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REVIEW ARTICLE

Newer therapeutic approaches for anti-ulcer drugs-a review

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ABSTRACT

The frequency and prevalence of this disease and its consequences have exhibited dramatic variation, according to epidemiological data. There has been a continuing search for an appropriate, palliative, and curative agent for the treatment of peptic ulcer disease using natural materials of plant and animal origin because these medications are complicated, expensive, and poisonous. Antioxidants aid in scavenging free radicals and regulating the oxidative stress that contributes to the development of peptic ulcers.

Keywords: Antioxidants, Free radicals, Peptic ulcers

INTRODUCTION

Apeptic ulcer is defined as a localized erosion or defect on the surface of the stomach with a mucosal break that is at least 5 mm in diameter, typically caused by the shedding of inflammatory necrotic tissue. Peptic ulcers are thought to be caused by an imbalance between protective and aggressive factors, such as mucin, bicarbonate, and prostaglandins. Numerous variables, including a sedentary lifestyle, alcohol, smoking, spicy food, physiological stress, and medications like non-steroidal anti-inflammatory medicines, are thought to play a significant part in the etiology of ulceration.[1]

EPIDEMIOLOGY OF PEPTIC ULCER

According to epidemiological research, the incidence of peptic ulcer (PU) rises with the use of non-steroidal anti-inflammatory drugs (NSAIDs) and ASA, as well as with population aging, and is a mirror of the incidence of *Helicobacter pylori* infection.[2]

The identification of powerful and efficient acid suppressants as well as the management and prevention of *H. pylori* infection, were listed as two more key findings that contributed to the decline in peptic ulcer disease (PUD) incidence. By the turn of the century, however, the increased use of NSAIDs had produced a rise in in gastric ulcers (NSAID-induced ulcers) and a decrease in duodenal ulcers (*H. pylori*-associated infections).[3]

In underdeveloped nations, the frequency of *H. pylori* infection peaks at more than 80% before the age of 50, according to studies, and a large percentage of children are infected before the age of 10.[4]

The lifetime risk of developing PU is estimated to be approximately 10% anyway; only a minority of cases with *H. pylori* infection will lead to an ulcer, while a larger proportion of people will get non-specific discomfort, abdominal pain, or gastritis.

SYMPTOMS AND CLINICAL FEATURES OF PEPTIC ULCER

The most typical PU symptom (for both stomach and duodenal ulcers) is epigastria pain, which is experienced by the majority of people with peptic ulcers. Compared to patients with in gastric ulcers, who experience nighttime discomfort in roughly 30–40% of cases, about 50–80% of duodenal ulcer patients do. Back pains may indicate that

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an ulcer has spread posteriorly, or they may originate in the pancreas. Patients may frequently be asymptomatic, with just 20–25% of them exhibiting suggestive peptic ulceration symptoms that were later confirmed to be peptic ulcers.[5]

PATHOGENESIS

A complicated and multifaceted etiology for PU has been discovered.[5] The involvement of various host and environmental variables that enhance stomach acid output, 1 weaken mucosal barriers, and/or both is crucial to the development of gastric ulcers. Environmental variables that are important to the etiology of PU development include emotional stress, smoking, dietary inadequacies, excessive alcohol intake, and long-term NSAID use.

In addition, *H. pylori* produces certain chemicals that are harmful to epithelial cells, including vacuolating cytotoxin, proteases, and ammonia that is created to control stomach pH.

This is followed the identification and management of the *H. pylori* infection. In fact, it has been reported that long-term use of NSAIDs can harm the mucosa lining of the stomach and duodenum through a number of mechanisms, including topical epithelial irritation brought on by the medication, impairment of the mucosal membrane's barrier function, suppression of prostaglandin synthesis in the stomach, decreased blood flow to the stomach, and interference with the healing of superficial wounds.

HISTORICAL ASPECT[7]

For the past 100 years, there has been much discussion about how gastric acid is secreted, with a focus on both the molecular and cellular mechanisms that are involved. When gastric juice was chemically analyzed, William Prout first extracted hydrochloric acid from it in 1824. James Black's discovery of the histamine (H2) receptor in 1971 led to the development of antagonists for the treatment of peptic ulcer. The treatment of peptic ulcers was changed after the spectacular discovery of proton-pump inhibitors in 1989 because it prevents the last stage of acid formation in the stomach lumen.

