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PHARMACOTHERAPY OF ULCER

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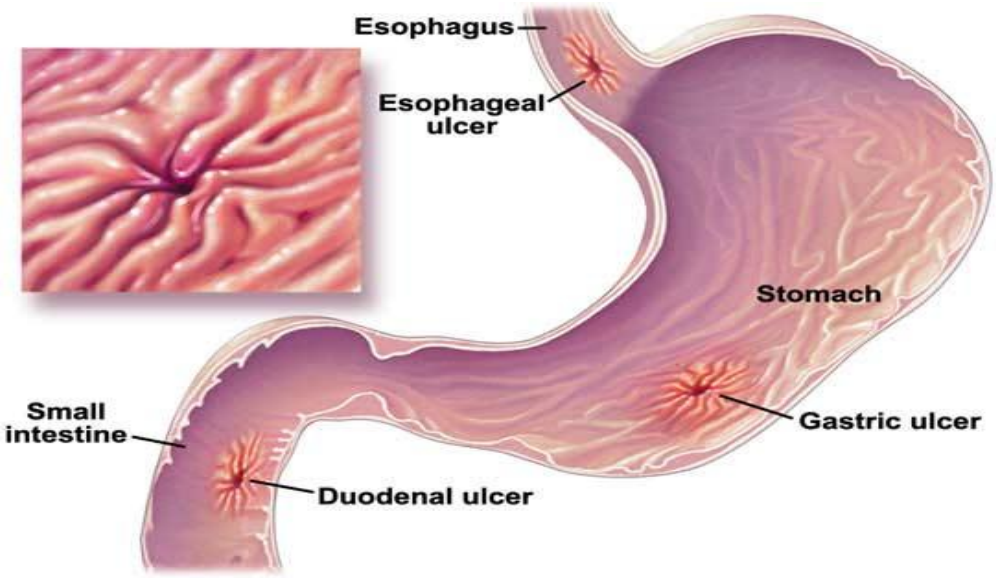
ABSTRACT
Peptic ulcer is a chronic disease affecting up to 10% of the world's population. The formation of peptic ulcers depends on the presence of gastric juice pH and the decrease in mucosal defenses. Non-steroidal anti-inflammatory drugs (NSAIDs) and Helicobacter pylori (H. pylori) infection are the two major factors disrupting the mucosal resistance to injury. Conventional treatments of peptic ulcers, such as proton pump inhibitors (PPIs) and histamine-2 (H2) receptor antagonists have demonstrated adverse effects, relapses, and various drug interactions. On the other hand, medicinal plants and their chemical compounds are useful in the prevention and treatment of numerous diseases. Hence, this review presents common medicinal plants that may be used for the treatment or prevention of peptic ulcers. In the last one hundred years much has been written on peptic ulcer disease and the treatment options for one of its most common complications perforation. The reason for reviewing the literature was evaluating most common ideas on how to treat perforated peptic ulcers (PPU) in general, opinions on conservative treatment and surgical treatment and summarizing ideas about necessary pre-, and perandpostoperative proceedings.

KEYWORDS: chronic disease, Helicobacter Pylori infection, conventional treatment, Medicinal treatment.

INTRODUCTION

Peptic ulcer is an acid-induced lesion of the digestive tract that is usually located in the stomach or proximal duodenum, and is characterized by denuded mucosa with the defect extending into the sub mucosa or muscular is propria. The estimated prevalence of peptic ulcer disease in the general population is 5–10% but recent epidemiological studies have shown a decrease in the incidence, rates of hospital admissions, and mortality associated with peptic ulcer. This is most likely secondary to the introduction of new therapies and improved hygiene, which resulted in a decline in Helicobacter pylori (H. pylori) infections. Traditionally, mucosal disruption in patients with the acid peptic disease is considered to be a result of a hyper secretory acidic environment together with dietary factors or stress. Risk factors for developing peptic ulcer include H. pylori infection, alcohol and tobacco consumption, non-steroidalanti-inflammatory drugs (NSAIDs) use, and Zollinger–Ellison syndrome. The main risk factors for both gastric and duodenal ulcers are H. pylori infection and NSAID use. However, only a small proportion of people affected with H. pylori or using NSAIDs develop peptic ulcer disease, meaning that individual susceptibility is important in the beginning of mucosal damage. Functional polymorphism.



