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AN OVERVIEW : ANTI ULCER ACTIVITY WITH MEDICINAL PLANTS

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ABSTRACT

Peptic ulcer disease is considered as one of the common disease in the world. Treatment of peptic ulcer with synthetic drugs such as proton pumb inhibitors, H_2 receptor antagonists and other non-steroidal anti-inflammatory drugs has shown adverse effects, relapses, drug interactions. Medicinal plants containing active chemical constituents are useful in prevention and treatment of various diseases. An ulcer is disease of epithelial cells of body or organ which represents an open sore in the lining of epithelial cells or deep lesion in the specific region resulting into its degradation thus disrupting the normal physiology of the organ affected. The damage can be to the extent of bleeding, which is commonly known as bleeding sore. Traditional medicines or to point out clearly, the medicinal plants have wider range of therapeutic advantages in the proper management of diseases, as they have better pharmacological activity along with low incidence of side effects or the adverse effects. Medicinal plants also thus have huge market for themselves in our ultimate goal of providing healing touch to the disease person.

INTRODUCTION:

Peptic ulcer is a gastro intestinal disorder due to an imbalance between the aggressive factors like acid, pepsin, *Helicobacter pylori* and defensive factors like bicarbonate secretion, prostaglandins, gastric mucus, innate resistance of the mucosal cell factors. Normally peptic ulcer develops when aggressive factors overcome the defensive. The major factors that disrupt the equilibrium between aggressive factors and defensive factors are *Helicobacter pyloro,* acid-pepsin hyper secretion, non-steroidal anti-inflammatory drugs, sometimes idiopatic due to usuage of cobacco, psychological stress, rapid gastric emptying and Zollinger-Ellisson syndrome where there is a high and uncontrollable production of acid also leads to ulcer formation. Sunthetic drugs such as proton pump inhibitors, H_2 receptors, cytoprotectants, demulcents, anti cholinergics, antacids and prostaglandin analogues are used for the treatment of ulceration but these drugs produce several side effects.

So herbal medicines are considered as better alternatives for the treatment of peptic ulcer for example, proton pump inhibitors (omeprazole, Lansoprazole) may cause gynaecomastia, loss of libido. Due to the coccurrence of many side effects by use of synthetic drugs as they have less or no side effects. As herbal medicines are considered as safe for the treatment of ulcers with lesser adverse effects, economical, effective, relatively less toxic, extensive research is carried out in search for potent antiulcer agents of plant origin.

Peptic ulcer disease represents a serious medical problem. Approximately 500,000 new cases are reported each year, with 5 million people affected in the United States alone. Interestingly, those at the highest risk of contracting peptic ulcer disease are those generations born around the middle of the 20^{th} century. Ulcer disease has become a disease predominantly affecting the older population, with the peak incidence occurring between 55 and 65 years of age. In men, duodenal ulcers were more common than gastric ulcers; in women, the converse was found to be true. Thiry-five percent of patients diagnosed with gastric ulcers will suffer serious complications. Although mortality rates form peptic ulcer disease are low, the high prevalence and the result in pain, suffering, and expense are very costly.

Ulcer can develop in the esophagus, stomach or duodenum, at the margin of a gastroenterostomy, in the jejunum, in Zollinger-Ellison syndrome, and in association with a meckel's diverticulum containing ectopic gastric mucosa. Peptic ulcers disease is one several disorders of the upper gastrointestinal tract that is caused, at least partially, by gastric acid. Patients with peptic ulcer dis

may present with a range of symptoms, form mild abdominal discomfort to catastrophic perforation and bleeding.

SYMPTOMS:

More patients with peptic ulcer disease present with abdominal discomfort, pain or nausea. The pain is located in the epiastrium and usually dose not radiate. However, these symptoms are neither sensitive nor specific. Pain radiating to the back may suggest that an ulcer has penetrated posteriorly, or the pain may be pancreatic in origin. Pain radiating to the right upper quadrant may suggest disease of the gallbladder or bile ducts.

Patients may describe the pain of peptic ulcer as bruning or gnawing, or as hunger pains slowly building up for 1-2 hours, the gradually decreasing. Use of antacids may provide temporary relief. Classically, gastric ulcer pain is aggravated by meals, whereas the pain of duodenal ulcers is relieved by meals. Hence, patients with gastric ulcers tend to avoid food and present with weight loss, while those with duodenal ulcers do not lose weight. It is important to remember that although these patterns are typical, they are not pathognomonic. The nature of the presenting symptoms alone not permit a clear differentiation between benign ulcers and gastric neoplasm.

TYPES OF ULCERS:

PEPTIC ULCER:

Any ulcer that is exposed to pepsin is referred to as peptic ulcers. Peptic ulcers are found in the lining of stomach or duodenum. Pepsin is normally present along with hydrochloric acid in the stomach lining.

DUODENAL ULCER:

When a peptic ulcer is in duodenum, it is called a duodenum ulcer. This type of peptic develops in the first part of the small intestine. Some of the symptoms of a duodenal ulcer are interestingly quite opposite to those of gastric ulcers. Duodenal ulcers are the most common ulcers found in western world.

GASTRIC ULCER:

When a peptic ulcer isnin stomach,it is called a gastric ulcer. The symptoms of gastric uvers are more specific than peptic uler symptoms.

