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The Impact of Helicobacter pylori Eradication on Extra-Gastric Conditions: A Comprehensive Review

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Abstract -

Environmental acidity, poor nutrition, stress, cigarette and alcohol use, nonsteroidal anti-inflammatory drugs (NSAIDs), Herpes simplex virus infection, and Zollinger-Ellison syndrome are the main causes of peptic ulcers, which are erosions in the digestive tract. Peptic ulcer problems are more likely to occur when aspirin and nonsteroidal anti-inflammatory medications (NSAIDs) are used, especially when combined with anticoagulants, corticosteroids, and selective serotonin reuptake inhibitors. Peptic ulcers mainly manifest as gastric ulcers and duodenal ulcers. Peptic ulcer disease (PUD) risk factors include a personal or family history of the infection, using nonsteroidal anti-inflammatory medicines (NSAIDs), and a Helicobacter pylori infection. In addition, there are a number of plant materials, herbs, and minerals that may have a role in preventing or assisting the healing of stomach ulcers; for example, Salvadora persica, Moringa oleifera, Aloe vera, and Allium sativum all contain chemical components that exhibit antiulcer action. In addition, there is a wide array of medications that target the causes of peptic ulcer formation that are now used in treatment. These include antacids, gastric acid secretion inhibitors, misoprostol, sucralfate, magnesium hydroxide, and anti-H. pylori drugs.

Keywords- Gastric ulcer, Duodenal ulcer, Helicobacter pylori infection, NSAID

Introduction -

Peptic ulcers, which are lesions in the digestive tract caused by acid, are commonly found in the stomach or proximal duodenum [1]. The mucosa eroding into the submucosa or muscularis propria is a hallmark of these ulcers. Many things, such an extremely acidic environment, certain foods, stress, NSAIDs, H. pylori infection, alcohol and tobacco use, and other risk factors like Zollinger-Ellison syndrome, are thought to contribute to the mucosal disturbance [2]. Patients who took NSAIDs on a regular basis had a fourfold increased chance of developing problems from peptic ulcers, according to the study. But for aspirin users, the risk is double [3]. The risk of upper gastrointestinal bleeding is significantly raised when anticoagulants, corticosteroids, and selective serotonin reuptake inhibitors are taken in conjunction with nonsteroidal anti-inflammatory medications

(NSAIDs) or aspirin [4]. Peptic ulcer disease is still not definitively linked to aspirin and nonsteroidal anti-inflammatory medicines (NSAIDs), even though many NSAID users also have H. pylori infections. A meta-analysis of observational studies found that aspirin use, nonsteroidal anti-inflammatory medication use, and Helicobacter pylori infection are risk factors for peptic ulcer disease [5]. While several additional factors contribute to the development of PUD, the most common ones are PUD caused by Helicobacter pylori and PUD caused by nonsteroidal anti-inflammatory drugs (NSAIDs) [6].

Types of ulcers –

On the basis of location, peptic ulcers are categorized as follows:

1. Gastric Ulcer: Occurrence of ulcer in the stomach.
2. Duodenal Ulcer: Occurrence of ulcer in the duodenum.

Peptic ulcers are categorized based on their severity.

1. Acute peptic ulcers – It affect the tissues up to the submucosa layer. They can occur as single or multiple lesions and are commonly found in various areas of the stomach and the initial centimeters of the duodenum.

2. Chronic peptic ulcers- It penetrate through the epithelial and muscle layers of the stomach wall. They can extend to involve the nearby pancreas or liver (42, 43).

Causes of ulcer –

There are a number of potential causes of ulcers. The most common reason is a Helicobacter pylori infection. Furthermore, ulcers can form after using NSAIDs such as aspirin and ibuprofen for an extended period of time. Hyperacidity, or an excess of stomach acid, can play a role as well; this condition can run in families and can be triggered by things like stress, smoking, and particular dietary habits. Another possible reason is the extremely rare Zollinger-Ellison syndrome, which causes the stomach to produce too much acid. Tobacco use, steroid use (e.g., for asthma treatment), hypercalcemia (excessive calcium production), a personal or family history of stomach ulcers, and advancing age (e.g., due to a decrease in stomach function) all raise the risk of developing stomach ulcers. One of the leading causes of ulcers is drinking too much alcohol (40).

