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PEPTIC ULCEROGENESIS: ETIOLOGY, PATHOGENESIS AND VARIOUS CLINICAL ASPECTS

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ABSTRACT: "Eat to live and don't live to eat" this is a principle to be followed for a healthy and wealthy life. According to the therapeutic point of view, the patient who suffers from peptic ulcer diseases was shown to have a reduced secreted amount of HCl and pepsin. The management of gastric and duodenal ulcers can be followed by the decreased or neutralized level of gastric acid. Peptic ulcer influences up to 10% of the all-out total populace accordingly called chronic disease. Peptic ulcer arrangement relies on the lessening in the mucosal guards and on the nearness of the gastric juice pH. The two central points which disturb the mucosal protection from damage is the *Helicobactor pylori* (*H. pylori*) contamination and Non-steroidal calming drugs (NSAIDs). The valuable medicines of peptic ulcer are Proton pump inhibitors, Histamine-2 (H_2) receptor antagonists, Antacids, Anticholinergics, Mucosal defensive agents, Bismuth compounds, Antimicrobial agents, and cholecystokinin-2-receptor antagonists drugs. The review contains the detailed study of H_2 receptor antagonist drugs used as anti ulcers and the recent advancements to cure peptic ulcer disease. To heal the ulcer, the following factors are implied- a strict diet, anti-secretory, and motor-inhibitory drugs, antacids, sedatives, physical and mental rest, and strict prohibition from alcohol and stimulants like alcohol and caffeine-containing products.

INTRODUCTION: A peptic ulcer is an illness of the digestive tract, which is alluded to as the corrosive peptic damage, brings about a mucosal break to arrive at the submucosa or muscularis propria [1]. Peptic ulcers can be found in the esophagus as well as Mackel's diverticulum, but it is located in the stomach or proximal duodenum [2]. The absence of keeping up a balance between some endogenous components or cytoprotective or defensive factors brings about a peptic ulcer.

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All the more early factors, for example, HCl, Pepsin, leukotrienes, Reactive Oxygen Species (ROS) and later factors, for example, a nitric oxide (NO), mucosal bloodstream, prostaglandins (PG), surface-dynamic phospholipids and cell movement, enzymatic and non-enzymatic antioxidants, and some growth factors are additionally answerable for the disease.

The etiological factors, for example, less eating routine, stress, hypersecretory acid environment, long haul utilization of NSAIDs, *H. pylori* disease, high intake of alcohol and smoking, and some hereditary variables are likewise responsible for this disease. In the past 30 years, a sharp decrement in the rates and incidence ratio of hospitalization and mortality rate was noticed [3-4].

Gastric and duodenal ulcers are significantly brought about by *H. pylori* diseases and more utilization of NSAIDs [5]. In various cytokine genes, the functional polymorphisms are related to peptic ulcers. Example- the mucosal interleukin 1 creation is influenced by polymorphisms of interleukin 1 beta (IL1β), which causes H. pylori-related gastric and duodenal diseases [6]. On another term, the individuals who use NSAIDs are four times in the more danger of difficulties of peptic ulcer and two times in aspirin users [7]. The danger of upper gastrointestinal draining is expanded by the resulting utilization of NSAIDs or aspirin with corticosteroids, anticoagulants, and particular serotonin reuptake [8]. As indicated by the consequence of different logical observational examinations, it has been presumed that NSAIDs, aspirin and *H. pylori* contaminations will in general increment the danger of peptic ulcer disease. As of the bleeding trauma patient cases, bleeding peptic ulcer must also be taken into consideration and requires a fast surgical/ medical approach for the stabilization of the clinical image [9].

Clinical conditions like stress, trauma, burn shock, head injury, and neurological disorders are associated with the stress ulceration of the stomach. It has resulted from the interactions between vascular, neuro-humoral, and mucosal factors, and ANS plays a crucial role in **Fig. 1**. The gastric emissions and gastric motility are expanded by the incitement of Medulla oblongata. The gastric secretions are increased, and gastric mucosal resistance is reduced due to stress releasing adrenocorticotropic hormone (ACTH) released by the disturbed functions of the anterior pituitary.