ESOPHAGEAL ULCER:

This type of ulcer occurs in the lower end of your esophagus. Esophageal ulcers are often associated with a bad case of acid reflux, of GERD as it is commonly called(short for Gasrto Esophageal Reflux Disease).

BLEEDING ULCER:

Internal bleeding is caused by a peptic ulcer which has been left untreated. When this happens, it is now referred to as a bleeding ulcer-this is the most dangerous type of ulcer. See your doctor immediately if you are showing symptoms.

REFRACTORY ULCER:

Refractory ulcers, are simply peptic ulcers that have not healed after at least 3 months of treatment.

STRESS ULCER:

Stress ulcers are a group of lesions found in the esophagus, stomach or duodenum. These are normally only found in critically ill or severely stressed patients.

DIAGNOSIS OF PEPTIC ULCER DISEASE:

Symptoms depend on ulcer location and patient age. Many, patients particularly elderly patients,have few or no symptoms. Pain is however the most common symptom, often localized to the epigastrium or mid-epigastrium and relieved by food or antacids. The pain is described as bruning, gnawing, constant or annoying, or sometimes a sensation of hunger. The course is usually chronic and recurrent. Only about 50% og patients present with the characteristic pattern of symptoms.

Gastric ulcer symptoms ofter do not follow a consistent pattern (for example, eating sometimes exacerbates rather than relieves, pain). This is especially ture for pyloric channel ulcers, which are often associated with symptoms of obstruction (for example bloating nausea and vomiting) caused by oedema and scarring. In general, however, in gastric ulcers, pain typically starts whenever the stomach is empty (usually approximately an hour after eating), and is generally relieved by antacids or food but aggravated by alcohol and caffeine. Weight loss and gastrointestinal bleding occur more frequently with gastric ulcers. Patients can experience weight loss of 5kg to 10kg and although this could indicate carcinoma, especially in people over 40 years, on investigation a benign gastric ulcer is found most of the time.

Duodenal ulcers tend to produce more consistent pain. Pain is absent when the patient awakens but appears midmorning, is relieved by food,but fecurs two to three hours after a meal. Pain that awakens a person at night, a few hours after falling asleep, is also common and is highly suggestive of duodenal ulcer. The pain then usually subsides by morning and is often relieved after eating. This is not commonly noticed in gastric ulceration. In neonates, perforation or haemorrhage may be the first manifestation of duodenal ulcer. Haemorrhage may also be the first recognized sing in later infancy and early childhood, although repeated vomithing or evidence of

abdominal pain may be a clue. Diagnosis of peptic ulcer is by patient history, and confirmed byendoscopy and testing for H phlori.

Carbon-13 urea breath tests detect active H phlori infection by testing for the enzymatic activity of bacterial urease. In the presence of urease produced by H pylori, labeled carbon dioxide is produced in the stomach, absorbed into the bloodstream, diffused into the lungs and exhaled.

Stool or faecal antigen testing identifies active H pylori infection by detecting the presence of H pylori antigens in stools.

Serology, which is immunoglobulin G(IgG) based, can be measured in serum, plasma or whole bloos. It will, however, not distinguish between a previous or a current infection.

Biopsy-based urease tests, which are invastive and canonly be done atr gastroscopy or in the acute hospital setting. There are two methods for this test. In the CLO test ("Campylobacter-like organisms" test, the rapid urease test) a fragment of mucosal membrane is placed into a special jelly which undergoes a colour change in 10 to 20 minutes, or the specimen is sent ofr histology which may take up to 24 hours to obtain the result.

ENDOSCOPY:

An endoscope is a thin, flexible tube with a tiny camera at the end. The patient is given a mild sedative, and then the tube is passed through mouth in to the lining of the stomach to diagnose a peptic ulcer. Tiny samples of the tissus will be taken (biopsy), which are examined under a microscope.

If a diagnostic imaging test reveals an ulcers, the patient will most likely have a test to see if H pylori bacteria are present.

CAUSES OF PEPTIC ULCER DISEASE:

PROTECTIVE VS.HOSTILE FACTORS:

"No gastric acid, no peptic ulcer" is a misconception. Excessive gastric acid secretion is only one factor in the pathogenesis of peptic ulcer disease. Decreased mucosal defense against acid is another cause. The integrity of the upper gastrointestinal tract is dependent upon the balance between "hostile" factors such as gastric acid, H. pylori, NSAIDs and pepsin, and "protective" factors such as prostaglandins, mucus, bicarbonate, and blood flow to mucosa affecting gastrointestinal mucosa injury to gastric and duodenal mucosa develops when deleterious effects of gastric acid overwhelm the defensive properties of the mucosa. Inhibition of endogenous peostaglandin synthesis leads to a decrease in epithelial mucus, bicarbonate secretion, mucosal blood flow, epithelial proliferation, and mucosal resistance to injury. Lower mucosal resistance

increases the incidence of injury by endohenous factors such as acid, pepsin, and bile salts as well as exogenous factors such as NSAIDs ethanol and other noxious agents.

HELICOBACTER PYLORI:

H. pylori is the etiologic factor in most patients with ulcer disease and may predispose individuals to the development of gastric carcinoma. H. pylori colonizes in the human stomach. The method of H.phlori transmission is ulcer, but seems to be person-to-person spread via a fecal-oral route. The prevalence of H. pulori in adults appears to be inversey related to the socioeconomic status. It is also thought that water is a reservoir for transmission of H. pylori.

