INTRODUCTION

INTRODUCTION

Peptic ulcer disease had a tremendous effect on morbidity and mortality until the last decades of the 20th century, when epidemiological trends started to point to an impressive fall in its incidence. Two important developments are associated with the decrease in rates of peptic ulcer disease: the discovery of effective and potent acid suppressants, and targeting *Helicobacter pylori*. Despite substantial advances, this disease remains an important clinical problem, largely because of the increasingly widespread use of non-steroidal anti-inflammatory drugs (NSAIDs) and low dose aspirin.[1]

Epidemiology

More than 500 000 new cases of peptic ulcer are diagnosed annually in the US, and 4 million patients with previously diagnosed peptic ulcer disease experience recurrence each year. The overall lifetime prevalence is changing and previously was approximately 12% in men and 9% in women. The annual mortality rate for patients with peptic ulcer disease in the US is less than 15000 and is mostly due to complications such as haemorrhage.[2]

The prevalence and incidence of peptic ulcer disease varies worldwide in relation to geographical, racial and social circumstances. Multiple risk factors previously suggested as important for peptic ulcer disease included family history, age, gender, race, social class, blood group, smoking, alcohol and coffee consumption, use of NSAIDs, stress and season of the year.[3,4,5] More recently, *Helicobacter pylori (H. pylori)* infection has also been implicated as one of the important risk factors.[6,7]

Previously, there was interest in genetic factors that might play an important role in the aetiology of peptic ulcer disease.[8,9] However, the pattern of inheritance was not simple and it was suggested that the genetic basis was multifactorial. Initially, the strongest evidence of a genetic influence on peptic ulcer disease came from studies showing an increased risk of duodenal ulcer in individuals with hyperpepsinogenaemia.[10,11] This evidence disappeared when it became evident that elevated serum pepsinogen I was also a feature of *H. pylori* infection.[12,13] The marked geographical variation in the incidence rates of peptic ulcer disease in different parts of the world along with the rapid rate of change in incidence provides strong evidence that environmental factors are the most important features that modulate the development of an ulcer.[14]

Changing in epidemiological pattern of peptic ulcer disease

Within the past 3 decades, the occurrence of peptic ulcer disease has declined remarkably in the US, Europe, Australia and Japan.[15-17] Risk of peptic ulcer disease was the highest among those born at the beginning of the century and has decreased in all subsequent generations.[18,19] The rapid change in the pattern of peptic ulcer disease in successive generations is more likely due to changes in environmental factors than changes in the genes of the affected patients.[18] Another possibility is that there was a change in the prevalence of a particularly virulent *H. pylori* strain.[20,21]

Many studies reported an association between peptic ulcer and other diseases both within and outside the gastrointestinal tract (e.g. liver cirrhosis, chronic obstructive pulmonary disease, rheumatoid arthritis, and cardiovascular diseases).[22-26] A recent study re-evaluated the associations of peptic ulcer disease with these diseases while controlling for *H. pylori* infection.[27] While the study found significant associations between peptic ulcer and liver, lung, and cardiovascular diseases, these associations disappeared after the

adjustment for *H. pylori* infection. The results not only demonstrated the lack of association between peptic ulcer disease and these other diseases but also confirmed the aetiological link between *H. pylori* infection and peptic ulcer disease.[28]

Pathogenesis

The pathogenesis of peptic ulcer viewed as representing a complex scenario involving an imbalance between defensive (mucus-bicarbonate layer, prostaglandins, cellular renovation, and blood flow) and aggressive factors (hydrochloric acid, pepsin, ethanol, bile salts, some medications, etc.) of which the most notable now appears to be *Helicobacter pylori*.[29,30]

The defensive mechanism represented by the ability of normal gastrodoudenal mucosa to resist the injury from the acid and peptic activity in gastric juice: surface epithelial cells secrete mucus and bicarbonate creating a pH gradient in the mucous layer from the acidic gastric lumen to nearly neutral surface of the mucosa,[31] gastric mucosal cells have special apical surfaces that resist the diffusion of acid back into the cell.[32] In addition, mucosal cells may directly resist the injury by intrinsic mechanisms, such as the extrusion of back-diffused hydrogen ions by means of basolateral carriers (e.g sodium hydrogen or sodium bicarbonate exchange). Blood flow in normal mucosa removes the acid that has diffused across a compromised mucosa. Prostaglandins enhance the mucosal resistance to injury by maintaining mucosal blood flow and stimulating the secretion of mucus and bicarbonate.[33] Figure (1): shows different gastric mucosal protective mechanisms.

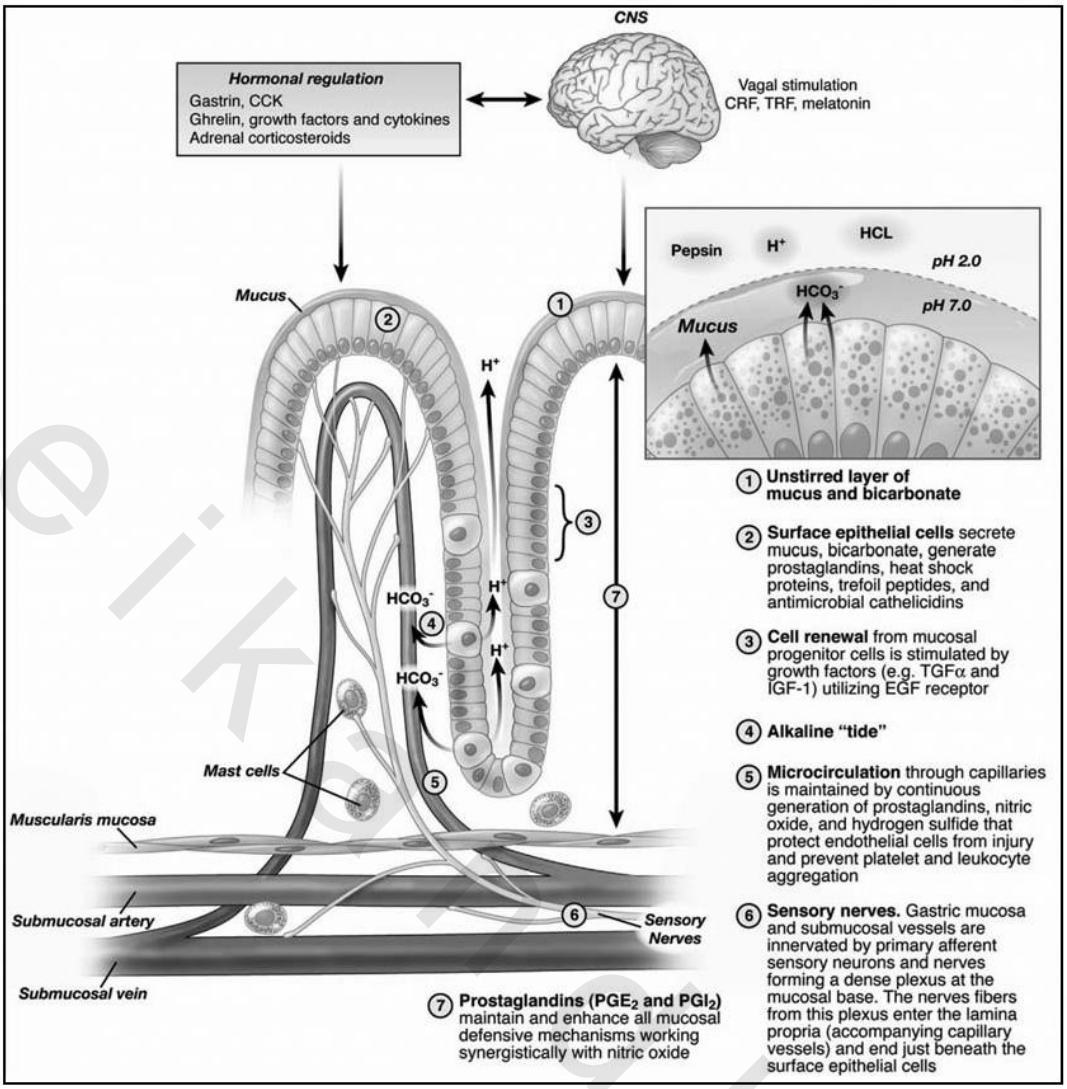

Figure (1). Schematic presentation of gastric mucosal defense mechanisms.[34]

(1) Unstirred layer of mucus/ bicarbonate/phospholipids constitutes the first line of defense. It maintains a "neutral" pH of ~ 7.0 at the luminal interface of the surface epithelial cells, while pH in the lumen is about 1.0 – 3.0.