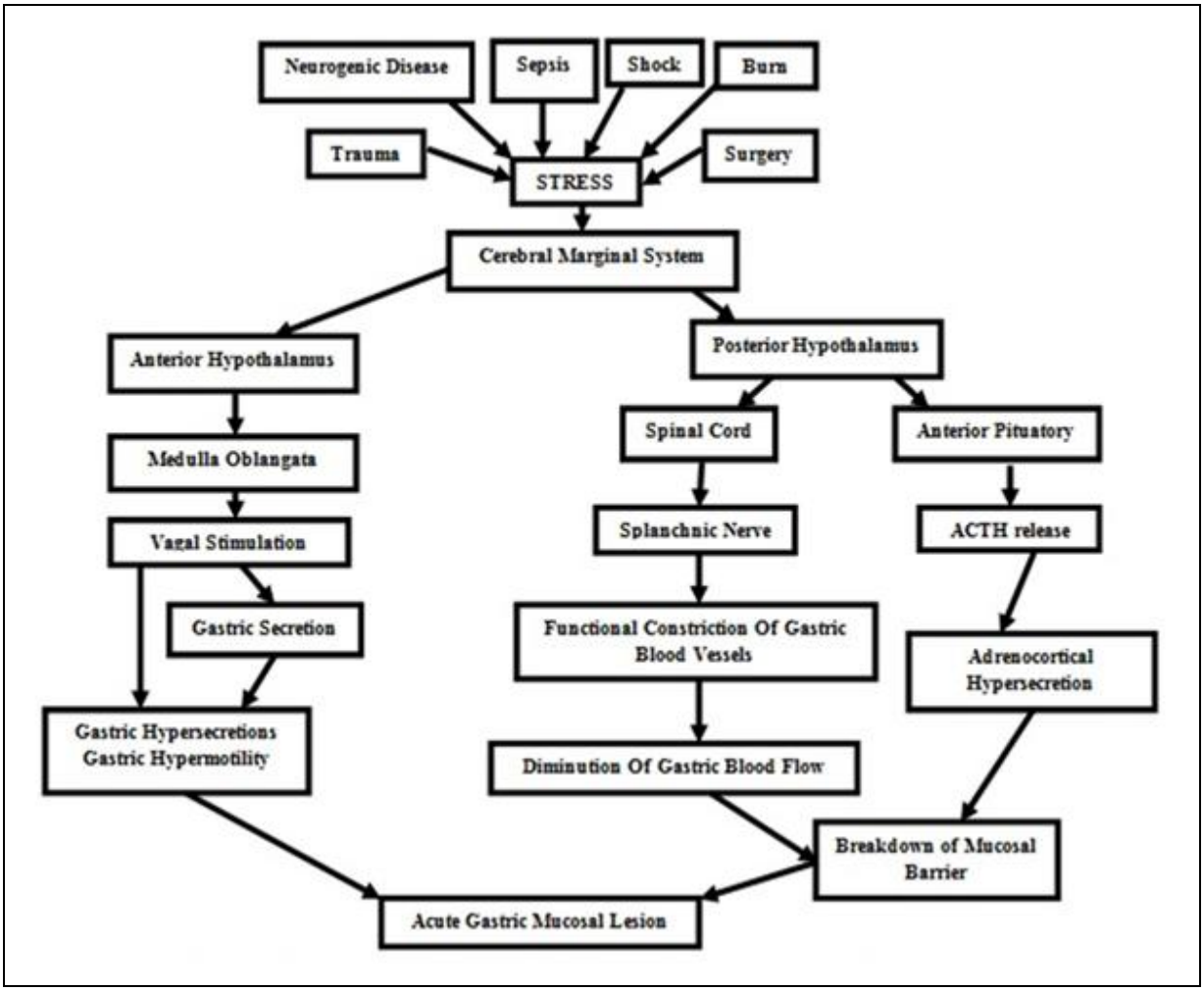

FIG. 1: ROLE OF AUTONOMIC NERVOUS SYSTEM (ANS) IN THE MECHANISM CAUSING PEPTIC ULCER

History: For more than a thousand years, sound individuals were seen with nausea, acute stomach torment, vomiting, and looseness of the bowels, which caused the demise of individuals in only a couple of hours or days. Individuals with these indications were given toxin and were sent to jail

for having such symptoms. Because of the pestilence changes in *H. pylori* contaminations, it has been seen that gastric and duodenal ulcers, peptic ulcer malady turned out to be progressively predominant in western nations in the nineteenth-century. This examination was, to a great extent, dependent on the clinical reports and the confirmations of individuals in the emergency clinics, **Fig. 2**.

The peptic ulcer has been the non-lethal ailment; it was not had the option to analyze before the twentieth century when endoscopy, medical procedure, and radiology got accessible. Until recent times, the autopsy was the only method to be known who allowed one peek, at which point the disease has occurred in life. In 1950 an encyclopedic book summarized peptic ulcer disease, 49 pages chapter was entitled by Ivy, Grossman, and Bachrach named "Postmortem incidence concerning pathogenesis" in which they gave the relevant data available for Europe in 19th century [10].

The perforated peptic ulcer (PPU) was closed by basic conclusion by the specialist Johan Mikulicz-Radecki (1850–1905) who said: "Every doctor, faced with a perforated duodenal ulcer of the stomach or intestine, must consider opening the abdomen, sewing up the hole, and averting a possible inflammation by careful cleansing of the abdominal cavity." Even though, this therapy sounds extremely easy to be operated perforated peptic ulcer remains a dangerous surgical operation which has a high number of morbidity and death rate that can't be disparaged.

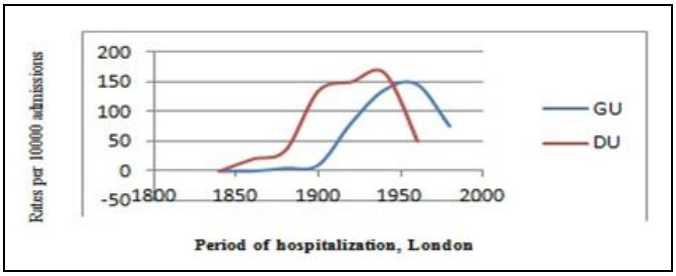

FIG. 2: PATIENTS ADMITTED FOR GASTRIC AND DUODENAL ULCER IN 12 HOSPITALS IN LONDON WITH RATE PER 10000 ADMISSIONS IN EACH 5 YEARS TIME INTERVAL

Epidemiology: About 5% of the worldwide populace is influenced by peptic ulcer disease. There are around 80-95% of patients with duodenal ulcers and about 70-90% of patients with gastric ulcer who are contaminated with *H. pylori*. Around 15,000 deaths have been assessed because of peptic ulcer disease. The contamination of *H. pylori* has been evaluated to ascend by around 29.7% under 30 years of age and is 63% at the age of 55-65.

In the overall public, the lifetime inescapability of peptic ulcer disease has been evaluated to be around 5-10% and incidence rate of about 0.1-0.3% per annum [2, 11]. Because of a sharp diminishing pattern in the occurrence rate that appeared in epidemiological examinations, conceding the patient in the emergency clinic and relationship of the mortality with the ailment before, the inescapability and rate of peptic ulcer sickness in high-pay nations is presently most likely lower than these evaluations worldwide. Although a fall in the frequency of gastric disease, it is the second driving reason for malignant growth-related deaths and fourth-most regular malignancy worldwide [12].

