Chapter

Pharmacotherapy of Peptic Ulcer Disease and Latest Research

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Abstract

Peptic ulcers have unquestionably been a disease of the twentieth century. Epidemiological data for this disease and its complications have shown striking variation in incidence and prevalence. Various drugs have been used to treat peptic ulcer disease like proton-pump inhibitors, histamine (H2) receptor antagonists, prostaglandin analogues and sucralfate. Because these drugs are complex, expensive and toxic, efforts have been constantly made to find a suitable, palliative and curative agent for the treatment of peptic ulcer disease from natural products of plant and animal origin. Recently, antioxidants are being used to treat peptic ulcer disease. Antioxidants help in scavenging the free radicals and controlling the oxidative stress responsible for the progression of peptic ulcer.

Keywords: gastritis, gastric ulcers, oxidative stress, antioxidant treatment

1. Introduction

Peptic ulcers have unquestionably been a disease of the twentieth century. Epidemiological data for this disease and its complications have shown striking variation in incidence and prevalence. Peptic ulcer is defined as a local defect or excavation on the surface of the stomach with a mucosal break of diameter 5 mm or larger, usually produced by sloughing of the inflammatory necrotic tissue. Aetiology of peptic ulcer is fiercely debated and is believed that peptic ulcers develop due to imbalance between aggressive factors (*Helicobacter pylori*, non-steroidal anti-inflammatory drugs, gastric acid) and protective factors (mucin, bicarbonate, prostaglandins) leading to interruption of mucosal integrity [1].

The major forms of peptic ulcer include chronic duodenal ulcer, chronic gastric ulcer, Zollinger-Ellison syndrome (ZES), drug-induced ulcers and stress-induced peptic ulcer. Various factors are implicated to play a pivotal role in pathogenesis of ulceration like sedentary life style, alcohol, smoking, spicy food, physiological stress, drugs like non-steroidal anti-inflammatory drugs (NSAIDs) and various bacterial infections [1]. Oxidative stress has emerged as one of the major pathogenic factors in progression of ulcer as it directly impairs the cellular function and promotes cellular organelle damage in mitochondria, lysosomes and nucleus [2].

Stress-induced peptic ulcer is a pathological condition affecting the gastrointestinal tract. Stress ulcers are commonly found in the gastric mucosa anywhere within the stomach to the duodenum. Pathogenesis is mainly due to reduction in mucosal blood flow or a breakdown in other normal mucosal defence mechanisms. Effective therapy remains elusive in the treatment of stress-induced peptic ulcers [3]. One of the common denominators for the occurrence of the disease is involvement of

free radicals, an increase in histamine release and decreased mucous production. Reactive oxygen species are generated by various metabolic activities, and antioxidant enzymes like superoxide dismutase, catalase, lipid peroxidase and glutathione peroxidase control their accumulation. Any imbalance in the activity of these enzymes leads to faulty disposal of free radical and their accumulation [4].

Alcohol is one of the leading causes of peptic ulcer disease. The mechanism of ethanol-induced gastric lesions is varied including the depletion of gastric mucus content, damaged mucosal blood flow and mucosal cell injury. It decreases bicarbonate and mucus production by which it produces necrotic lesion in gastric mucosa. Ethanol initiates apoptosis which leads to cell death. It also releases superoxide dismutase and hydroperoxyl free radical species in the biological system [4].

Various drugs have been used to treat peptic ulcer disease like proton-pump inhibitors, histamine (H_2) receptor antagonists, prostaglandin analogues and sucralfate. Because these drugs are complex, expensive and toxic, efforts have been constantly made to find a suitable, palliative and curative agent for the treatment of peptic ulcer disease from natural products of plant and animal origin. Recently antioxidants are being used to treat peptic ulcer disease. Antioxidants help in scavenging the free radicals and controlling the oxidative stress responsible for the progression of peptic ulcer [2]. Coenzyme Q10 (CoQ10) and L-glutamine have antioxidant property, and their role as antioxidants has been documented in the literature in treating medical conditions [5–8].

2. Historical aspect

Gastric acid secretion had always been the topic of debate for the last 100 years with greater emphasis thrown on molecular as well cellular mechanisms involved in gastric acid secretion. Gastric juice was chemically analysed, and hydrochloric acid (HCL) was first isolated from gastric juice in 1824 by William Prout [9]. After the discovery of histamine (H_2) receptor by James Black in 1971, antagonists were available for the treatment of peptic ulcer [10]. After the scintillating discovery of proton-pump inhibitors in 1989, the treatment of peptic ulcer was revolutionized as it blocks the final step of acid synthesis in the stomach lumen.

2.1 Gastric acid regulation

2.1.1 Central regulation

The central nervous system and enteric nervous system play a major role in the regulation of acid secretion along with hormones, paracrine agents as well as second messengers. The acid secretion occurs in three phases, namely, the cephalic, gastric, and intestinal phases [11]. The dorsal motor nucleus of the vagus (DMNV), the nucleus tractus solitarius (NTS) and the hypothalamus play a major role in central regulation of acid secretion. The DMNV plays a crucial role in integrating the sensory input from the hypothalamus and visceral input from the NTS and supplies efferent fibres to the stomach via the vagus, thereby primarily helping in motility rather than secretion. The ventromedial hypothalamus exerts an inhibitory influence on acid secretion with its stimulation causing decreased acid secretion and vice versa [11]. The sensory receptors of the stomach present within the muscle layer as well as mucosa of the stomach help in detecting the mechanical, chemical as well as the thermal stimuli, and these sensory impulses are carried to the central nervous system via sympathetic afferent as well as the vagal nerve fibres [11].