(2) The surface epithelial cells are capable of secreting mucus, bicarbonate and synthesizing prostaglandins and heat shock proteins.

(3) Continuous mucosal cell renewal from mucosal progenitor cells (driven by growth factors and EGF receptors) maintains structural integrity of epithelial structures. Expression of surviving in progenitor cells prevents apoptosis and is the key for immortality of these cells under normal conditions.

(4) "Alkaline tide" - parietal cells secreting HCl into the gastric gland lumen concurrently secrete bicarbonate into the lumen of adjacent capillary blood vessels.
It is transported to the surface, where it contributes to the first line of defense.

(5) Mucosal microcirculation through the capillary microvessels is essential for delivery of oxygen and nutrients. Endothelial cells of microvessels generate
prostaglandins, mainly PGI2 (prostacyclin) and nitric oxide, which exert mucosal protective actions.

(6) Sensory nerve stimulation leads to the release of neurotransmitters such as calcitonin gene related peptide (CGRP) and substance P in nerve terminals, which cause vasodilatation and enhance mucosal blood flow.

(7) Continuous generation of prostaglandin E2 (PGE2) and prostacyclin (PGI2) by gastric mucosal cells is crucial for the maintenance of mucosal integrity.

Almost all of the above (1-6) mucosal defense mechanisms are stimulated or facilitated by endogenous or exogenous prostaglandins.

The aggressive factors are represented by the presence of acid and peptic activity in the gastric juice. Most of the patients with duodenal ulcer, not gastric ulcer, secrete excess gastric acid,[35] and the hypersecretion of acid is due to vagal overactivity.[36] Figure (2): shows physiology of gastric acid secretion.[37]

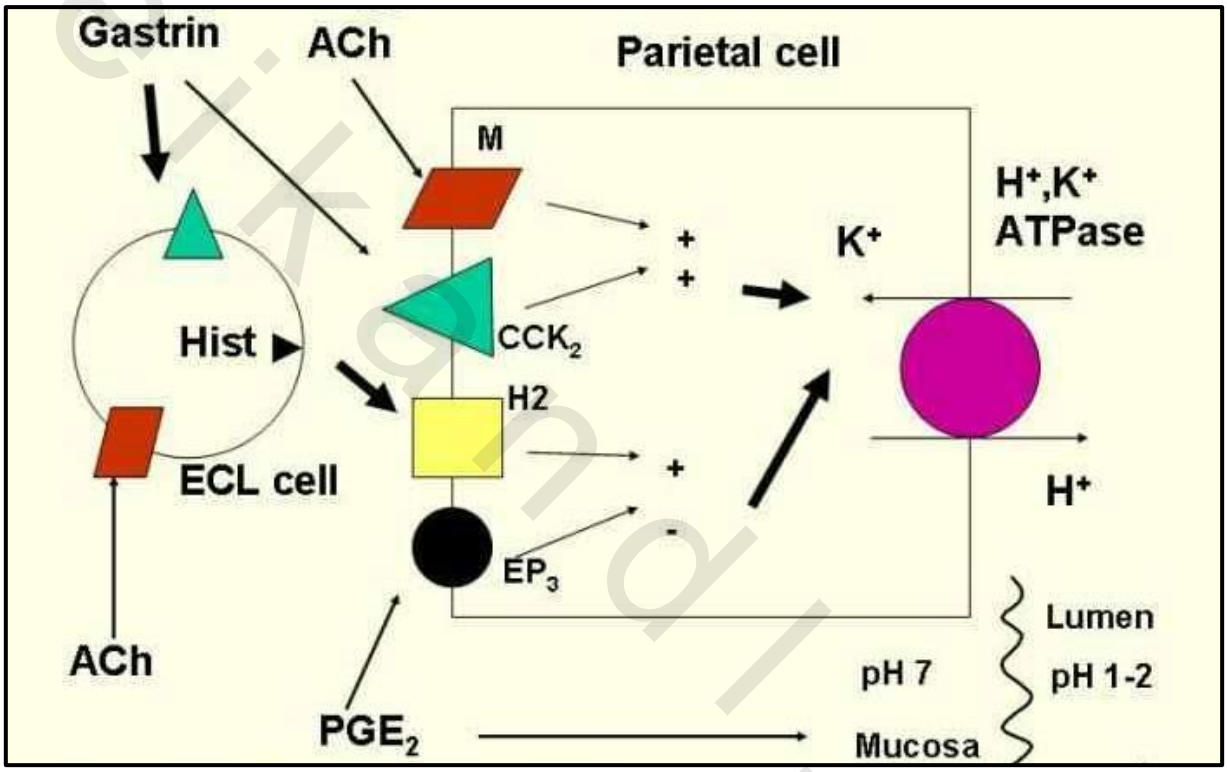

Figure (2): Physiology of gastric acid secretion.

Ach: Acetylecholine, Hist: Histamin, ECL: enterochromaffine-like cells, CCK: cholecystokinin, M: muscarinic receptor, H2: Histamin receptor. EP_3: Procyclin EP_3.

Peptic activity is a fundamental component of the pathogenesis of ulcers; acid without pepsin has little digestive power. Pepsin is secreted as pepsinogen, which is activated only in acidic media; its proteolytic activity is reduced above pH 3.5.[38]

The development of peptic ulcer requires a breakdown in mucosal defense. Peptic ulcer is a product of self digestion; it results from an excess of autopeptic power in gastric juice over the defensive power of gastric and intestinal mucosa.[39]

Any small shift in the standoff between the acid secretion and mucosal defense tips the equilibrium toward health or ulcers. Although occasional ulcers result from large increases in the secretion of acid, peptic ulcers generally develop only when mucosal defense is perturbed.[40]

Role of oxidative stress in peptic ulcer

Oxidative stress is a state of elevated levels of reactive oxygen species (ROS), resulting from a variety of conditions that stimulate either additional ROS production or a decline in antioxidant defenses, [41] and it is defined as a state in which oxidation exceeds the antioxidant systems in the body secondary to the loss of balance between them.[42] Oxidative stress is involved in several lifestylerelated diseases including atherosclerosis, hypertension, diabetes mellitus, ischemic heart diseases, and malignancies.[43]

Several phenotypes of gastrointestinal diseases, such as peptic ulcer disease and gastroparesis, are known to be related to antioxidant property dysfunction.[41]

In peptic ulcer, oxidative stress is involved in ulcerogenesis and carcinogenesis induced by *H. pylori*. Also, NSAIDs induced peptic ulcer by different mechanisms including the generation of ROS by the adherence and accumulation of leukocytes specially neutrophils on the damaged vascular endothelium, and inhibition of prostaglandins synthesis.

This ROS can damage or may cause complete degradation (i.e., perioxidation) of essential complex molecules in the cells, including lipids, proteins, and DNA.[44]

Because ROS form naturally during many metabolic processes, cells have developed several protective mechanisms to prevent ROS formation or to detoxify the ROS. These mechanisms employ molecules called antioxidants and involve enzymatic and nonenzymatic mechanisms. Enzymes involved in the elimination of ROS include superoxide dismutases (SODs), catalase, and glutathione peroxidase.[45]

Enzymatic mechanism

SODs catalyze the rapid removal of superoxide radicals. There are several types of SODs, which differ with respect to their location in the cells and the metal ions they require for their function. For example, a copper zinc SOD is present in the fluid filling the cell (i.e., the cytosol) and in the space between the two membranes surrounding the mitochondria. Furthermore, a manganese-containing SOD is present in the mitochondrial interior (i.e., matrix). Both of these enzymes are critical for prevention of ROS-induced toxicity.[46]

The glutathione peroxidase system consists of several components, including the enzymes glutathione peroxidase and glutathione reductase and the cofactors glutathione (GSH) and reduced nicotinamide adenosine dinucleotide phosphate (NADPH).[47] Together, these molecules effectively remove hydrogen peroxide. Moreover, GSH can interact directly with certain ROS (e.g., the hydroxyl radical) to detoxify them, as well as performing other critical activities in the cell.[44]

Nonenzymatic mechanisms

GSH is probably the most important antioxidant present in cells. Therefore, enzymes that help generate GSH are critical to the body's ability to protect itself against oxidative stress.

(NADPH) is involved in a much more diverse range of reactions in the cell than GSH. Nevertheless, because of its role in the glutathione peroxidase system, NADPH or the enzymes that generate this compound are sometimes considered antioxidants.

In addition to GSH and NADPH, numerous other nonenzymatic antioxidants are present in the cells, most prominently vitamin E (α-tocopherol) and vitamin C (ascorbate).