NONSTEROIDAI ANTI-INFLAMMATORY DRUGS(NSAIDS):

A small but important percentage of patients have adverse gastrointestinal events associated with NSAID use that results in substantial morbidity and mortality. Risk factors for the development of NSAID-associated gastric and duodenal ulcers include advanced age, history of ptevious ulcer disease, concomitant use of corticosteroids and anticoagulatns, higher doses of NSAIDs, and serious systemic disorders. The concept of gastroduodenal mucosal injury has evolved from the notion of topical injury to concepts that involve multiple mechanism.

NSAIDs initiate mucosal injury topically by their acidic properties. By diminishing the hydrophobicity of gastric mucus, endogenous gastric acid and pepsin may injure surface epithelium. Systemic effects of NSAIDs appear to play a predominant role through the decreased synthesis of mucosal prostaglandins. The precursor of prostaglandins, arachidonic acid, is catalyzed by the cyclo-oxygenase isoenzymes, cyclo-oxygenase-1 and cyclo-oxygenase-2. The gene for cyclo-oxygenase-1. The housekeeping enzyme, maintains the homeostasis of organs. Cyclo-oxygenase-2. the inflammatory enzyme, is inducible. Although NSAIDs can inhibit both pathways, only the gene for cyclo-oxygenase-2 contains corticosteroid-resonsive repressor glement. Literature suggests that the anti-inflammatory properties of NSAIDs are mediated through inhibition of cyclo-oxgenase-2, and adverse effects, such as gastric and duodenal ulceration, occur as a result of effects on the constitutively expressed cyclo-oxygenase-1. H. pylori is prevalent among22-63% of patients taking NSAIDs. Most studies do not show a significant different in H. pylori prevalence between NSAIDs users and nonusers. Gastritis in patients on NSADI therapy appears to be related to underlying H.pylori rather than drug use. The lower incidence of H.pylori among patients with gastric ulcers than those with duodenalucers is persumbaly the result of NSAID use. NSAIDs are more likely to cause gsstric than duodenal ulcers. NSAIDs appear to

cause ulcers by a mechanism independent of H.pylori based on the inhibition of prostaglandin synthesis.

GASTRINOMA (ZOLLINGER-ELLISON SYNDROME:

The classic triad to Zollinger-Ellison syndrome involves peptic ulcers in unusual locations (i.e., the jejunum), massive gastric acid hypersecretion and a gastrin-producing islet cell tumor of the pancreas (gastrinoma). Gastrinoma in the pancreas appears in approximately 50% of patients. Another 20% patients have it in the duodenum and others have it in the stomach, peripancreatic lymph nodes, liver, ovary, or small-bowel mesentery.

Zollinger-Ellison syndrome accounts for only 0.1% of all duodenal ulcer disease. One fourth of patients have this syndrome as part of the multiple neoplasia syndrome type I (MEN I).

Patients with gastrinoma may have intractable ulcer disease. Because gastrin is trophic to the gastric mucosa, endoscopy or x-ray may demonstrate hypertrophy of the gastric rugae. Patients may also experience diarrhea (including steatorrhea from acid inactication of lipase) and gastroesophageal reflux. These symptoms are episodic in 75% of patients.

HYPERCALCEMIA:

Hypercalcemia has a direct bearing on the gastric acid hypersecretory state found in patients with Zollinger-Ellison syndrome and MEN I. Intravenous calcium infusion in normal volunteers induces gastric acid hypersecretion. Additionally, calcium has been demonstrated in vivo and in vitro to stimulate gastrin release directly from gastrinomas. Resolution of hypercalcemia (by parathyroidectomy) reduces the basal acid output and serum gastrin concentration in fasting gastrinoma patients and those with MEN I, suggesting that resolution of hypercalcemia plays an important role in the therapy of this subgroup of patients.

GENETIC FACTORS:

Genetic factors play a role in the pathogenesis of ulcer disease. The lifetime prevalence of developing ulcer disease in first-degree relatives of ulcer patients is about three times greater than the general population. Approximately 20-50% of duodenal ulcer patients report a positive family history; gastric ulcer patients also report clusters of family members who are likewise affected.

SMOKING:

The literature reveals a strong positive correlation between cigarette smoking and the incidence of ulcer disease, mortality, complications, recurrences and delay in healing rates. Smokers are about two times more likely to develop ulcer disease than nonsmokers. Cigarette smoking and H.pylori are co-factors for the formation of peptic ulcer disease. There is a strong association between H.

pylori infection and cigarette smoking in patients with and without peptic ulcers. Cigarette smoking may increase susceptibility, diminish the gastic mucosal defensive factors, or may provide a more favorable milieu for H. pylori infection.

STRESS:

Numerous studies have revealed conflicting conclusions regarding the role of psychological factors in the pathogenesis and natural history of peptic ulcer disease. The role of psychological factors is far from established. Acute stress-results in increases in pulse rate, blood pressure and anxiety, but only in those patients with duodenal ulcers did acute stress actually result in significant increases in basal acid secretion. There is no clearly established "clear –type " personality. Ulcer patients typically exhibit the same psychological makeup as the general population, but they appear to perceive greater degress of stress. In addition, there is no evidence that distinct occupational factors influence the incidence of ulcer disease.