2.1.2 Peripheral mechanism

Intrinsic mechanisms of the stomach regulate acid secretion, and these include neural stimulation via the vagus and gastrin and histamine release from G cells and enterochromaffin-like (ECL) cells, respectively. All these stimuli directly act on the parietal cells. Acetylcholine also helps in the regulation of acid secretion [12]. The histamine released acts on the histamine receptor type 2 (H_2) on the parietal cells, leading to activation of cyclic adenosine monophosphate pathway and calcium-sensitive pathway resulting in stimulation of H^+ K^+-ATPase on parietal cells [13].

2.2 Mechanisms of cytoprotection

The term cytoprotection coined by Robert is defined as protection against gastric mucosal injury by mechanisms other than neutralisation of gastric acid [14]. An explosion of investigations led to the discovery that endogenous prostaglandins are involved in cytoprotection via putative mechanisms which includes mucus secretion, release of bicarbonate, maintenance and strengthening of mucosal blood flow and free radical scavenging [15–18]. The normal gastric mucosa without exogenous insult remains hostile to the acidic milieu of gastric lumen. Gastric mucosal defence can be categorised into pre-epithelial defence which is secretion of mucus gel, epithelial defence with surface epithelial cells withstanding pH <2.5 and the post-epithelial barrier with parietal cells at the base of the gland [19].

2.2.1 Stimulation of mucus and bicarbonate secretion

The mucus barrier is made of mucus, lipids and proteins. These form a continuous gel and along with bicarbonate secretion protect the stomach from acidic insult [20]. Cytoprotective agents like prostaglandins have shown to increase the mucus gel thickness but does not protect the surface epithelium in contrast to protection of the deeper layers [21]. Mucin also helps in reepithelization of mucosa. It was identified that bicarbonate helps in cytoprotection and acts by metabolically dependent process as well as by passive diffusion [22]. Prostaglandins help in increasing the bicarbonate secretion, and bicarbonate in turn forms the mucus bicarbonate barrier [23]. Bicarbonate also directly helps in lowering the hydrogen ion concentration in the gastric mucosa [14].

2.2.2 Strengthening of gastric mucosal barrier

The apical membrane, the so-called tight junctions between the surface epithelial cells, prevents back diffusion of acid and hence forms a major mucosal barrier. Phospholipids on the luminal surface of gastric epithelium form a hydrophobic lining and thereby contribute in preventing the water-soluble hydrogen ions to pass through. Prostaglandins increase concentration of these phospholipids [24].

2.2.3 Regulation of mucosal blood flow

Vascular injuries to sub-epithelial capillaries with increased vascular permeability and circulatory stasis lead to functional impairment of gastric microcirculation. Upregulation of mucosal blood flow maintains oxygenation and nutrient supply. Increase in blood supply to mucosa helps in regulating bicarbonate mediated acid neutralisation and in absorption of injurious agents [25].

2.2.4 Effects on gastric motility

Mucosal compression is said to play an important role in epithelial necrosis and ulceration. Gastric hypercontraction accounts for mucosal compression. The gastric mucosa is protected by the action of circular muscles which causes flattening of gastric mucosal folds, thereby leading to increase in mucosal surface area ultimately reducing volume of irritants coming in contact with the mucosa. Various substances like prostaglandins and mast cell stabilisers aid in this process adding to cytoprotection [26].

2.2.5 Scavenging free radicals

Free radicals cause lipid peroxidation and damage to intracellular components. It leads to ischemia of gastric mucosa, thereby causing severe damage to the mucosa. Vitamin E and selenium are well-known antioxidants shown to have protective effect on stress and chemical-induced gastric lesions [27].

2.2.6 Endogenous mediators on gastric cytoprotection

Prostaglandins, L-cysteine, methionine and epidermal growth factor are said to be cytoprotective. Imbalance between two metabolites of arachidonic pathway is also said to contribute to gastric injury. Literature data suggests prostaglandins help in gastric protection by increasing the gastric blood supply and decreasing the synthesis of leukotrienes, thus playing a significant role in cytoprotection [28]. Therefore, cytoprotection is a multifactorial phenomenon.

2.3 Pathogenesis of peptic ulcer

Peptic ulcers are chronic with ~99% ulcers occurring in the duodenum and stomach with the former being four times higher than the latter [29]. Factors causing peptic ulcers include increased acid secretion, impaired mucosal defence, free radical and lipid peroxidation.

2.3.1 Increased acid secretion

Pepsin activity in gastric juice and acidity of gastric juice are important determinants of ulcer formation. The famous Schwartz's dictum "no acid-no ulcer" becomes accurate when amplified to "no acid and peptic activity", as pepsin contributes to the digestive power of the stomach. This dictum is supported by various therapeutic drugs like antacids and anti-secretory drugs, but much to everyone's anguish, ulcer recurs once therapy is stopped [30].

2.3.2 Impaired mucosal defence

The tight epithelial junctions form a barrier preventing hydrogen ion back diffusion. Recent evidences suggest surface phospholipids form a hydrophobic lining on the gastric epithelium and hence retard the passage of hydrogen ions. NSAIDS and *Helicobacter pylori* infection disrupt the mucosal barrier and are known to increase the diffusion of hydrogen ions [31].