Vitamin E is a major antioxidant found in the lipid phase of membranes and, like other chemically related molecules, acts as a powerful terminator of lipid peroxidation. During the reaction between vitamin E and a lipid radical, the vitamin E radical is formed, from which vitamin E can be regenerated in a reaction involving GSH and ascorbate.[47]

Malondialdehyde (MDA)

MDA is the end product of lipid peroxidation and is used to determine lipid peroxidation. [48] MDA is an endogenous genotoxic product of enzymatic and oxygen radical-induced lipid peroxidation,[49] and is formed only by fatty acids with three or more double bonds.

The cyclic peroxide radicals are the precursors of cyclic endoperoxide and MDA. It can cause cross linking and polymerization of membrane components.[50,51] This can alter intrinsic membrane properties, such as deformability, iron transport, enzyme activity and the aggregation state of the cell surface determinant.

Because MDA is diffusible, it will also react with the nitrogenous bases of DNA.[52] This may explain why MDA is mutagenic, genotoxic and carcinogenic.[53,54,55]

Nuclear E2_related factor 2 in oxidative stress

There are many transcription factors that have antioxidant effects which prevent the cell damage with different mechanisms, e;g Forkhead transcription factor FOXO3a (also known as FKHR-L1) which protects quiescent cells from oxidative stress by directly increasing their quantities of manganese superoxide dismutase (MnSOD) messenger RNA and protein. This increase in protection from reactive oxygen species was shown to antagonize apoptosis caused by glucose deprivation.[56]

On the other hand, vascular cell adhesion molecule-1 (VCAM-1) is involved in vascular endothelial dysfunction which is an early feature in the pathogenesis of atherosclerosis and other inflammatory diseases. Regulation of VCAM-1 gene expression may be coupled to oxidative stress through specific reduction-oxidation (redox) sensitive transcriptional or posttranscriptional regulatory factors.[57] More than 20 redox_sensitive transcription factors have been found in mammalian cells, among which Nrf2 (nuclear E2_related factor 2) takes a special place.[58]

Nrf2 has been postulated to be a key regulator of antioxidant enzyme genes,[59] it regulates transcription of genes containing ARE (antioxidant responsive element, 5′_A/GTGAC/TnnnGCA/G_3′) in their promoter. ARE controls expression of more than 100 genes, among which we can emphasize large groups of antioxidant enzymes including: heme oxygenase, glutathione peroxidase, glutathione reductase, and, NADPH: quinoneoxidoreductase.[56]

In cells, Nrf2 is sequestrated in the cytoplasm by a protein known as keap1.[60] Keap1 is an adaptor protein for Cullin3-based ubiquitin E3 ligase and interacts with Nrf2.[61] Nrf2 accumulates in the nucleus and heterodimerizes with small Maf proteins (sMaf). The Nrf2–sMaf heterodimer coordinately induces multiple cellular defense enzymes.[62-64] This stress-mediated gene regulation system is referred to as the Keap1-Nrf2 system, which acts as a key regulator for protective responses against ROS,[65] inflammatory, carcinogenic and proapoptotic conditions.[58]

Mechanism of functioning of the keap1/nrf2/are signaling system

The activity of the Keap1/Nrf2/ARE signaling system, which is dependent upon redox homeostasis in cells, changes during stages of transcription, translation, posttranslational modification of proteins, transport of Nrf2 transcription factor into the nucleus, and also its binding to regulated gene promoters.[66]

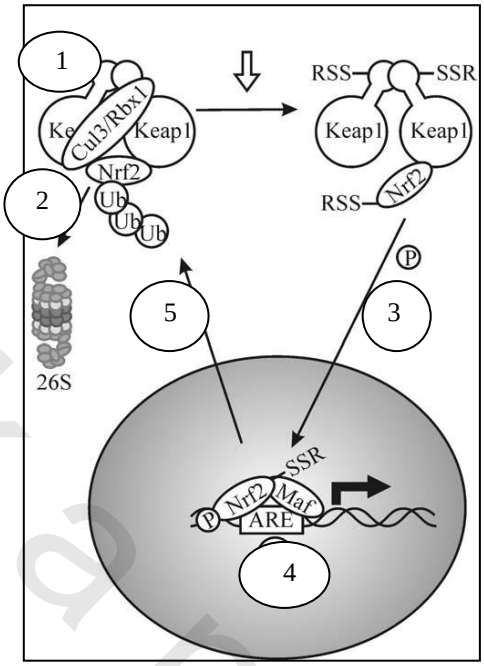

Figure (3): Key aspects of Nrf2 activation: 1) binding to Keap1 inhibitor; *2*) ubiquitination and proteasome degradation; *3*) phosphorylation and transport into the nucleus; *4*) binding to ARE; *5*) export from the nucleus.[66]

The relation between activation of Nrf2 and proteasomes is of dual nature. On one hand, induction of the Keap1/Nrf2/ARE signaling system is naturally increased upon proteasome inhibition,[67,68] mutations, or effects disrupting the interaction of Keap1 with ligase, increasing the stability and levels of Nrf2 in cells.[69,70] On the other hand, because Keap1/Nrf2/ARE system activation usually happens as a response to oxidative stress, it is associated with an increase in expression of different proteasome subunits and overall proteasome activity, which leads to effective removal of modified proteins,[71,72] Oxidation and electrophilic modification in Keap1 cysteine residues play a key role in depression of transcription factor Nrf2.[66,73]

The biological importance of the Keap1/Nrf2/ARE system, has recently been evaluated in different disease conditions as it regulates intracellular redox balance and the activity of a number of redox sensitive transcription factors. Thus, it is easy to understand researchers' interest towards development of activators as well as inhibitors of Nrf2 transcription activity to prevent and treat a wide spectrum of pathologies.[74-79]

Some studies revealed that Nrf2 is essential for protection against chemically induced carcinogenesis. Molecular basis of this protection can be attributed to increased expression of detoxifying enzymes that enhance the chemical hydrophilicity and excretion of the carcinogen, the removal of reactive oxygen species, and the clearance of damage caused by ROS.[80]

Nrf2 loss led to an increase in the intracellular reactive oxygen species (ROS) level and the ratio of oxidized to reduced glutathione.[81]

Etiology of peptic ulcer

Peptic ulcer disease is multifactorial:

1-*Helicobacter pylori*

H. pylori exclusively colonize gastric epithelium, suggesting the specific recognition of cell type by the bacterium. Many factors enable its survival and persistence within the gastric mucosa, including protein glycosylation. The presence of tight adherence of *H. pylori* to the gastric epithelial cell surface through formation of membrane attachment pedestal requires bacterial adhesions to recognize and specifically bind to host receptors expressed on the cell surface.[82]

H. pylori also secrete several enzymes that can cause cellular damage by direct or indirect mechanisms. Urea, when hydrolyzed by bacterial urease, can form compounds such as ammonium chloride and monochloramine that can directly damage epithelial cells. It also alters the viscosity of gastric mucosa. In addition, the urease enzyme itself is antigenic and indirectly produces injury by stimulating inflammatory cells.[83]

2- DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs):

NSAIDs produce a wide spectrum of injury to the gastroduodenal mucosa, ranging from hemorrhage and petechiae to erosion and ulcer. The superficial lesion may have less clinical importance, except that which extends to cause occult gastrointestinal bleeding and cause chronic anaemia. The risk associated with ulcer complication is higher in elderly people and more in women because this group consume the most NSAIDs.[84]

Many NSAIDs have topical irritative effect on the mucosa.[85] However, the ulcerogenic effect of NSAIDs is attributable mainly to the systemic inhibition of prostaglandin production, NSAIDs also produce gastropathy by inducing (ROS) mediated mitochondrial pathology and apoptosis in gastric mucosa.[86]

Other medications that could induce gastric mucosal injury include, corticosteroids which are often used to treat inflammation and auto-immune conditions, and bisphosphonates which are used in treatment of osteoporosis, and potassium chloride which is used to treat (hypokalaemia).[87,88]

Other predisposing factors

1-Cigarette smoking

Cigarette smoking impair healing and promotes the recurrence of ulcers. Smoking increases the likelihood that surgery will be required and increase the risks of surgery. Numerous mechanisms explain the effect of smoking including: stimulation of acid secretion, alteration of blood flow or motility, induction of bile reflux and reduction in the generation of prostaglandins.[89-98]

2-Lifestyle factors [99]

Ethanol is known to cause gastric mucosal irritation and nonspecific gastritis and increase the risk of ulcer.