Perforated ulcer disease (PUD) causes the death of more than 70% due to the occurrence of perforation in 2-10% of patients. Perforation is regularly observed as the principal clinical examination of perforated ulcer disease. The perforation site contains 60% of the foremost mass of the duodenum, which may happen in antral for about 20% and lesser-curvature gastric ulcer for about 20%. The pace of occurrence of duodenal perforation is among 7-10 cases in 100,000 grown-ups per year. The present pinnacle age for Perforated Peptic Ulcer (PPU) is 40-60%. Previously, PPU was said to be the disease in younger patients (usually males), but in recent times, the age of patients suffering from PPU is gradually increasing (predominantly females) Since the presentation of H_2 receptor antagonists, the death pace of peptic ulcer medical procedure has not diminished which causes the passing of 20,000-30,000 patients for each year in Europe. This is caused because of the extreme utilization of aspirin or NSAIDs.

Pathogenesis: One of the fundamental normal reasons for peptic ulcers by which practically 50% of the total populace is colonized is *H. pylori*. The presence of *H. pylori* is particularly high in developing areas, generally in Africa, Central Asia, Eastern Europe, and Central America [13] **Fig. 3**.

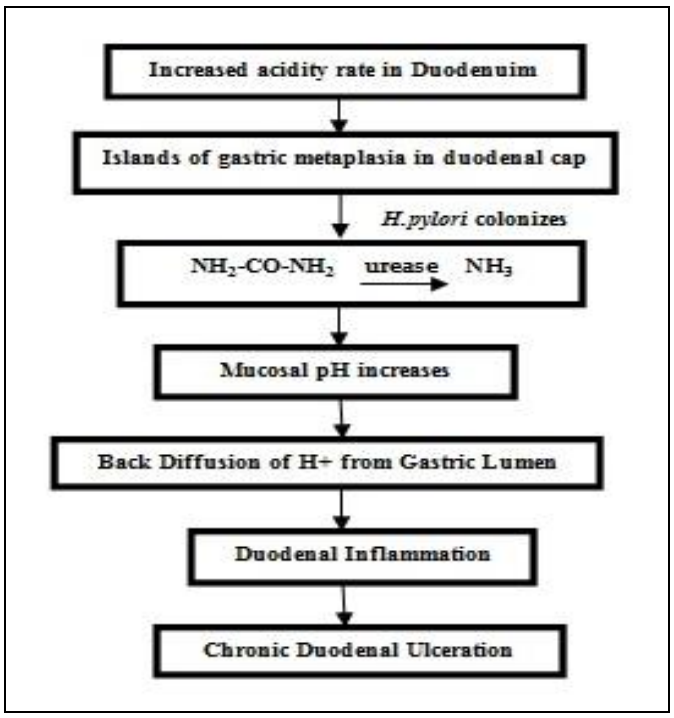

FIG. 3: PATHOGENESIS OF CHRONIC DUODENAL ULCERATION

Role of *H. pylori*: About 95% of the patient with Gastric Ulcer is found to have *H. pylori* in their antrum [14]. *H. pylori* are found in the mucus layer or underneath the mucus layer, adhered to the gastric epithelium close to intracellular intersections. As the patients with positive *H. pylori* infection decreases worldwide, it causes the decrement in the duodenal ulcer patients as well as the decrease in the growth of *H. pylori* infection [15]. Even though having its abnormal living, *H. pylori* is an amazing maker of urease and discharge ammonia consequently which may bring about giving a microenvironment of raised Ph, which encourages the living organism to survive in the body. This ammonia released in the body might be cytotoxic in nature. It involves a genome of around 1,600 genes and is profoundly heterogeneous. Genes related to virulence are *CagA* (Cytotoxin-Associated Gene A Product), *VacA* (Vacuolating Cytotoxin), *OipA* (Outer Inflammatory Protein) and *DupA* (Duodenal Ulcer Promoting) **Fig. 4**.

1. *CagA* (Cytotoxin-Associated Gene A Product): It is arranged at the one finish of cag pathogenicity island. It structures syringe-like pilus and is moved to the host cell via a type IV secretory system, which brings about the translocation of peptidoglycan, CagA, and other bacterial components into host epithelial cells.

2. VacA (Vacuolating Cytotoxin): This gene encodes vacuolating cytotoxin. This gene is associated with the formation of membrane channel, *i.e.,* cytochrome c, which releases from mitochondria and prompts apoptosis and ties to the receptors of cell membrane followed by the commencement of pro-inflammatory responses.

3. OipA (Outer Inflammatory Protein):- This gene is the external membrane protein that involves adhesion. It is known to be the better marker of extreme clinical results than CagA.

4. DupA (Duodenal Ulcer Promoting): The notable attributes of duodenal ulcers include the induction of IL-8 production in the antrum, which drives to tantrum predominant gastritis. As indicated by the reports, it has been noticed that *H. pylori,* which contains a high amount of DupA, causes a high measure of IL-12 created in monocytes.

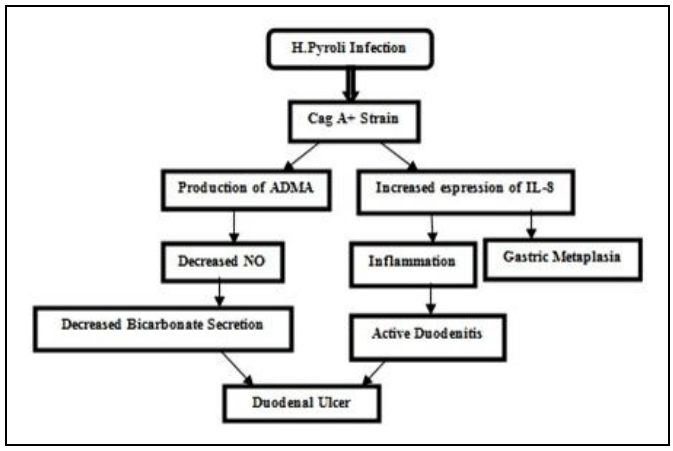

FIG. 4: A COMPARATIVE FLOW CHART SHOWING THE ROLE OF *H. PYLORI* RESPONSIBLE FOR INDUCTION OF DUODENAL ULCERATION AND GASTRIC METAPLASIA

The ADMA is produced by the actuated *H. pylori* CagA + strain, which prompts a diminished synthesis of NO. This outcome in the suppression of bicarbonate secretion and causes more measures of acidification. IL-8 production is likewise actuated by *H. pylori,* and IL-8 causes inflammation in the duodenum and gastric metaplasia due to having cancer-causing and proangiogenic factors. Proton pump inhibitors are known as the most useful, beneficial, and popular prophylactic agents to treat peptic ulcer [18]. For the destruction of *H. pylori,* first-line therapy is used, which is known as triple therapy as it includes PPIs

and two antibiotics like metronidazole or Clarithromycin plus amoxicillin to be given for 14 days period [16]. In case the first-line therapy fails to treat a patient, then second-line therapy is used, which does not contain the use of Clarithromycin or metronidazole [17].