2.3.3 Free radical and peroxidation

Free radical contains unpaired electrons, and it plays an important role in pathogenesis of ischemia/reperfusion injury. Free radicals can nick deoxyribonucleic acid

(DNA) and provoke uncontrolled chain reactions like lipid peroxidation. Acute and chronic gastric ulcers are caused by oxygen-derived free radicals, and in one study, infusion of superoxide-generating system into rat celiac artery-induced gastrointestinal bleeding was shown [32].

2.4 Predisposing factors for peptic ulceration

2.4.1 Helicobacter infection

Helicobacter pylori causes antral gastritis in more than 95% of patients with duodenal ulcer than 75% with gastric ulcer. This organism adheres to the mucosal epithelium close to the gap junctions and releases urea and ammonia producing an alkaline environment with raised pH. This creates an environment for the organism to survive, and release of ammonia is cytotoxic to the gastric cells. Gastric metaplasia occurs, and colonisation of these heterotrophic islands results in mucosal injury and gastric ulceration. Oxidative stress has been implicated in the pathogenesis of *Helicobacter pylori* infections, and increased oxidative damage by *Helicobacter pylori* is responsible for epithelial injury, altered epithelial proliferation and increased apoptosis [33].

2.4.2 Non-steroidal anti-inflammatory drugs

NSAIDs are known to cause various injuries in the gastric tract ranging from haemorrhages and petechiae to erosions with ulcers. These drugs are known to cause mucus glycoprotein denaturation in the stomach and sloughing of epithelial cells. Also, drugs like aspirin causes intracellular protons to accumulate in the parietal cells and leads to localised acid accumulation by the process called back diffusion of acid. These drugs also cause labialization of lysosomes leading to cellular autolytic reactions, inhibition of prostaglandins and mast cell degranulation leading to histamine release, inhibition of glucose oxidation and enzymes involved in anabolic reactions. It also increases the production of free radicals [34].

2.4.3 Cigarette smoking

Healing of ulcers is affected by smoking, and it is a known fact that gastric ulcers occur more frequently in smokers. Various theories are put forward as to why cigarette smoking causes ulcers, and some of them includes stimulation of acid secretion, blood flow alteration to gastric mucosa, induction of bile reflux and reduced prostaglandin synthesis [35].

2.4.4 Psychological stress

The CNS and brain gut axis play an important role in stress ulcerogenesis. Various conditions like shock, sepsis, trauma and neurological disorders are now regarded as multifactorial phenomenon. Various interactions between vascular, mucosal and neurohumoral factors and the autonomic nervous system play a critical role in stress ulcerogenesis. Limbic area plays a pertinent role in modulating acid secretion, motility and blood flow [36].

2.4.5 Alcohol

Ethanol causes cell and plasma membrane damage leading to increased membrane permeability finally causing accumulation of sodium and water. It also causes

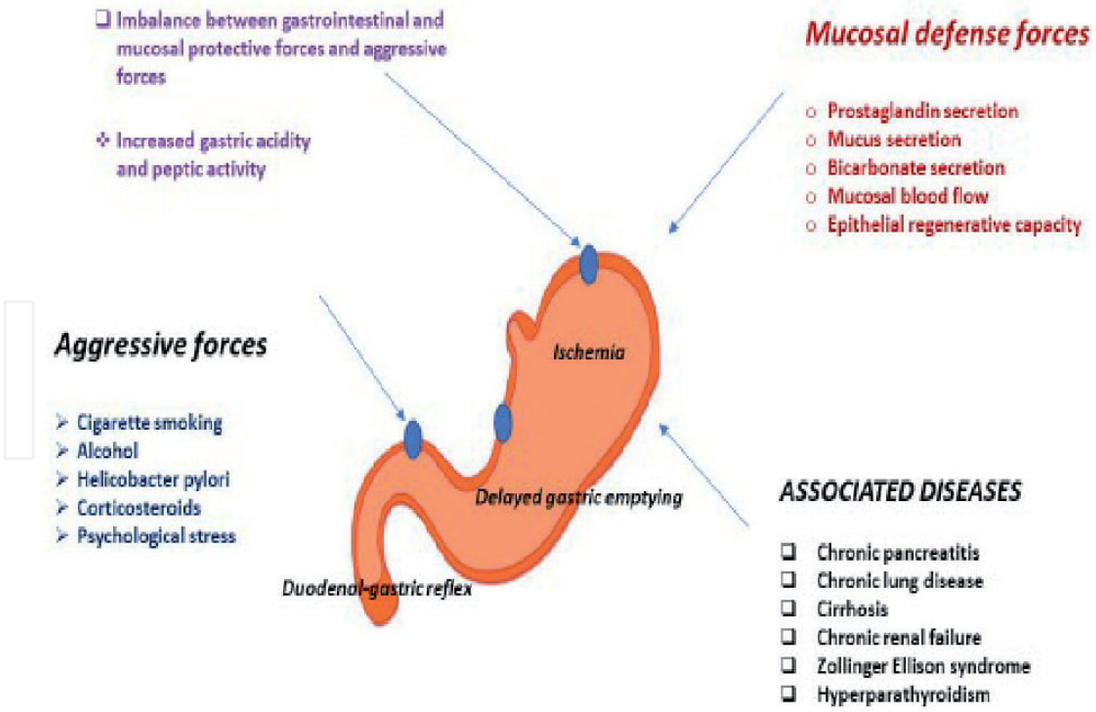

Figure 1.
Pathogenesis of peptic ulcer.

free radical release leading to lipid peroxidation causing gastric lesions. Patients with cirrhosis due to alcohol also have increased incidence of peptic ulcer [37] (**Figure 1**).