3- Stress

Acute gastric ulceration in the setting of burns and head injury, which are states of extreme physiological stress, have been referred to as Curling and Cushing ulcers, respectively. The syndrome of stress-related mucosal damage of the gastrointestinal tract was first described in 1971 by Lucas et al who termed this 'stress-related erosive syndrome.[100]

4-Genetics

More than 20% of patients have a family history of duodenal ulcer, compared with 5-10% in control groups.[35]

5-Caffeine and diet

Coffee is a strong acid secretagogue, it can induce dyspepsia. Whether non coffee caffeine containing beverages (tea, soft drinks) induce peptic ulcer is unknown, but they are acid secretion stimulators. Decaffeinated coffee has an acid stimulating effect. It is reasonable to have peptic ulcer patients restrict decaffeinated coffee and all caffeine containing beverages.

Spices, in particular black pepper, red pepper, and cilli powder, may produce dyspepsia. Peptic ulcer patients should avoid any spice that causes discomfort, especially during exacerbation of peptic disease. The high fiber containing food on the other hand may possess factors that are protective against ulcer disease.[101]

6-Certain diseases, e.g (hepatic cirrhosis) [102]

Changes in gastric microcirculation in cirrhosis, such as increased number of straight arterioles and dilated precapillaries and veins have been reported. These alterations might contribute to gastroduodenal ulcers and other putative acid peptic lesions.[103,104]

Clinical manifestations of peptic ulcer

Typical symptoms of peptic ulcer disease include episodic gnawing or burning epigastric pain; pain occurring two to five hours after meals or on an empty stomach; and nocturnal pain relieved by food intake, antacids, or antisecretory agents. A history of episodic or epigastric pain, relief of pain after food intake, and nighttime awakening because of pain with relief following food intake are the most specific findings for peptic ulcer and help rule in the diagnosis. Less common features include indigestion, vomiting, loss of appetite, intolerance of fatty foods, heartburn, and a positive family history.[105]

Complication of peptic ulcer

If ulcers are not treated or treatment is not effective, serious complications may occur. The most common complications include:

1. Duodenal ulcer perforation, which is still a common complication of chronic peptic ulcer disease, despite the wide use of anti-secretory and *H. Pylori* eradication therapy. Many studies showed that the disease is largely confined to elderly patients taking

ulcerogenic medications.[106-110] Perforation and penetration are specially dangerous when the ulcer continues into adjacent organs such as the liver and pancreas.

2. Gastrointestinal bleeding is also a common complication. Sudden large bleeding can be life-threatening.[111] It occurs when the ulcer erodes one of the blood vessels, such as the gastroduodenal artery.
3. Gastric outlet obstruction has been reported to affect less than 5% of patients with peptic ulcer of the distal stomach, pylorus or proximal duodenum.[112] Gastric outlet obstruction is not a single entity; it is the clinical and pathophysiological consequence of any disease process that produces a mechanical impediment to gastric emptying.[113]
4. Choledocho-duodenal fistulisation (CDF); choledocho-duodenal fistulisation (CDF) from duodenal bulb ulcer is currently exceptional, reflecting the low prevalence of peptic disease. Combination of clinical data (occurrence in middle-aged males, ulcer history, absent jaundice and cholangitis) and CT findings including (pneumobilia, normal gallbladder, adhesion with fistulous track between posterior duodenum and pancreatic head) allow diagnosis of CDF.[114]

Treatment

Despite advances in medicine, peptic ulcer disease is still a common disease in elderly patients and also patients with multiple comorbid conditions.[1,115]

The treatment of PUD involves the following strategies:

I-Eradication of *H. pylori*

First-line therapy

It consists of a triple therapy using a proton pump inhibitor (PPI) or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole for those individuals with penicillin allergy, all given twice daily. The recommended duration of treatment range is between 7 and 14 days. The emergence of drug resistance and decreasing drug efficacy has made the second line therapy necessary.[116-119]

Second-line therapy

H. pylori may develop resistance to the prescribed antibiotics used for the first-line therapy. Subsequently, quadruple therapy which consists of a PPI, bismuth, metronidazole and tetracycline is a recommended alternative to first-line treatment, which may be advocated in areas of high antibiotic resistance.[116,120]

Third-line therapy

This is given after multiple treatment failures with different regimens. It was noted that most of *H. pylori* isolates after two eradication failures are resistant to metronidazole and clarithromycin.[121] Therefore, it is recommended that these two drugs should be excluded from the third-line therapy.[122,123]As a result, the third-line therapy is now being applied in some countries.[124,125] These third-line therapies are the new emerging therapies.

Emerging therapies

Fluroquinolone-based therapies

Levofloxacin-based triple therapies are now becoming the second-line treatment of choice in some European countries.[116] It has proven very effective in the treatment of *H. pylori* infection. Levofloxacin has been advocated for use in second and third-line regimens, in combination with amoxicillin and a PPI. [126,127]

Rifabutin and rifampicin-based therapies

These are anti-tuberculous compounds. They are expensive and associated with some side effects like myelotoxicity, leucopaenia and thrombocytopaenia.[128,129] This therapy has been found to be effective in combination with a PPI and amoxicillin.[121,130,131] However, the main problem with a widespread use of rifabutin and rifampicin is the concern that antibiotic resistance may develop against *Mycobacterium avium* and *M.Tuberculosis* in HIV infected patients.[132]

Furazolidone-based therapy

Furazolidone is active against gram-negative, gram-positive bacteria (including *H. Pylori*) and protozoa by inhibiting bacterial enzymes.[133] It is widely used in low-income populations because it is inexpensive.[130] Strains resistant to furazolidone are rare and its potential to develop resistance is as low as bismuth compounds or amoxicillin.[134] Furazolidone has systemic toxicity (tremors, convulsions, peripheral neuritis and gastrointestinal disturbances).[135]

Doxycycline-based therapy

Doxycycline is a widely used tetracycline antibiotic for several infections. This treatment has proved to be a highly effective in a third-line regimen, achieving 91% eradication rate in patients having metronidazole and clarithromycin resistant *H. pylori* strains. This regimen includes a combination of doxycycline, amoxicillin, omeprazole and bismuth salts, it is showing excellent compliance (99%) and mild side-effects, may well constitute the best available option for the third line rescue treatment.[121]

With respect to tetracycline, doxycycline requires the administration of only two capsules per day, leading to a better compliance in patients undergoing eradication therapies.[130]

II-Antisecretory drugs

Decreasing gastric acid secretion is one of the most important factors in the treatment of peptic ulcer. This group include the proton pump inhibitors and histamine receptors antagonists (H_2RAs).[136]

Proton Pump Inhibitors (PPIs)

The discovery of inhibitors of the ATPase began with serendipity, omeprazole was synthesized and became the first drug of this class to be introduced into clinical use in 1989. Omeprazole was followed by lansoprazole, pantoprazole, rabeprazole and more recently, by the S-enantiomer of omeprazole (esomeprazole). All of this class of drugs are currently the standard treatment for acid-related diseases; although sharing a similar mechanism of action, there are subtle chemical differences between the PPIs that affect the precise mechanism by which they inhibit the pump. This may result in clinical differences in their effectiveness.[137]

Mechanism of action

The proton pump inhibitors act by irreversibly blocking the hydrogen/potassium adenosine triphosphate enzyme system (H/K^+ATPase) the final step of acid secretion, there is no bypass of inhibition and no tolerance of the effect. PPIs are prodrugs, effective only after diprotonation. After accumulation in the stimulated secretory canaliculus of the parietal cell and binding to the ATPase, the second protonation occurs and they are then

activated to form the thiophilic drug that reacts with luminally accessed cysteines on the pump. It follows that the presence of acid secretion is necessary for their action. Hence it is recommended that they be given ~30 min after a meal to ensure that the pump is active.[138]

Therapeutic uses

Peptic ulcer disease, Gastroeosophageal reflux disease (GERD), Zollinger-Ellison syndrome.[135]

Adverse effects

Occur infrequently, diarrhea, abdominal pain, and headache. Several studies have suggested a modest increase in the risk of hip fracture in patients taking PPIs especially those with risk factors for osteoporosis, and increased risk of both community acquired respiratory infection and nosocomial pneumonia. Clinically significant drug interactions are rare, omeprazole may inhibit metabolism of warfarin, diazepam, and phenytoin. Lanzoprazole may enhance clearance of theophylline.[135]

Histamine receptor antagonists

The histamine receptor antagonists developed initially in the 1950s were effective against the vascular effects of histamine. The first agent discovered that selectively targeted the H_2 receptor was burimamide.[139] Subsequently, metiamide and then finally cimetidine were introduced in 1977.[140] Cimetidine (Figure:3) represented the first anti-ulcer medication which was well tolerated. Several other H_2RAs as were then developed, such as ranitidine, famotidine and nizatidine, Famotidine is 30 times more potent than cimetidine, whereas nizatidine possesses the same potency as ranitidine.[141] All were successful in accelerating the healing of peptic ulcers, but had to be given chronically to avoid ulcer recurrence.[139]