(Fig.1.Ulcer type)

PATHOGENESIS OF PEPTIC ULCER

Almost half of the world's population is colonized by H. pylori, which remains one of the most common causes of peptic ulcer disease. The prevalence of H. pylori is higher in developing countries, especially in Africa, Central America, Central Asia, and Eastern Europe. The organism is usually acquired in childhood in an environment of unsanitary conditions and crowding, mostly in countries with lower socioeconomic status. H. pylori causes epithelial cell degeneration and injury, which is usually more severe in the antrum, by the inflammatory response with neutrophils, lymphocytes, plasma cells, and macrophages.

The mechanism by which H. pylori induces the development of different types of lesions in the gastroduodenal mucosa is not fully explained. H. pylori infection can result in either hypochlorhydria or hyperchlorhydria, thus determining the type of peptic ulcer. The main mediators of H. pylori infection are cytokines that inhibit parietal cell secretion, but H. pylori can directly affect the H+/K+ ATPase α-subunit, activate calcitonin gene-related peptide (CGRP) sensory neurons linked to somatostatin, or inhibit the production of gastrin. Although the formation of gastric ulcers is associated with hyposecretion, 10–15% of patients with H. pylori infection have increased gastric secretion caused by hypergastrinemia and reduced antral somatostatin content. This leads to increased histamine secretion, and subsequently the increased secretion of acid or pepsin from parietal and gastric cells. Additionally, the eradication of H. pylori leads to a decrease in gastrin mRNA expression and an increase in somatostatin mRNA expression. In the remaining majority of patients, gastric ulcers are associated with hypochlorhydria and mucosal atrophy.

The main mechanism of NSAID-associated damage of the gastroduodenal mucosa is the systemic inhibition of constitutively expressed cyclooxygenase-1 (COX-1), which is responsible for prostaglandin synthesis, and is associated with decreased mucosal blood flow, low mucus and bicarbonate secretion, and the inhibition of cell proliferation. NSAIDs inhibit the enzyme reversibly in a concentration-dependent manner. The co-administration of exogenous prostaglandins and cyclooxygenase-2 (COX-2)-selective NSAIDs use reduces mucosal damage and the risk of ulcers. However, the different physicochemical properties of NSAIDs cause differences in their toxicity. NSAIDs disrupt mucus phospholipids and lead to the uncoupling of mitochondrial oxidative phosphorylation, thus initiating mucosal damage. When exposed to acidic gastric juice (pH 2), NSAIDs become protonated and cross lipid membranes to enter epithelial cells (pH 7.4), where they ionize and release H+. In that form, NSAIDs cannot cross the lipid membrane, and are trapped in epithelial cells, leading to the uncoupling of oxidative phosphorylation, decreased mitochondrial energy production, increased cellular permeability, and reduced cellular integrity. Patients who have a history of peptic ulcers or hemorrhage, are over the age of 65, also use steroids or anticoagulants, and take high doses or combinations of NSAIDs are at the highest risk for acquiring NSAID-induced ulcers.