2.5 Therapy for acute peptic ulcer

Gastric acid secretion and mucosal defence mechanism have been the target to treat peptic ulcer disease. This has led to discovery of many drugs to treat peptic ulcer disease, and few treatment options have stood the test of time as shown in **Table 1** [38].

2.5.1 H^+/K^+ ATPase inhibitors

It acts by directly blocking the gastric proton pump rather than blocking histamine and cholinergic receptors. There are many drugs available in this class, namely, omeprazole, lansoprazole, rabeprazole and pantoprazole. They block the final step in the acid secretion and thereby have better control over basal as well as nocturnal acid secretion. They are also known to inhibit the growth of *Helicobacter pylor*i [38]. They are now used as first-line agents in the treatment of peptic ulcer, and it has replaced H_2 antagonists.

2.5.2 Prostaglandins

Robert in 1979 showed prostaglandins inhibit gastric acid secretion and help in protection against ulcers caused by NSAIDs, diet, alcohol, smoking and stress. Misoprostol, a prostaglandin analogue, acts by increasing the secretion of mucus as well as bicarbonate, thereby protecting against chronic ulcers. But it helps only in protection against gastric ulcer and not against duodenal ulcers [39]. It is contra-indicated in pregnancy due to its abortifacient property. Enprostil, rioprostil and arbaprostil are other known compounds. Other drugs in clinical trials are noclo-prost, enisoprost and mexiprost [39].

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*

Table 1.
Class of drugs with effect on healing of peptic ulcer.

2.5.3 H_2 receptor antagonists

These drugs act by blocking the H_2 receptor and thereby reduce the release of gastric acid. It is very helpful in reducing 90% of the basal, food-stimulated and nocturnal secretion of gastric acid as well. Literature evidence says it also helps in prevention of stress-induced gastric ulcers. They are used in combination with antacids in the treatment of stress-induced ulcers. These drugs include mainly ranitidine, cimetidine, famotidine and nizatidine. One of the major drawbacks is long duration of administration for ulcer therapy, and recurrence of ulcer after healing is a frequent complication [40].

2.5.4 Muscarinic receptor antagonists

Pirenzepine has more cytoprotective effects when compared with histamine receptor antagonists. It helps in protection against gastric mucosal lesions induced by alcohol, sodium hydroxide (NAOH) and taurocholate. It exerts its action via inhibition of muscarinic (M_1) receptor present in the stomach and reduces basal as well as stimulated acid secretion [41].

2.5.5 Mucosal coating agents

Sucralfate is a basic sulphated disaccharide with aluminium sulphate complex. It helps in forming an adherent coating at the mucosal sites which are ulcerated. It acts by reducing pepsin activity, adsorbs bile salts and acts as barrier to hydrogen ion diffusion. It also binds to both epidermal growth factor (EGF) and fibroblast growth factor (FGF) and helps in enhancing ulcer healing. It is found effective in *Helicobacter pylori* infection [42].

3. Coenzyme Q10

Morton in 1955 in Liverpool identified a quinone-like substance with an ultraviolet absorption at 272 nm from intestinal mucosa of horses and named it as ubiquinone.

Crane and his colleagues in the University of Wisconsin isolated quinone in lipid extracts of mitochondria and named it coenzyme Q because of its unique role in cellular metabolism and energy production. Ernster, a Swedish scientist, expanded the benefits of this molecule as an antioxidant and free radical scavenger. Coenzyme Q10 also plays a major proton-motive role in the energy transfer systems [43].

Coenzyme Q10 is an active quinone with a benzoquinone ring along with 10 isoprenoid side chains. It is structurally related to vitamin K and vitamin E. Naturally it is orange in colour without odour and taste with a molecular weight of 863.34 g/mol. It is stable at temperatures below 46°C. CoQ10 is the prevalent form in humans in contrast to CoQ9 in rats and Q6, Q7 and Q8 in yeast and bacteria. It exists in three forms, the fully oxidised ubiquinone; semiquinone, the free radical form; and ubiquinol, the reduced form [44].

CoQ10 is found in every cell of the human body, mainly located in the phospholipid bilayer of various membranes. It is found in higher concentrations in the heart, liver, muscles and pancreas, which have high energy requirements. It is derived from tyrosine with several vitamins and trace elements as cofactors. Because of this complex biosynthesis, human enzyme and protein defects may cause deficiency of CoQ10 in infants as well as adults. Cellular functions depend on production of adenosine triphosphate (ATP) in mitochondria making electron and proton transfer functions of quinone ring very important in all life forms [43].

Coenzyme Q10 is usually absorbed from the small intestine, and bioavailability depends on the type of preparation and on the route of administration. Evidence says it is absorbed orally with almost 178% increase in serum levels. Some studies also say it is absorbed very minimally due to its lipophilic nature and huge molecular weight. Oil-based preparations of CoQ10 have better absorption [44].

