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Review Article

PEPTIC ULCER DISEASE: A REVIEW ON ETIOLOGY, PATHOGENESIS, AND MARKET FORMULATIONS

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ABSTRACT

Peptic ulcers are a broad term that includes ulcers of the digestive tract in the stomach or the duodenum. The formation of peptic ulcers depends on the presence of acid and peptic function in the gastric juice and the deterioration of mucosal defense. Two major factors can disrupt the mucosal resistance to injury: non-steroidal anti-inflammatory drugs (NSAIDs) example, aspirin, and *Helicobacter pylori* infection. Numerous natural products have been evaluated as therapeutics for the treatment of a variety of diseases, including peptic ulcers. There has been a considerable pharmacological investigation into the antiulcer activity of some compounds. In this work, we shall review the literature on different medicinal plants and alkaloids with antiulcer activity. This article reviews the anti-peptic, gastro-protective, and/or antiulcer properties of the most commonly employed herbal medicines and their identified active constituents. The best goals for the treatment of peptic ulcer disease are to reduce pain, heal the wound and delay the recurrence of ulcers. About 70% of patients with peptic ulcer disease are infected by *Helicobacter pylori* and eradication of this microorganism seems to be curative for this disease. This article reviews drugs derived from the medicinal plant more commonly used in the world for peptic ulcers and, if reported, the antiulcer activity. This article will be concerned only with the antiulcer and gastro-protective effects.

Keywords: Peptic ulcer, Causes, Pathogenesis, Pathophysiology, Treatment.

INTRODUCTION

A peptic ulcer is an acid lesion of the digestive tract, located in the stomach or duodenum. It is characterized by denuded mucosa with the defect extending into the submucosa or muscularis propria.

These are open sores. It is the break in the inner lining or sometimes the lower esophagus. A 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 submucosa or muscularis propria[1].

Species of *H.Pylori*: Helicobacter is a Proteobacteria subdivision; order *Campylobacter*, and family *Helicobacteraceae*. *Wolinella*, *Flexispira*, *Sulfurimonas*, *Thiomicrospira*, *and Thiovulum* are also members of this family. There are currently over 20 recognized species in the genus *Helicobacter*, with many more awaiting formal recognitions. *Helicobacter* members are all microaerophilic organisms that are catalase and oxidase positive in most cases, and many, but not all, species are also urease positive. *Helicobacter* species[2] are classified into two groups: gastric *Helicobacter* species and enterohepatic (non-gastric) *Helicobacter* species. Both groups exhibit a high level of organ specificity, such that gastric *Helicobacter* cannot colonize the intestinal mucosa or liver in general, and vice versa. *H. pylori*

- *H. Acinonyx*
- *H. mustelae*
- *H. nemestrinae*
- *H. heilmannii*
- *H. fells*
- *H. bizzozeromii*
- *H. suls*

Causes

- **H. Pylori[3] –** The bacteria cause a decrease in acid and a decrease in parietal cell volume, which leads to ulcer formation. Furthermore, hypergastrinemia causes low pH, which reduces bicarbonate secretion, resulting in gastric metaplasia and ulcer formation.
- **NSAIDs[3]-** These reduce blood flow, mucus production, and leukocyte adhesion by inhibiting systemic prostaglandin production.
- **Gastric bypass surgery[4]-** Ulcers can develop within the gastric pouch or at any point following gastric bypass. These ulcers can be caused by anastomotic tension, the formation of a gastro gastric fistula, or the retention of pouch parietal cells.
- **Cigarette smoking[5]-** It causes mucosal damage, reduces prostaglandin production, and causes bile acid reflux into the duodenum, resulting in a change in blood flow and ischemia.
- **Zollinger-Ellison syndrome[6]-** Zollinger-Ellison syndrome tumors are made up of cells that secrete a large amount of the hormone gastrin. When gastrin levels rise, the stomach produces far too much acid. Peptic ulcers develop as a result of the excess acid.
- **Autoimmune diseases[7]-** Corticosteroids are commonly used to treat patients with autoimmune diseases. Patients receiving long-term steroid treatment may suffer from prostaglandin deficiency, which causes an increase in gastric acid production.
- **Genetic factors[8]-** First-degree relatives of ulcer patients have a three-times higher lifetime risk of developing ulcer disease than the general population. Positive family history was

reported by 20-50 percent of duodenal ulcer and gastric ulcer patients.