Peptic Ulcer and Oxidative Stress: Peptic ulcer and gastric carcinoma are accepted to be started and aggravated because of the oxidative stress actuated by *H. pylori* and NSAIDs. Patients saw with increment serum LPO and diminished level in SOD and CAT levels show a positive correlation between oxidative stress in ulcers and gastric carcinoma. Glutathione, an antioxidant, helps in forestalling cell damage, which is brought about by ROS, for example, peroxides and free radicals. Cellular GSH levels are decreased by incitement of ROS production from gastric epithelial cells by *H. pylori*.

Prostaglandins (PGs) are said to carry on the best ulcer healing agents. The decrease in the synthesis of PGs causes decline mucosal defense and increases the hazard to ulcers because of a decreased level of linoleic acid (LA), α- linolenic acid (ALA), and essential fatty acids (EFA) in duodenal ulcer patients. Nitric oxide (NO) I said to be an efficient vasodilator as it provides protection against ischemic injury by maintaining the mucosal blood flow and is also a defense factor for mucosa. Manjari and Das found that degree of liquid peroxidation and NO were in the high sum in patients with DU through catalase, GSH, arachidonic acid, α-linolenic acid docosahexaenoic acid and concentration of SOD were in low levels so these irregularities can get typical by the treatment of the patient with proton pump inhibitors. This investigation demonstrated that polyunsaturated fatty acids (PUFAs) could be utilized as anti-ulcers drugs as they repress the development of *H. pylori*.

NSAIDs bring about the diminished production of PGs by restraining the enzyme cyclooxygenase (COX). NSAIDs cause mucosal harm by the enrollment of leukocytes and production of reactive oxygen species (ROS), which leads to mucosal injury and apoptosis because of the ROS intervened mitochondrial damage, lipid, protein and DNA oxidation **Fig. 5**. Numerous preventive therapies are available to prevent NSAIDs and aspirin caused peptic and duodenal ulcers with a variety of complications like co-therapy of NSAIDs with H_2 receptor antagonist, PPIs, or misoprostol; COX-2-selective NSAIDs can also be used, or their combinations with gastroprotective agents can also be taken into usage [18].

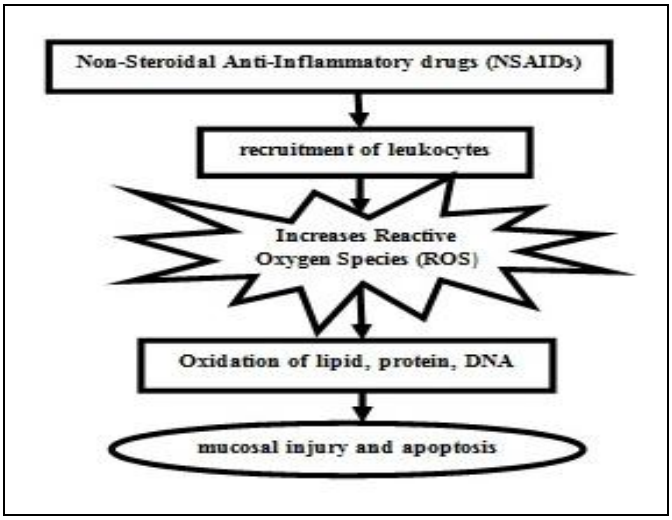

FIG. 5: NSAIDs INDUCED OXIDATIVE STRESS CAUSES MUCOSAL INJURY AND APOPTOSIS

Pathogenesis of Peptic Ulcer *via* Inflammatory Cytokines: The creation of various pro-inflammatory cytokines in gastric mucosae for example, interleukin-1β, interleukin-8 (IL-8) and tumor necrosis factor- α is enhanced by *H. pylori* and causes the infiltration of mononuclear leukocytes and polymorphonuclear (PMN). IL-8 has been overexpressed in gastric malignancy cells as indicated by the correlation of normal mucosa cells in this way found to be an as carcinogenic and pro-angiogenic factor. In nude mice, tumorigenesis and angiogenesis of human gastric carcinoma cells increment by the transfection of IL-8. The neutrophils are initiated by the water extract *H. pylori*. Further, the adhesion is caused between CD11b/CD18 on neutrophils and ICAM-1 on endothelial cells. A bacterial cytosol protein that is H.pylori neutrophil-activating protein (HP-NAP) helps in advancing the adhesion of neutrophil to endothelial cells. *H. pylori* neutrophil-activating protein (HP-NAP) goes about as a chemotactic factor for monocytes and neutrophils as it works on the human immune system as an antigen by activating NADPH oxidase. The synthesis of plasminogen activator inhibitor-2 (PAI-2) and tissue factor is also stimulated by HP-NAP.

Tyrosine phosphorylation and NF-kB is activated by the induction of epithelial IL-8 by living bacteria. An NF-Kb-inducing kinase (NIK) is enacted by *H. pylori* using TNF receptor-associated factor 2 (TRAF2) and TRAF6, then this activated NIK phosphorylates and in result activates IKK-α and IKK-β, which again on phosphorylation turns to IkBα, causes the proteasomal degradation. By binding to the promoting district of the IL-8 gene, the homo or heterodimer of NF-Kb translocates into nucleus adapting expressions of IL-8. Inducible Nitric oxide synthase (iNOS) is therefore activated by the induction of NF-Kb, which causes Tumor necrosis factor α (TNF-α) mediated apoptosis, induction of human β defensin-2 (HBD-2) by expanding the expression of apoptotic proteins and anti-apoptotic proteins **Fig. 6**.