Mechanism of action

The H_2 RAs are competitive antagonists of histamine at the parietal cell H_2 receptor. They suppress the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid.[135]

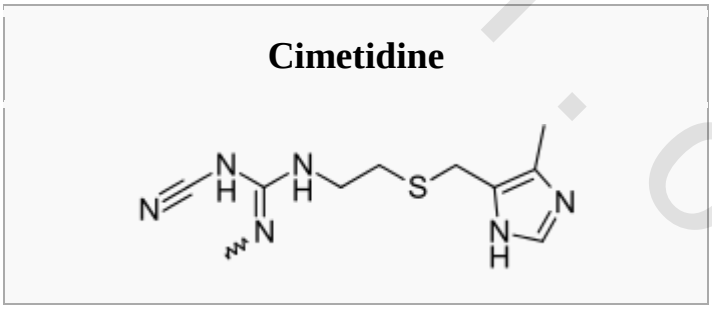

Figure (4): chemical structure of cimetidine.[142]

Therapeutic uses

H_2RAs are used by clinicians in the treatment of acid related gastrointestinal conditions, including: peptic ulcer disease, Zollinger-Ellison syndrome, and prevention of stress ulcer .[135] Two therapeutic problems exist for H_2RAs: first, these drugs were more effective in controlling nighttime acid secretion than daytime acid secretion, and their effectiveness was diminished by ~ 50% after 1 week of therapy due to tolerance. Moreover, these drugs were also relatively ineffective in treating gastroeosophageal reflux disease (GERD).[143]

Adverse effects

H_2RAs are extremely safe and well tolerated drugs. Adverse effects occur in less than 30% of patients and include diarrhea, headache, mayalgia. Some studies suggests that intravenous H_2RAs may increase the risk of nosocomial pneumonia in critically ill patients.

They have a central nervous system toxicity manifested by confusion, hallucination and agitation, particularly in the elderly and in patients with renal and liver failure. It has also been associated with dysrhythmias characterized by bradycardia and hypotension after the rapid intravenous infusion, therefore, intravenous doses should be given over 30 minutes.[135,144]

III-Medications that protect the lining of stomach and small intestine (Cytoprotective)

Gastric mucosal integrity is maintained by pre-epithelial, epithelial and post-epithelial defense mechanisms permitting the mucosa to withstand exposure to the damaging factors. When mucosal defense is weakened or overwhelmed by injurious factors, injury develops in the form of erosions or ulcers.

Prostaglandin E2 analogs such as misoprostol (Cytotec) protect the gastric mucosa against a variety of ulcerogenic and necrotizing agents, even such strong inducers of injury as 100% ethanol and boiling water They proposed a new concept of cytoprotection. Other cytoprotective agents include the prescription medication sucralfate (Carafate) which acts by formation of a viscous tenacious paste that binds selectively to ulcers or erosions and another nonprescription cytoprotective agent which is bismuth subsalicylate (Pepto-Bismol) that creats a protective layer against acid and pepsin, it also stimulates prostaglandins, bicarbonate and mucus secretion. [34]

Refractory ulcers

Refractory peptic ulcer disease (i.e., disease that fails to heal after eight to 12 weeks of therapy) may be caused by persistent or resistant H. pylori infection, continued NSAID use, giant ulcers requiring longer healing time, cancer, tolerance of or resistance to medications, or hypersecretory states. Therapy for refractory peptic ulcer disease involves treatment of the underlying cause and prolonged administration of standard doses of a proton pump inhibitor Up to 25 percent of patients with gastric ulcers who continue to take NSAIDs may require proton pump inhibitor therapy for longer than eight weeks.[145,146]

Despite the availability of different treatment modalities and the decrease incidence of PUD, still there is no complete 100% cure of this disease. Drugs are frequently incompletely sufficient for controlling the ulcer manifestations and also could have adverse effects not tolerated by all patients. Antibiotic resistance and cost of the drugs constitute problems in several countries.

Experimental models of peptic ulcer

Different models have been established to induce peptic ulcer with different mechanisms.

1. Non steroidal anti-inflammatory drugs (NSAIDs) induce peptic ulcer by inhibiting cyclooxygenase and decreasing prostaglandin production. NSAIDs also induce mucosal

damage via Reactive Oxygen Species (ROS) produced by recruited leukocyte. ROS mediate mitochondrial damage as well as lipid, protein, and DNA oxidation leading to apoptosis and mucosal injury.[41] NSAIDs are a useful family of therapeutics, accounting for nearly 5% of all prescribed medications.[147]An inhibitory effect of NSAIDs on cyclooxygenase (COX) activity is responsible for their anti-inflammatory actions because COX is an enzyme essential for the synthesis of prostaglandins (PGs) (Figure:5), which have a strong capacity to induce inflammation. On the other hand, NSAID use is associated with gastrointestinal complications; with about 15–30% of chronic users of NSAIDs suffering from gastrointestinal ulcers and bleeding.[148-152]

There are at least two subtypes of cyclooxygenase (COX), COX-1 and COX-2, which are responsible for the majority of COX activity at the gastric mucosa and in inflamed tissues, respectively.[153,154] Therefore, it is reasonable to speculate that selective COX-2 inhibitors could have anti-inflammatory activity without gastrointestinal side effects. Although PGE2 has a strong protective effect on gastrointestinal mucosa, the inhibition of COX by NSAIDs is not the only explanation for the gastrointestinal side effects of NSAIDs. [155,156] Recently studies demonstrated that NSAIDs induce apoptosis in cultured gastric cells and at gastric mucosa in a manner that is independent of COX inhibition.[157-161]

NSAIDs induced reduction in anti-apoptotic genes (e.g., Bcl and Bcl-2) while inhibiting increases in Fas and Fas ligand as well as pro-apoptotic genes (e.g., Bax and Bak).[41]

The development of increased gut permeability and mucosal inflammation are the most frequent abnormalities in NSAIDs users. Increased gut permeability can be seen as soon as 12 hours after the ingestion of single doses of most NSAIDs.[162-165] Some studies have found that NSAIDs increase fecal calprotectin in rheumatoid arthritis or osteoarthritis patients taking NSAIDs. Calprotectin, that represent >50% of neutrophil cytosol protein, is present in increased concentrations in inflamed tissues. It belongs to the S-100 protein family composed of two subunits of molecular mass of 8 and 14 kDa. Calprotectin is released from leukocytes both due to cell death and in an active mechanism of secretion. Calprotectin is involved in inflammatory processes; its proapoptotic and antibacterial properties have been shown (probably by binding zinc and calcium ions essential for the development of individual microorganisms) and also its abuity to inhibit in vitro the proliferation of proliferating cells, like bone marrow cells, cancer cells or stimulated lymphocytes. However, it should be noted that its significance in the development of inflammatory lesions in various diseases has not been fully understood.[166-168]

The most commonly drugs used for induction of peptic ulcer in rats are indomethacin with does 20,30 mg/kg,[169] aspirin 300 mg/kg.[170]

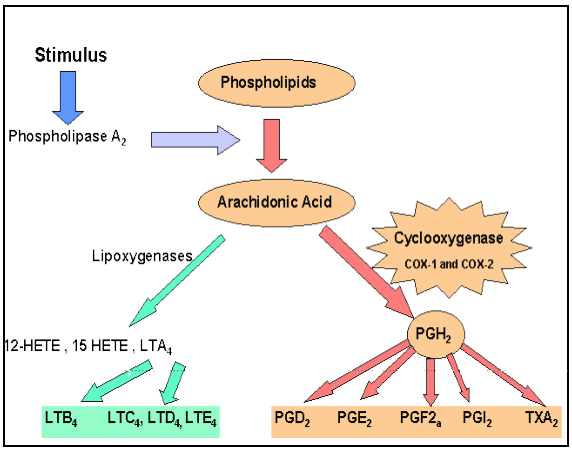

Figure (5): Biosynthesis of prostaglandins.[171]

2. Ethanol: The model of ethanol-induced experimental gastric injury is widely used to cause gastric ulcer independently from acid secretion. Ethanol causes necrotic lesions in the gastric mucosa through multiple pathways, directly producing necrotic lesions, which in turn reduces defensive factors, bicarbonate secretion and mucus production.[172] The gastric wall mucus is thought to play an important role as a defensive barrier against gastrointestinal damage.[173] Many studies showed that ethanol decreases the levels of plasma endothelin-1 (ET-1), serum nitric oxide (NO) and gastric mucosal prostaglandin E2 (PGE2).[174]
3. Water immersion restraint stress-induced gastric lesion models by immobilization and immersion in water for 24 hours.[175]
4. Ischemic reperfusion gastric ulcer injury, at which the injury is produced by clamping the coeliac artery which causes damage and fall off of muscularis mucosa.[176]

