Research Journal of Pharmaceutical, Biological and Chemical Sciences

Molecular pathogenesis of gastric ulcers and strategies for prevention

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ABSTRACT

The purpose of this review is to summarize the pertinent literature published in the present era regarding ulcerogenic effectors, and all available therapeutic concepts in this regard including; different physiological/pathological changes in response to H. pylori infection, nonsteroidal anti-inflammatory drugs (NSAID), bile acids, nitric oxide, copper complexes, acid pump inhibitors, histamine blockers, curcuminoids, cytokines and/or growth factors and finally probiotics. Because of the partial understanding of gastric ulcer pathogenesis three major hypotheses were strongly speculated and widely documented. Firstly, the hyperacidity hypothesis entailing the disturbance of the gastric acid, histamine, gastrin and somatostatin. Secondly, the eicosanoid imbalance hypothesis exploiting changes in the microcirculation through the vasoconstrictor eicosanoids such as TXA_2 and vasodilator cytoprotectant eicosanoids such as PGE_2. Thirdly, the infective hypothesis implementing H. pylori as the major pathogenic effectror for the gastroduodenal ulceration. In fact, all of the previous effectors could be involved and possibly employing inflammatory/antiinflammatory, oxidative stress and/or angiogenic disturbance.

Keywords, Oxidative stress, Non-steroidal anti-inflammatory drugs, entero- chromaffin-like (ECL) cells, Proton pump inhibitors (PPIs), Probiotics.

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1. Background

Gastric ulcer is a deep lesion penetrating through the entire thickness of the gastrointestinal mucosa and muscularis mucosa (Tarnawski et al., 2001). Ulcer disease whatever in the esophagus, stomach and or in the duodenum is one of the main prevalent still unresolved medical problems that faces many patients in a wide rang of age of both sexes worldwide. It is indisputable that H. pylori infection is the most important etiologic factor for gastroduodenal ulcer however neither eicosanoids nor bacterial infection alone or combined could explain the pathogenic effectors of the disease due to recurrence after cessation of the treatment for each. Additionally, the most effective combination therapy to eradicate H. pylori has not yet been found (Sontag et al., 2001). The discovery of H. pylori as a causal factor in a variety of upper gastrointestinal disorders has had a major clinical impact and has in particular changed the management of patients with peptic ulcer disease (Kuipers et al., 2003). However, in developed countries at least, ulcers related to H. pylori infection are becoming rarer (Wallace, 2005). Thus, ulcers associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) remain a major clinical problem, which has not been solved through the introduction of selective inhibitors of cyclooxygenase (COX)-2 (Wallace and Muscara, 2001;Wallace, 2005). On the other hand, the cytoprotective role of cytokines and growth factors in this process is not well understood. The role of copper complexes with vitamins or amino acids as gastric cytoprotective agents were scarcely investigated in few reports (Tuorkey and bdul-Aziz, 2009).

2. Part A. Gastric Ulcer Mediators

2. 1. Gastric acid

A great deal has been learned about the pathogenesis of gastric ulcer over the past two decades, as a result of the painstaking efforts of inspired researchers. In an attempt to protect the gastric mucosa from gastric acid, enhance ulcer healing, and prevent ulcer recurrence, pharmacological control of gastric acid secretion has long represented a desirable goal (Aihara et al., 2003;Tuorkey and bdul-Aziz, 2009;Tuorkey and Karolin, 2009b). Since, gastric acid hypersecretion is one of the major pathogenic factors for the induction of gastric ulcer disease. Furthermore, luminal acid interferes with the process of restitution, resulting in the conversion of superficial injury to deeper mucosal lesion and inactivates the acid-labile growth factors important for maintenance of mucosal integrity and repair of superficial injury (Wallace and Muscara, 2001). Impairment of gastric ulcer healing depends upon the increased release of proinflammatory cytokines, a decrease in the gastric mucosal blood flow and angiogenesis through reducing vascular endothelial cell growth factor (VEGF) expression (Harsch et al., 2003). On the other hand, mucins are heavily glycosylated glycoproteins that are the major components of the mucus viscous gel covering epithelial tissues. They form lubricants protective selective barrier on epithelial surfaces, and modulate cell-cell and cell-extracellular matrix interactions, lymphocyte trafficking and anti- immune recognition. Their expression is regulated by several cytokines and local and endocrine hormones (Gum, Jr., 1992;Shimizu and Shaw, 1993;Wittel et al., 2001). Various pharmaceuticals, such as histamine H_2 receptor (H_2R)

antagonists and H$^+$/K$^+$-ATPase (acid pump) inhibitors have been developed and utilized for the treatment of acid-related peptic diseases (Black et al., 1972). For several years ago, gastric acid established as one of the major ulcerogenic effectors, for instance, about 50% of gastric ulcer patients are pepsin and acid hypersecretors (Szabo, 1988). But, on the other hand, gastric acid plays a stringent role in gastric defense; hence, it is the first line of mucosal defense to prevent bacterial colonization and reduced their ability to entrance in the mucosal layer e.g., Helicobacter pylori, which is the major effector for the pathogenesis of gastric ulcer.

2. 2. Histamine

Histamine is a chemical messenger that mediates a wide rang of cellular responses, including allergic and inflammatory reactions, gastric acid secretion and possibly neurotransmission in parts of the brain. Additionally, it is secreted by mast cells as a result of allergic reactions or trauma. Pharmacologically, histamine produces vasodilatation and increase in permeability of blood vessel walls that may contribute to gastric hemorrhage (Hung and Wang, 2004). In the experimental animal, increased mucosal histamine has been reported to elicit gastric secretion and mucosal lesion (Andersson et al., 1990). Since, histamine may cause increase in gastric mucosal permeability to electrolytes and renders the stomach more susceptible to acid-induced damage (Gislason et al., 1995). The role of histamine in the secretion of acid from acid-producing parietal cells is widely reported (Tairov et al., 1983;Tairov et al., 1984;Norlen et al., 2000). Where, histamine activates histamine-2 receptors on the acid-producing parietal cells to stimulate acid production, the over production of acid inhibits through low antral pH gastrin release from G-cells, thus preventing the stimulatory effect of gastrin on enterochromaffin-like (ECL) cells and further histamine release (El-Omar et al., 1997). This inhibitory control is mediated via the release of somatostatin from D-cells situated in close proximity to the G-cells. The mechanism of stimulating and inhibiting acid production in the stomach wall was summarized in fig.
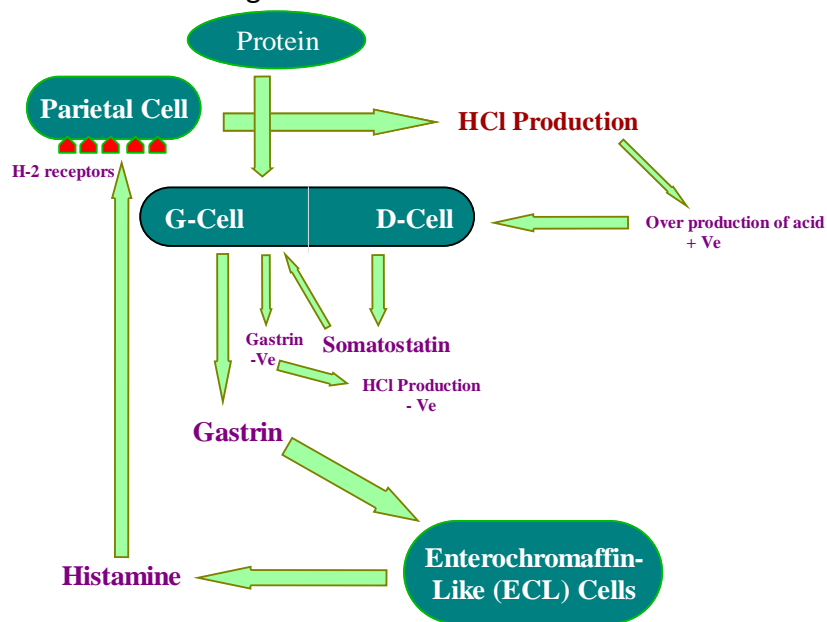
Figure 1: **The mechanism of acid secretion and acid inhibition in stomach, and the role of histamine, gastrin, and somatostain in this process.**

1. Protein stimulates G-cell to release gastrin.
2. Gastrin stimulates enterochromaffin-like cells to secrete histamine.
3. Histamine stimulates H-2 receptors on Parietal cells to produce HCl.
4. Over production of acid is prevented through release of somatostain from D-cells.
5. Somatostatin inhibits gastrin secretion from G-cells.