Gastric acid regulation

Central regulation

Along with hormones, paracrine agents, and second messengers, the central nervous system, enteric nervous system, and other neurological systems all play a significant role in controlling acid secretion. The three stages of acid secretion are the cephalic, gastric, and intestinal phases.[8] The nucleus tractus solitarius (NTS), the hypothalamus, and the dorsal motor nucleus of the vagus (DMNV) are key players in the central control of acid secretion. By providing efferent fibers to the stomach via the vagus, the DMNV primarily aids in motility rather than secretion and is essential in integrating sensory input from the hypothalamus and visceral input from the NTS. The ventromedial hypothalamus inhibits acid secretion; stimulation of this region results in less acid secretion, and vice versa. The stomach's muscle layer and mucosa contain sensory receptors that aid in the detection of mechanical, chemical, and thermal stimuli. These sensory impulses are sent to the central nervous system via sympathetic afferent and vagal nerve fibers.

Peripheral mechanism

Gastrin and histamine are released from G cells and enterochromaffin-like cells, respectively, as part of the intrinsic mechanisms of the stomach that control acid secretion. The parietal cells are immediately affected by each of these stimuli. In addition acetylcholine aids in controlling acid output.[9] The histamine released interacts with the histamine receptor type 2 (H2) on the parietal cells, activating the calcium-sensitive pathway and the cyclic adenosine monophosphate pathway and stimulating the parietal cells' H + K + -ATPase.

Mechanisms of cytoprotection

Robert first used the term "cytoprotection," which is defined as defense against gastrointestinal mucosal damage by means other than gastric acid neutralization. Endogenous prostaglandins have been implicated in cytoprotection through potential processes including mucus secretion, bicarbonate release, maintenance and enhancement of mucosal blood flow, and

free radical scavenging, according to a flood of research. Without an external injury, the normal gastric mucosa continues to be hostile to the acidic environment of the stomach lumen. Pre-epithelial defense, which is the secretion of mucus gel; epithelial defense, which consists of surface epithelial cells that can survive pH levels below 2.5; and post-epithelial barrier, which is composed of parietal cells at the gland's base, are the three categories of gastric mucosal defense.

Stimulation of mucus and bicarbonate secretion

Mucus, lipids, and proteins make up the mucous membrane barrier. Together with bicarbonate secretion, they provide a constant gel that shields the stomach from acid damage. Prostaglandins, a cytoprotective substance, have been found to thicken the mucus gel while protecting the deeper layers but not the surface epithelium.[10] The reepithelization of mucosa is aided by mucin. Bicarbonate has been found to aid in cytoprotection and works through both passive diffusion and metabolically dependent processes. Prostaglandins aid in boosting the secretion of bicarbonate, which in turn helps to build the mucus bicarbonate barrier. Additionally, bicarbonate directly aids in reducing the amount of hydrogen ions present in the gastrointestinal mucosa.

Strengthening of the gastric mucosal barrier

A significant mucosal barrier is formed by the apical membrane, also known as tight junctions, between the surface epithelial cells because it inhibits acid from diffusing backward. The hydrophobic coating created by phospholipids on the luminal surface of the gastric epithelium helps to block the passage of water-soluble hydrogen ions. These phospholipids are more concentrated when prostaglandins are present.

Regulation of mucosal blood flow

Functional impairment of gastric microcirculation results from vascular injuries to sub-epithelial capillaries with increased vascular permeability and circulatory stasis. Oxygenation and nutrition delivery are maintained by upregulating mucosal blood flow. The regulation of bicarbonate-mediated acid neutralization and the absorption of harmful substances are both aided by an increase in blood flow to the mucosa.

Effects on gastric motility

Epithelial necrosis and ulceration are both thought to be significantly influenced by mucosal compression. Mucosal compression is due to gastric hypercontraction. By flattening the stomach mucosal folds and increasing the mucosal surface area, circular muscles protect the gastric mucosa by decreasing the volume of irritants that come into contact with it. This process is aided by a variety of chemicals, including mast cell stabilizers and prostaglandins, which increase cytoprotection.