ALCOHOL AND DIET:

Although alcohol has been shown to induce damage to the gastric mucosa in animals, it seems to be related to the absolute ethanol administered (200 proof). Pure ethanol is lipid soluble and results in frank, acute mucosal damage. Because most humans do not drink absolute ehtnol, it is unlikely there is mucosal injury at ethanol concentrations of less than 10% (20 proof). Ethanol at low concentrations (5%) may modestly stimaulate gastric acid secretions; higher concentrations diminish acid secretion. Though physiologically interesting, this has no direct link to ulcerogenesis or therapy.

Some types of food and beverages are reported to cause dyspepsia. There is no convincing evidence that indicates any specific diet causes ulcer disease. Epidemiologic studies have failed to reveal a correlation between caffeinated, decaffeinated,or cola-type beverages, beer, or milk with an increased risk of ulcer disease. Dietary alteration, other than avoidance of pain-causing foods, is unnecessary in ulcer patients.

THE CHANGING SPECTRUM OF THERAPY FOR ACTIVE PEPTIC ULCER DISEASE:

Conventional therapy for the prevention of peptic ulcers: Cimetidine and later ranitidine revolutionized the treatment of peptic ulcers, with H_2 receptor antagonists being the most widely used and effective novel drugs over the past decade. However, relapse ulceration following cessation of treatment with such agents is a frequent clinical observation. It is against this background that we have to deal with the current status and future advances in drug development for the therapy of gastroduodenal ulceration.

H_2 RECEPTOR ANTAGONISTS:

H_2 receptor antagonists are capable of reducing over 90% of basal, food stimulated, and nocturnal secretion of gastriac acid stimulated by histamine, gastrin, cholinomimetic drugs and vagal stimulation. Histamine antagonists prevent occurrence of stress induced ulcers. However, their use in combination with antacids may be preferred. In addition, they are important in the medical management of Zollinger Ellison Syndrome and gastric hypersecretory states seen in systemic mastocytosis. As described earlier, recurrence of ulcer after healing is a frequent complicant of therapy with H_2-receptor antagonists, and therefore long term treatment is required. H_2.receptor antagonists are thus remarkable but not prefect drugs. These drugs include mainly cimetidine, ranitidine, famotidine, roxatidine and nizatidine. Saltidine, mifentidine, TZU-0460, CM-57755 etc. are also under investigation and have shown better antiulcer activity.

Ranitidine Bismuth Citrate: Ranitidine bismuth citrate (RBC) is the new anti-ulcer drug developed by Glaxo Laboratories (U.K.), which when combined with clarithromycin can eradicate H.*pylori in* 94% of patients. This has been confirmed in a clinical trial on 232 patients with duodenal ulcers. RBC was given 400 mg twice daily for 28 days and clarithromycin for times a day for first 14 days.

PROSTAGLANDINS:

In 1979, Robert recognised that PGs inhibits gastric acid secretion and protect against experimental ulcers caused by NSAIDs, diet and life styles(eg. alcohol, smoking and stress). Misoprostol (Cytotec) is a synthetic prostaglandin E analog with acid reducing and cytoprotective properties. Prostaglandins enhance mechanisms thought to be involved in mucosal defense of the chronic peptic ulcer (e.g., the secretion of mucus, output of bicarbonate, and blood flow). It is indicated for the prevention of NSAID-induced gastric ulceration. Short term co-administration of enprostil lowered the serum gastrin levels in patients on long term treatment with omeprazole. Misoprostol does not prevent duodenal ulcer. It is contraindicated in pregnancy because of itsss abortifacient property and requires special precautions if prescribed in pregnancy because of its abortifacient property and requires special precautions if prescribed to women of child bearing potential. The main side effect is diarrhoea in 6 to 30% of users. The synthetic PGs currently available in market are misoprostol, enprostil, rioprostil, arbaprostil and trimoprostil like compounds. Several other compounds like nocloprost, enisoprost, mexiprost, nileprost, rosaprostol etc. are undergoing clinical trials.

H^+ LK^+-ATPASE INHIBITORS:

Blocked of the gastric proton pump constitutes a more direct mechanism for acid secretion inhibition compared to blockade of histamine and cholinergic receptors. Omeprazole is not the active inhibitor of **H^+K^+ APS**ase enzyme but is reversibly transformed in acidic media to the sulphenamide which can react with thiols to form disculfides, thus representing a model for the covalently linked enzyme-drug complex. Omeprazole has been show to inhibit the growth of H. pylori . Recently, lansoprazole has been introduced in the markets of United States of America. NC-1300, RO 18-5362, B831-56 are series of fluorinated benzimidazoles and are potent and long acting inhibitors of acid secretion in animals and have shown mechanism similar to that of omeprazolr.

MUSCARINIC RECEPTOR ANTAGONISTS:

Pirenzepine, a selective muscarinic M-1 receptor antagonists, reduces basal and stimulated acid secretion, in animals and man. Its efficacy in duodenal ulcer is equivalent to cimetidine. It has more cytoprotective effect than of histamine receptor antagonists against gastric mucosal lesions induced by ethanol, HCL, NaOH and taur0cholate. Telenzepine is 4-10 times more potent than pirenzepine,as an inhibitor of acid secretion in rats and dogs.