2. 3. Oxidative stress

In the biological system, small amounts of the potentially toxic reactive oxygen species (ROS) could be generated in eukaryotic cells by normal oxidase action or during the course of electron transport in the mitochondria or in the endoplasmic reticulum. Since electron seeks stability through electron pairing with biological macromolecules e.g. proteins, lipids and DNA, which in turn, leads to protein and DNA damage along with lipid peroxidation. Additionally, a variety of cells, including neutrophils, macrophages, neurons, and endothelial cells can produce both O_2^- and NO^- through the respective actions of various oxidases and nitric oxide synthases. Superoxide radical (O_2^-) reacts extremely rapid with the naturally produced nitric oxide (NO^-) to give rise of peroxynitrite ($ONOO^-$)/peroxynitrous acid (ONOOH). Therefore, Oxidative stress has involved as one of the major pathogenic factors that directly impaired cells functions, promotes cellular organelles damage in the cells, including particularly, mitochondria, lysosomes, and nucleus. Since, ROS could directly disrupt the mitochondrial membrane that subsequently leads to release of cytochrome c; the later becomes a part of apoptosome complex. Or in an additive way leads to membrane rupture of the lysosomes leads to release of cathepsins, the later activate caspase and apoptosis cascade, and finally leads to cell death via apoptosis. In the contrary, the cells protect themselves against the destructive effects of ROS through scavenging them by enzymes defense system, or, by the antioxidant activities of the dietary compounds. Several studies concluded that polyunsaturated fatty acids are the most vulnerable to free radical attacks and the initial products of lipid peroxidation are conjugated dienic hydroperoxides. Although ROS production is difficult to measure in biological tissues, there are various indirect manifestations of oxidative stress, including lipid peroxidation, DNA oxidation, protein oxidation, and a shift in the redox states of thiol/disulfide redox couples. The lipid peroxidation and appearance of lipid free radicals and malondialdehyde (MDA) in the blood and gastric juice could result from ROS-initiated chain reactions or initiated by indirect mechanisms that suppress the antioxidant capacity in both blood and gastric wall to scavenge ROS. The fundamental primary product is lipid hydroperoxides, which are capable of initiating lipid peroxidation chain reaction and decompose giving rise to secondary oxidation products including: aldehydes, hydrocarbons, acids, ketones and higher polymers. Among these, is MDA that is mutagenic and carcinogenic, and its reaction with thiobarbituric acid is marker for lipid peroxidation as thiobarbituric acid reactive substances. Identifying lipid peroxidation, as the mediator of acute injury is complicated since MDA, the major component of TBARS undergoes

rapid further metabolism. Therefore, it was reported that the use of TBARS is not adequate due to its low sensitivity and interferences with several other substances (Dotan et al., 2004).

2. 4- Incidence of apoptosis

Apoptosis was initially defined by Kerr et al. (1972) who suggested that cells dying in this process goes through defined morphological changes that involve chromatin condensation, cytoplasmic and nuclear blebbing, and eventual cellular demise without loss of membrane integrity (Kerr et al., 1972). Its investigation requires specific parameters including the executer caspase-3 shown to be a key component involved in the underlying mechanisms of apoptosis and relies on the action of the initiator caspases including caspase-8 and caspase-9 for its action (Raffray and Cohen, 1997;Cohen, 1997). These investigations include also the intra-nucleosomal DNA fragmentation as a gold-standard for the process previously reported in gastric ulceration (Xia et al., 1999;Salvesen and Dixit, 1999). Caspase-3 has a central role in this cascade, and is known to activate cytoplasmic DNase, which subsequently migrates to the nucleus and fragments the DNA. Therefore, DNA fragmentation - particularly when it is inter-nucleosomal is one of the gold standards for detection of apoptosis (Goel et al., 2003;Bhattacharya et al., 2006). Under normal physiological conditions, the balance between gastric epithelial cell proliferation and death is of great importance in maintaining gastric mucosal integrity. Since, the balance between cell apoptosis and cell proliferation has important role to keep the gastric mucosa healthy (Kalia et al., 2000). Since, the gastric epithelial cells proliferate in the lower part of the glandular neck and migrate up the crypt towards the surface and then are shed into the lumen by apoptosis (Ohkura et al., 2003). Disturbance of this balance could result in either cell loss, leading to mucosal damage and ulcer formation, or cell accumulation, leading to cancer development (Kohda et al., 1999)..

2. 5. Non-steroidal anti-inflammatory drugs

NSAID-induced ulcers develop in achlorhydric individuals, has contributed to a widely held belief that acid is not involved in the pathogenesis of these lesions (Wallace, 2000). Thus, the prevention of NSAID-related gastropathy is an important clinical issue, and therapeutic strategies for both the primary and secondary prevention of adverse events are continually evolving (Schlansky and Hwang, 2009). Further reinforcing for this hypothesis, their are several studies demonstrating that treatment with histamine H_2-receptor antagonists did not reduce the incidence of NSAID-induced ulceration (Agrawal, 1995). Furthermore, NSAID-induced gastropathy is an intricate process involving gastric mucus depletion, increased microvascular permeability, nitric oxide imbalance, as well as free radical production (Abdallah, 2010). Several studies have demonstrated that H_2-antagonists and proton pump inhibitors can prevent NSAID-induced gastric lesions but not the formation of the clinically more significant ulcers as well as ulcer complications. Recently it has reported that a high dose of famotidine (40 mg twice daily) was effective in preventing NSAID-induced ulcers (Taha et al., 1999). Omeprazole could significantly reduce the incidence of NSAID-induced ulceration. A profound suppression of acid secretion whether by omeprazole or by a high dose of famotidine was necessary in order to