- **Psychological stress[8]-** These factors cause an increase in gastric acid production, which increases the risk of ulcer formation.
- **Consumption of alcohol[5]-** A lot of alcohol irritates the stomach lining, making it red, raw, and inflamed, which can lead to bleeding.

Symptoms[9]

- GI bleeding
- Obstruction (e.g., nausea with vomiting)
- Severe abdominal pain
- Blood in stole
- Trouble breathing
- Feeling faint.
- Nausea
- Unexplained weight loss
- Appetite[10]
- Heartburn changes

Virulence Factors: There are 3 categories of factor-

1. Colonization[11]:

- BabA
- SabA
- Lewis antigen

2. Immune-escape[12]:

- LPS & flagella
- CagA
- VacA

3. Disease-induction[13]**:**

- CagA& T4SS
- Vac[14]
- OipA

Pathogenesis

Pathogenesis and disease outcomes in Helicobacter pylori are mediated by a complex interplay of bacterial virulence factors, host factors, and environmental factors. After *H. pylori* enter the stomach, four steps are required for bacteria to colonize the stomach, remain infected, and cause disease pathogenesis:

(1) Survival in the acidic stomach
(2) Movement toward epithelium cells by flagella-mediated motility
(3) Attachment to host cells by adhesions/receptors interaction.
(4) Causing tissue damage by toxin release[15].

Pathophysiology

A physiologic balance exists between gastric acid secretion and duodenal mucosal defence systems under normal conditions. When the balance between aggressive and protective factors is disrupted, mucosal injury occurs. Peptic ulcers are thus defined as defects in the mucosa and submucosa of the stomach or duodenum that extend through the mucosa layer.

Mucus is secreted by stomach and duodenum epithelial cells in response to cholinergic stimulation or epithelial lining irritation. Mucus and bicarbonate are secreted by the foveolar cells, which combine to form a gel layer that is impermeable to aggressive factors such as acid and pepsin. This layer is important because it keeps the stomach from digesting itself.

In the event of an injury, additional mechanisms help prevent acid and pepsin from entering epithelial cells in the event of an injury. Increased blood flow, for example, removes acid that has diffused through the damaged mucosa while also providing epithelial cells with sufficient bicarbonate levels in the gel layer. Furthermore, epithelial cells regulate intracellular pH by using basolateral cell membrane ion pumps to remove excess hydrogen ions.

As previously stated, when the balance between aggressive and defensive factors is disrupted, mucosal damage and, as a result, peptic ulcers occur. Infection with *H. pylori*, NSAIDs, alcohol, b ile salts, acid, and pepsin are all aggravating factors. The defense process includes mucus, bicarbonate, prostaglandin, adequate mucosal blood flow, and epithelial regeneration[16].The mucosal barrier is made up of three components:

- A layer of epithelial cell lining bound by fluid-repelling tight junctions; a mucus layer secreted by surface epithelial cells and foveolar cells that forms a protective gel-like coating over the entire mucosal surface of the stomach.
- A mucus layer secreted by surface epithelial cells and foveolar cells that forms a protective gel-like coating over the entire mucosal
- A layer of bicarbonate ions secreted by epithelial cells on the surface of the skin that neutralizes acids[17].