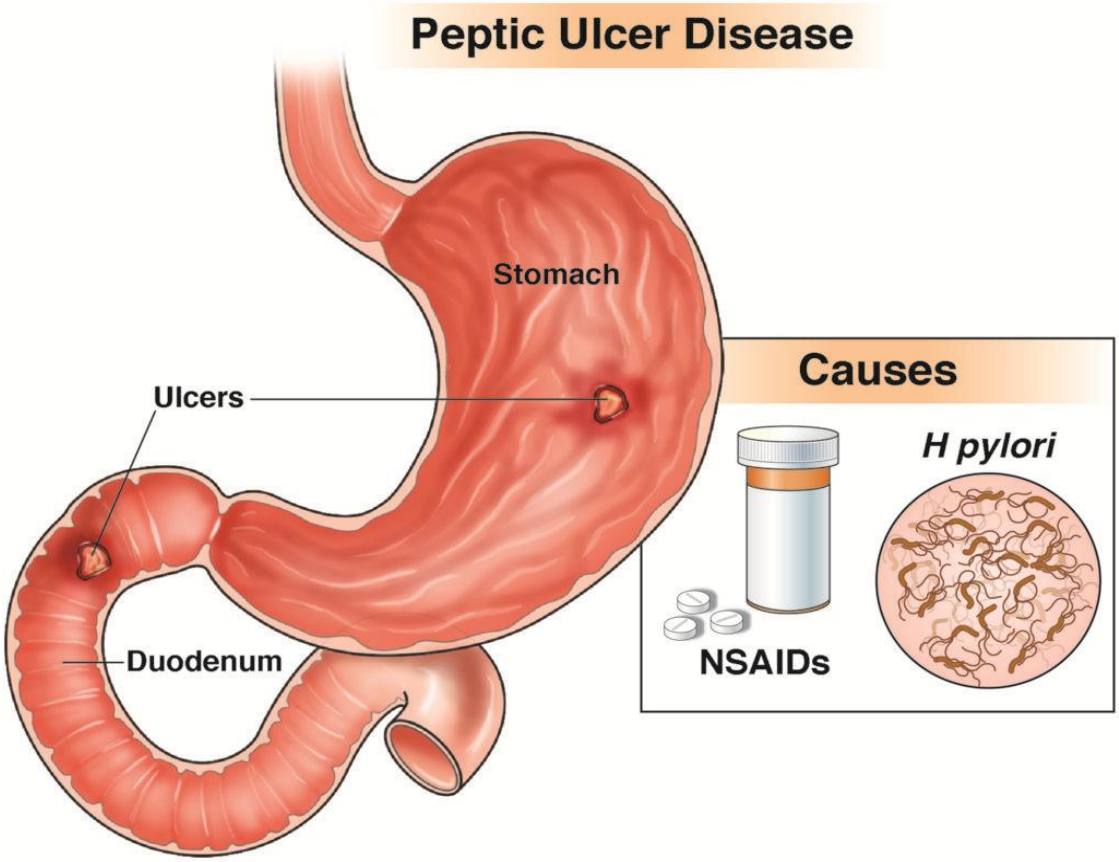
TYPES OF ULCER

1. Peptic Ulcer

Peptic ulcer is a broad term which includes ulcers of digestive tract in the stomach or the duodenum. Earlier it was believed that one developed this type of ulcers due to stress and spicy food. However, recent research has shown that these are just the aggravating factors.

The causative agent is infection caused by the bacteria H. pylori or reaction to certain medicines like non-steroidal anti-inflammatory drugs (NSAIDs)1.

Symptoms of peptic ulcers include abdominal discomfort and pain. Other symptoms include weight loss, poor appetite, bloating, nausea, and vomiting. Some may also experience blood in stool and vomit, and black stools that indicate gastrointestinal bleeding.



(Fig.2.Peptic ulcer)