have a significant impact on the incidence of NSAID-induced ulcers. Furthermore, acid may contribute to NSAID-induced ulcer formation in several ways. First, acid can exacerbate damage to the gastric mucosa induced by other agents, e.g., acid can convert regions of ethanol-induced vascular congestion in the mucosa to actively bleeding erosions (Wallace, 2005). Second, acid will contribute to ulcer formation by interfering with haemostasis, for instance, platelet aggregation is inhibited at a pH of less than 4 (Green, Jr. et al., 1978). Third, acid can convert superficial injury to deeper mucosal necrosis by interfering with the process of restitution. Fourth, acid can inactivate several growth factors (e.g., fibroblast growth factor) that are important for the maintenance of mucosal integrity and for the repair of superficial injury, since these growth factors are acid-labile (Szabo et al., 1994). So the inhibition of their synthesis by NSAIDs can result in an increase in gastric acid secretion (Ligumsky et al., 1983). For these reasons, NSAIDs are still more dangerous due to the higher base-line risk of ulcer complications. In support of this argument, the size of risk for ulcer complications in patients who have a suitability for ulceration rises to approximately 12-fold when compared to patients unexposed to NSAIDs and with no ulcer history (Aalykke and Lauritsen, 2001). Since, the corresponding annual risk of hospitalization of ulcer complications in patients with a history of peptic ulcer also using NSAIDs has been estimated to be about 6±7%. On the other hand, PPIs have long been suggested to reduce the incidence of serious gastrointestinal complications during NSAID use. A study by Pilotto et al. (2004) added further support for this notion, since, the use of PPIs was associated with a significant reduction in the risk of ulcer in both acute and chronic users of NSAIDs (Pilotto et al., 2004). Aspirin is the most popular and effective pain killer and antipyretic, it has antiinflammatory action, which may be mediated by inhibition of the prostaglandin synthetase enzyme complex. Additionally, it inhibits platelets aggregation in minimal dose, so it has been used in various thromboembolic diseases to reduce recurrent transient ischemic attacks of the brain and it has also beneficial effects in prevention of myocardial infraction. The combination of low-dose aspirin for cardiovascular protection, plus a PPI for gastroprotection, resulted in a low rate of ulcer bleeding (Wallace, 2005). At high doses aspirin in the acidic environment of gastric juice become un-ionized and freely penetrate the mucosal barrier reaching to gastric wall. Due to the weak basic nature of cytoplasm of gastric mucosal cells, aspirin could accumulate at high concentrations into mucosal cells, and yields a negatively charged anion that is unable to exit the cell. Thus, superficial or deeper erosions are produced and bleeding takes place, within minutes. Although adverse effects of nonsteroidal anti-inflammatory drugs occur in only a small proportion of users, the widespread use of these drugs has resulted in a substantial overall number of affected persons who experience serious gastrointestinal complications (Lazzaroni et al., 2007). It is now well established that the point prevalence of peptic ulcer disease in patients receiving conventional nonsteroidal anti-inflammatory drug therapy ranges between 10 and 30%, representing a 10- to 30-fold increase over that found in the general population. One out of 175 users of conventional nonsteroidal anti-inflammatory drugs in the USA will be hospitalized each year for nonsteroidal anti-inflammatory drug-induced gastrointestinal damage. The mortality of hospitalized patients remains about 5-10%, with an expected annual death rate of 0.08%. The selective COX-2 inhibitors consistently show comparable efficacy to that of conventional nonsteroidal anti-inflammatory drugs in patients with rheumatoid arthritis and osteoarthritis, but have a reduced

propensity to cause gastrointestinal toxicity. In many cases, the gastric effects of therapeutically active doses of COX-2 inhibitors are indistinguishable from placebo. The safety benefits of COX-2 inhibitors given alone appear similar to those of combined therapy with conventional nonsteroidal anti-inflammatory drugs and gastroprotective agents. These findings warrant the consideration of COX-2 inhibitors as first-line therapy in patients requiring long-term pain control (Lazzaroni et al., 2007). In this context, Michiel W et al (2009) have been compared hospitalization rates for serious upper and lower gastrointestinal (GI) events between chronic and acute users of a traditional non-steroidal anti-inflammatory drugs (tNSAID) proton pump inhibitor (PPI) and users of a COX-2 selective inhibitor (Coxib). The cohort in this study included 23 999 new tNSAIDs + PPI users and 25 977 new Coxib users, with main characteristics: mean±SD age 58.1±15.5 vs. 56.7±17.5; female 55.3% vs. 62.2%; duration of treatment (days): 137±217 vs. 138±179, respectively. Among acute users, adjusted hazard ratios (95% Confidence Interval) were 0.21 (0.14–0.32) for upper and 0.26 (0.16–0.42) for lower GI events, for Coxib versus tNSAIDs + PPI users. Among chronic users, these were 0.35 (0.22–0.55) for upper GI and 0.43 (0.25–0.75) for lower GI events. Among all tNSAIDs users, Coxib users had significantly lower rates of GI events.

2. 6. Helicobacter pylori

The initial response to H. pylori infection is an interaction of the host epithelial cells with the bacteria (Correa, 1988) and had been reported to be implicated in various gastrointestinal diseases, such as gastric ulcer, adenocarcinoma and lymphoproliferative disorders (Uemura et al., 2001). However, the pathogenetic mechanisms of chronic infection with H. pylori and gastric ulcer are yet to be full determined (Rad et al., 2004). H. pylori-infected gastric mucosa showed infiltration of polymorphonuclear leukocytes, lymphocytes, monocytes and plasma cells in the lamina propria, and intraepithelial severe neutrophil infiltration (Fan et al., 1996). The later well documented to correlate mucosal damage due to the effects of various cytokines, free radicals, and monochloramine (Karttunen, 1991). Moreover, H. pylori-induced inflammation is implicated in the development of mucosal damage and is characterized by strong granulocytic and lymphocytic infiltration (Rad et al., 2004). These changes would accelerate apoptosis and proliferation in the mucosal layer (Ohkura et al., 2003). In addition, it had been reported that H. pylori infection induced a three-fold increase in the serum gastrin concentration but was without effect on the thickness of the oxyntic mucosa (Zhao et al., 2003). H. pylori infection is associated with low acid secretion in gastric cancer patients and with high gastric acid secretion in patients with duodenal ulcers (Calam et al., 1997b). Certain cytokines released in H. pylori gastritis, such as tumor necrosis factor alpha and specific products of H. pylori, such as ammonia, release gastrin from G cells and might be responsible. The infection also diminishes mucosal expression of somatostatin. Exposure of canine D cells to tumor necrosis factor alpha in vitro reproduces this effect. These changes in gastrin and somatostatin increase acid secretion and lead to duodenal ulceration. But the acid response depends on the state of the gastric corpus mucosa. The net effect of corpus gastritis is to decrease acid secretion. Specific products of H. pylori inhibit parietal cells. Also, interleukin 1 beta, which is overexpressed in H. pylori gastritis, inhibits both parietal cells and histamine release from

enterochromaffin-like cells. H. pylori also promotes gastric atrophy, leading to loss of parietal cells. Factors such as a high-salt diet and a lack of dietary antioxidants, which also increase corpus gastritis and atrophy, may protect against duodenal ulcers by decreasing acid output. However, the resulting increase of intragastric pH may predispose to gastric cancer by allowing other bacteria to persist and produce carcinogens in the stomach. (Calam et al., 1997a). H. pylori infection results in the increased secretion of pro-inflammatory cytokines such as IL-1α and IL-6 (Thomson et al., 2003), and IL-8 activity correlates with the histological severity in H. pylori-associated antral gastritis (Ando et al., 1996). Thus, the H. pylori infection causes chronic inflammation that results in the release of pro-inflammatory cytokines that may reduce acid secretion, and thereby appear to increase the antisecretory effect of omeprazole (Thomson et al., 2003). This inflammation resolves after eradication of the infection, and presumably the concentrations of the pro-inflammatory and antisecretory cytokines also fall. The aim of treatment is eradication of the bacterium, defined as negative tests for the organism for one month after completion of the course of the antimicrobial (Pakodi et al., 2000). An international working party recommended three therapeutic regimens. One is omeprazole and amoxycillin; the other two comprise bismuth, metronidazole and either tetracycline or amoxycillin (Tytgat, 1991). However, the most effective combination therapy to eradicate Helicobacter pylori has not yet been found (Sontag et al., 2001). De Francesco V et al. (2004) have been performed a prospective randomized study to evaluate whether the triple therapy prolongation may improve its effectiveness and comparing its outcome with that of sequential regimen (De, V et al., 2004). In the previous study, three hundred and forty-two H. pylori positive patients were subjected to the study. They were randomized to receive one of the following treatments: (i) a 7-day triple therapy comprising of rabeprazole (20 mg, b.i.d.) plus clarithromycin (500 mg, b.i.d.) and amoxycillin (1 g, b.i.d.); (ii) a 10-day triple therapy comprising the same scheme; (iii) a 10-day sequential regimen comprising of rabeprazole (20 mg, b.i.d.) plus amoxycillin (1 g, b.i.d.) for 5 days followed by rabeprazole (20 mg, b.i.d.) plus clarithromycin (500 mg, b.i.d.) and tinidazole (500 mg, b.i.d.) for the next 5 days. Sequential regimen showed a significant gain in the eradication rate as compared to the 7-day ($P < 0.0001$) and the 10-day ($P < 0.01$) triple therapies, respectively. Overall eradication was lower in smokers than in non-smokers, but the difference remained significant only in the 7-day triple therapy ($P < 0.01$). Additionally, the overall eradication was higher in peptic ulcer than dyspepsia ($P < 0.01$), even if this difference was significant only for both triple therapies. The authors concluded that Seven-day triple therapy achieves disappointing eradication rates in dyspeptics and smokers. Prolonging triple therapy to 10 days does not significantly improve the eradication rate. The novel 10-day sequential regimen is more effective and equally tolerated than the 10-day triple therapy.