New trends in treatment of peptic ulcer, the evident role of oxidative stress in pathogenesis of peptic ulcer motivated for the development of new drugs with antioxidant properties to help healing of peptic ulcer such as; rebamipide.[177] Some plant extracts are also being used for treatment of PUD such as; Curcumin, [178] Nigella sativa [179] and cinnamon for their antioxidant and inflammatory properties.[180]

Moreover; many antidepressant drug have shown benefits for patients with PUD; a study has shown that imipramine and amitriptyline dose dependently prevent gastric ulcer.[181]

Rebamipide

Rebamipide, 2-(4-chlorobenzoylamino)-3-[2(1H)-quinolion-4-yl] propionic acid, (figure 5) is a therapeutic agent used for mucosal protection, healing of gastroduodenal disorder (e.g gastritis) and scavenging the free radicals.[177]

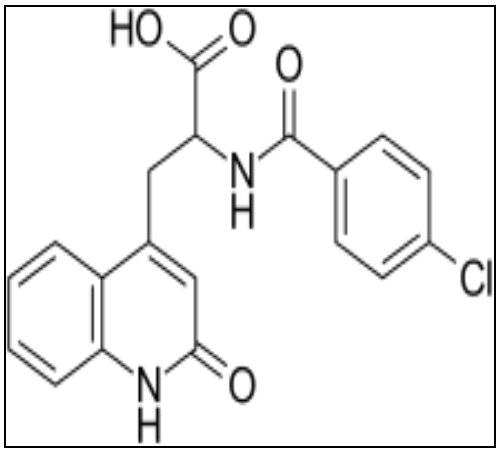

Figure (6): chemical structure of Rebamipide [177]

Mechanism of action figure (7)

Rebamipide exerts a positive effect on the digestive epithelial barrier by increasing the induction of endogenous prostaglandins (PGs), and scavenging free radicals.[182] Recently it has been demonstrated that this drug has unique properties such as anti-inflammatory actions.[183] The protection by rebamipide against the deleterious effect of IL-1b on the epithelium may be an important element of its anti-inflammatory properties on the gastric mucosa, and could be related in part to its anti-apoptotic effects.[184]

PGs have been shown to modulate gastric functions such as acid suppression, cytoprotection, mucus secretion, bicarbonate secretion, blood flow and motility,[185-187] and dramatically increases vascular endothelial growth factor (VEGF), a known angiogenic factor and a vascular permeable factor, by activated macrophages through specific PGE receptor and peroxisome proliferator activated receptor γ (PPARγ, a nuclear receptor of PG) mediated process.[188] In vitro study at basal conditions, rebamipide at concentrations of 1 mM and 2 mM increased the integrity of the monolayer of epithethial barrier as reflected by increased electrical resistance and decreased mannitol fluxes across the epithelium. The reinforcement of the barrier in basal conditions may play an important role in the protective action of rebamipide on the epithelium of the digestive tract. It is known that rebamipide can protect the gastric mucosa against different damaging factors such as NSAIDs,[189] ischaemia reperfusion injury,[190] platelet-activating factor induced gastric injury,[191] ethanol induced injury [192] and oxygen radical mediated gastric injury.[193]

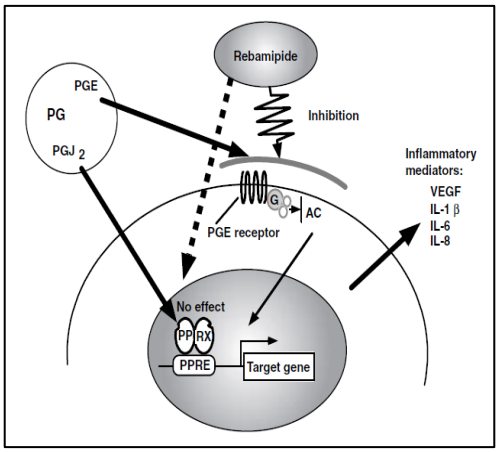

Figure (7): Action of Rebamipid. PGs induce increase of inflammatory mediators. Rebamipide suppresses membrane, but not nuclear PG receptor (PPARγ), mediated increase of inflammatory cytokines. PG, prostaglandin; PPRE, peroxisome proliferator response element; PPAR, peroxisome proliferator activated receptors; RX, retinoid X receptor-α; G, G protein; AC, adenylate cyclase; VEGF, vascular endothelial growth factor; IL-1b, interleukin-1b; IL-6, interleukin-6; IL-8, interleukin-8.[188]

Pharmacokinetics

Rebamipide exhibitis a low aqueous solubility and a poor oral bioavailability, and pH-dependent solubility profiles,[194] rebamipide is soluble in dimethylformamide, very slightly soluble in methanol and ethanol, and practically insoluble in ether and water.

The aqueous solubility of rebamipide has been reported to be approximately 0.0001 and 0.013% (w/v) at pH 3 and 7, respectively.[195] Various efforts have been made to improve the oral absorption potential of drugs with poor water solubility, i.e., by incorporating absorption enhancers and adjuvants,[196,197] and synthesizing various salt forms.[198-200] Salt formation techniques may be utilized to improve the solubility profile and oral bioavailability of rebamipide.[201]

Up to 98.4% of ingested repbamipide is bound to plasma proteins. It is metabolized in the liver by human cytochrome P450 enzyme. The cytochrome P450 enzyme acts on rebamipide through hydroxylation and glucoronidation, resulting in the formation of 6-hydroxy and 8-hydroxyrebamipide.[202] The role of glucoronidation in the metabolism of rebamipide is very low and nonsignificant. Drug interactions of rebmipide with other drugs is very low and it is safely used concomitantly with other drugs.[203]

Rebamipide is commercially available in tablet form, each contains 100 mg of Rebamipide, (Mucosta; Otsuka).

For research purposes, rebamipide is also available in enema and drops forms.

Clinical uses of rebamipide

1-Rebamipide in ulcerative colitis (UC) and proctitis

The efficacy of rebamipide enemas was studied in active distal ulcerative colitis and proctitis, the drug was given enemas containing 150 mg rebamipide per dose. It was concluded that rebamipide topical therapy might be effective in mild to moderate active distal UC.[204]

2-Rebamipide in dermatology

Rebamipide has been used in the following conditions: stomatitis, recurrent oral aphthae, Behcet's disease.[205]

3-Rebamipide in ischemic colitis

Rectal administration of rebamipide in the treatment of ischemic colitis was tested and evaluated in patients with colonic ulcer. The study concluded that in left side ischemic colitis with ulcers rebamipide enema therapy can significantly reduce the duration of hospitalization, and it recommended the use of this drug as a new and effective therapeutic alternative.[206]

4-Rebamipide as ophthalmic suspension for dry eye

A study was conducted in Japan on 188 patients with signs and symptoms of dry eye, to examine the efficacy and safety of 2% rebamipide ophthalmic suspension in comparison with 0.1% sodium hyaluronate ophthalmic solution. The result confirmed that in addition to the improvement in corneal-conjunctival damage in patients with dry eye, rebamipide ophthalmic solution also showed improvements in subjective symptoms such as foreign body sensation and eye pain.[207]

Side-effects of rebamipide

Adverse drug reactions to rebamipide is not common, side effects seen are mild and can be corrected with dose adjustment. The common side effects noticed after rebamipide use is gastrointestinal, like constipation, bloating, diarrhea, nausea and vomiting.[208] Hypersensitivity and rash was seen in less than 1% of patients.[209]

Contraindication

Rebamipide is contraindicated in patients with known history of drug hypersensitivity.[177]

Precautions

- Use in elderly
  Special care is required in elderly patients to minimize the risk of gastrointestinal side effects, because these patients may be physiologically more sensitive than younger patients.
- Use during pregnancy, delivary, or lactation
  This drug should be administered to pregnant or possibly pregnant only if the anticipated therapeutic benefit is thought to outweigh any potential risk. (The safety of this drug in pregnant women has not been established). Nursing should be interrupted when this drug is administered. (Rat studies have shown that rebamipide is excreted in breast milk).
- Pediatric use
  The safety of this drug in low birth weight infants, newborns, suckling infants, and children has not been established. (Clinical experience is insufficient).[177]