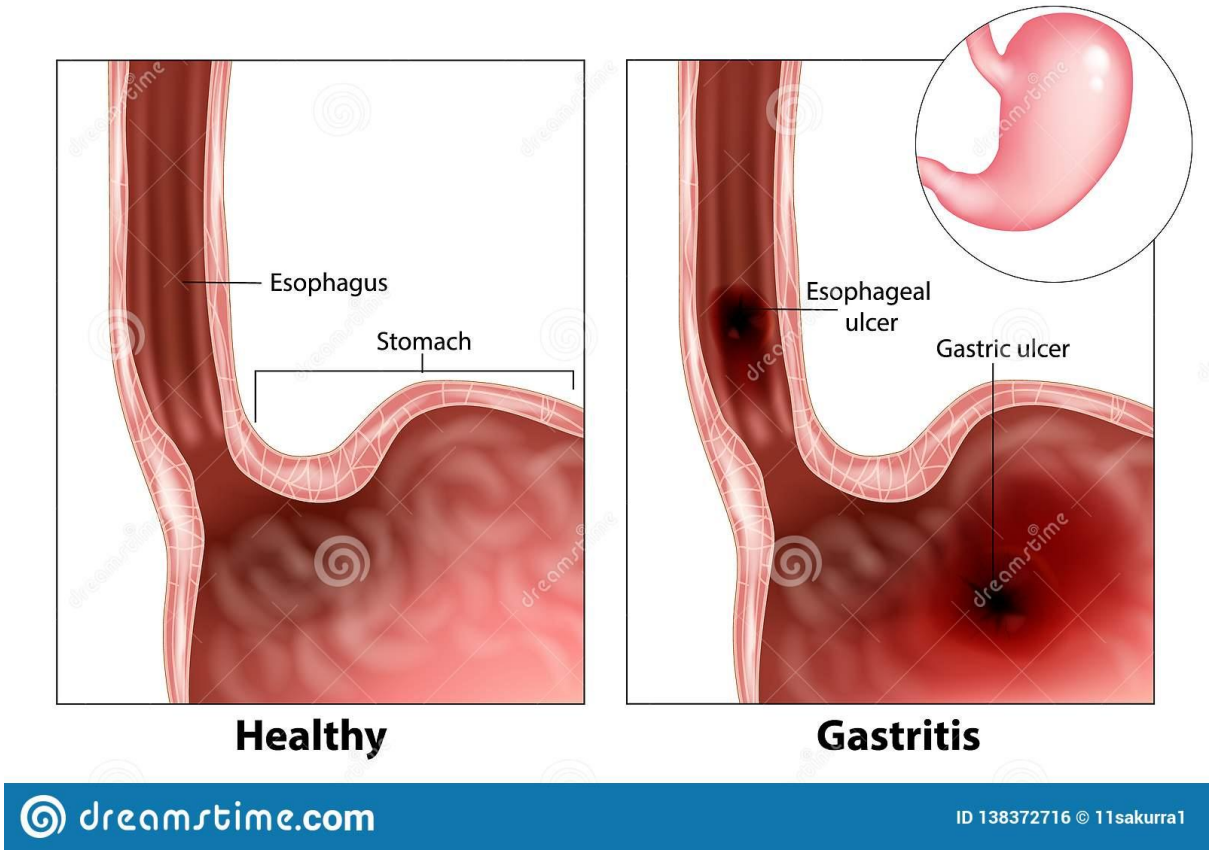
2. Aphthous Ulcers

it' develop in the inner lining of the mouth are referred to as mouth ulcers. Mouth ulcers are common and are usually due to trauma such as from ill-fitting dentures, fractured teeth, or fillings. Anemia, measles, viral infection, oral candidiasis, chronic infections, throat cancer, mouth cancer and vitamin B deficiency are some of the common causes of ulcers or sores in the mouth 3. Aphthous minor is amongst the most common form of oral ulcerative diseases and affects an estimated 15-20% of the population worldwide. In some populations, the prevalence has been documented as being as high as 50-66% and it is especially common in North America 4-5. The incidence of aphthous ulcers has been found to be lower in smokers than in non-smokers.

(Fig.3.Apthous ulcer)

3. Esophageal Ulcers

Esophageal ulcers are lesions that occur in the esophagus (the food pipe). These are most commonly formed at the end of the food pipe and can be felt as a pain right below the breastbone, in the same area where symptoms of heartburn are felt. Esophageal ulcers are associated with acid reflux or GERD, prolonged use of drugs like NSIDs & Smoking.



(Fig.4.Esophageal Ulcer)

TREATMENT

An overview of conventional antiulcer treatment options is summarized in Tables 1 and 2.