2. 7. Bile acids

It is established that primary bile acids constitute 90% of the total bile acid pool, while cholic acid makes up about 50% of the total and 60% of glycine-conjugated bile acids (Oktar et al., 2001). Bile acids have strong preventive effect against the overgrowth of intraluminal bacteria (Auer et al., 1983;Masclee et al., 1989). Since, the exogenous bile acid in bile duct ligated rats has attenuated the severity of colonic damage and reduced neutrophil

accumulation in a similar manner as in the ileitis model (Oktar et al., 2001). Interleuki-1, interleukin-6, and tumor necrosis factor–α can inhibit the production of bile acids (Calmus et al., 1992). However, blockage of normal bile flow also had an ameliorating effect on colonic neutrophil infiltration. Bile salts are known to destroy the permeability barrier of gastric mucosa, since, bile salts not only increase mucosal permeability to acid but also produce direct injury to the surface cells of the stomach and render the gastric mucosa more susceptible to acid injury (Min et al., 2005). In the contrary, withdrawal of bile flow, either by inhibiting the enterohepatic circulation mechanism or by removing the cytotoxic constituents of the bile, ameliorates the mucosal injuries of the stomach, intestine or colon (Oktar et al., 2001). There are four different bile acids; taurocholic acid (TCA), taurodeoxycholic acid (TDCA), taurochenodeoxycholic acid (TCDCA) and tauroursodeoxycholic acid (TUDCA). Bile acids are synthesis in the liver by a multistep, multi-organelle pathway in which hydroxyl groups are inserted at specific positions on the steroid structure, the double bond of the cholesterol B ring is reduced and the hydrocarbon chain is shortened by three carbons, introducing a carboxyl group at the end chain. The most common resulting compounds, cholic acid and chenodeoxy-cholic acid, and before the bile acids leave the liver, they are conjugated to a molecule of either glycine or taurine by an amide bond between the carboxyl group of the bile acid and the amino group of the added compound. These new structure are called bile salts. Unconjugated bile acids are suspected to induce damage on the gastric mucosa. The mechanism for the presence of unconjugated bile acid in the serum after infusion of taurine conjugated bile acid is unknown. High serum level of bile acids may diffuse though intestinal mucosa to the lumen in the obstructive cholestasis (Yohei Fukumoto et al., 1999), UDCA and TUDCA have been suggested to have a protective effect on hepatocyte structure and function and UDCA treatment for patients with chronic cholestatic liver disease has been reported to improve clinical and biological manifestations (Thibault and Ballet, 1993;Hillaire et al., 1995). Increased serum bile acids due to common bile duct ligation were the primary bile acid of cholic acid and the secondary bile acid of deoxycholic acid (Yohei Fukumoto et al., 1999). As cholic acid is a main serum bile acid in animals, levels of the cholic acid group were considered to be increased in peripheral blood by obstruction of bile flow. Patient that has liver cirrhosis demonstrate high rates of either gastric or duodenal mucosal lesions and potential cytotoxic bile acids are accumulated in their peripheral blood (Fischer et al., 1996). In cases of portal hypertension, an increase of gastric blood flow with morphologic changes of dilated microvessels in the gastric mucosa was observed (Calatayud et al., 2001). Regarding the relationship between gastric ulcer and bile salts, the direct detergent effect of bile salts to mucosa due to bile regurgitation from the duodenum to the stomach is presumed (Yohei Fukumoto et al., 1999). The resistance of gastric mucosa to damage has also been observed after exposure to low levels of deoxycholic or glycodeoxycholic acid by stimulation of glycoprotein secretion in cultured rabbit gastric mucosal cells.

3. Part B. Strategies for prevention/healing

3. 1. Gastroprotective effects of Nitric Oxide

Initially, nitric oxide (NO) is recognized as a mediator in a broad array of biologic system and it is the endothelium-derived relaxing factor, which caused vasodiluation by relaxing vascular smooth muscle. Additionally it acts as a neurotransmitter, prevents platelet aggregation, and plays an important role in macrophage function. The events related to the gastroprotective effects of nitric oxide include a reduction in acid secretion (Takeuchi et al., 1995) and promotion of angiogenesis (Ma and Wallace, 2000). Gastroprotective effects of nitric oxide may be due to it is rapid reactivity with various oxygen species in the biologic system. Hence, NO has a very short half-life in tissue (three to ten seconds) because it reacts with oxygen and superoxide, and then is converted into nitrates and nitrites. That also causes additional decrease in acid secretion. H. pylori infection may induce nitric oxide (NO) synthase expression and NO release (Mannick et al., 1996), which in turn may inhibit acid secretion and unmask luminal alkalinization caused by bicarbonate leakage from the plasma into the gastric juice (Takeuchi et al., 1995;Thomson et al., 2003). The development of nitric oxide releasing nonsteroidal anti-inflammatory drugs has shown that even nonselective cyclooxygenase inhibitors exerted no deleterious effects on gastric mucosa (Takeuchi et al., 2001). Nitric oxide production in gastric mucosa and the substance(s) accountable for this effect are still to be discovered. Nitric oxide inhibits gastric secretion by suppression of histamine release from enterochromaffin-like cells (Kato et al., 1998;Freitas et al., 2004). Clinical importance of nitric oxide (endogenous or exogenous) needs to be considered as possibilities for new therapeutic approaches (Freitas et al., 2004). Use of nitro-vasodilators in animal studies may reduce the NSAID-associated gastric damage, but nitric oxide may also inhibit platelet aggregation. The results from a large case-control study suggest that nitro-vasodilators are associated with a decreased risk of ulcer (Lanas et al., 2000). On the other hand, nitric oxide (NO) has well documented to has a marginal role against resistance and killing pathogenic bacteria, thus, it is a central component of innate immunity (Nathan and Shiloh, 2000). This antimicrobial activity is especially marked for intracellular pathogens such as Mycobacterium tuberculosis (Bekker et al., 2001) and Leishmania major (Vouldoukis et al., 1995), which are killed by an NO-dependent mechanism. Chemical sources of NO and peroxynitrite have a direct toxic effect on H. pylori (Dykhuizen et al., 1998;Kuwahara et al., 2000). Despite eliciting a vigorous immune response, Nuruddeen D et al. (2010) have been reported that macrophages cocultured with H. pylori have the ability to kill the bacterium by an NO-dependent mechanism (Lewis et al., 2010). However, this killing is incomplete in vitro, and, moreover, there is clearly a failure of this mechanism in vivo despite the expression of iNOS in the infected mucosa. The survival of H. pylori, despite marked induction of inducible NO synthase (iNOS) in the gastric tissues (Fu et al., 1999) and macrophages (Wilson et al., 1996), which confirmed that the bacterium has developed mechanisms to avoid NO-dependent killing. A study by Nuruddeen D et al. (2010) have been implicated arginase II (Arg2) in the immune evasion of H. pylori by causing intracellular depletion of L-arginine and thus reduction of NO-dependent bactericidal activity (Lewis et al., 2010). However, their are some indications that H. pylori can induce apoptosis of macrophages

by generation of polyamines from ornithine decarboxylase (ODC), which is dependent on c-Myc as a transcriptional enhancer. (Asim et al., 2010). Since, expression of c-Myc requires phosphorylation and nuclear translocation of extracellular signal regulated kinase (ERK), which results in phosphorylation of c-Fos and formation of a specific activator protein (AP)-1 complex (Shaulian and Karin, 2002). Therefore, a unique AP-1 complex in gastric macrophages may contribute to the immune escape of H. pylori (Asim et al., 2010).