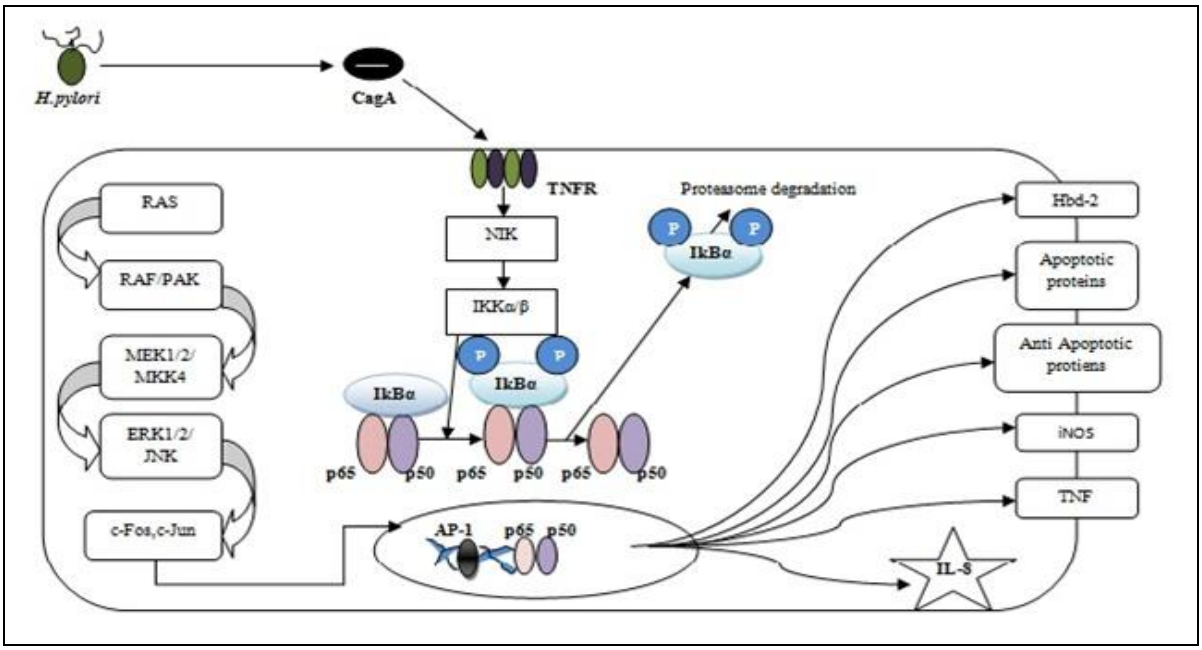

FIG. 6: *H. PYLORI* INDUCED INFLAMMATORY MEDIATORS

Pharmacological Treatments: An overview of useful antiulcer drugs are summarized in the given **Table 1**.

TABLE 1: VARIOUS ANTI-ULCER DRUGS WITH THEIR MECHANISM OF ACTION, USES AND SIDE EFFECTS

Class	Example	Mechanism of action	Uses	Side effects
Ant acids	Sodium bicarbonate Calcium carbonate Aluminum hydroxide Magnesium hydroxide / Combination	Increases gastric pH to greater than four, and inhibits the proteolytic activity of pepsin and Causes osmotic retention of fluid	Helps in neutralizing gastric acid, reducing acid delivery in duodenum and pepsin activity, besides to bind bile acids	Frequency not defined: Nausea, Vomiting, Hypophosphatemia, Chalky taste, Constipation, Abdominal cramping, Diarrhea, Electrolyte imbalance, Rebound acid secretion [19]
H_2 receptor antagonist	Cimetidine, Ranitidine Famotidine, Nizatidine Roxatidine, Lafutidine	Blocking the action of histamine at the histamine H_2 receptors of parietal cells	Inhibits acid production by reversibly competing with histamine for binding to H_2 receptors on the basolateral membrane of the parietal cells, suppress acid production by 70%	Headache, Anxiety, Depression, Dizziness, Cardiovascular events, thrombocytopenia [20]
Mucosal defensive agents	Prostaglandin analogs (Misoprostol) Sucralfate	Stimulate mucus production and enhance blood flow throughout the lining of the gastrointestinal tract	-Prophylaxis of stress ulcers in critically ill patients -Conditions with mucosal ulceration not due to acid production as aphthous ulcers	Diarrhea, contraindicated in pregnancy, Constipation, Abdominal pain [21]

Proton pump inhibitors (PPIs)	Omiprazole Esomeprazole Lansoprozole Rabeprazole Pantoprazole	Inhibition of the gastric H+/K+-ATPase (proton pump) enzyme system	- GERD maintenance therapy - Erosive esophagitis - Short-term treatment of active duodenal and begin gastric ulcers	Headache, Abdominal pain, Diarrhea, Nausea, Vomiting, Constipation, Flatulence, Vitamin B12 deficiency, Osteoporosis [22, 23]
Potassium-Competitive Acid Blocker	Vonoprazan	Inhibits H+, K+-ATPase in gastric parietal cells at the final stage of the acid secretory pathway	It is a new acid suppressant drug. GERD maintenance therapy	Nasopharyngitis Fall, Contusion, Diarrhea, Upper respiratory tract inflammation, Eczema, Constipation, Back pain [24-28]

H_2-Receptor Antagonist- The acid secretion that is stimulated by histamine, caffeine, bethanechol, 2-deoxyglucose, insulin, sham feeding, pentagastrin, and food, and nocturnal and basal gastric acid secretion are both markedly inhibited by Histamine H_2-receptor antagonists. Some patients are diagnosed by the ulcer and other patients with non-ulcer dyspepsia by the primary care physicians. Many of these patients are treated with the H_2-receptor antagonists.