It plays a vital role as intermediate in mitochondrial electron transport chain. CoQ10, an endogenously synthesised lipid-soluble antioxidant along with alpha-tocopherol, acts in scavenging the free radicals generated in the inner mitochondrial membrane. CoQ10 also prevents lipid peroxidation in cells depleted of alpha-tocopherol. It helps in protection of DNA from free radical injury, in recycling of antioxidants such as tocopherol and ascorbate with additional role in cell signalling and gene expression. A direct evidence for the antioxidant property of CoQ10 is shown in literature, where luminescence is eliminated from free radicals when skin cream containing coenzyme Q10 is applied demonstrating the elimination of free radicals by CoQ10. It also helps in maintaining cellular respiration and ATP synthesis. It also helps in decreasing calcium overload in tissues by indirectly stabilising calcium channels [45].

CoQ_{10} deficiencies are due to autosomal recessive mutations, mitochondrial diseases, ageing-related oxidative stress, carcinogenesis processes and also treatment with statins. Many neurodegenerative disorders, diabetes, cancer and muscular and cardiovascular diseases have been associated with low CoQ_{10} levels as well as different ataxias and encephalomyopathies [45, 46]. CoQ10 is generally very well tolerated at doses not exceeding 500 mg. Gastrointestinal (digestive) distress is reported with doses up to 3000 mg daily [45]. Recent evidence also says coenzyme Q10 is used in treatment of peptic ulcer. Few animal studies have tried the use of coenzyme Q10; in one study, indomethacin-induced ulcer in Wistar rats was treated using coenzyme Q10, and favourable results were obtained [47]. CoQ10-mediated gastroprotective effect involves preservation of microvascular permeability, elevation of prostaglandin E_2, improvement of redox status as well as boosting of nitric oxide.

4. Glutamine

Glutamine is one of the 20 amino acids encoded by standard genetic code. It is considered a conditionally essential amino acid. Its side chain is an amide formed by

replacing hydroxyl side chain of glutamic acid. In humans, blood glutamine is the most abundant free amino acid, with concentration of about 500–900 μmol/L. It is mainly helpful in protein synthesis, acid base balance, cellular energy (next to glucose), nitrogen donation for anabolic process, carbon donation in citric acid cycle and ammonia transporter in blood circulation. It is produced by enzyme glutamine synthetase from glutamate/ammonia in muscles. Almost 90% of glutamine is synthesized in the muscles [48]. Consumers are cells of the intestine, kidney cells and immune/cancer cells. It is used in cachexia, to reduce infections and to control gut leak after surgery. It also increased intestinal barrier and intestinal permeability. As a preferred substrate for enterocytes, glutamine has shown to support the normal immunological structure and function of the gastrointestinal tract. In animal studies glutamine deprivation is associated with loss of intestinal epithelial integrity, while glutamine supplementation decreases gastrointestinal tract mucosal atrophy. Glutamine also restored ATP levels and reduces cell apoptosis. It is very important during stress and catabolic conditions [49]. So far only one animal study has evaluated the use of L-glutamine in aspirin-induced peptic ulcer model. They found out the L-glutamine was effective in protecting against aspirin-induced gastric lesions in rats [50]. L-Glutamine, commonly used in sports medicine for muscle recovery, has gained medical importance because of its antioxidant properties [51]. The antioxidant properties of L-glutamine has been claimed to be useful in the treatment of peptic ulcer disease in animal studies as well as in very few human studies. Only a few animal studies have been done so far to investigate the role of L-glutamine in the treatment of *Helicobacter pylori* infections, and it was found to be positive, yet human trials have not been done in large [52, 53].

4.1 Ulcer induction methods

Clinical ulcers are usually chronic and are penetrating lesions in comparison with experimentally induced lesions which are acute non-penetrating ulcers healing at faster rates without scar formation. Even though experimental lesions have some limitation, it is still possible to evaluate the therapeutic agents rapidly with reasonable predictability for their therapeutic use. There are various animal models used for evaluating gastric ulcers, and some of the most important will be described below.

Criteria for experimental ulcers proposed by Lee and Bianchi are as follows [54]:

1. It should be simple and easily reproducible with easy quantification of results.

2. Variety of animal species should be made use of.

3. Ulcer should be produced in characteristic sites like the stomach and the first part of the duodenum.

4. Models should include different mechanisms by which ulcers are produced.

5. There should not be any spontaneous healing of ulcers during the observation period.

The various methods available are discussed in the next subsections.

4.1.1 Pylorus ligated rat

Ulcers produced by this method are also called as Shay ulcers as it was first demonstrated by Shay in 1945. In this model, the animals are usually housed in individual

cages and fasted for 36 h before ligating the pylorus. The abdomen is opened after anesthetising the rats by a small midline incision just below the xiphoid process. Then the pyloric part of the stomach is ligated without compromising its vascularity. Later the abdomen is closed in layers using interrupted sutures. The animal is made to starve completely without water and is sacrificed after 19 h. The stomach is then dissected out, and the contents of the stomach are used to determine the pH, volume of gastric juice and free and total acidity. The stomach is then cut open along the greater curvature and examined for ulceration. Circular lesions and linear lesions are observed. This model usually has a greater predictive value for antiulcer agents though ulcers in this model are usually localised in the ruminal area of the stomach in comparison to human ulcers which are usually located in the glandular portion of the stomach and duodenal region [55].