MUCOSAL COATING AGENTS:

Sucralfate: Sucralfate is a sulfated disaccharide-basic aluminium sulfate complex. It forms an adherent coating with proteinaceous material at ulcerated mucosal sites. When pH is low, there is extensive polymerization and crosslinking of sucralfate. The coating provides barrier to hydrogen ion diffusion, reduces peptic activity and adsorbs bile salts. Further, sucralfate can bind to both epidermal growth factor (FGF),which also enhance ulcer healing. Recently, sucralfate has also been reported to suppress the associated *H pylori* infection.

BISMUTH COMPOUNDS:

Bismuth subcitrate, formerly called tripotassium dicitrate bismuthate (TDB) is the most recent of the bismuth salts to be tested and found effective clinically. The substance is a colloidal suspension. When the pH is above 3.5 to 4.0; it forms a white precipitate in gastric acid. Bismuth subcitrate has a strong affinity for mucosal glycoproteins, especially in the necrotic tissue in ulcer craters. Ulcer craters become preferentially and visibly coated with a white layer of polymer glycoprotein complex, which is only slowly permeated by H_30^+, such that the layer constitutes a diffusion barrier to gastric acid. Bismuth salts also have some antimicrobial activity against

H.pylori infection. However, the chronic use of other bismuth salts has caused encephalopathy and osteodystrophy .

CARBENOXOLONE:

It is a synthetic derivative of glycyrrhizic acid (a constituent of liqyorice) which has been shown to be of value in promoting healing of peptic ulcers. The mechanism of action is not understood but, is believed to involve an effect on mucus, increasing its secretion and viscosity and thus protecting mucosa from attack by acid and pepsin. Its principal adverse effect is sodium retention which may lead to edema, hypertension and heart failure and this limits its use especially in the old people.

MISCELLANEOUS GROUP:

The anti-ulcer activity of calcium channel blockers namely verapamil, nifedipine and diltiazem against experimental ulcers has been established. Proglumide, a cholecystokinin and gastrin receptor antagonist is also found to possess antisecretory and antiulcer activity. The histidine decarboxylase inhibitors like(+) -

PATHOPHYSIOLOGY OF ULCER:

Peptic ulcer is basically a lesion located at the level of the stomach, duodenum or esophagus. Ulcer tends to affect the entire gastrointestinal tract, stating from the lining of the mouth and ending with the rectal region. Peptic ulcer suggests the involnement of hydrochloric acid and pepsin in the development of the disorder. when gastric acid is produced in excess, the mucosal membrane that protects the stomach and internal orgfans from danger is damaged, enabling the bacteria Helicobacter pylori to penetrate the barrier and cause internal infections. Therefore, in the case of peptic ulcer, both gastric acid and bacteria are responsible for the developmebt of the disorder. peptic ulcer located in the stomach is called gastric ulcer; peptic ulcer located at the level of the duodenum is called duodenal ulcer and peptic ulcer developed at the level of the esophagus is called esophagealulcer.

Despite extensive research, the etiology of peptic ulcer disease remains unclear. Given the multiple processes that control acid and pepsin secretrion and defense and repair of the gastroduodenal mucosa, it is likely that the cause of ulceration differs between individuals. Acid and pepsin appear to be necessary but not sufficient ingredients in the ulcerative process. It is clear that the majority of gastric ulcers and a substantial number of duodenal ulcers do not have increased gastric acid secretion. Recent research has focused more on protection and repair of the stomach and duodenum.

Historically, our understanding of the pathophysiology of peptic ulcer disease focused on abnormalities in the secretion of gastric acid and pepsin, and on the suppression of acid as a treatment strategy. Today, gastric hypersecretion-associated with gastrinoma in Zollinger- Ellison syndrome, antral G-cell hyperplasia, an increase in parietal-cell mass, and a physiological imbalance between the antagonistic gastric hormones gastrin and somatostatin-is still an important issue in peptic ulcer disease. Moreover, it is known that cholinergic hypersensitivity and parasympathetic dominance are related ot the stimulation not only of hydrochloric acid but also pepsin, which is often neglected as a cofactor in the development of erosive injury to the gastric mucosa. Psychologic stess, cigarette smoking, alcohol consumption, use of nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin, oral bisphosphonates, potassium choloride, immunosuppressive medications, and an age-related decline in prostaglandin levels have all beeb shown to contribute to peptic ulcer disease. It was, however, the isolation of *H.plori* and its identification as the most important cause of peptic ulcer disease that led to exploration of the role of inflammation and its associated cytokine cascade in gastric acid secretion.

H. pylori evades attack by the host immune system and causes chronic, indolent inflammation by several mechanisms. *H.pylori* can damage the mucosal defense system by reducing the thickness of the mucus gel layer, diminishing mucosal blood flow, and interacting with the gastric epithelium throughour all stages of the infection. *H. pylori* infection can also increase gastriac acid secretion; by producing various antigens, cirulence factors, and soluble mediators, *H.pylori* induces inflammation, which increases parietal-cell mass and, therefor, he capacity to secrete acid. The H. pylori cytotoxin-associated gene CagA also has an important role: it interferes with gastric epithelial cell-signaling pathways, thereby regulating cellular responses and possibly contributing to apical junction barrier disruption, interleukin-8 secretion and phenotypic changes to gastric epithelial cells.