Scavenging free radicals

Lipid peroxidation and damage to intracellular components are caused by free radicals. It results in ischemia of the stomach mucosa, severely damaging the mucosa. Well-known antioxidants like Vitamin E and selenium have been found to protect against stress- and chemical-induced stomach lesions.

Pathogenesis of peptic ulcer

The duodenum and stomach account for 99% of all peptic ulcer cases, with the incidence of the former being 4 times higher than the latter. Increased acid secretion, weakened mucosal defense, free radicals, and lipid peroxidation are some of the causes of peptic ulcers.

Increased acid secretion

Gastric juice acidity and pepsin activity both play significant roles in preventing the development of ulcers. The adage "no acid, no ulcer" popularized by Schwartz is valid when expanded to "no acid and peptic activity" since pepsin helps the stomach's digesting process. Various therapeutic treatments, such as antacids and anti-secretory medications, support this maxim, but to everyone's dismay, ulcer recurrence occurs after treatment is stopped.

Free radicals and peroxidation

Free radicals are critical in the pathogenesis of ischemia/reperfusion injury because they contain unpaired electrons. Deoxyribonucleic acid can be damaged by free radicals, and they can also start uncontrollable chain reactions like lipid peroxidation. Free radicals created from oxygen are what cause both acute and chronic stomach ulcers, and one study found that injecting a system that produces superoxide into a rat's celiac artery causes gastrointestinal bleeding [Figure 1].

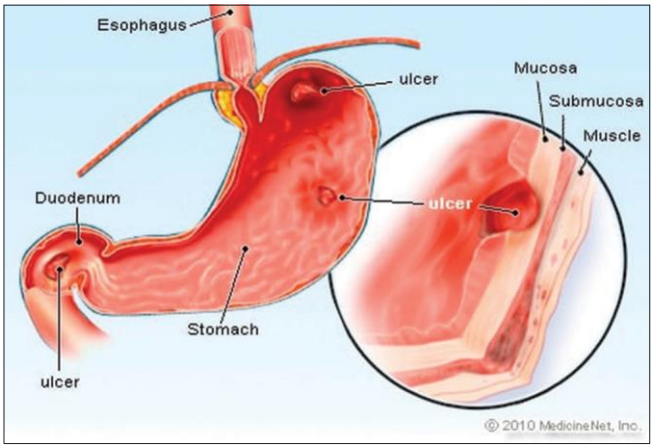

Figure 1: Peptic ulcer[6]

Predisposing factors for peptic ulceration

Helicobacter infection

More than 95% of patients with duodenal ulcers and 75% of patients with gastric ulcers are affected by antral gastritis due to *H. pylori*. This bacterium attaches to the mucosal epithelium near the gap junctions and excretes urea and ammonia, which raise the pH and create an alkaline environment. The organism can survive in this environment, and the stomach cells are cytotoxic when ammonia is released. Stomach metaplasia takes place, and colonization of these heterotrophic islands causes stomach ulceration and mucosal damage. The etiology of *H. pylori* infections has been linked to oxidative stress, and *H. pylori* infections because more oxidative damage, which leads to epithelial injury, altered epithelial proliferation, and more apoptosis.

NSAIDs

NSAIDs have been linked to a number of lesions in the gastric tract, including erosions and ulcers as well as hemorrhages and petechiae. These medications are known to result in stomach mucus glycoprotein denaturation and epithelial cell sloughing. Additionally, aspirin and other medications induce the parietal cells to store intracellular protons, which causes localized acid accumulation through a process known as back diffusion of acid. Additionally, these medications suppress prostaglandins, mast cell degranulation leading to histamine release, glucose oxidation, and enzymes involved in anabolic responses. Lysosome labialization results in cellular autolytic reactions