Tianeptine

Tianeptine (figure: 8) is an atypical antidepressant drug with structural similarities to the tricyclic antidepressant agents but a novel neurochemical profile, also called Selective Seretonin Reuptake Enhancer (SSRE). The main differences between this and other antidepressant agents are its action on serotonin (5-hydroxytryptamine; 5-HT): tianeptine increases serotonin uptake in the brain and platelets.[210,211] The behavioural (in animal models) and physical (atrophy of neuronal dendrites) effects of stress on the hypothalamic-pituitary-adrenal axis are reduced by tianeptine, and levels of noradrenaline (norepinephrine) and dopamine are indirectly increased in several regions of the brain.[212-215] The main active metabolite (MC5; pentanoic acid) has some minor antidepressant activity.[216,217] Like the selective serotonin reuptake inhibitors (SSRIs) and in contrast with the tricyclic antidepressants, tianeptine has a favourable cardiovascular profile in healthy volunteers and patients with depression, with and without concurrent alcoholism.[218,219]

Pharmacokinetics

The bioavailability of tianeptine is 99% after a single oral dose of 12.5 mg in healthy people. The drug is not subject to first-pass hepatic metabolism. Food decreases C_{max} and prolongs t_{max} but does not affect the extent of absorption. Although the distribution of tianeptine is rapid (distribution half-life 0.7 hours) protein binding is high (95%), resulting in a low volume of distribution (0.5 to 0.8 L/kg) in healthy people.[220]

Tianeptine undergoes extensive extrarenal metabolism and has a short elimination half-life (t1⁄2; 2.5 hours in healthy people). The major metabolic pathway of tianeptine is a 2-step β-oxidation process of the aliphatic chain, leading to the formation of 2 main metabolites MC5 and MC3 (propionic acid). MC3 is the main metabolite of tianeptine in urine and MC5 is the main metabolite in plasma.[221,217] Tianeptine does not undergo cytochrome P450–dependent biotransformation to any significant extent, thus reducing the risk of drug interactions.[217] The pharmacokinetics of oral tianeptine was not significantly altered in patients with compromised renal function. However, the t1⁄2β and AUC of the MC5 metabolite were increased compared with controls, suggesting a decreased clearance of this metabolite in patients with renal failure.[222] Although bioavailability of tianeptine remained high (85%) in elderly individuals, clearance was lower than that reported in younger individuals. The pharmacokinetics of tianeptine is not altered in patients with alcoholic cirrhosis and depression.[223]

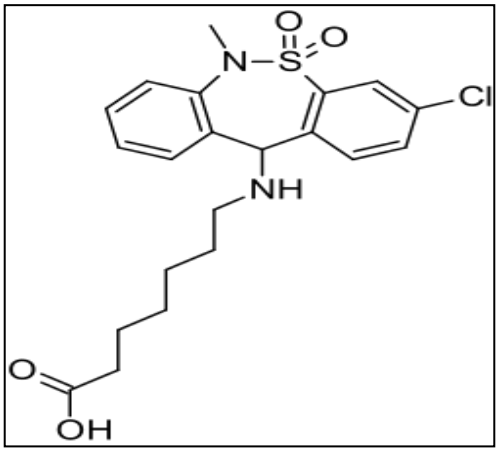

Figure (8): chemical structure of Tianeptine [224]

Clinical uses

Tianeptine 25 to 37.5 mg/day for 1.5 to 3 months had equivalent antidepressant efficacy to fluoxetine 20 mg/day in patients with major depression (single episode or recurrent), bipolar disorder (depressed) or dysthymic disorder in several studies. The anxiolytic efficacy of tianeptine was assessed in several comparative trials of patients with concurrent depression and anxiety.[225,226] Tianeptine 25 to 50 mg/day appears to have equivalent anxiolytic efficacy to fluoxetine 20 mg/day for 1.5 to 3 months, sertraline 50 mg/day for 1.5 months, amitriptyline 50 to 100 mg/day for 1 to 1.5 months, clomipramine 100 to 200 mg/day for 6 months and mianserin 30 to 80 mg/day for 1.5 or 6 months. Superior anxiolytic efficacy was attributed to tianeptine over maprotiline 75 mg/day for 2 months in a study of perimenopausal women with anxio-depressive symptoms.[227]

Tianeptine 25 to 50 mg/day is effective as long term treatment to prevent relapse or recurrence in patients with depression. The efficacy of tianeptine was established in elderly patients and in patients with chronic alcoholism especially on withdrawal of alcohol. [228]

Clinical studies have shown that anxiolytic and antidepressant drug therapy benefits patients with gastrointestinal disorders; e.,g imipramine and imitriptiline (Tricyclic antidepressants TCA) dose dependently prevent gastric ulcers in different ulcer models.[229] Disimipramin, an active metabolite of imipramine, has also potentially inhibited gastric acid secretion and produced gastroprotective effects in various ulcer models. And flouxitine (Selective serotonin reuptake inhibitors, SSRIs) also has been shown experimentally to elicit antiulcer activity in various ulcer models.[230]

Tianeptine was shown to exert a direct gastroprotective effect via the alpha 2 adrenoreceptors in rats, [231] and prevent the reduction of glutathione (GSH) content that occurred in the indomethacin damaged stomach tissue in rats.[229]

Adverse effects

The adverse effects of tianeptine appear to be similar in many respects to that of the SSRIs, in that cognitive, cardiovascular and body weight effects are minimal in comparison with the classical tricyclic antidepressant agents, the only symptom appearing significantly more often with tianeptine was headache. In clinical trials, the most common adverse effects seen in patients with depressive disorders receiving tianeptine were gastrointestinal (nausea, constipation, abdominal pain) or CNS (headache, dizziness, change in dreaming) disturbances, which decreased in frequency with continued treatment.[232-236]

Effects such as dry mouth, hot flushes, somnolence, vertigo, gastrointestinal disturbances, increased body weight, increased heart rate and tremor occurred significantly more often in patients receiving tri- or tetracyclic antidepressant agents than in those receiving tianeptine. In studies comparing tianeptine with fluoxetine, paroxetine or sertraline, in contrast, the incidence of most adverse effects was similar; nausea, tremors and palpitation tended to occur more often in fluoxetine recipients, and the incidence of dry mouth tended to be higher in tianeptine recipients. Tianeptine has only rarely been associated with hepatoxicity.[237-240,225]

The favourable tolerability of tianeptine has been confirmed in long term trials, and in elderly patients (including those with cardiovascular pathology before treatment initiation) and patients with alcoholism. Tianeptine has a wide therapeutic margin; overdosage has been associated with only minor transient adverse effects.[241]

Oleum cinnamomi

Botanical (Vegetative) Name: *Cinnamomum verum* J. Presl.

Synonyms: *Cinnamomum zeylanicum* Nees; Ceylon cinnamon; true cinnamon.

Family: Lauraceae.

Common Names: **French**: cannellier, canella de Ceylan; **German**: Ceylon-Zimtbaum; **Italian**: canella; **Spanish**: canelo de Ceilan.[242]

Introduction

Cinnamon is one of the finest sweet spices, with cassia as a coarser substitute. The botanical name *Cinnamomum* is derived from the Hebraic and Arabic term *amomon*, meaning fragrant spice plant. *Cinnamon* is a popular spice in Greece and Rome. *Cinnamon's* name is derived from the Greek word, *kinamon*. *Cinnamon* is widely used by humans, both as a spice and as a traditional medicine. It is, perhaps, one of the oldest herbal medicines, having been mentioned in Chinese texts as long as 4,000 years ago,[243]and imported to Eygpt over 3,600 years ago.[244] It consists of 250 species and represented by 26 species.

Cinnamon is native to Sri Lanka and parts of India. It is cultivated commercially in India, Africa, South America, the West Indies, Indonesia, and the Seychelles.[242]

Botanical description

A tropical medium-sized, evergreen tree up to 15-m (50 ft) high. It has long, very stiff, lanceolated, leathery, bright green leaves, with small yellow flowers in clusters and small ovoid bluish or blackish fruits. The bark and leaves are highly aromatic. The commercial cinnamon bark is a dull, pale brown. The cinnamon quills of commerce are known as cinnamon sticks. The broken quills of various grades are called quillings. There are other varieties of cinnamon. *Cinnamomum* cassia or Chinese cassia, *C. burmanii* or Indonesian cinnamon, *C.loureirii* or Vietnamese cinnamon.[244]

Bark (quills), bark powder, bark essential oil, leaf essential oil, and oleoresin are the mostly used products. The spice is reddish-brown and has a sweet, warm, spicy, and woody aroma. The flavor is warm, spicy, and aromatic. The essential oil has a sweet, aromatic, spicy, slightly woody, and clove-like aroma.[242]

Active constitute

Cinnamon bark contains essential oil (up to 2%), with *cinnamaldehyde (*60–80%) as the major constituent. Other minor constituents are *trans-cinnamic* acid,o-methoxycinnamaldehyde, eugenol, and monoterpenoids. The bark also contains procyanidins, diterpenes, phenylpropanoids, mucilage, and polysaccharides. The leaf oil has eugenol (70–90%) as the major constituent. The methanol extract has tannins, flavonoids, glycosides, terpenoids, coumarins, and anthraquinones.[245]

Medicinal uses and functional properties

It is a traditional remedy for dyspeptic conditions like flatulence, gastrointestinal spasms, loss of appetite, and diarrhea. It is also used to improve the flavor of other nonmedicinal products. In folk medicine it is used to treat colds, nausea, inflammation, rheumatism, vomiting, and menstrual disorders. It has carminative and astringent properties.