Currently, about 77%-92% of duodenal ulcers at 4 weeks intervals were cured by the marketed dose of Histamine H_2-receptor antagonists, and this rate are increased by the treatment provided for the eradication of *H. pylori*. Rather than a more frequent dosing regimen, once-daily administration is very effective and results in higher healing rates. Though the rate of healing of gastric ulcers is slower after the interval of 8 weeks of treatment, about 75%-88% of ulcers are being treated.

The development of H_2-receptor antagonists played a has revolutionized role in the treatment of peptic ulceration by the introduction of cimetidine to clinical practice in 1976, and then the development of ranitidine, famotidine, and nizatidine. They are best known for their overall effectiveness. As the market is in progress and huge, thus 3 more H_2-receptor antagonists, roxatidine, mifentidine, and sufotidine, are currently going under the clinical trials.

Clinical Pharmacology of H_2-receptor Antagonists: The four H_2-receptor antagonists that are currently marketed in the US are cimetidine, ranitidine, famotidine, and nizatidine and their chemical structures are shown in **Fig. 7**.

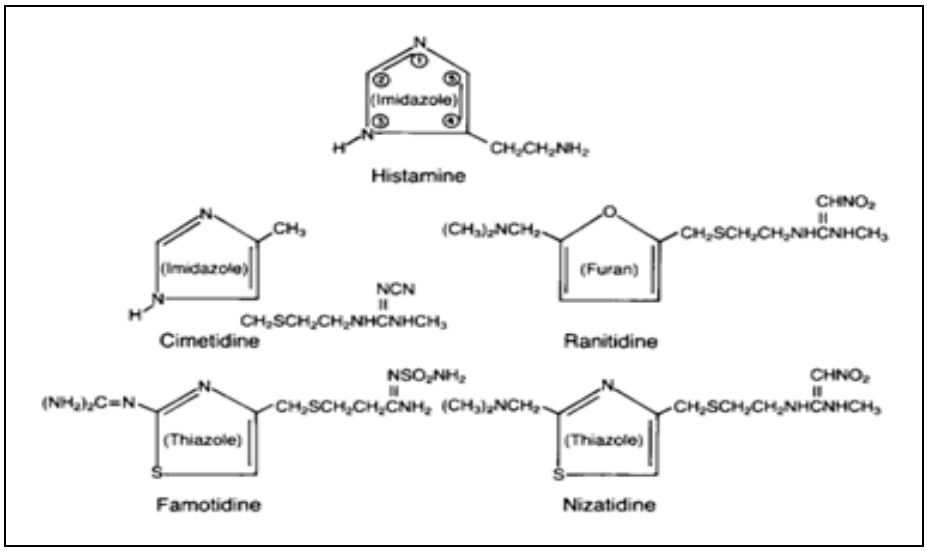

FIG. 7: CHEMICAL STRUCTURES OF CIMETIDINE CONTAINS IMIDAZOLE RING, RANITIDINE CONTAINS FURAN RING, FAMOTIDINE AND NIZATIDINE CONTAINS THIAZOLE RING

Gastric Action of H_2-receptor Antagonist: The basolateral membrane of acid-secreting parietal cells has histamine receptors of H_2 type, thus not blocked by H_1 antihistamines. The working of the H_2 receptor by histamine, which is released from mast cells and other cells, activates adenylate cyclase and increases the intracellular concentrations of cyclic AMP. When the level of cyclic

AMP increases, it activates the proton pump of the parietal calls, potassium-ATPase, and hydrogen, which helps in the secretion of hydrogen ions in exchange for potassium ions against a large concentration gradient. Both secretions of acid by the parietal cells and the intracellular concentrations of cyclic AMP are reduced by the H_2 blockers, which inhibit the binding of histamine to H_2 receptors selectively. The possible in vivo interactions take place between the calcium pathway, which is activated by the acetylcholine or gastrin or both or by histamine and cyclic AMP pathway, which is activated by the histamine.

Cimetidine is said to be the less potent, and famotidine is said to be the most potent among the relative potencies of four H_2 blockers in the inhibition of the secretion of the gastric acid, which varies from 20-50 folds. The suitable concentrations required for the inhibition of 50% of pentagastrin-stimulated secretion of gastric acid are approximately 6 h for cimetidine to 10 hours for famotidine, ranitidine, and nizatidine. After the discontinuation of the therapy with H_2 blockers, the acid secretion is increased rapidly to the pretreatment rate or even slightly more than it for the few days or week is known as rebound hypersecretion. The role of rebound hypersecretion is in the deterioration of the acid-pepsin disease for weeks or months since the end of the therapy.

Pharmacokinetics: Cimetidine, ranitidine, and famotidine have rapid absorption due to the extensive first-pass hepatic metabolism. After the oral administration of these drugs, their bioavailability is average that is 43-60% **Table 2**. The bioavailability of nizatidine in normal subjects is close to 100% and in renal failure patients; it is approximately 75% due to less first-pass hepatic metabolism.

After the oral administration of four H_2-blockers, the average time to peak serum concentrations is approximately 1-3 h, and binding to serum protein range from 13-35%. The total body content of the cimetidine found in the skeletal muscles is approximately 70% and is distributed in most of the organs except in fat. All four drugs can be excreted in the breast milk and are found in the cerebrospinal fluid, which crosses the placental barrier.

Clearance and elimination half-lives of the H_2-receptor antagonist shows the huge variations as their half-lives in serum are 1.5-4 h in normal terms **Table 2**. All four drugs are eliminated by the combination of all hepatic metabolism, glomerular filtration, and renal tubular secretion.

For oral doses of cimetidine, famotidine, and ranitidine, hepatic metabolism is the principal pathway of the excretion, and for nizatidine is the renal excretion. With I.V administration, only 25-40% of the dose is metabolized by the rest, and the rest is eliminated by the kidney. Nizatidine is the only drug to have active metabolites with the activity of 60% of the parent drug.