Pathophysiology of ulcer-

An imbalance between the stomach mucosa's protective and destructive elements causes peptic ulcer disease (PUD). H. pylori infection, NSAID usage, and a first-degree relative with PUD are three of the risk factors that might raise the probability of getting PUD. (7). Gastric acid secretion is controlled by three pathways: the vagus nerve (ACh), gastrin, and the local release of histamine. Each pathway acts through its own receptors. In response to these receptors, parietal cells secrete hydrogen ions (H) into the stomach lumen via their proton pump, H KATPase. Hydrogen reacts with plasma chloride ions (Cl) in the stomach lumen to produce hydrochloric acid (HCl).Hydrogen ions (IH) are secreted at the apical canaliculi of parietal cells by the terminal enzyme HK-ATPa, which is also called the proton pump. The basolateral membrane of these cells contains

receptors for histamine, acetylcholine, and gastrin, which can activate this enzyme. The main regulator of the process is histamine, which binds to H receptors. The oxyntic glands include paracrine enterochromaffin-like (ECL) cells known as "histaminocytes," which secrete histamine together with Gastrin and ACh (8). In contrast to H IH receptors, which activate HK ATPase by generating cyclic adenosine monophosphate (cAMP), muscarinic and gastrin cholecystokinin (CCK) receptors mobilise intracellular calcium through the phospholipase C IP-DAG pathway. Aside from cyclic adenosine monophosphate (cAMP), calcium plays a role in the proton pump's activity. Only when H activation produces cAMP is the whole secretomotor response to gastrin and cholinergic agonists seen. Histamine, gastrin, and ACh all have different but interrelated roles in the acid response. Aside from histamine, histamine antagonists block all stimuli for stomach acid production, including ACh, pentagastrin, and others (9).

Herbs used in treatment of peptic ulcer-

There are a lot of plant-based nutrients, herbs, and materials that can help prevent or speed up the healing process of stomach ulcers. Animal and in vitro investigations, in addition to human trials, have shown encouraging results. Although there have been reports of antiulcer activities in many botanical preparations, most of the research on these items has focused on their pharmacologic effects in animal studies. The usefulness and safety of herbs as gastro-protective agents are not well-documented due to a lack of clinical evidence. Nonetheless, a number of botanical compounds have demonstrated both minimal toxicity and promising medicinal uses. Many current drugs can produce ulcers, hence it is important to note that chemical elements like Flavonoids, aescin, succulent gel, and others have distinct therapeutic value owing to their antiulcer action (10). Sula, parinamsula, and amlapitta are the three categories of gastrointestinal illnesses in Ayurveda, the traditional medicine of ancient India. These categories reflect the symptoms and signs of peptic ulcers and functional dyspepsia, respectively (38).

Some are as follows-

1-Allium sativum

Commonly known as "vellapundu" in the local language, garlic is really technically classified as Allium sativum and is a member of the Liliaceae family. The Indian subcontinent is a major producer. Starch, mucilage, albumen, sugar, and an acrid volatile oil make up this plant's chemical makeup, which acts as the active ingredient. Garlic seeds are ground into a fragrant oil. The oil-containing components of the juice, in particular, are rich in sulfur, iodine, and salicylic acid compounds that are organically bonded. There are also other minerals and substances that contain vitamins that are important (11). According to Ayurveda, garlic is a powerful tool for getting rid of maggots. Also, many have found relief from infected ulcers and ulcerations after applying coconut oil or mustard to the affected area. A cleansing lotion for wounds and bad ulcers has been made from a mixture of several extracts, usually three or four components, either in ordinary or watery form (12).