The available in vitro and animal in vivo evidence suggests that cinnamon has anti-inflammatory, antimicrobial, antibacterial, antioxidant, antitumor, cholesterol lowering, and immunomodulatory effects.[246-253]

Cinnamaldehyde (CA), one of the active components of cinnamon, has been known to exert several pharmacological effects such as anti-inflammatory, antioxidant, antitumor, and antidiabetic activities.[254]

(CA) from cinnamon displayed significant antiproliferative effects on human colon cancer cells in concentration and kinetic dependent manners,[255] and antitumor effect of cinnamon extracts is directly linked with enhanced proapoptotic activity and inhibition of NF-kappa B and AP1 activities and modulation of their target genes in vitro and in vivo mouse melanoma.[256]

Cinnamon extract was shown to induce apoptosis in the cervical cancer cells through increase in intracellular calcium signaling as well as loss of mitochondrial membrane potential and thus cinnamon could be used as a potent chemopreventive drug in cervical cancer.[257] *Cinnamon* was identified a natural vascular endothelial growth factor (VEGF) inhibitor and could thus be useful in cancer prevention and/or treatment.[258]

Cinnamaldehyde exhibit chemopreventive dietary factor targeting colorectal carcinogenesis.[259]

It has inhibitory effects on Gentamycin-Induced Nephrotoxicity in mail adult rats by decreasing blood urea nitrogen, serum creatinine and uric acid.[260] (Eugenol) was shown to inhibit COX-2.[261]

In vitro studies have demonstrated that cinnamon may act as an insulin mimetic to potentiate insulin activity or to stimulate cellular glucose metabolism. Furthermore, animal studies have demonstrated strong hypoglycemic properties.[262-264]

Polyphenolic polymers from cinnamon function as antioxidants and control glucose intolerance and diabetes.[265] The methanol extract of cinnamon displayed excellent NO-scavenging ability, and the inhibition of inducible nitric oxide synthase (iNOS) expression was the primary mechanism of action as regards its NO-suppressing activity.[266]

Metabolic syndrome is associated with insulin resistance, elevated glucose and lipids, inflammation, decreased antioxidant activity, increased weight gain, and increased glycation of proteins. *Cinnamon* was shown to improve all of these variables in vitro, animal, and/or human studies. Daily cinnamon and usual care were found to lower HbA1C in patients with type 2 diabetes.[267] Human studies involving control subjects and subjects with metabolic syndrome, type 2 diabetes mellitus, and polycystic ovary syndrome all showed beneficial effects of whole cinnamon and/or aqueous extracts of *cinnamon* on glucose, insulin, insulin sensitivity, lipids, antioxidant status, blood pressure, lean body mass, and gastric emptying.[268]

Cinnamon exhibits also effects against obesity and insulin resistance.[269] The methanol *cinnamon* bark extract effectively inhibited the α-glucosidase leading to suppression of postprandial hyperglycemia in STZ-induced diabetic rats loaded with maltose and sucrose.[245]

Another study showed that cinnamon bark extracts were useful for the control of postprandial glucose in diabetic patients by inhibiting intestinal α-glucosidase and pancreatic a -amylase. *Cinnamon* extract and/or *cinnamon* was shown to improve fasting

blood glucose in people with type 2 diabetes or prediabetes.[270] The A and B-type procyanidin oligomers in different *Cinnamon* species had hypoglycemic activities and may improve insulin sensitivity in type 2 DM.[271]

Cinnamon extract was found to significantly increase insulin sensitivity, reduce serum and hepatic lipids, and improve hyperglycemia and hyperlipidemia possibly by regulating the peroxisome proliferator activated receptor (PPAR) medicated glucose and lipid metabolism.[272]

Cinnamon oil had a regulating role in blood glucose level and lipids, and improved the function of pancreatic islets and thus may be useful in the treatment of type 2 diabetes mellitus, and a good natural food preservatives.[273,274]

Trans-cinnamaldehyde (TC) exerted antimicrobial effects by several mechanisms, including disruption of and carbohydrate, amino acid, and lipid metabolism.[275] Also *cinnamon* extract could be a good source of natural antimicrobial substances for the treatment of cases of M. cattarhalis.[276]

The essential oil of *cinnamon* showed promising larvicidal and repellant agent against C. tritaeniorhynchus; [277] in another study the essential oil showed anticandidal activity against C. orthopsilosis and C. parapsilosis in both suspension and biofilm cultures,[278]and antibacterial activity against *P. aeruginosa*.[279]

Also essential oil was also shown to have good antifungal activity,[280] and the Cinnamomum zeylanicum was found to protect against kidney and renal disorder.[281]

Cinnamon extract induce the production of low levels of proinflammatory cytokines [interleukin (IL)-1 b , IL-6, IL-12, interferon (IFN) γ , and tumor necrosis factor (TNF)- α] while expressing high levels of immunoregulatory cytokines (IL-10 and transforming growth factor- β). In addition, cinnamon extract inhibited APC-dependent T-cell proliferation and converted CD4(+) T cells into IL-10(high) CD4(+) T cells. Furthermore, oral administration of cinnamon extract inhibited development and progression of intestinal colitis by inhibiting expression of COX-2 and proinflammatory cytokines (IL-1 β, IFN- γ, and TNF- α), while enhancing IL-10 levels.

These results indicate that its anti-inflammatory action is because of antioxidative effect and the restoration of redox balance. Several phenolic compounds from an aqueous extract of cinnamon bark showed significant inhibitory effects on the formation of advanced glycation end products (AGE) by effectively scavenging reactive carbonyl species.[282]

In addition, *cinnamon* has been shown to alleviate factors associated with Alzheimer's disease by blocking and reversing tau formation (protein associated with microtubules and is implicated in neurodegenerative disease) in vitro and in ischemic stroke by blocking cell swelling and also *cinnamon* extract was shown to inhibit the toxic oligomeric A β species formation in Alzheimer's disease.[283]

The *cinnamon*-coated gold nanoparticles could serve as excellent CT/photoacoustic contrast-enhancement agents and could provide a novel approach towards tumor detection through nanopharmaceuticals.[284]

Antioxidant properties

Cinnamon has been shown to have strong antioxidant activity.[285-288] *Cinnamon* increased the antioxidant enzyme activities and restored the GSH content in rats fed a fat diet.[289] The essential oils were reported to show strong antioxidant activity using in vitro models.[290]

Many studies found cinnamate, a phenolic compound in cinnamon bark, to significantly lower hepatic cholesterol and triglyceride levels in rats fed high cholesterol diet. The dietary cinnamate inhibited hepatic HMG-CoA reductase activity, which resulted in lowered hepatic cholesterol content, and suppressed lipid peroxidation via enhancement of hepatic antioxidant enzyme activities. A concentrated water extract of defatted cinnamon fruit powder contained the maximum amount of phenolics and showed highest antioxidant activities.[291] The purified compounds from this extract showed strong antioxidant and radical scavenging activities.

An elevated serum AST and ALT enzymatic activities in rats induced by CCL4 were significantly restored to near normal by oral administration of either aqueous or ethanolic extract of cinnamon as compared to untreated rats. However, the ethanolic extract was found to have more potent hepatoprotective action against CCL4 by lowering MDA level and elevating antioxidant enzyme activities (SOD and CAT). The possible mechanism may be the radical scavenging activity of the polyphenol compounds.[292] Another study on high cholesterol group (HCD) found that cinnamon provided protection against the lipemic-oxidative disorder and acts as hypocholesterolemic, hepatoprotective agent and improves cardiovascular function through modulation of oxidative stress.[268]

The essential oil of *cinnamon* was also found to confer significant dose dependent protection against alloxan-induced renal damage.[293]