Understanding the pathophysiology of peptic ulcer disease is at something of a crossroads: mechanisms of injury differ distinctly between duodenal and gastric ulcers. Duodenal ulcer is essentially an *H.pylori* related disease and is caused mainly by an increase in acid and pepsin load, and gastric metaplasia in the duodenal cap[25]. Gastric ulcer, least in Western countries, is most commonly associated with NSAID ongestion, although *H.pylori* infection might also be present[26]. Chronic, superficial and atrophic gastritis predominate in patients with gastric ulcers, when even normal acid levels can be asociaged with mucosal ulceration[27]. In both conditions, ulcer is

associated with an inbalance between protective and aggressive factors, with inflammation being a leasing cause of this imbalance.

The isolation of *H.pylori* in the early 1980s was one of the most exciting advances in the history of peptic ulcer disease[28], and it has dramatically changed the management of peptic ulcer. Eradication of *H.pyori* infection is now the mainstay of treatment for peptic ulcer disease, and has resulted in very high ulcer healing rates and recurrence rates that have dropped dramatically, espedially for individuals with a duodenal ulcer. The greater recognition of the role of NSAIDs and aspirin in gastrointestinal-tract injury has led to the development of therapeutic and preventive strategies that rely on the use of antisecretory drugs, the prostaglandin analog misoprostol, or selective cyclo-oxygenase (COX)-2 inhibitors(coxibs).

TESTS FOR DIAGNOSING HELICOBACTER PYLORI:

The following tests are used to diagnose *Helicobacter pylori* infection Testing may also be done after treatment to ensure the bacteria are fully eradicated.

1. **BREATH TEST:** A simple test called the carbon isotope-urea breath test (UBT) can identify up to 99% of people who harbor *Helicabacter pylori.* Up to 2 weeks before the test, the patient must descontiune taking any antibiotics, bismuth-containing agents such as Pepto-Bismol and proton-pump inhibitors (PPIs). As part of the test, the patient swallows a special substance containing *urea* (a compound in mammals metabolized from nitrogen) that has been treated with carbon atoms. *If Helicobacter pylori* are present, the bacteria convert the urea into carbon dioxide, which is detected and recorded in the patients's exhaled breath after 10 minutes. This test can also be used to confirm that *Helicobacter pylori* have been fully treated.
2. **BLOOD TESTS:** Blood tests are used ot measure antibodies to *Helicobacter pylori,* with results available in minutes. Diagnostic accuracy is reported at 80-90%. One such important test is called enzyme-linked immunosorbent assay (ELISA). An ELISA test of the urine is also showing promise in children.
3. **STOOL TEST:** A test to detect genetic fingerprints of *Hekucibacter pylori* in the feces appears to be as accurate as the breath test for initial detection of the bacteria and for detecting recurrences after antibiotic therapy. This test can also be used to confirm that the *Helicobacter pylori* infection has been fully treated.
4. **TISSUE BIOPSY:** The most accurate way to identify the presence of *Helicobacter pylori* is a tissue biopsy from the lining of the stomach. However, this is clearly an

incasive task and many patients are treated for *Helocobacter pylori* based on the above three noninvasive tests.

It should be noted that such tests are not as accurate as endoscopy, an invasive procedure, which is needed to confirm a diagnosis of *Helicobacter pylori*. The breath and stool tests, however, can be – are used most often. Other durgs that may be useful include H_2 blockers, such as Famotidine(Pepcid AC), Cimetidine (Tagamet), and Ranitidine (Zantac). Sucralfate is another drug used to heal ulcers and reduce the stomach upset caused byNSAIDs.

A number of alternative medications may be tried for people with chornic pain, to minimize the risk of ulcers associated with NSAIDs.

1. **COX-2 INHIBITORS (COXIBS):** Coxibs block an inflammation-promotin enzyme called COX-2. This drug class was initially thought to work as well as NSAIDs, while causing less gastrointestinal distress. However, following numerous reports of cardiovascular events, the FDA banned Rofecoxib (Celebrex) is still available, but patients should discuss with their doctor wheter this drug is appropriate and safe for them. The use of Cox-2 inhibitors may provide a decrease in uncomplicated ulcers, but more serious events do not seem to be reduced by the use of these medications
2. **ARTHROTEC:** Arthrotec is a combination of Misoprostal and the NSAID Diclofenac. It may reduce the risk for gastrointestinal bleeding. This drug can cause miscarriage (abortion) at any stage of pregnancy and therefore should not be used during pregnancy.
3. **ACETAMINOPHEN:** Acetaminophen (Tylenol, Anacin-3) is the most common alternative to NSAIDs. Acetaminophen is inexpensive and generally safe. It poses fat less of a risk of gastrointestinal problems than NSAIDs. It dose should not exceed 4 grams (4,000mg); some studies suggest that ulcer risk is increased even in dose exceeding 2 grams (2,000 mg) a day, if the dryg is used on a long-term basis. Patients who take high doses of Acetaminophen for long periods are also at risk for liver damage, particularly if they drink alcohol. It may pose a small risk for serious kidney complication in people with preexisting kidney disease, although Acetaminophen remains the drug of choice for patients with impaired kidney fuction.
4. **TRAMADOL:** Tramadol (Ultram) is a pain reliever that has been used as an alternative to opioids. It has opioid-like properties, but is not as addictive. However, dependence and abuse have been reported. It can cause nausea, but does not cause severe gastrointestinal problems, as NSAIDs can. Some patients experience severe itching. A

combination of Tramadol and Acetaminophen (Ultracet) provides more rapid pain relief than Tramadol alone and more durable relief than Acetaminophen alone. Side effects are the same as for each of these agents.