TABLE 2: CLINICAL PHARMACOKINETICS OF FOUR H_2-RECEPTOR ANTAGONIST DRUGS

Variable	Cimetidine	Ranitidine	Famotidine	Nizatidine
Absorption				
Bioavailability (%)	30-80	30-88	37-45	75-100
Time to peak serum concentration (hr)	1-2	1-3	1-3.5	1-3
Distribution				
Volume (liters/kg of body weight)	0.8-1.2	1.2-1.9	1.1-1.4	1.2-1.6
Protein binding in serum (%)	13-26	15	16	26-35
CSF: serum ratio	0.18	0.06-0.17	0.05-0.09	Unknown
Breast milk: serum ratio	4.6-11.8:1	1.9-23.8:1	0.41-1.78:1	Unknown
Fetal: maternal ratio	0.4-0.8:1	Unknown	0.06:1	Unknown
Elimination				
Totalsystemic clearance (ml/min)	450-650	568-709	417-483	667-850
Half-life in serum (hr)	1.5-2.3	1.6-2.4	2.5-4	1.1-1.6
Hepatic clearance (%)	60	73	50-80	22
Oral Intravenous	25-40	30	25-30	25
Renal clearance (%)	40	27	25-30	57-65
Oral Intravenous	50-80	50	65-80	75

Immunological Actions of H_2-receptor Antagonists: The cell-mediated immunity *in-vitro* has been seen in cimetidine by the blockage of the H_2 receptor on T lymphocytes. The part of lymphocytes in which response to the mitogen stimulation was increased simultaneously in the patients who receive cimetidine. Ranitidine and famotidine do not show such actions. In immuno-compromised patients, cimetidine has been used in the uncontrolled studies in the acceleration of the herpes zoster lesions.

Adverse Effects: All four drugs do not show severe adverse effects. Various risk factors include hepatic or renal dysfunction and multiple medical illnesses. Some of the most common adverse drug reactions for H_2 blockers shown in patients are diarrhea (1-3%), drowsiness (1-2%), fatigue (2%), headache (2-3%), constipation (1%) and muscular pain (2%), chronic kidney disease [29]. More side effects less than 1% rates are dizziness, mental confusion, galactorrhea, impotence, thrombo-cytopenia, loss of libido, gynecomastia, neutropenia, drug fever, allergic reactions, hypotension, tachycardia, cardiac arrhythmias, bradycardia, minor or severe skin reactions, polymyositis, myalgia, arthralgia, intestinal nephritis, agranulocytosis, somnolence, increased serum creatinine levels and elevated serum levels of liver enzymes with or without hepatitis.

Bradycardia is caused by both cimetidine and ranitidine through an effect on cardiac H_2 receptors. In the recent analysis of 15 normal patients were given ranitidine (150 mg orally twice a day) or cimetidine (300 mg orally four times a day), after taking a complete dose and submaximal exercise, 5 patients had a small heart rate reduction and blood pressure. Famotidine does not have any changes in the heart rate and blood pressure in normal patients but showed the negative inotropic effect that is decreased cardiac output and stroke volume. Nizatidine has very little information on hemodynamic effects.

Drug Interactions: Several drug interactions have been marked between H_2 blockers, among which cimetidine is common. As the normal subjects are involved in most of the studies, the true existence of interactions in patients who receive the H_2 blocker is unknown. The impairment of the hepatic metabolism of another drug is the primary drug interaction shown with cimetidine because cimetidine binds with the heme-a portion of the cytochrome P-450 system of mixed-function oxidases and interacts by this mechanism with 41 drugs. Though, ranitidine is 4-10 times more potent than cimetidine though binds 5-10 folds less desirable to cytochrome P-450. Ranitidine has quantitatively less potential for the alteration of the oxidative metabolism of another drug than cimetidine in the equipotent doses. Famotidine and nizatidine have very limited potential for the inhibition of the metabolism of other drugs as they do not bind to the cytochrome P-450 enzyme.

All four H_2 blockers are highly potential to affect the absorption rate of some of the drugs by increasing the gastric pH. Like cimetidine, it reduces the absorption rate of ketoconazole, which is a weak base by the increase in the gastric pH caused by cimetidine results in the slower dissolution rate of ketoconazole. Cimetidine inhibits gastric alcohol dehydrogenase enzyme and enhances the absorption rate of the ethanol from the stomach. Ranitidine increases the absorption rate of bismuth from tri potassium dicitratobismuthate.

Recent Advancements: Due to the unknown causes of ulcers, the present medical scenario is based on the accepted theory in the neutralization of the peptic ulcer gastric HCl and to relieve the pain. Further, efforts are emphasized on increasing the mucosal resistance against the aggressive acid-pepsin factor. Thus to heal the ulcer, the following factors are implied- a strict diet, anti-secretory, and motor-inhibitory drugs, antacids, sedatives, physical and mental rest, and strict prohibition from alcohol and stimulants like alcohol and caffeine-containing products.

Diet: Traditionally, milk and cream and small feedings in small terms of the time of soft foods are more emphasized in treating peptic ulcers. More emphasis has been given on the increase of the nutritive adequate diet food which absorbs or chemically combines with HCl and to exclude such food from a diet that acts as thermal, mechanical, or chemical irritants or increases gastric secretion in the stomach or increase the motility.

In peptic ulcer, the role of protein metabolism is also taken into consideration. Sappington and

Bockus surveyed 5 hospitalized patients suffering from chronic peptic ulcer disease. These patients were given a high protein diet and found that three showed increased retention of nitrogen and showed previously existing protein deficiency. Kirsner, Brandt, and Scheffner studied the excretion of various amino acids and plasma concentrations in normal and ulcer patients and resulted in no differences. The analyzed that the patients who received protein like milk and eggs or skim milk showed greater utilization of amino acids than when the dietary source was protein hydrolysate.