Class of drugs	Mechanisms	Use
H2 receptor antagonists (cimetidine, ranitidine, famotidine, nizatidine, roxatidine)	Acid inhibition	*H. pylori*-negative peptic ulcer; replaced by PPI because of inferiority in acid suppression
PPI (omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole)	Most potent acid inhibition	Standard treatment for all *H. pylori*-negative peptic ulcers; prevention of NSAID or aspirin ulcers; essential component in eradication regimen; given intravenously in bleeding ulcers
Prostaglandin analogues (misoprostol*)	Increase mucosal resistance; weak acid inhibition	*H. pylori*-negative gastric ulcer; prevention of NSAID ulcers
***H. pylori* eradication regimens** (PPI plus two antibiotics)	Cure of *H. pylori* infection	Standard therapy in all *H. pylori*-positive ulcers
Bismuth salts (subcitrate, subsalicylate)	Weak antibacterial effect; increase of mucosal prostaglandin synthesis	In quadruple therapy for *H. pylori* eradication

*PPI = proton-pump inhibitor, NSAID = non-steroidal anti-inflammatory drug *Contraindicated in pregnancy*

Figure 2: Class of drugs with effect on healing of peptic ulcer

Drug Classes	Characteristics	Types
Antacids	Help in neutralizing gastric acid, reducing acid delivery in duodenum and pepsin activity, besides to bind bile acids	Calcium and magnesium carbonates, aluminum hydroxide and magnesium trisilicate
Anti-secretory agents	Reduce gastric acid secretion, help relieve ulcer pain and stimulate ulcer healing, inhibit *H. pylori* growth and proliferation in gastric tissues	Histamine H2-receptor antagonist (cimetidine, famotidine, nizatidine and ranitidine), proton pump inhibitors (esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole)
Cytoprotective agents	Reduce/prevent gastric mucosal damage (increase mucus and bicarbonate secretion, strengthen gastric mucosal barrier, decrease gastric motility, increase blood flow to gastric mucosa, increase prostaglandins and sulfhydryl biosynthesis, scavenge free radicals, stimulate cell growth and repair and decrease leukotrienes release)	Prostaglandins, fatty acids, sulfhydryl compounds, aluminum-containing antacids, sucralfate, bismuth chelate and liquorice

Figure 3: Class of anti-ulcer drugs[17]

[Figure 2]. Additionally, it boosts the generation of free radicals.

Psychological stress

The CNS and brain-gut axis are crucial in the development of stress ulcers.

Table 1: Plant extract with antiulcerogenic activity

Order	Family	Biological Name	Mechanism of Gastrorotection
Apiales	Apiaceae	Centella asiatica	Wound healing, mucus production, antioxidant, anti- inflammatory
Asterales	Asteraceae	*Baccharis dracunculifolia*	Wound healing, antioxidant, mucus production
		Baccharis trimera	Wound healing, anti-secretory, antioxidant
		Hieracium gymnocephalum	Wound healing, anti- inflammatory
		Tanacetum larvatum	Wound healing, anti- inflammatory, antioxidant
Boraginales	Boraginaceae	*Cordia dichotoma*	Wound healing, antioxidant, anti- inflammatory
Brassicales	Capparaceae	*Capparis zeylanica*	Wound healing
	Moringaceae	*Moringa oleifera*	Wound healing, serotonin release, anti- secretory, cytoprotective, anti- inflammatory
Cucurbitales	Cucurbitaceae	*Momordica cymbalaria*	Wound healing, anti-secretory
Cyperales	Cyperaceae	*Cyperus rotundus*	Wound healing, antioxidant activity, anti- inflammatory
Fabales	Fabaceae	*Parkia speciosa*	HSP70 up-regulation, Bax protein down-regulation

Today, a number of illnesses, including shock, sepsis, trauma, and neurological problems, are thought to be complex phenomena. Stress ulcerogenesis is significantly influenced by a number of interactions involving the autonomic nervous system, vascular, mucosal, and neurohumoral variables. The limbic area is important for controlling blood flow, motility, and acid secretion.

Others

Other factors include smoking, alcohol, etc.

Therapy for acute peptic ulcer[11]

The treatment of PUD has focused on mucosal defense mechanisms and gastric acid secretion. Few therapeutic methods for PUD have withstood the test of time, as demonstrated by the development of numerous medications to treat the condition [Figure 3].