Diagnosis[18]

Test	Comments
EGD	For patients with evidence of bleeding, weight loss, chronicity, or vomiting; and people more than 55 years.
	More than 90 per cent sensitivity and specificity in diagnosing gastric and duodenal ulcers and cancers.
Barium and diatrizoate sodium (Gastrografin) contrast radiography (double-contrast hypotonic duodenal graphy)	Indicated when endoscopy is unsuitable or not affordable, or if complications such as gastric outlet obstruction are suspected.
	Diagnostic accuracy increases with the extent of disease; 80 to 90 per cent sensitivity in detecting duodenal ulcers.
***Helicobacter pylori* testing**	
Serologic ELISA	Useful only for initial testing cannot be used to confirm eradication.
Urea breath test	These are costly.
	Sensitivity, 95 to 100 per cent; specific features, 91 to 98 per cent; can be used to ensure completion.
Stool antigen test	It is accurate (sensitivity, 91 to 98 per cent; specificity, 94 to 99 per cent). It can be used to ensure completion.
ELISA based urine and rapid urine	Sensitivity, 70 to 96 per cent; average, from 77 to 85%.
Endoscopic biopsy	Culture (sensitivity, 70 to 80 percent; specificity, 100 percent), histology (sensitivity,> 95 percent; specificity, 100 percent).

Treatment

The ulcer is a relapsing, chronic disease that can last for years. The goals of anti-ulcer therapy are pain relief, ulcer healing, avoiding complications, and avoiding relapse. Anti-ulcer medications are classified as follows:

1. Agents that contribute to the reduction of gastric acid secretion
2. Agents reduce stomach acid
3. Ulcer protective agents and
4. Anti-Helicobacter pylori.

Table 1 and 2 describes the possible medicines for the management of ulcer.

Table 1: Drugs[21] used in peptic ulcer

S.No.	Drug	Market Name	Mechanism of action	Adverse effect
1.	Amoxicillin[19]	Trimox, Acmox DS, Aglomox, Allmox INJ	Inhibits and kills bacteria	Nausea, Jaundice, Anxiety, Itching
2.	Clarithromycin	Clarinix, Celex-OD, Clarimin,	Binds to 50S ribosomal Subunit & inhibits protein synthesis	Insomnia, Abdominal pain, Candidiasis
3.	Metronidazole	Balgyl gel, Acrogyl, Antamebin	Inhibits protein synthesis &causes cell death	Dermatitis, Influenza, Skin irritation
4.	Carbenoxolone	Carbenoxolone	Protects mucosal barrier from acid pepsin attack	Hypokalemia
5.	Famotidine[20]	Acicon, Facid, Famtac	Inhibits histamine H2 receptor & suppresses the gastric secretion	Headache, diarrhoea, constipation

Table 2: Combination of drugs used in peptic ulcer

S.No.	Drug	Market Name	Mechanism of action	Adverse effect
1.	Amoxicillin+ Dicloxacillin	Abclox, Aclowell-L, Adcil, Adclox-D, Abimax-DC	Inhibits bacterial cell wall synthesis by binding with penicillin-binding proteins	Leukopenia, Urticaria, Seizures, Vaginitis
2.	Ofloxacin+ Tinidazole[22]	Aflox-TZ, Agroflox-T, Bofloden-T, Casflox-TZ	Exerts bactericidal activity by inhibiting bacterial topoisomerase IV and DNA gyrase.	Chest pain, Pruritus, Flatulence, Pharyngitis
3.	Diazepam+ Propantheline	Pepler	Blocks action of acetylcholine at postganglionic parasympathetic receptor site & inhibit gastrointestinal motility.	Confusions, Vomiting, Mydriasis, Blurred vision
4.	Famotidine+ Domperidone[23]	BDOM-F, Dicka-F	Blocks histamine H2 receptors.	Dizziness, Acne, Arrhythmia, Dry skin
5.	Ranitidine+ Ondansetron	Reden-O, Ranidom ON+RANTDN, Acidom-O	Inhibits histamine H2 receptor of gastric parietal cells, which inhibits gastric acid secretion.	Bradycardia, Drowsiness, Insomnia, Pancreatitis

No matter that the further allopathic medicine or chemotherapy has progressed, the possibility of adverse effects cannot be ruled out. As a result, the use of herbal remedies is associated with a low incidence of side effects. Table 3 lists the medicinal plants that have antiulcer properties.