4.1.2 Stress ulcers

These ulcers are usually produced by subjecting any species to different types of stress. This model is very easy as it is devoid of any experimental surgery and usage of anaesthesia. It mainly involves the central nervous system, and produced lesions are located in the glandular portion of the stomach.

5. Restraint ulcers

This method was first used by Brodie and Hansen in 1960. Rats are usually fasted for 36 h before the experiment. Later each rat is placed in a piece of galvanised steel window screen of appropriate size. The screen is then moulded around each rat and is held together with wire staples. The animals are made immobile by tightening the limbs together. The test drug is administered 30 min before subjecting the animals to restraint. After 24 h the animals are sacrificed, and their stomach is dissected out along the greater curvature and is subjected to assessment. One drawback of this method was the ulcers were not deep as they did not penetrate the muscularis mucosa and penetrating ulcers were not produced. Some commonly used modifications of this method to overcome the drawbacks include water immersion-induced restraint ulcer, cold and restraint ulcer, swimming stress ulcers and also stress with concurrent administration of NSAIDs and also haemorrhagic shock-induced gastric ulcers in rats [56].

5.1 NSAID-induced gastric mucosal damage

The routinely used drug for experimental induction of ulcers includes diclofenac, ibuprofen, indomethacin, phenylbutazone and aspirin. Usually the test agents are administered 30 min–1 h before the noxious challenge. Later after 4 h the animals are sacrificed and examined for mucosal lesions in the stomach [57].

5.1.1 Histamine-induced gastric ulcers

The vasospastic and the gastric secretion increases shown via the histamine receptors attribute to ulcer formation in this model. It was first described in 1947 in guinea pigs. It was noted that in this model 100% ulceration was produced with notable increase in volume of gastric secretion as well as increment in free and total acidity. Usually the animals are fasted for 36 h, and ulcers are induced by injecting 1 ml of histamine acid phosphate (50 mg base) via intraperitoneal route. Histamine toxicity to animals are prevented using promethazine hydrochloride

5 mg intraperitoneally 15 min prior to and 15 min after histamine administration, respectively. The investigational drug is usually administered 45 min before injecting histamine. After 4 h the animals are sacrificed; and assessment of the stomach is done after dissection, and various indices are calculated [58].

5.1.2 Acetic acid-induced chronic gastric ulcers

Acetic acid at a concentration of 1–30% is used, and usually 0.05 ml per rat is used. It is injected to the submucosal layer of the stomach, penetrating ulcers usually produced can be noted with gross examination, and ulcers are mostly confined by adhesion to contiguous organs. It can be successfully used to screen new antiulcer agents [59].

5.1.3 Serotonin-induced gastric ulcers

Wilhelmi, Wedinger and Veraguth described this method in Wistar rats. Usually rats are fasted for 24 h, and later serotonin creatinine sulphate is dissolved in saline and injected subcutaneously into rats. Usually serotonin is used at a dose of 20 mg/kg, and with this dose, moderate gastric lesions are noted [60].

5.1.4 Ethanol-induced gastric ulcers.

Eighty percent of ethanol in a dose of 5 ml/kg of body weight is usually given orally to the albino rats. If administered intraperitoneally, 40% of ethanol is given, and usually animals are observed for a period of 7–14 days [61].

6. Conclusion

Peptic ulcer being a global problem proper treatment is warranted. Proper screening of *Helicobacter pylori* and ruling out other possible causes could benefit the patient in getting cured with the correct treatment. The latest research proves oxidative stress as one of the major contributing factors for peptic ulcer disease, so the use of antioxidants as a potential agent is highly warranted. Further clinical trials can be done to elicit the efficacy of these antioxidants as potential anti-peptic ulcer drugs.

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References

[1] Prabhu V, Shivani A. An overview of history, pathogenesis and treatment of perforated peptic ulcer disease with evaluation of prognostic scoring in adults. Annals of Medical and Health Sciences Research. 2014;**4**(1):22-29

[2] Tandon R, Khanna RD, Dorababu M, Goel RK. Oxidative stress and antioxidants status in peptic ulcer and gastric carcinoma. Indian Journal of Physiology and Pharmacology. 2004;**48**(1):115-118

[3] Das D, Bandyopadhyay D, Bhattacharjee M, Banerjee RK. Hydroxyl radical is the major causative factor in stress-induced gastric ulceration. Free Radical Biology and Medicine. 1997;**23**(1):8-18

[4] Ko JK, Cho CH. Alcohol drinking and cigarette smoking: A "partner" for gastric ulceration. Chinese Medical Journal; Free China ed. 2000;**63**(12):845-854

[5] Denny N, Chapple IL, Matthews JB. Antioxidant, and anti-inflammatory effects of coenzyme Q10: A preliminary study. Journal of Dental Research. 1999;**78**(543):00008

[6] Heyland DK, Elke G, Cook D, Berger MM, Wischmeyer PE, Albert M, et al. Glutamine and antioxidants in the critically ill patient: A post hoc analysis of a large-scale randomized trial. Journal of Parenteral and Enteral Nutrition. 2015;**39**(4):401-409

[7] Okabe S, Ohtsu K, Takeuch K, Takhal K. Effect of L-glutamine on indomethacin induced gastric lesions in the rat. The Japanese Journal of Pharmacology. 1974;**24**:169-171