H^+/K^+ ATPase inhibitors[12]

As opposed to blocking histamine and cholinergic receptors, it works by directly inhibiting the gastric proton pump. This class of medications includes omeprazole, lansoprazole, rabeprazole, and pantoprazole, among others. They improve control over both basal and nocturnal acid secretion by blocking the last stage of the process. They are also known to stop *H. pylori* from growing. They have taken the position that H2 antagonists are the first-line treatment for peptic ulcers.

Prostaglandins[13]

In 1979, Robert demonstrated that prostaglandins reduce gastric acid production and aid in the prevention of ulcers brought on by NSAIDs, food, alcohol, smoking, and stress. Misoprostol, a prostaglandin analogue, works by boosting mucus and bicarbonate secretion, preventing the development of chronic ulcers. However, it does not protect against duodenal ulcers; it only protects against stomach ulcers. Due to its abortifacient qualities, it should not be used during pregnancy. Other recognized substances include enprostil, rioprostil, and arbaprostil. These medications include mexiprost, enisoprost, and nocloprost.

H_2 receptor antagonist[14]

By inhibiting the H2 receptor, these medications limit the release of stomach acid. Additionally, it significantly lowers 90% of the basal, food-stimulated, and nocturnal releases of stomach acid. According to published research, it also aids in preventing stomach ulcers brought on by stress.When treating ulcers brought on by stress, they are treated with antacids. Ranitidine, cimetidine, famotidine, and nizatidine are the primary medications in this group. Long administration times for ulcer therapy are one of the main downsides, and ulcer recurrence after healing is a common consequence [Figure 2].

Muscarinic receptor antagonists[15]

When compared to histamine receptor antagonists, pirenzepine has more cytoprotective effects. It aids in defense against taurocholate, sodium hydroxide, and

alcohol-induced stomach mucosal lesions. It works by suppressing the muscarinic (M1) receptor in the stomach, which lowers both baseline and induced acid secretion.

PHARMACOLOGICAL MANAGEMENT OF PU CONTINUES TO EVOLVE DESPITE THE AVAILABILITY OF DIVERSE TYPES

In order to focus treatment on pain relief, ulcer healing, and ulcer recurrence delay, novel therapeutic agents have been developed. However, a large number of the pharmaceutical treatments for PU are directed either at reducing the aggressive variables or at enhancing the mucosal defense.[16]

PLANT PRODUCTS AND PHYTOCHEMICALS AS ANTIULCEROGENIC AND GASTROPROTECTIVE AGENTS[18]

Plants and items derived from plants have been utilized for treating a variety of illnesses and disorders in folklore for centuries. Nowadays, herbal therapy is gaining acceptance as a legitimate alternative to synthetic medications that are sold commercially for the management and treatment of PU. This is supported by its reduced price, perceived effectiveness, accessibility, and lack of or little side effects. These herbal treatments contain a variety of gastroprotective qualities [Table 1].

COMPONENTS AND THEIR ANTIULCER INHIBITORY EFFECTS

Alkaloids[19]

Alkaloids are a class of nitrogen-containing phosphate-solubilizing microorganisms that are found in nature and have strong antiulcer properties. By decreasing pro-inflammatory cytokines and oxidative stress and improving gastric mucosal blood flow, the imidazole alkaloid epiisopiloturine hydrochloride, which was isolated from *Pilocarpus microphyllus* leaves, protects against naproxen-induced gastrointestinal injury in rats. With maximum effects at 10 mg/kg, pretreatment with epiisopiloturine reduced naproxen-induced macro and microscopic stomach damages. In mice with ethanol-induced acute gastric ulcers, cavidine, a significant alkaloid substance derived from Corydalis impatiens, reduced stomach damage when administered at 10 mg/kg. Additionally, cavidine therapy boosted mucosa glutathione, superoxide dismutase, and prostaglandin E2 levels while lowering Interleukin-6 IL-6 and tumor necrosis factor levels.

Terpenes and terpenoids[20]

Citrus aurantium monoterpene myrcene raised mucosal malondialdehyde levels, decreased gastric and duodenal lesions, and boosted gastric mucus production.