3.2. Regeneration of gastric mucosa and the role of growth factors in ulcer healing

Growth factors are local polypeptide hormones that modulate the rate of cellular proliferation of their target cells carrying functional specific receptors. Chai et al. (2004) demonstrated that vascular endothelial growth factor (VEGF)-induced angiogenesis is dependent upon the presence of serum response factor (SRF) (Chai et al., 2004). SRF is a transcription factor that plays an important role in immediate early gene expression and embryonic development (Wallace, 2005). Inhibition of the activity of SRF, through injection of an antisense expression plasmid into gastric ulcers in rats, led to marked inhibition of angiogenesis in the ulcer bed (Wallace, 2005). VEGF is released by endothelial cells themselves, and by platelets. Indeed, release of VEGF is likely to be a primary mechanism through which platelets contribute to ulcer healing (Ma and Wallace, 2000;Wallace, 2005). In experimental models of acute gastric damage, the expression of VEGF increases during healing (Jones et al., 2001), while the pre-treatment of rats with a single dose of oral VEGF exerted a protective effect against acute ethanol damage in the gastric mucosa. Furthermore, the daily administration of VEGF has been found to promote the healing of cysteamine duodenal ulcer in rats by stimulation of angiogenesis and formation of granulation tissue (Szabo et al., 1998;Szabo et al., 2000). Since, expression of VEGF and its receptors has been demonstrated in the ulcer margin of human peptic ulcer disease (Takahashi et al., 1997). In support of this notion, Wozniak et al. (2009) have been determined the role of vascular endothelial growth factor (VEGF) administered intraperitoneally in the gastroprotective response to stress-induced acute gastric ulcers in rats. A dramatic increase in the number of blood vessels was observed when VEGF was injected 24 h before stress exposure. Gastric secretion, depth of ulceration and ulceration index decreased significantly after VEGF application. The results demonstrate the gastroprotective effect of VEGF on stress-induced ulceration (Wozniak-Holecka et al., 2009). Systemic administration of leptin to ob/ob mice was accompanied by an increase in VEGF expression and angiogenesis, and thus, reversed the impairment of gastric ulcer healing (Tanigawa et al., 2010). These data suggested that VEGF might play a dual role in mucosal protection and repair. On the one hand, it might improve mucosal resistance by an increase of vascular permeability that dilutes gastrotoxic agents and reduces the area of the hemorrhagic lesions. On the other hand, it might contribute to the development of the angiogenic response together with other growth factors. Thus, VEGF is a reparative factor for ulcerated gastric mucosa through maintaining endothelial cell viability, inducing their proliferation, chemotaxis and vascular permeability (Milani and Calabro, 2001). A high level of IL-8 and TNFα from the gastric epithelium as well as neutrophils and macrophages was observed in the inflamed gastric mucosa (Crabtree et al., 1993;Crabtree, 1996). Several studies have observed a positive

correlation between the density of H. pylori and the increase in IL-8, an interleukin having chemotactic and activating properties for neutrophils (Ando et al., 1996), and thus influencing the inflammatory scores. Moreover, proinflammatory cytokines cause a reduction of somatostatin and gastrin releases from the D and the G cells, respectively. IL-10 inhibits the synthesis of IFN-γ, IL-1, IL-6, IL-8 and TNF-α and may act as a feedback mechanism, which dampens down these cytokines (Andersen et al., 2005). Immunohistochemical analysis of the duodenal mucosa after administration of cysteamine revealed a decreased cytoplasmic bFGF immunostaining especially on the top of the villi, while the submucosa was not affected (Kusstatscher et al., 1995;Sandor et al., 1995). The elevated level of bFGF was at least partially the consequence of de novo protein synthesis. However, it seemed to be mainly the release of the growth factor from presyntethized pools (Szabo and Vincze, 2000). IL-6 was first recognized as a T-cell-derived factor acting on B-cells to induce immunoglobulin secretion, and acts on a wide variety of tissues (Kishimoto et al., 1992). One hand, IL-6 promotes the growth of myeloma/plasmacytoma/hybridoma cells, T-cells, keratinocytes, and renal mesangial cells. And, on the other hand, IL-6 transsignaling promotes caspase-3 mediated neutrophil apoptosis to resolve the neutrophil infiltrate (McLoughlin et al., 2003). The role of IL-6 has not completely understood yet in gastric ulcer arena, however, it has been widely established in several other diseases. TGF-α is released locally in the gastric mucosa, particularly when the mucosa is exposed to topical irritants. TGF-α includes the stimulation of the restitution and proliferation of mucosal cells, gastroprotection, vasodilatation, gastric adaptation to noxious substances, healing of acute and chronic lesions and inhibition of gastric acid secretion (Kobayashi et al., 1996). Kazumori et al. (2004) have been noticed that during the process of ulcer healing, expression of TGF-alpha mRNA was markedly augmented (Kazumori et al., 2004). TGF-α has been shown to share common receptor (EGFR) and to accelerate ulcer healing due to stimulation of cell proliferation (Konturek et al., 1997). Vongthavaravat et al. (2003) have concluded that: 1) TGF-α caused dose-dependent gastroprotection against ulceration, 2) TGF-α-mediates gastric mucosal protection is prevented by capsaicin-induced sensory denervation and, 3) stress-induced injury was associated with significant reduction in gastric content of TGF-α (Vongthavaravat et al., 2003).

3. 3. Proton pump inhibitors and Histamine blockers

Undoubtedly, the most effective suppressors of gastric acid secretion are the gastric H^+,K^+-ATPase (proton pump) inhibitors such as omeprazole or ranitidine. Proton pump inhibitors (PPIs) are the most potent acid suppressants available and are significantly more effective than histamine H_2 receptor antagonists (Fock et al., 2008). Acid pump inhibitors were found to accumulate in parietal cell secretory canaliculi resulting in an antisecretory effect that lasts much longer than that of H_2 receptor antagonists. Brzozowski et al. (2000) noticed that the suppression of gastric acid secretion by omeprazole or ranitidine prevents the progression of gastric erosions into ulcers, and the addition of exogenous acid restores the progression of the acute lesions into gastric ulcers, indicating that gastric acid plays a key role in ulcerogenesis induced by ischemia-reperfusion (Brzozowski et al., 2000). Similar to adults, PPIs are rapidly metabolized in children, with short elimination half-lives of around 1 hour (Litalien et al., 2005).