2- Aloe vera

The dehydrated latex of several species of Aloes, including Curacao Aloe, Cape Aloe, Socotrine Aloe, Aloe Africana Miller, and Aloe spicata Baker, is known as aloe. Other species of Aloes include Aloe perryi Baker, Aloe ferox Miller, and Aloe Africana Miller. You may find all of these plants in the Liliaceae family. The three isomeric alones found in aloe vera—barboloin, isobarbaloin, and crystalline alin—make up the plant. In addition, it has emodin, sap, Aloe-emodin, and translucent Aaloin. Essential polysaccharides, complex sugars, and anthraquinones, which are strong laxatives, are all present in the gel. On top of that, it has lignin, vitamins, amino acids, phospholipids, and minerals (13). Possible explanations for A. vera's anti-ulcer actions include the presence of lectins, its anti-inflammatory characteristics, its healing activities, its promotion of mucus formation, and its management of stomach secretions. The parietal cells that produce stomach acid can have their aminopyrine absorption impeded by these lectins. So, the extract may have an effect on the activity of these acid-producing cells, which would lower the production of stomach acid (14).

3- Moringa oleifera (MO)-

A wealth of carotenoids, tocopherols, flavonoids, phenolic acids, folate, and polyunsaturated fatty acids are found in Moringa oleifera, sometimes known as the drumstick tree. It has antibacterial properties in both its roots and its leaves (15). Furthermore, laboratory rats protected against gastrointestinal ulcers produced by acetylsalicylic acid, serotonin, and indomethacin were those that were given a methanolic extract of Moringa oleifera (16). Furthermore, it aids in the recovery of animals from chronic stomach ulcers caused by acetic acid (17).

4- Salvadora persica

Miswak, short for "brush," is a member of the Salvadoraceae family of plants. In India's dry and arid regions, you may find this plant, which is also called kharijal or Salvadora persica. Meethijal, or Salvadora oleoides, is a near relative of this massive, densely branching shrub or tree (18). Research has shown that Salvadora persica has significant protective properties against ulcers induced by ethanol and stress. The essential oil extracted from the stem of this toothbrush tree contains major components such as 1,8-cineole (eucalyptol), α-caryophellene, β-pinene, and 9-epi-(E)-caryophellene (19). Using optical microscopy, researchers looked at the antiulcer properties of a Salvadora persica decoction. According to the findings, the gastric mucosa components in the rats that were evaluated tended to revert to their original state (20).

5- Momordica cymbalaria

Momordica cymbalaria, also known as Luffa tuberose or Momordica tuberose, is a vine belonging to the Momordica genus. Tamil Nadu, Karnataka, Madhya Pradesh, Maharashtra, and Andhra Pradesh are among the Indian states where it grows. A variety of bioactive components, including phenolic acids, carotenoids, cucurbitane triterpenoid, phytosterol, and flavonoids, are found in this medicinal plant. The Cucurbitaceae family is mostly composed of triterpenoids among these chemicals (21). In an animal model of ethanol-induced ulcers, the antiulcerogenic properties of this plant's extract were observed. The most notable effect was a

significant reduction in acid production, gastric juice volume, and H+-K+ATPase levels. Contrarily, levels of stomach wall mucus and catalase enzyme were significantly elevated. Nevertheless, superoxide dismutase levels, an antioxidant enzyme, were shown to be lowered (22).

6- Cyperus rotundus

The monocotyledonous Cyperaceae family includes several species of grass-like plants. It includes 5,600 species distributed over both tropical and temperate climates. The genus Cyperus, which is part of the family Cyperaceae, has a lot of promise as a nutritional supplement. Cyperus rotundus L. has been the subject of the greatest amount of research on its pharmacological characteristics among the over 950 species that make up this group. Cyperus spp. has a long history of use in traditional medicine for the treatment of a broad variety of symptoms, including those related to the respiratory and digestive systems, blood abnormalities, menstrual cycle irregularities, and inflammatory diseases. Cereotundone, mustakone, zierone, germacrene D, α-cyperone, α-corymbolol, α-pinene, caryophyllene oxide, and other bioactive compounds may be discovered in Cyperus species. These compounds improve the pharmacological effects of Cyperus spp. extracts (23).