It is recommended that a minimum daily intake of 90-95gms of protein is necessary on a daily basis for the body. The food that contains high protein contents is milk, eggs, casein, milk powder, and cheese.

Antacids: Some authorities believed that the uptake of cream and milk on the interval feedings make the antacid therapy of no use; that is why antacid importance was in debate for a while. Benjamin and Ivy gave their statement that the patients with gastric hypersecretion who were given the feedings of cream and milk alone are ineffective in neutralizing the stomach content so the additional use of antacids is useful for neutralization. As the prolonged use of sodium bicarbonate, tends to produce alkalosis because of which soluble alkalis is been discarded on a larger amount thus, sodium bicarbonate shows the fastest relief of pain for ulcer patients. Calcium carbonate is also been referred by some gastroenterologists.

Aluminum hydroxide preparations have been more popular for some time but shown some dis-satisfactory results with their clinical effectiveness results as well as their constipating effects on peptic ulcer disease.

Milk of magnesia with the aluminum hydroxide gel combination was a strong antacid than the aluminum hydroxide alone been given. It has been assumed that the inappropriate dosage was the main cause of the dissatisfaction. The combined preparation of milk of magnesia and aluminum hydroxide prevents constipation and leads to diarrhea. There has been the important development of hypercalcemia and clinical syndrome of alkalosis without hypercalcinuria and renal failure in the peptic ulcer patients who were the long term ulcer patients, which includes absorbable alkali-frequently (Burnett's syndrome), milk and cream.

Abstinence from Stimulants: Secretion of gastric juice in ulcer patients is stimulated by caffeine (in tea and coffee). Alcohol is used as a test meal for years and said to be the gastric secretory stimulant, as in the case of smoking, Hartiala gave his theory that the dogs with duodenal pouches were given nicotine and analyzed that the output of secretion from these pouches was reduced by 50%. On comparing, the duodenal contents of a significant amount of aHcaline secretion were deprived of neutralizing the upcoming acid gastric juice. Batterman and Ehrenfeld did the comparison of the 56 ulcer patients (smokers) with the results in 39 nonsmokers. They concluded the result that tobacco smoking causes great harm to the welfare of ulcer patients. It will not only harm the results of antacid therapy, but the risk factor increases 3-4 times in nonsmokers or the patients who have given up smoking. Patients who cannot quit smoking are recommended to use denicotinized tobacco. It is insisted to completely quit tobacco, alcohol, and caffeine-containing products during the acute ulcer therapy.

Sedatives: One of the commonly used treatments in peptic ulcers is the use of sedatives. They cause relaxation in the cerebral cortex and subcortical centers of the brain by their depressant action. Sedatives converted a refractory patient into a cooperative and relaxed patient. A routine dose of 16-35 mg Phenobarbital (three times daily, hour-an-hour before meal) is recommended during the acute ulcer attack and pentobarbital sodium (100 mg) at bedtime. Merendino, in his study on the effect of barbiturates on gastric secretion, reported that Phenobarbital, when given orally (120-180 mg), shows that gastric secretion is depressed in both denervated and innervated gastric pouches in dogs. Such high doses are hardly used in ulcer patients.

Antisecretory and Motor-Inhibitory Drugs: Belladonna and atropine are used since long in the treatment of ulcers. If given in ordinary amount, they have less effect on gastric secretion or motility in man. The standardized dose for the effective tincture of belladonna must be 15 drops before

every three main meals and the dose to be increased by one drop daily until there are tachycardia, mydriasis, and dryness of the mouth. There must be an effective standardized dose of atropine for each patient. Recently introduced, anticholinergics are of great promise. Grimson, with his colleagues, firstly introduced Banthine with the other similarly acting new drugs such as Prantal, Pamine, Pro-Banthine, Monadral, Antrenyl, Darstine, Centrine, *etc*. when these drugs are administered parenterally; they cause inhibition of motility and gastric secretion. When these drugs are administered orally in large doses, the antacid nature is shown in a few patients Administration of the oral dose thus relieves pain in over 80% of ulcer patients, useful in patients with nocturnal pain. Patients with obstruction, hypertrophied prostate, and glaucoma should not use these drugs.

The two enzymes must be inhibited; which are useful in the formation of HCL for the inhibition of such enzymes, antisecretory drugs are used. The known drugs, p-chloromercuribenzoate in combination with sulfhydryl groups, block the gastric secretory response to mecholyl and acetazoleamide (Diamox) which results in the inhibition of carbonic anhydrase. Janowitz, Dreiling, and Hollander told that the gastric HCl secretion is inhibited by acetazoIeamide (Diamox) in man.

CONCLUSION: A peptic ulcer is a common digestive system disease. Gastric and duodenal ulcers are majorly caused by *H. pylori* infections and more use of NSAIDs. Peptic ulcer and gastric carcinoma are believed to be initiated and aggravated due to the oxidative stress induced by *H. pylori* and NSAIDs. Currently, about 77%-92% of duodenal ulcers at 4 weeks intervals were cured by the marketed dose of Histamine H_2-receptor antagonists, and this rate is increased by the treatment provided for the eradication of H.pylori. Rather than a more frequent dosing regimen, once-daily administration is very effective and results in higher healing rates. Though the rate of healing of gastric ulcers is slower after the interval of 8 weeks of treatment, about 75%-88% of ulcers are being treated.

The present medical scenario is based on the accepted theory in the neutralization of the peptic ulcer gastric HCl and to relieve the pain. Traditionally, milk and cream and small feedings in small terms of the time of soft foods are more emphasized in treating peptic ulcers. As the prolonged use of sodium bicarbonate tends to produce alkalosis because of which soluble alkalis has been discarded on a larger amount; thus, sodium bicarbonate shows the fastest relief of pain for ulcer patients. Tobacco, alcohol and caffeine-containing products must be avoided. Sedatives help in the physical and mental rest. Administration of the oral dose of anticholinergics, thus relieves pain in over 80% of ulcer patients and is useful in patients with nocturnal pain.

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