Furthermore, similar to that seen in adults, the absolute bioavailability of omeprazole increases with repeated dosing in children; this phenomenon is thought to be due to a combination of decreased first-pass elimination and reduced systemic clearance. Currently, there are several different proton pump inhibitors available for clinical use: omeprazole, lansoprazole, rabeprazol and pantoprazole. They are α-pyridyl-methyl-sulfinyl benzimidazoles with different substitutions on the pyridine or the benzimidazole groups. PPIs are "prodrugs" requiring activation in an acid environment (**fig 2).** These agents enter the parietal cells from the blood and, accumulate in the acidic secretory canaliculi of the parietal cell. They are the activated by a proton-catalized process resulting in the formation of a thiophilic sulfenamide or sulfenic acid. The later reacts covalently with the sulfhydryl group of cysteines o the extracellular domain of the H^+/K^+-ATPase. Binding to cysteine 813, in particular, is essential for the irreversible inhibition of acid production. PPIs are unstable at a low pH; therefore, the oral dosage forms ("delayed release") are supplied as enteric-coated granules or tablets that dissolve only at the alkaline proximal small intestinal pH to prevent degradation by acid in the esophagus and stomach. PPIs are rapidly absorbed; highly protein bound, Peak absorption occurs 3 to 4 hours after oral administration, and the plasma levels are undetectable by about 11 hours after a single dose of the drug where it is extensively metabolized in the liver by the cytochrome P450 system (particularly CYP2C19 and CYP3A4) (Ozawa, 2002). Their sulfated metabolites are excreted in the urine or feces. Their plasma half-lives are about 1 to 2 hours, but their durations of action are much longer. Gastric acid inhibition approaches 98% following omeprazole 30 mg daily for one week. Acid secretion resumes only after new pump molecules are inserted into the luminal membrane. Inhibition of this final common pathway of gastric acid secretion is able to abolish the secretory response to all known secretagogues. Omeprazole also selectively inhibits gastric mucosal carbonic anhydrase, which may contribute to its acid suppressive properties. The antisecretory effect of omeprazole results in an elevation of serum gastrin concentrations, which in humans appear to be related to the degree of acid suppression. The bioavailability of omeprazole increases with repeated doses up to about four days, probably as a result of increasing drug absorption as intragastric acidity decreases. Omeprazole is an effective agent in the treatment of peptic ulcer disease and reflux esophagitis. Omeprazole inhibits the hepatic microsomal P-450 monooxygenase system, and the plasma half-life of drugs metabolized by this route may be extended (Hoogerwerf and Pasricha, 2001).
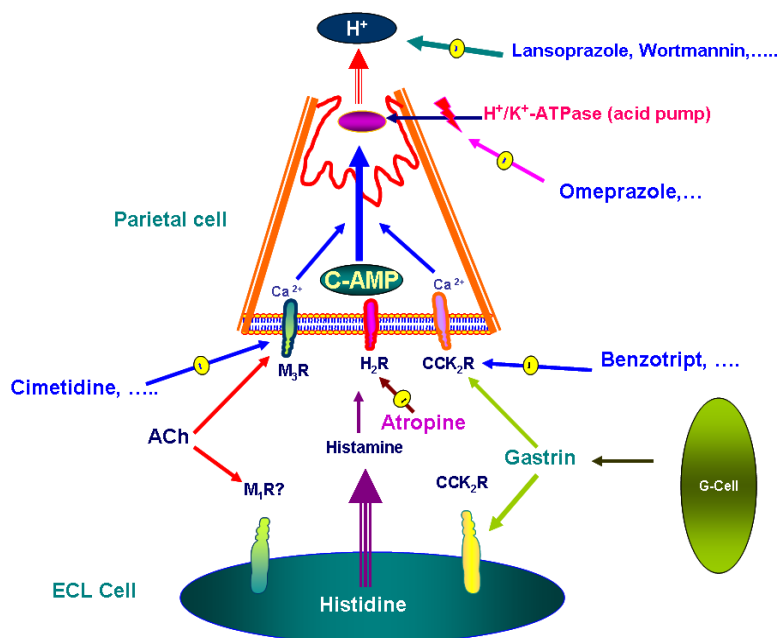
Figure 2: Schematic drawing of a parietal cell and the various targets for antisecretory drugs (in italics). ACh, acetylcholine; cAMP, cyclic AMP; ECL, enterochromaffin-like or mast cell; HDC, histidine decarboxylase. M_1R, acetylcholine M_1 receptor; CCK_2R, gastrin CCK_2 receptor; H_2R, histamine H_2 receptor

In fact, the antioxidant ability for PPIs is closely related to the present of sulfonamide group, which could react with hypochlorous acid (HOCI) (Harwood et al., 2008;Lissi et al., 2009), which is the most toxic and abundant oxidant generated by phagocytes. It is remarkable that protonated omeprazole can also bind-inactivate the prooxidant effects of both free iron and copper. Since omeprazole has inhibitory effects on neutrophil function, the final antioxidant potential of the drug may be result from 'direct' and 'indirect' antioxidant mechanisms (Lapenna et al., 1996). However, toxicologic studies in the rat in which massive doses of omeprazole have been used have shown markedly elevated gastrin levels associated with ECL-cell hyperplasia and gastric carcinoid tumors, which have been found after long-term treatment. Unfortunately, animal studies have indicated that long-term inhibition of gastric acid secretion increases circulating gastrin levels resulting in mucosal hyperplasia and carcinoid tumor development in rat gastric mucosa (Carlsson et al., 1990;Havu et al., 1990;Berlin, 1991;Mattsson et al., 1991;Sundler et al., 1991;Feurle, 1994;Gilligan et al., 1995;Hammer et al., 1998;Norsett et al., 2005).

3. 4. Curcuminoids

Curcumin, a yellow pigment obtained from the rhizomes of Curcuma longa (Family: Zingiberaceae) is a major component of turmeric and is commonly used as a spice and food colouring agent (Huang et al., 1994;Rukkumani et al., 2004). Curcuma longa, has been used in traditional remedy for a wide range of ailments, including wound healing, urinary tract infection, and liver ailments (Kim et al., 2005). Although, curcumin has been defined as the