7- carica papaya

There are four genera in the tiny family Caricaceae, to which the papaya tree belongs on a global scale. The most popular and extensively grown species in India is Carica papaya Linn, one of four species in the genus Carica Linn. Papaya, formally known as Carica papaya, is a plant that belongs to the Caricaceae family. The papaya melon tree goes by several names: pawpaw, fan mu gua, kapaya, lapaya, papyas, papye, and tapayas (24). Key chemical components of papaya include crypto glavine, pectin, carposide, carpaine, pseudocarpaine, dehydrocarpines, carotenoids, chymopapain, cis-violaxanthin, and antheraxanthin (25). The main reason papaya is famous is its ability to aid digestion. As a medical help to digestion, the tree's leaves as well as its ripe and uncooked fruit are utilised. Curiously, when it comes to therapeutic uses, the unripe papaya fruit is said to be more useful. External use of the papaya tree's milky white sap speeds the healing of cuts, ulcers, boils, warts, and malignant tumours; the sap is also a valuable medicine (26).

8- Acacia Arabica

Native to the Leguminosae family, this tree's bark goes by several names in India, including Babul, Babur, and Kikar in Punjabi. It has a high tannin content, anything from 12-20%. Further analysis of the bark revealed the presence of several polyphenolic chemicals. A phytochemical analysis of the stem bark has identified glycosides, saponins, alkaloids, and terpenoids (27). For hemorrhagic ulcers and wounds, Ayurvedic practitioners recommend gargling with it or washing the affected area with it. The delicate leaves have a stimulating and astringent effect on ulcers when crushed and used as a poultice. Acacia senegal gum protects rats from cold restraint stress-induced stomach ulcers, according to recent studies. In addition, the intestinal enzyme activity in the intestines has been reduced and meloxicam-induced intestinal damage has been prevented by an aqueous extract of A. arabica gum (28).

Allopathic Drug For Ulcer-

The treatment of gastrointestinal ulcers has undergone significant advancements since the initial days of therapy involving diet and antacids. At present, there exists a wide range of medications that effectively target the underlying causes of ulcer formation. Antacids, histamine2-receptor antagonists, and sucralfate are presently recognized as primary treatment options, catering to the needs of the majority of patients (29).

Classification Of Drug Used In Treatment Of Peptic Ulcer-

1- Gastric Acid Secretion Inhibitor-
   H2 Antihistamine- Cimetidine , Famotidine , Ranitidine , Lafutidine.
   Proton Pump Inhibitor – Pantoprazole , Lansoprazole , Omeprazole , Rabeprazole.
   Anticholinergics – Pirenzepine , Propantheline , Oxyphenonium .
   Prostaglandin Analogue – Misoprostol
2- Ulcer Protectives – Sucralfate , Colloidal Bismuth Subcitrate .
3- Antacid-
   Non-Systemic – Magnesium Hydroxide , Alumin. Hydroxide , Calcium Carbonate.
   Systemic – Sodium Citrate , Sodium Bicarbonate.
4- Anti H.Pylori Drugs – Amoxicillin , Tinidazole , Tetracycline , Metronidazole (8).

Cimetidine

Cimetidine is a popular medicine for the short-term treatment of gastric and duodenal ulcers because it decreases stomach acid. Not only does it control gastric hypersecretion, but it's also used to treat reflux esophagitis and stop stress ulcers from developing in the stomach. A competitive blocker of histamine's ability to stimulate the H2-receptors on stomach parietal cells, cimetidine is an H2-receptor antagonist. The release of hydrochloric acid and the intrinsic factor are both regulated by these cells (30) . Histamine, meals, caffeine, and insulin are among the stimuli that cause a decrease in the amount of stomach acid output. Some medications, such warfarin, phenytoin, propranolol, nifedipine, theophylline, and metronidazole, may be affected by cimetidine's effects on hepatic metabolism. Thus, it may be necessary to change the dosage of these treatments and other medications that are similarly metabolised when starting or stopping cimetidine. This is particularly true for patients with a low therapeutic ratio or renal and/or hepatic impairment. Furthermore, variations in pH may influence the absorption of certain medications like ketoconazole. At least two hours should pass between the administration of these medications and cimetidine for the best possible absorption (31).