The traditional use of *Cedrus deodara* to treat peptic ulcers is justified by the volatile oil's ability to considerably reduce ulcers when administered at a level of 100 mg/kg. The percentages of ulcer inhibition for rabeprazole (20 mg/kg) and *C. deodara* (100 mg/kg) were 41.5% and 67.7%, respectively. In both *in vivo* and *in vitro* experimental models, the essential oil of *Gallesia integrifolia*, which is high in santalene, had strong gastroprotective and curative properties. This is likely because of its antioxidant, nitrergic, mucogenic, anti-secretory, and anti-inflammatory actions.

Flavonoids[21]

Flavonoids are naturally occurring antioxidants with a distinctive C6-C3-C6 carbon skeleton structure that can be found in a variety of fruits and vegetables. Recent research has shown that flavonoids have a wide range of pharmacological effects, including those that are anti-inflammatory, anti-allergic, anti-cancer, and anti-diarrheal. They have antioxidant activity because their aromatic ring(s) include a hydroxyl group(s). The plant kingdom contains large amounts of quercetin, rutin, and kaempferol. In rats with stomach injuries brought on by acidified ethanol, they decreased the mucosal content of platelet-activating factor.

ANTIULCER ACTIVITY OF INDIAN MEDICINAL PLANTS

Acacia arabica[22-24]

Arabic acacia. In arid and sandy areas, *Acacia arabica* (family Mimosaceae) is widespread throughout India. Both locally and generally, it is referred to as the "babul tree" or "Karuvelam." The gum in this plant, which contains arabic acid mixed with calcium, magnesium, and potassium as well as a tiny amount of malic acid, sugar, moisture at 14%, and ash at 3–4%, has been found to include a number of chemical components. There is a lot of tannin in the bark, and pods have a tannin content of about 22.44%.

Antiulcer activity

Within Ayurveda. It works well as a wash for wounds and hemorrhagic ulcers. A poultice made from bruised, fragile leaves that is put on ulcers acts as an astringent and stimulant. In current studies. The rat stomach ulcer caused by cold restraint stress was prevented by *Acacia Senegal* gum. The intestinal damage caused by meloxicam was prevented by an aqueous extract of A. Arabica gum, which also revealed reduced intestinal enzyme activity.

Allium sativum[8]

The plant *A. sativum*, a member of the *Liliaceae* family, is also known as "Vellapundu" in several parts of the world. It is grown throughout India. This plant's chemical components include an acrid volatile oil, which is the active ingredient, as well as starch, mucilage, albumen, and sugar. Seeds produce fragrant oil. In addition to crucial nutrients and supportive materials comprising vitamins, the juice, and especially its oil contents are rich in combinations of salicylic acid, iodine, and sulfur that are organically bound.

Antiulcer activity

Within Ayurveda. Applying fried garlic in mustard or coconut oil is a great way to get rid of maggots that are infesting wounds, ulcerated surfaces, and ulcers. Garlic juice has been used as a lotion for cleansing wounds and nasty ulcers when combined with three or four parts of ordinary or distilled water in current studies. Rats were treated with *A. sativum* bulb juice extract at doses of 250 and 500 mg/kg orally in order to treat cysteamine-induced stomach ulcers.

Aloe vera[9]

A. vera from the *Liliaceae* family is frequently referred to as "Aloe gel." In India, it is referred to as "Gawarpetha" or "Kattalai" regionally. This plant contains aloin, isobarbaloin, and emodin as chemical components.

Antiulcer activity[25,26]

Inside of Ayurveda. In America, isolated chronic ulcers are successfully treated using leaves. The ulcers heal after a few weeks after the discomfort first lessens in current studies. *A. vera* powder and gum *Acacia* were combined, and 200 mg/kg of the resulting solution was given orally to rats to treat indomethacin-induced stomach ulcers. Significant antiulcer activity comparable to control was shown by the extract. Activated components. Considerations include barbalin, isobarbolin, and saponins.

CONCLUSION

There has been a continuing search for an appropriate, palliative, and curative agent for the treatment of peptic ulcer disease using natural materials of plant and animal origin because these medications are complicated, expensive, and poisonous. Antioxidants aid in scavenging free radicals and regulating the oxidative stress that contributes to the development of peptic ulcers.

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