Table 3: Medicinal plants[24-25] having anti-ulcer property

S.No	Botanical name and family	Common and English name	Part used	Active constituent	Site of action and mechanism	Adverse effect	Medicinal use
1.	*Annona squamosa, Annonaceae*	Sitaphal, Sugar apple	Bark, seed, Leaves, fruit.	Tannic acid, flavonoids, Saponins	Anti-inflammatory activities due to the presence of cyclic peptides	Stomach irritation, nausea, vomiting, and liver damage	The bark is used as astringent and tonic, fruit is considered demulcent, anti-diarrhoeal activity, used in diabetes, antiulcer.
2.	*Bauhinia variegata Linn. Fabaceae*	Kachnar, Kantar, Camel's foot	Flowers, buds, Stem, roots, bark, seeds, and leaves.	Flavonoid, Quercetin, rutin, aspirin	Inducing the volume of gastric acid secretion, neutralizing the acidic condition, increase the mucus secretion	Headache, flushing, rashes, stomach upset	The bark is useful in ulcers, scrofula, asthma and skin disease. Used to remove intestinal worms
3.	*Strophanthus hispidus Apocynaceae*	Petai, bitter bean or stink bean	Root, fruit	Glycoside, alkaloids, resin	Possess antiulcerogenic effect. Inhibition of writhing reflex with a peak effect of 73.13%	Change in taste, blurred vision. Fatigue, headache, anxiety	Treat hypertension, diabetes, and kidney problems, Treatment of ulcer
4.	*Nigella sativa Linn. Ranunculaceae*	Kalonji, black cumin	Seed	Campesterol, quinazoline, tannin,	Inhibits h. *pylori* infection and inhibits it's	Allergic rashes in some People,	Diuretic, hypoglycemic, anti-tumor, antiulcer

				alkaloids, Nigellicin	activity	Increase the risk of seizures in some people	
5.	*Calliandra portoricensis, Mimosoideae*	Red Powder Puff, Babool family	Leaves	Phenolic compounds, saponin, protein, flavonoids	Decrease in gastric acid secretion, Modulation of oxidative stress	Drowsiness, dizziness, hypotension or headache	Antiulcer, leprosy, anti-inflammatory
6.	*Curcuma longa, Zingiberaceae*	Haldi, turmeric	Rhizome	Phenolic, tannins, flavonoids	protects against gastric ulcer by blocking, the H2 histamine receptor, shows anti-inflammatory effect	Increase the level of urinary oxalate, risk of kidney stone, acid reflux, diarrhoea	Antiulcer, wound healings, anti-inflammatory
7.	*Ficus arnottiana Miq. Moraceae*	Paras papal, Banyan tree	Leaf	β-sitosterol, alkaloids, carbohydrate, tannins, phenols	Mucus-protective activity and gastric anti-secretary activity. The extract is non-toxic even when relatively high	Decrease in blood sugar level, Hypoglycemic	Useful against inflammation, leprosy, scabies, ulcer, burning sensation
8.	*Acacia niloticadelile, Fabaceae*	*Kikar, Gum arabic tree*	Bark tender Leaves, pods	Phenolic Compounds, saponin, flavonoids	Seedless pods on pylorus ligation induced gastric ulcer	The danger of drug interaction, increased incidence of relapses during Ulcer treatments	Antiulcer, sore-throat, toothache, diarrhea, dysentery
9.	*Jatropha curcas linn., Euphorbiaceae*	Ratanjot, Spanish Bugloss	Leaves	Phenolic compounds, saponin, Flavonoids	Protect the gastrointestinal mucosa from lesions produced by various experimental ulcer models	Vomiting, diarrhoea, abdominal pain and burning sensation in the throat	Insecticidal and used in foul ulcers, tumors, and scabies, in jaundice
10.	*Zingiber officinale, Zingiberaceae*	A dark, Ginger, ginger root	Root	Phenolic compounds, Flavonoids	Inhibiting parietal cell H+-K+-ATPase, inhibition of an ulcerogenic—*H. pylori*, exhibiting anti-oxidative properties	Heartburn, burping and general stomach discomfort	Antiulcer, motion sickness, Sea sickness and pregnancy, Gastrointestinal benefits