Table 1: Mechanisms of action and adverse effects of the most commonly used antiulcer treatment options.

Medicine		Mechanism of Action	Adverse Effects	References
Proton Pump Inhibitors (PPIs)	Omeprazole Lansoprazole Rabeprazole Esomeprazole Pantoprazole	Inhibition of the gastric H^+/K^+-ATPase (proton pump) enzyme system	Headache Abdominal pain Diarrhea Nausea Vomiting Constipation Flatulence Vitamin B12 deficiency Osteoporosis	[1,2]
H2 Receptor Blockers	Cimetidine Famotidine Nizatidine Ranitidine	Blocking the action of histamine at the histamine H2 receptors of parietal cells	Headache Anxiety Depression Dizziness Cardiovascular events Thrombocytopenia	[3]
Antacids	Aluminum hydroxide	Increases gastric pH to greater than four, and inhibits the proteolytic activity of pepsin	Frequency not defined: Nausea Vomiting Hypophosphatemia Chalky taste Constipation	[4]
	Magnesium hydroxide	Causes osmotic retention of fluid		

			Abdominal cramping Diarrhea Electrolyte imbalance	
Potassium-Competitive Acid Blocker	Vonoprazan	Inhibits H^+, K^+-ATPase in gastric parietal cells at the final stage of the acid secretory pathway	Nasopharyngitis Fall Contusion Diarrhea Upper respiratory tract inflammation Eczema Constipation Back pain	[5,6,7,8,9]
Cytoprotective Agents	Misoprostol Sucralfate	Stimulate mucus production and enhance blood flow throughout the lining of the gastrointestinal tract	Diarrhea Abdominal pain Headache Constipation	[10,11]

Table 2: Types and efficiency of *Helicobacter pylori (H. pylori)* eradication treatment options.

Type	Duration	Efficiency	References
First line			
Standard triple therapy:			
PPI + two antibiotics (clarithromycin + metronidazile or amoxicilin)	7–14 days	70–85%	[12]
Second line			
Bismuth-containing quadruple therapy:			
PPI + bismuth salt + tetracycline + metronidazole	14 days	77–93%	[13,14]
Non-bismuth based concomitant therapy:			
PPI + clarithromycin + amoxicillin + metronidazole	14 days	75–90%	
Levofloxacin triple therapy:			
PPI + amoxicillin + levofloxacin	14 days	74–81%	
Salvage regimens			
Rifabutin-based triple therapy:			
PPI + rifabutin + amoxicillin	10 days	66–70%	[15]

PPI: proton pump inhibitors.

ALTERNATIVE THERAPY FOR PEPTIC ULCER

The usage of medicinal plants in healing numerous diseases is as old as human beings, and well-known as phytotherapy. Moreover, in the past few years, there has been a rising interest in alternative therapies and the usage of herbal products, in particular, those produced from medicinal plants. Also, due to appearance of various side effects by usage of conventional drugs for numerous diseases, medicinal plants are considered the major reservoir of potentially new drugs. Plant extracts and their crude are the most significant sources of new drugs, and have been shown to cause promising results in the treatment of gastric ulcer as well. It is known that numerous pharmaceutical agents such as proton pump inhibitors, anticholinergic, antacids, antimicrobial agents, H2-receptor antagonists, sucralfate, and bismuth are not fully effective, and produce numerous adverse effects such as impotence, arrhythmia, hematopoietic alterations, hypersensitivity, and gynecomastia. Due to that, investigations of the new pharmacologically active agents through the screening of different plant extracts led to the discovery of effective and safe drugs with gastro protective activity. Especially, plants with antioxidant capability as the main mechanism are used as the herbal reservoir for the treatment of ulcer disease.

Medicinal plants have achieved their therapeutic properties from their capability to produce renewable and various secondary metabolites, which are known as phytochemical constituents. Hence, numerous plants have used these phytochemicals as a protection mechanism against pathogens.