5. If continuation of NSAIDs is necessary, the lowest possible dose should be used.

PROTON-PUMP INHIBITORS(PPIs):

ACTIONS AGAINST ULCERS:

PPIs are the drugs of choice for managing patients with peptic ulcers, regardless of the cause. They suppress the production of stomach acid by blocking the gastric acid pump --- the molecule in the stomach glands that is responsible for acid secretion[30].

PPIs can be used either as part of a multidrug regimen for *Helicobacter pylori* or alone for preventing and healing NSAID-caused ulcers. They are also useful in treating ulcers caused by Zollinger-Ellison syndrome. They are considered to be more effective than H2 blockers.

STANDARD BRANDS:

Most PPIs anr available by presctiption as oral drugs. There is no evidence that one brand of PPI works better than another. Brands approved for ulcer prevention and treatment include:

1). Omeprazole (generic, Prilosec OTC)

2). Esomeprazole (Nexium)

3). Lansoprazole (Prevacid)

4). Rabeprazole (Aciphex)

H_2 BLOCKERS:

H_2 blockers interfere with acid production by blocking histamine, a substance produced by the body that encourages acid secretion in the stomach. H_2 blockers were the standard treatment for peptic ulcers until proton pump inhibitor and anticiotic regimens against *H. pylori* were developed. These drugs cannot cure ulcers, but they are useful in certain cases. They are effective only for duodenal ulcers, however.

Four H_2 blockers are currently available over-the-conter in the U.S.: Famotidine (Pepcid AC), Cimetidine (Tagamet), Ranitidine (Zantac), and Nizatidine (Axid). All have good safety profiles and fews side effects. There are some differences between these drugs:

1. **FAMOTIDINE (PEPCID AC):**

Famotidine is the most potent H2 blocker. The most common side effect is headache, which occurs in 4.7 % of people who take it. Famotidine is virtually free of drug interactions, but it may have significant adverse effects in patients with kindbey problems.

2. **CIMETIDINE (TAGAMET):**

Cimetifine has few side effects; about 1%of people taking Cimetidine experience mild temporary dearrhea, dizziness, rash, or headache. Cimeridine interats with a number of commonly used medications, including phenytoin, teophylline, and warfairn. Long-term use of excessive doses (more than 3 grams a day) may cause impotence or breast enlargement in men. These problems resolve after the drug is discontinued.

3. **RANTITDINE (ZANTAC):**

Ranitidine interacts with very few drugs. In one study, Ranitidine provided more pain frlief and heald ulcers more quickly than Cimetidine in people younger than age 60, but there was no difference in older patients. A common side effect of Ranitidine is headache, which occurs in about 3% of people who take it.

4. **NIZATIDINE (AXID):**

Nizatidine is nearly free of side effects and drug interactions.

TREATMENT OF H.*PYLORI* INFECTION:

Ultrastructural studies have shown that following an exposure to bismuth preparations *H.pylori* detaches from the gastric epithelium and gers lysed within 30-90min. in spite if tge clinical syooressuib of *H. pylori* with oral bismuth, recrudescence is extremely common following monotherapy with bismuth. Therefore, it seems obvious that short term treatment with bismuth alone is inadequate for *H.pylori* infection. Chronic administration of bismuth for the treatment of *H.pylori* is sensitive to a wide range of anti-microbials including ampicillin, erythromycin, tetracyclines, ciprofloxaxcin, olfloxacin, metronidazole, tinidazole and nitrofutantion. But, monotherapy with antibiotics has been shown to lead to the rapid onset of resistant organisms in some circumstances. Acquired resistance to quinolones has been demonstrated in *H.pylori* after olflozacin and ciprofloxacin. The inadequacy of single agent therapy has les some workers to propose that a combination of bismuth with antibiotics, may provide the optimum approach. Combination therapy has provided the best results todate. Eradication rates vary from 40% with TDB and amoxicillin to 80% with TDB and metronidazole. Triple therapy has been found still more effective and 96% of patients will eradicate the oraganism with TDB, metronidazole and

tetracycline (or amoxicillin) combination. Further, it is reported that the efficacy of many antibiotics is pH dependent. Hence , there is a ratinlae for combination of acid inhibitory drugs with antibiotics in the treatment of *H.pylori* infection. A controlled study of combination therapy with omeprazole and amoxicillin in patient with duodenal ulcer showed eradication of *H.pylori* in 82% of patients. Over the past five years, several workers have suggested that eradication of *H.pylori* significantly reduces the rate of duodenal ulcer relapse. Recently, National Institute of Health (NIH) Consensus Conference recommended H.pylori eradication regimen as the first line medical therapy for patients with peptic ulcer disease who are *H.pylori* positive .