[8] Karkaya K, Barut F, Hanci V, Can M, Comert M, Ucan HB, et al. Gastroprotective effects of CoQ10 on ethanol-induced acute gastric lesions. Bratislavské Lekárske Listy. 2015;**116**(1):51-56

[9] Heinz E, Öbrink KJ. Acid formation and acidity control in the stomach. Physiological Reviews. 1954;**34**(4):643-673

[10] Angus JA, Black JW. The interaction of choline esters, vagal stimulation, and H2-receptor blockade on acid secretion in vitro. European Journal of Pharmacology. 1982;**80**(2-3):217-224

[11] Hersey SJ, Sachs G. Gastric acid secretion. Physiological Reviews. 1995;**75**(1):155-190

[12] Goldschmiedt M, Feldman M. Gastric secretion in health and disease. In: Sleisenger MH, editor. Gastrointestinal Disease. Philadelphia: WB Saunders Company; 1993. pp. 521-544

[13] Soll AH. Pathogenesis of peptic ulcer and implications for therapy. New England Journal of Medicine. 1990;**322**(13):909-916

[14] Robert A, Nezamis JE, Lancaster C, Hanchar AJ. Cytoprotection by prostaglandins in rats. Gastroenterology. 1979;**77**(3):433-443

[15] Lacy ER, Ito S. Microscopic analysis of ethanol damage to rat gastric mucosa after treatment with a prostaglandin. Gastroenterology. 1982;**83**(3):619-625

[16] Szabo S, Szelenyi I. Cytoprotection'in gastrointestinal pharmacology. Trends in Pharmacological Sciences. 1987;**8**(4):149-154

[17] Schmidt KL, Miller TA. Morphological characteristics of prostaglandin cytoprotection. Toxicologic Pathology. 1988;**16**(2):223-236

[18] Soll AH, Weinstein WM, Kurata J, McCarthy D. Nonsteroidal anti-inflammatory drugs and peptic

ulcer disease. Annals of Internal Medicine. 1991;**114**(4):307-319

[19] Sanders MJ, Ayalon A, Roll M, Soll AH. The apical surface of canine chief cell monolayers resists H+ back-diffusion. Nature. 1985;**313**(5997):52-54

[20] Younan F, Pearson J, Allen A, Venables C. Changes in the structure of the mucous gel on the mucosal surface of the stomach in association with peptic ulcer disease. Gastroenterology. 1982;**82**(5):827-831

[21] Bickel M, Kauffman GL. Gastric gel mucus thickness: Effect of distention, 16,16-dimethyl prostaglandin E2, and carbenoxolone. Gastroenterology. 1981;**80**(4):770-775

[22] Rees WD, Turnberg LA. Mechanisms of gastric mucosal protection: A role for the 'mucus-bicarbonate' barrier. Clinical Science. 1982;**62**(4):343-348

[23] Allen A, Garner A. Mucus and bicarbonate secretion in the stomach and their possible role in mucosal protection. Gut. 1980;**21**(3):249

[24] Fromm D. Gastric mucosal "barrier". Gastroenterology. 1979;**77**(2):396-398

[25] Pihan G, Rogers C, Szabo S. Vascular injury in acute gastric mucosal damage. Digestive Diseases and Sciences. 1988;**33**(5):625-632

[26] Takeuchi K, Nobuhara Y. Inhibition of gastric motor activity by 16,16-dimethyl prostaglandin E 2. Digestive Diseases and Sciences. 1985;**30**(12):1181-1188

[27] Itoh M, Guth PH. Role of oxygen-derived free radicals in hemorrhagic shock-induced gastric lesions in the rat. Gastroenterology. 1985;**88**(5):1162-1167

[28] Peskar BM, Hoppe U, Lange K, Peskar BA. Effect of nonsteroidal anti-inflammatory drugs (NSAID) on rat gastric leukotriene formation. Gastroenterology. 1987;**92**(5):1573-1573

[29] Desai JK, Goyal RK, Parmar NS. Pathogenesis of peptic ulcer disease and current trends in therapy. Indian Journal of Physiology and Pharmacology. 1997;**41**(1):3-15

[30] Du Plessis DJ. Pathogenesis of gastric ulceration. The Lancet. 1965;**285**(7393):974-978

[31] Isenberg JI, Selling JA, Hogan DL, Koss MA. Impaired proximal duodenal mucosal bicarbonate secretion in patients with duodenal ulcer. New England Journal of Medicine. 1987;**316**(7):374-379

[32] Demir S, Yilmaz M, Koseoglu M, Akalin N, Aslan D, Aydin A. Role of free radicals in peptic ulcer and gastritis. Turkish Journal of Gastroenterology. 2003;**14**(1):39-43

[33] Kuipers EJ, Thijs JC, Festen HP. The prevalence of *Helicobacter pylori* in peptic ulcer disease. Alimentary Pharmacology & Therapeutics. 1995;**9**:59-69

[34] Huang JQ, Sridhar S, Hunt RH. Role of *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: A meta-analysis. The Lancet. 2002;**359**(9300):14-22

[35] Kurata JH, Nogawa AN. Meta-analysis of risk factors for peptic ulcer: Nonsteroidal antiinflammatory drugs, *Helicobacter pylori*, and smoking. Journal of Clinical Gastroenterology. 1997;**24**(1):2-17

