibacterial, antiviral, antioxidant, antimutagenic, and antimalarial properties. [57]

10. PREVENTION AND CONTROL

Certain lifestyle choices and habits can reduce your risk of developing peptic ulcers. Theseinclude:

- ✓ not mixing alcohol with medication
- ✓ not drinking more than two alcoholic beverages a day
- ✓ washing your hands frequently to avoid infections
- ✓ limiting your use of ibuprofen, aspirin, and naproxen

Maintaining a healthy lifestyle by quitting smoking cigarettes and other tobacco use andeating a balanced diet rich in fruits, vegetables, and whole grains will help you prevent developing a peptic ulcer.[58]

11. CONCLUSION

The combination of herbal products and standard anti-gastric ulcer drugs might present a synergistic effect against H. pylori and gastric ulcer disease and improve the outcome for patients with gastric ulcer. With only a few human studies, it is suggested to conduct further clinical studies with larger sample sizes on the efficacy and safety of medicinal plants with antiulcer activity. Also, it would be beneficial to design studies to investigate and further elucidate the mechanisms of action of medicinal plants used for the treatment or prevention of peptic ulcer.

Finally, herbal products used for medicinal purposes require licensing in order to ameliorate their safety and quality, and ensure that randomized controlled investigations validate demands of its possible efficacy. With increased reports of herb–drug interactions, there is still a problem of deficient research in this field, with no measures taken to address this problem. Hence, pharmacists and doctors should be aware especially of the risks associated with the usage of herbal preparations, whether on their own or in combination with other herbal or standard conventional therapy.

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