Pantoprazole-

Pantoprazole blocks the proton pump in an irreversible way. With the most prevalent side effects being diarrhoea (1.5% of cases), headache (1.3%), dizziness (0.7%), pruritus (0.5%), and skin rash (0.4%), it appears to be well tolerated with short-term oral treatment (32). Pharmacodynamic effects of pantoprazole are similar to those of other proton pump inhibitors (PPIs) since it binds to the parietal cells' proton pump (H+,K+-adenosine triphosphatase). Pantoprazole may bind more selectively to the proton pump than other proton pump

inhibitors. Pantoprazole has a high oral bioavailability of about 77% when taken as a delayed-release tablet that is coated with the enteric lining. Hepatic metabolism occurs via cytochrome P2C19, resulting in the formation of the inactive metabolite hydroxy-pantoprazole, which is then conjugated with sulphate. Regardless of dose, pantoprazole has an elimination half-life of 0.9–1.9 hours (33).

Pirenzepine-

As a selective tantimuscarinic agent, pirenzepine stands apart from the crowd of conventional anticholinergics. When taken at lower dosages, it reduces stomach acid secretion efficiently without affecting the motility of the gastrointestinal tract, the salivary glands, the central nervous system, the cardiovascular system, the eyes, or the urinary tract. When using therapeutic levels, dry mouth and impaired vision are the most commonly reported adverse effects. When used in smaller quantities, pirenzepine suppresses stomach secretion-regulating muscarinic receptors. Both the natural production of stomach acid and that induced by pentagastrin, histamine, and food are effectively suppressed by it (34).

Misoprostol-

After learning that prostaglandins of the E series can protect the stomach from acid secretion and other chemicals, the first prostaglandin E1 analogue to be commercially available was developed: misoprostol. Both the prevention and treatment of stomach ulcers are aided by this drug. The acid form of misoprostol is rapidly converted upon oral intake (35). It takes 30–60 minutes for the blood concentration of free acid to reach its maximum. When it comes to suppressing acid secretion, misoprostol and its free acid metabolite are on par. It binds to serum proteins around 85% of the time. Abdominal discomfort, dyspepsia, diarrhoea, and nausea are the most common adverse effects of misoprostol (36).

Sucralfate -

For the treatment of peptic ulcer disease, sucralfate is prescribed as a sulphated sucrose basic aluminium salt. Oral administration results in limited absorption, and its primary mechanism of action is believed to be protecting the ulcer site from pepsin, acid, and even bile salts. Sucralfate has a stellar reputation for being very well-tolerated. In 37% of instances, the most common adverse effect mentioned was constipation (37).

Magnesium Hydroxide-

Commonly used OTC drugs include antacids. They have a variety of salts and compounds including magnesium, aluminium, and calcium carbonate (38). Partially neutralising gastric hydrochloric acid and inhibiting the proteolytic enzyme pepsin are the mechanisms by which antacids affect the stomach (40). A number of medical conditions and conditions related to digestion and bile acid production, such as ulcers of the duodenum and stomach, stress gastritis, GERD, pancreatic insufficiency, non-ulcer dyspepsia, constipation, osteoporosis, urinary alkalinization, and chronic renal failure, have been treated with antacids (39).

Conclusion-

Peptic ulcers are primarily caused by an imbalance between the protective and destructive factors of the gastric mucosa, with risk factors including H. Pylori infection, NSAID use, and genetic predisposition. Various herbs and plant materials have shown potential in protecting or aiding in the healing of abdominal ulcers. Furthermore, the treatment of peptic ulcers has advanced to include a wide range of medications targeting the underlying causes of ulcer formation, such as gastric acid secretion inhibitors, antacids, ulcer protectives, and anti-H. Pylori drugs.

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