[36] Levenstein S, Ackerman S, Kiecolt-Glaser JK, Dubois A. Stress and peptic ulcer disease. JAMA. 1999;**281**(1):10-11

[37] Friedman GD, Siegelaub AB, Seltzer CC. Cigarettes, alcohol, coffee

and peptic ulcer. New England Journal of Medicine. 1974;**290**(9):469-473

[38] Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. The Lancet. 2009;**374**(9699):1449-1461

[39] Freston JW. Overview of medical therapy of peptic ulcer disease. Gastroenterology Clinics of North America. 1990;**19**(1):121-140

[40] Nash J, Lambert L, Deakin M. Histamine H2-receptor antagonists in peptic ulcer disease. Drugs. 1994;**47**(6):862-871

[41] Giorgi-Conciato M, Daniotti S, Ferrari PA, Gaetani M, Petrin G, Sala P, et al. Efficacy and safety of pirenzepine in peptic ulcer and in non-ulcerous gastroduodenal diseases. A multicentre controlled clinical trial. Scandinavian Journal of Gastroenterology. Supplement. 1982;**81**:1

[42] Guth PH. Mucosal coating agents and other non-anti-secretory agents. Digestive Diseases and Sciences. 1987;**32**(6):647-654

[43] Crane FL. Discovery of ubiquinone (coenzyme Q) and an overview of function. Mitochondrion. 2007;**7**:S2-S7

[44] Bhagavan HN, Chopra RK. Coenzyme Q10: Absorption, tissue uptake, metabolism and pharmacokinetics. Free Radical Research. 2006;**40**(5):445-453

[45] Overvad K, Diamant B, Holm L, Holmer G, Mortensen SA, Stender S. Coenzyme Q10 in health and disease. European Journal of Clinical Nutrition. 1999;**53**(10):764-770

[46] Shults CW. Coenzyme Q10 in neurodegenerative diseases. Current Medicinal Chemistry. 2003;**10**(19):1917-1921

[47] Malash AM, Abdallah DM, Agha AM, Kenawy SA. Gastroprotective efficacy of coenzyme Q10 in indomethacin-induced gastropathy: Other potential mechanisms. Ulcers. 2012;**6**:2012

[48] Miller AL. Therapeutic considerations of L-glutamine: A review of the literature. Alternative Medicine Review: A Journal of Clinical Therapeutic. 1999 Aug;**4**(4):239-248

[49] Novak F, Heyland DK, Avenell A, Drover JW, Su X. Glutamine supplementation in serious illness: A systematic review of the evidence. Critical Care Medicine. 2002;**30**(9):2022-2029

[50] Okabe S, Takeuchi K, Nakamura K, Takagi K. Inhibitory effects of L-glutamine on the aspirin-induced gastric lesions in the rat. Journal of Pharmacy and Pharmacology. 1974;**26**(8):605-611

[51] Heyland DK, Dhaliwal R, Day AG, Muscedere J, Drover J, Suchner U, et al. Reducing deaths due to oxidative stress (The REDOXS© Study): Rationale and study design for a randomized trial of glutamine and antioxidant supplementation in critically-ill patients. Proceedings of the Nutrition Society. 2006;**65**(3):250-263

[52] Hagen SJ, Ohtani M, Zhou JR, Taylor NS, Rickman BH, Blackburn GL, et al. Inflammation and foveolar hyperplasia are reduced by supplemental dietary glutamine during *Helicobacter pylori* infection in mice. The Journal of Nutrition. 2009;**139**(5):912-918

[53] Amagase K, Nakamura E, Endo T, Hayashi S, Hasumura M, Uneyama H, et al. New frontiers in gut nutrient sensor research: Prophylactic effect of glutamine against *Helicobacter pylori*-induced gastric diseases in Mongolian gerbils. Journal of Pharmacological Sciences. 2010;**112**(1):25-32

[54] Lee YH, Bianchi RG. Use of experimental peptic ulcer models for drug screening. Peptic Ulcer. 1971:329-348

[55] Shay H. A simple method for the uniform production of gastric ulceration in rat. Gastroenterology. 1945;**5**:43-61

[56] Levine RJ. A method for rapid production of stress ulcers in rats. In: Peptic Ulcer. Copenhagen: Munksgaard; 1971. pp. 92-97

[57] Djahanguiri B. The production of acute gastric ulceration by indomethacin in the rat. Scandinavian Journal of Gastroenterology. 1968;**4**(3):265-267

[58] Hay LJ, Varco RL, Code CF, Wangensteen OH. The experimental production of gastric and duodenal ulcers in laboratory animals by the intramuscular injection of histamine in beeswax. Surgery, Gynecology & Obstetrics. 1942;**75**:170-182

[59] Okabe S, Pfeiffer CJ. Chronicity of acetic acid ulcer in the rat stomach. Digestive Diseases and Sciences. 1972;**17**(7):619-629

[60] LePard KJ, Stephens RL. Serotonin inhibits gastric acid secretion through a 5-hydroxytryptamine1-like receptor in the rat. Journal of Pharmacology and Experimental Therapeutics. 1994;**270**(3):1139-1144

[61] Oates PJ, Hakkinen JP. Studies on the mechanism of ethanol-induced gastric damage in rats. Gastroenterology. 1988;**94**(1):10-21