GLOBAL MARKET FOR ANTI-ULCER DRUGS

During a review of the literature, it was discovered that anti-ulcer drugs have a sizable market in the global pharmaceutical industry. Gastrointestinal tract drugs account for 11% of the global pharmaceutical market. In the Indian context, the Indian pharmaceutical market is currently valued at $ 20 billion. 11 percent of the $ 20 billion drug market accounts for $ 2.2 billion in revenue. According to the IMS 2015 report, the anti-ulcer market, which falls under the Gastrointestinal drug market, is worth around Rs. 8413 crore. It is estimated that the Indian pharmaceutical market will reach $ 55 billion by 2035, bringing the total GIT (gastrointestinal tract) market to $ 6.05 billion by 2035.

CLINICAL TRIAL STATUS

Clinical trials are a component of the drug development process that includes human testing of the lead compound. Clinical trials are conducted in several stages. To begin the trials, the companies must first obtain permission from the governing body. Clinical trials are only conducted when the lead compound has the potential to be useful to a large number of people. The current clinical trials being conducted around the world have been included in this review.

Clinical Trial with Status and Region

A pilot trial of the ReCell Allogeneic Cell Harvesting Device for Venous - Active, recruiting, UK

Helicobacter eradication Aspirin Trial (HEAT) is currently recruiting in the United Kingdom.

Evaluation of lightweight fibreglass heel casts in the treatment of diabetic heel ulcers-Active, recruiting, UK

Misoprostol for small intestinal ulcers and unclear bleeding caused by aspirin or NSAIDs- Active, recruiting in the UK

A clinical trial of *Vranadi guggulu* and *Vranya lep*a in the treatment of diabetic foot ulcers is currently recruiting participants in India.

Herbal medicine's impact Diabetics can benefit from *Vranadi Guggulu* and VranaIepa INDIA, active, recruiting

A clinical trial to evaluate exudate management and adhesion of Aquarelle A foam adhesive dressing in the treatment of pressure ulcers -Active, recruiting, INDIA

An open clinical trial will be conducted to assess the efficacy of *Manjitti kudineer* in non-healing chronic ulcers, burns, and scalds-INDIA is actively recruiting.

A clinical trial to compare the efficacy and safety of Revaprazan tablets with Omeprazole capsules in patients suffering from a peptic ulcer or an acute stomach ulcer.

CONCLUSION

The combined effect of herbal preparations and standard anti-gastric ulcer drugs may have a synergic activity against *H. pylori* and gastric ulcer disease, improving patient outcomes. With only a few human studies, it is proposed that future clinical studies be conducted with a number of observation sizes on the safety and effectiveness of antiulcer medicinal herbs. It would also be advantageous to design data to determine and elucidate the

mechanisms of action of plants that are used in the treatment or prevention of peptic ulcers. Doctors and pharmacists should be aware of the dangers associated with the use of herbal remedies.

FUTURE PROSPECTS

The causative agents of *H. pylori*-related gastric ulcers is still unknown. Its growth has always been currently caused by a variety of *H. pylori* virulent factors and the host immune response. It is also unknown why some patients are more susceptible to the gastric toxicity of NSAIDs like aspirin than others. Antibiotic resistance remains a major challenge in the absence of a potential breakout.

The genetic diversity of the *H. pylori* virulence proteome directs future anti-virulence developments toward more conserved assembly and secretion pathways, leaving the question of how these inhibitors can make a contribution to *H. pylori* treatment.

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