most active component in C longa and has a considerable gastroprotective and antiulcerogenic effect, its antiulcer potential activity was recently confirmed and reviewed by our laboratory (Tuorkey and Karolin, 2009a). Various metabolites of curcumin have been reported, including dihydrocurcumin (DHC), tetrahydrocurcumin (THC), hexahydrocurcumin (HHC), octahydrocurcumin (OHC), curcumin glucuronide, and curcumin sulphate (Anand et al., 2008). Curcumin has been speculated to have promising chemotherapeutic and preventive activities, which could approve avenues for alternative treatments for many diseases. Recently, much attention has been directed to study the medical applications of curcumin in the treatment of human diseases. Since, curcumin has been shown to exhibit anti-tumor activity and apoptosis in many human cancer cell lines including that of lung and liver cancer (Huang et al., 2008), that is a side its prospective role as a potential immunomodulatory effector in vivo and in vitro studies (Churchill et al., 2000;Kurup et al., 2007;Varalakshmi et al., 2008). Currently, several clinical trails have been applied curcumin for treatment of pancreatic cancer (Swamy et al., 2008;Glienke et al., 2009), multiple myeloma (Milacic et al., 2008;Jiao et al., 2009), Alzheimer's (Wang et al., 2005;Kim et al., 2007), colorectal cancer (Half and Arber, 2009). Due to various effects of curcumin, such as decreased Beta-amyloid plaques, delayed degradation of neurons, metal-chelation, anti-inflammatory, antioxidant and decreased microglia formation, the overall memory in patients with Alzheimer's disease has improved (Mishra and Palanivelu, 2008). On the other hand, curcumin has a potent effect in the inhibition of matrix metalloproteinase (MMP-3) and MMP-13 gene expression by inhibiting the c-Jun-N terminal kinase (JNK), activation protein-1(AP-1), nuclear factor kappa B (NF-kB) pathways in human chondrocytes (Salahuddin A et al., 2005). Curcumin is also known to activate and regulated endritic cells, inhibit IL-1, IL-6, and TNF-α along with inhibition of NF-kB activation (Vojdani A and Erde J, 2006). Curcumin could prevent production of interleukin-8 (IL-8), monocyte inflammatory protein-1(MIP-1 α), monocyte chemotactic protein-1(MCP-1), IL-1β, tumornecrosis factor-α (TNF-α), 4-β-phorbor-12-β-myristate-13-α acetate (PMA) or lipopolysaccharide (LPS) stimulated monocytesand macrophages (Abe Y et al., 1999). The anti-ulcer activity of curcumin was displayed by attenuating the different ulcerative effectors including gastric acid hyper-secretion, total peroxides, myeloperoxiase (MPO) activity, IL-6 and apoptotic incidence, along with its inhibitory activity for pepsin (Mei et al., 2009). The antiulcer activities of curcumin arise from its antioxidant activity. Since, the antioxidant or scavenging reactive free radicals ability of curcumin arise whether from the phenolic OH group or from the CH_2 group of the β-diketone moiety. Since, reactive free radicals can undergo electron transfer or abstract H-atom from either of these two sites. Some studies attributed the antioxidant activity to the phenolic OH group (Kapoor and Priyadarsini, 2001), however, other studies indicated that hydrogen abstraction from the methylene CH_2 group is responsible for the remarkable antioxidant activity of curcumin (Jovanovic et al., 2001). By following the inhibition of styrene oxidation by a number of curcumin derivatives, Barclay et al. (2000) have been suggested that curcumin is a classical phenolic chain-breaking antioxidant, donating H atoms from the phenolic groups not the CH_2 (Barclay et al., 2000). A very important study as carried out with curcumin and dimethoxy curcumin (1,7-bis[3, 4-dimethoxy phenyl]-1,6-heptadiene-3,5-dione) to investigate the major function group in curcumin, the phenolic OH plays a major role in the activity of curcumin (Priyadarsini et al., 2003). Curcumin was found to be more active against COX-2

compared with COX-1 and exhibited potential inhibition of PGE_2 production with an IC_{50} value of 0.45 mM, compared with other curcuminoids demethoxycurcumin and bisdemethoxycurcumin. Inhibition of PGE_2 by curcuminoids is believed to be due to the inhibition of COX-2 expression. Curcumin at 1.3 mM (0.5 mg/mL) concentration caused more than 50% decrease in COX-2 expression, however, other curcuminoids did not cause any significant decrease in COX-2 expression even at 10 mg/mL concentrations. (Lantz et al., 2005). Despite curcumin is more effective for PGE_2 inhibition, its cytotoxic effect is not much different from other curcuminoids against these cell lines.(Khan and Lee, 2009). Surprisingly, curcumin showed immense therapeutic potential against H. pylori infection as it was highly effective in eradication of H. pylori from infected mice as well as in restoration of H. pylori-induced gastric damage. This study provides novel insights into the therapeutic effect of curcumin against H. pylori infection, suggesting its potential as an alternative therapy, and opens the way for further studies on identification of novel antimicrobial targets of curcumin (De et al., 2009).

3. 5. Copper complexes as antiulcer agents

The most effective suppressors of gastric acid secretion undoubtedly are the gastric H^+,K^+-ATPase (proton pump) inhibitors such as omeprazole. Nevertheless, several studies have indicated that long-term inhibition of gastric acid secretion increases circulating gastrin levels and this, in turn, results in mucosal hyperplasia and carcinoid tumor development (Ryberg et al., 1990). Therefore, several copper complexes were synthesized and investigated as promising alternative antiulcer therapy, since; they may be formed naturally in the body whenever appropriate proportions of copper and the organic ligands were established in the intestinal milieu. The hypothesized homeostasis of copper complexes was proposed by Sorenson (1989, **fig 3**) suggested their possible distribution by systemic circulation to all tissues to be: (**1**) utilized by tissues following ligand exchange with apoenzymes and apoproteins into metalloenzymes and metalloproteins, (**2**) stored in the liver following ligand exchange with thioneine to form copper-thioneine, or, (**3**) excreted in the event tissue needs have been met and stores replenished. Copper is mobilized from the liver in a complex form with ceruloplasmin, albumin and amino acids. These complexes rather than the ever existence of copper in their form, they facilitate copper absorption, tissue distribution and utilization (Robinson, 1987;Sorenson, 1989a). The anti-inflammatory action of copper complexes is an important activity of their antiulcer effect achieved by their intermediary role as a transport form of copper that allow activation of the several copper-dependent enzymes (Sorenson, 1989b;Shuff et al., 1992;Sorenson, 2002;Wangila et al., 2006). Dietary copper has a direct influence on the functional activity of lysyl oxidase responsible for the formation of lysine-derived cross-links in connective tissue collagen and elastin that is also essential for providing resistance to elastolysis and collagenolysis by non-specific proteinases (Rucker et al., 1998). Copper affect enzymes activity both as a cofactor and as a prosthetic component of several cuproenzymes controlling oxidation-reduction reactions including: cytochrome-c oxidase, superoxide dismutase (Babich et al., 2009;Broderius and Prohaska, 2009;Lalioti et al., 2009;Zadrozna et al., 2009;White et al., 2009). Sorenson pioneered the research on the antiulcer activity of copper complexes including the copper nicotinate (Sorenson, 1989a;Sorenson, 1989b;Sorenson, 2002;Zadrozna et al., 2009)
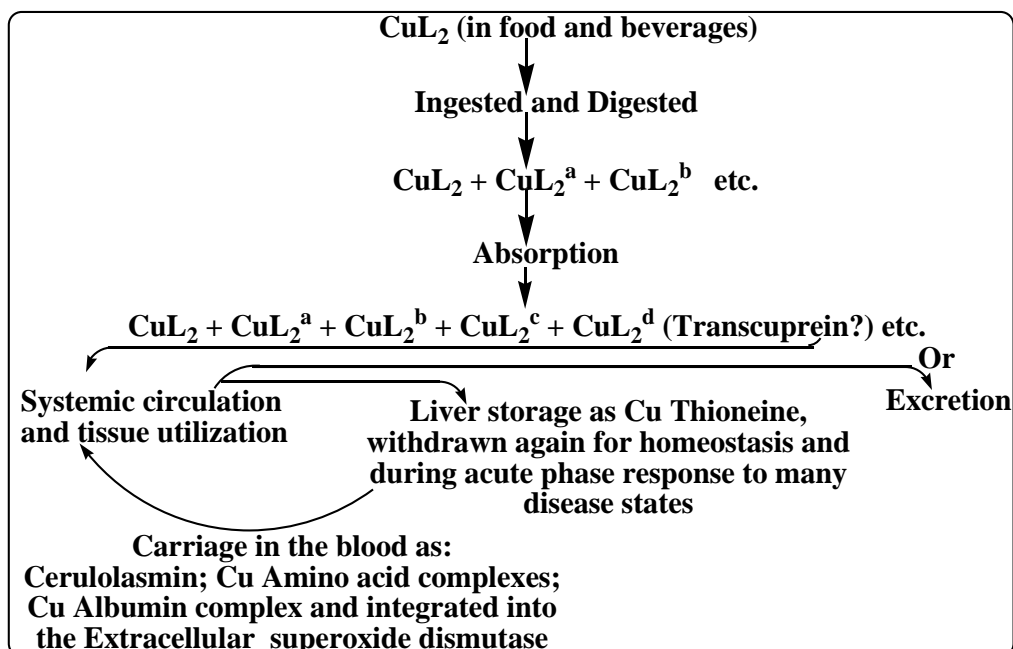
$$CuL_2 \text{ (in food and beverages)}$$

$$\downarrow$$

$$\text{Ingested and Digested}$$

$$\downarrow$$

$$CuL_2 + CuL_2^a + CuL_2^b \quad \text{etc.}$$

$$\downarrow$$

$$\text{Absorption}$$

$$\downarrow$$

$$CuL_2 + CuL_2^a + CuL_2^b + CuL_2^c + CuL_2^d \text{ (Transcuprein?) etc.}$$

**Or
Excretion**

**Systemic circulation
and tissue utilization**

**Liver storage as Cu Thioneine,
withdrawn again for homeostasis and
during acute phase response to many
disease states**