THERAPY AND PREVENTION OF NSAID ASSOCIATED ULCERS:

Ulcers associated with NSAIDs usually heal spontaneously when the NSAIDs are withdrawn. Even with the continued use of NSAIDs, ulcers may heal spontaneously. Limited studies suggest that H_2 blockers, prostaglandins, and omeprazole accelerate jealing as compared to placebo. Omeprazloe is emerging as the most promising agent for troublesome ulcers, especially when NSAIDs cannot be discontinued. A few trials have tested regimens for the prophylactic treatment of NSAID-associated ulceration. A three month trial indicated that misoprostol prevented NSAID-associated gastric ulcer, but data is lacking on the efficacy of PGs in preventing NSAID-associated duodenal ulcer. One short term study proved higher efficacy of PGs than H_2 blockers in preventing NSAID-associated gastric damage whereas H_2-blockers were effective in preventing duodenal damage.

TREATMENT OF REFRACTORY ULCERS:

Regardless of the mode of therapy, the healing of ulcers is time dependent; 90 to 95 precent of all ulcers heal if therapy is continued for 12 weeks. After that, ulcers or symptoms (or both) can be considered refractory to therapy. Since persisten symptoms may not be due to persistent ulcer disease, endoscopy is essential to establish the diagnosis. If persistent ulceration is found on endoscopy, a few possibilities ulceration is found on endoscopy, a few possibilities warrant consideration. Poor patient compliance, use of NSAIDs, smoking and gastrinoma are common causes of refractory ulceration. The role of *H.pylori* infection in refractory ulceration also remains uncertain. A 40mg dose of omeprazole or a full dose antisecretory therapy will probably have to be continued to maintain the healing of refractory ulcers, since it does not alter the natural history of ulcer disease. Treatment with bismuth or the eradication of *H.pylori* (or both) deserves consideration for patents who do not respond to conventional therapy.

RECURRENCE OF DUODENAL ULCERS:

Duodenal ulcers recur in 70 to 90% of paients within 1 year of the cessation of drug therapy. The evidence suggests that the rate of refurrrenfe differs depending on the initial therapy used.

The relapse rates are higher after healing with H_2 antagonists as compared ot tri-potassium di-citrato bismuthate therapy. Maintenance therapy with an H_2-receptor antagonists reduces this rate to 40%. Patients with complications of recurrence or those takingNSAIDs, and those who have pulmonary, renal or heart diseases are considered to be at a higher risk and should be placed on maintencnce therapy to avoid recurrence. A single night time administration of H_2 antagoinst at a dose of one half of the normal therapeutic dose is appropriate. This should be caontiuned for one year. Sucralfate, 1g at bedtime, is also an effective maintenance regimen. Patients should be then reassessed for further therapy. Patients who have a minimal risk and who experience a recurrence should be reevaluated and reassingned to maintenance therapy. Maintenance therapy is also appropriate for recurrent gastric ulcer, but the response rate may not be as high as that for duodenal ulcer.

MEDICINAL PLATNS FOR THE TREATMENT OF ANTIULCER:

In this modern era also 75-80% of the world populations still use herbal medicine mainly in developing countries, for primary health care because of better cultural acceptability, better compatibility with the human body and lesser side effects. The chemical constiruents present in the herbal medicine or plant are a part of the physiological functions of living flora and hence they are belived to have better compatibility with human body.

Natural products from plants are a rich resource used for centuries to cure various ailments. The use of natural medicine in the treatment of various diseases like peptic ulcer is an absolute requirement of our time. Therefore, alternative approach in recent days is the research of medicaments from traditional medicine. The use of phyto constituents as drug therapy to treat major ailments has proved to be clinically effective and relatively less toxic than the existing drugs and also reduces the offensive factors serving as a tool in the prevention of peptic ulcer.

ANTI ULCER ACTIVITY OF THE SOME IMPORTANT MEDICINAL PLANTS:

Jasminum grandi florum, Anogeissus latifolia, Alchornea castaneaefolia, Utleria salicifolia, solanum nigrum, Oimum sanctum, Scoparia dulcis, Bry sonima crassa, Asparaagus racemosus, centaurs Solstitialis, Anacardium Occidentale, callophyllum brasiliense, Rhizophora mangle, Larrea diraricata, Hemidesmus indicus, Spaartium junceum, Amomum subulatum, Aloe vera, Butea frondosa,Capsicum annuum, curcuma longa, Desmostachya bipinnata, Exocoecaria

agallocha, mangifera indica, morus alba, Ocimum Sanctum, Panax ginseng, Piper betel, Polyalthia longifolia, Rhizophora mangle, Sapindus trifoliatus, Sollanum nigurm, Syzygiym aromaticum, Terminalia chebula, Triticum aestivum, Vinca minor, Zingiber officinalis, Ficus religiosa, Hibiscus roasainensis, Indigofera tinctoria, Lawsonia alba, Myrtus Communis, Momordica charantia,carica papaya, Adansonia digitata, Allium sativum, Psidium gujava, Rhuscoriaria, Sesbania grandiflora, Shorea robusta.

CONCLUSION:

Preliminary phytochemical screening of this medicinal plants identified the presence of important secondary merabolities like flavonoids and tannins. There are several botanical products with potential therapeutic applications because of their high efficaly and low toxicity. These plants provide leads to find therapeutically useful compounds, thus more efforts should be made towards isolation and characterization of the active principles and their structure active relation ship. From this study, it is clear that the medicinal plants paly a vital role against various diseases.

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