On the other hand, the appearance of resistant pathogens has had a significant influence on the pharmaceutical companies to change their strategy in the development of conventional antibiotics and design new antimicrobial drugs derived from medicinal plants. Nevertheless, the synthetic antibiotics are still dominant as antimicrobial drugs.

As a matter of fact, incidences of infectious diseases have enlarged within the last three decades, involving infections with different properties as well as new infections, and it has been shown that around 60% of them are of zoonotic origin (spread among human and animals). *H. pylori* is one of the major representatives in that group, and may cause chronic gastritis, peptic ulcer disease, and stomach cancer. Therefore, one of the aims in this review was to highlight some medicinal plants that demonstrated significant antibacterial and

antioxidant activity against *H. pylori* and peptic ulcer disease. However, some of plants lose their efficiency against *H. pylori* consequent to the emergence of resistant strains. Consequently, the isolation of various constituents from the most active plant extracts is encouraged.

It is important to emphasize that herbal products may contain numerous bioactive constituents with dangerous, but also beneficial effects. Therefore, the higher education of doctors and patients about herbal therapy is necessary, as well as legislation to control the quality of herbal products, especially for further randomized investigations to determine the effectiveness and safety of many products in digestive and other disorders.

Finally, the Ayurvedic knowledge and modern medicine could generate preferable antiulcer drugs derived from medicinal plants with less side effects.

Numerous medicinal plants with significant antibacterial activity against *H. pylori* and benefits for gastric ulcer disease are shown in.

Table 3: Overview of herbal antiulcer treatment and *H. pylori* eradication.

Medicinal Plant	Possible Mechanisms	Effect	Adverse Effects	References
Korean red ginseng	Inhibition of *H. pylori*-induced 5-lipoxygenase (5-LOX) activity; preventing pro-inflammatory interleukin (IL)-8 or 5-LOX mRNA	Anti-inflammatory effect; increase eradication rates of *H. pylori*; reduction of gastric inflammation and oxidative DNA damage	Interaction with conventional drugs	[16,17]
Allium sativum	Inhibition of lipoprotein oxidation and lower serum glucose induction of antioxidant enzymes; mechanisms need to be more investigated	Antioxidant; suppressive effect of *H. pylori*-induced gastric inflammation in vivo and in vitro	Interaction with conventional drugs	[18]
Curcuma loga	Inhibition of *H. pylori*-induced 5-LOX activity	Anti-inflammatory; antioxidant	Not determined	[19]
Zingiber officinalis	Inhibition of PGE2 and parietal cell H^+, K^+-ATPase	Anti-inflammatory effect; antioxidant	Nausea and vomiting in pregnant women; restless, heartburn; interaction with conventional drugs (anticoagulants, analgesics)	[20,21,22]
Zingiber zerumbet	Gastroprotective mechanism of zerumbone (significant increase in the endogenous antioxidant GSH, reduction of lipid peroxidation level); other mechanism need to be investigated	Antioxidant, antiproliferative, anti-inflammatory, antisecretory effect; reduction of ulcer area formation	Nausea and vomiting in pregnant women; restless, heartburn; interaction with conventional drugs (anticoagulants, analgesics)	[23,24]
Camellia sinensis (Green tea polyphenols)	Suppression of tumor necrosis factor-alpha (TNF-α) gene expression; inhibition of urease	Antioxidant; improvement in the function of intestinal bacterial flora	Interaction with conventional drugs; dizziness, diarrhea, headaches, insomnia, heartbeat, may cause deficiency of iron	[25,26]

CONCLUSIONS

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

Finally, herbal products used for medicinal purposes require licensing in order to ameliorate their safety and quality, and ensure that randomized controlled investigations validate demands of its possible efficacy. With increased reports of herb–drug interactions, there is still a problem of deficient research in this field, with no measures taken to address this problem. Hence,

pharmacists and doctors should be aware especially of the risks associated with the usage of herbal preparations, whether on their own or in combination with other herbal or standard conventional therapy.

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