**Carriage in the blood as:
Cerulolasmin; Cu Amino acid complexes;
Cu Albumin complex and integrated into
the Extracellular superoxide dismutase**

Figure 3: Distribution of copper complexes following ingestion, digestion and absorption. L_2 is the original ligand and L_2^a, L_2^b, L_2^c, L_2^d, are new ligand exchange products (Modified from, Sorenson, 1989). (Sorenson, 1989a)

3. 6. Probiotics

Probiotics are live microorganisms, which could interact with the gastrointestinal upon administration (Brzozowski et al., 2006). They are widely used as functional foods, which have been advocated for the maintenance of gastrointestinal microflora equilibrium and treatment of gastrointestinal disorders (Lam et al., 2007). Probiotics are consisting of Saccharomyces boulardii yeast or lactic acid bacteria.e.g. Lactobacillus and Bifidobacterium species (Williams, 2010). The importance of using protmics came from their abilities to eradicate H. pylori and their notable role in the exaggeration the effect of multiple antibiotic regimens used for the H. pylori infection. In this concern, it is important to highlight promising data obtained with sulforaphane an isothiocyanate abundant as its glucosinolate precursor in certain varieties of broccoli and broccoli sprouts (Fahey et al., 2002). This compound specifically enriched in broccoli sprouts, inhibits extracellular, intracellular and antibiotic-resistant strains of H. pylori and prevents benzopyrene-induced gastric tumors (Fahey et al., 2002;Penner et al., 2005). furthermore, the yeast and lactobacilli found in yoghurt form a hardy symbiotic culture and that the organisms secrete soluble factors like some organic by-products of fermentation capable of killing H. pylori (Oh et al., 2002). Probiotic lactic acid bacteria offer one approach of stimulating the gastrointestinal immune system (Brzozowski et al., 2006). This last effect appears to be mediated via regulatory T-cell activation by intestinal dendritic cells and the low activation of T-helper 1 and 2 (Th1 and Th2) cell inflammatory responses (Gomez-Llorente et al., 2010).

Probiotics may modulate the intestinal immune response through the stimulation of certain cytokine and IgA secretion in intestinal mucosa, and this effect is depend on the strain used (Ohashi and Ushida, 2009). They also could induce a specific stimulation of natural killer cells (NK) and the innate immune system including the defensins and IL-10 (Brzozowski et al., 2006). A short cohort study was carried out to investigate the effects of the probiotic bifiform on efficacy of H. pylori eradication in patients with chronic gastritis and ulcer disease (Iakovenko et al., 2006). A total of 98 patients with verified H. pylori infection were divided into two groups. The studied group received a week three-component anti- H. pylori therapy plus a probiotic; the control group received the same treatment without the probiotic. All the patients were tested for H. pylori before the treatment and one month after the end of the treatment. The results of this study revealed that H. pylori eradication rate in the probiotic treated group was higher than in the control group (89.1 vs 63.5, respectively, $p < 0.05$). After the treatment, patients of the study group had lower rates of side effects, impaired intestinal biocenosis, tissue cytokines levels but higher concentration of plasmatic cells in CO and cIgA in coprofiltrates. The study recommended the addition of probiotic bifiform to the standard three-component antihelicobacter scheme of the treatment raises its efficacy and is promising treatment of H. pylori. A study by Brzozowski T et al. (2006), have compared the effects of intragastric inoculation of gerbils with H. pylori strain (cagA+ vacA+, $5x10^6$ colony forming units/ml) with or without triple therapy including omeprazole, amoxicillin, and tinidazol or probiotic bacteria Lacidofil (Brzozowski et al., 2006). Surprisingly, results of this study indicated that the basal gastric acid was significantly reduced in H. pylori-infected animals but not in those with triple therapy or Lacidofil. Furthermore, gastric blood flow and gastrin-somatostatin link were reversed by anti-H. pylori triple therapy and attenuated by probiotics.
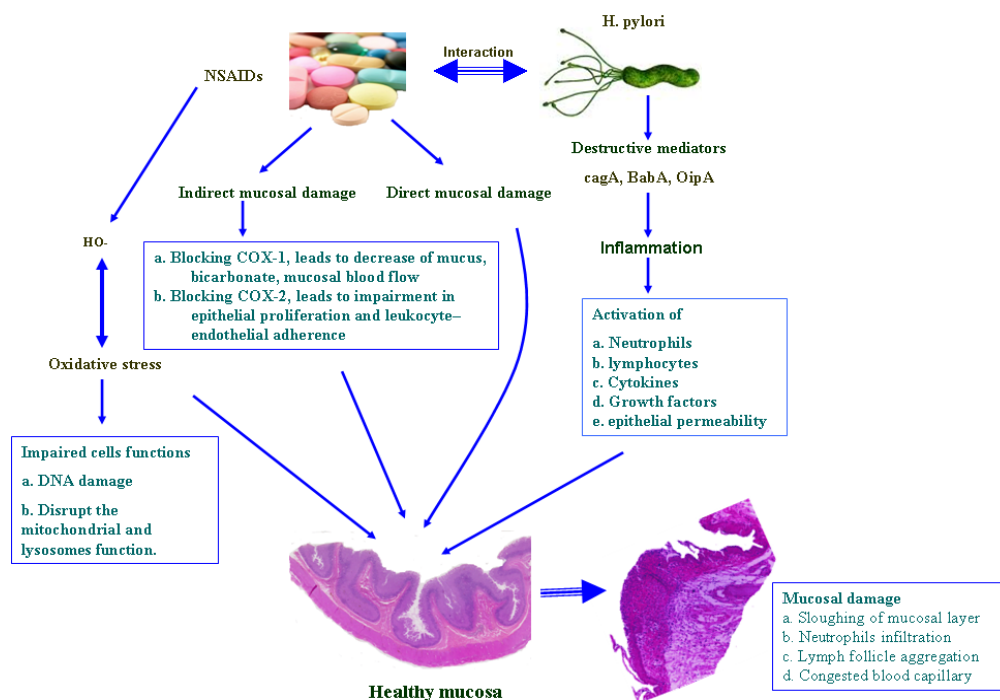
Figure 4: The possible mechanisms for gastric ulcer induction by the main ulcerogenic effectors, implementing infection with *Helicobacter pylori* use of nonsteroidal anti-inflammatory drugs (NSAIDs) and oxidative stress whatever exogenous or endogenous.

CONCLUSION

Gastric ulcer occurs due to imbalance between cytoprotectant and ulcerogenic effectors in the stomach wall. The main destructive effect for NSAIDs is due to blocking cyclooxygenase I and II. Since, gastro-duodenal mucosal prostaglandins (PGs) generated from COX-1 and COX-2 play a critical role in defense mechanisms and in repair processes including in blood flow, bicarbonate, and mucus secretion and in the ability of the damaged mucosa to repair itself. In this concern, Wallace (2005) has been summarized the roles of COX-1 and COX-2 in gastric mucosal defense (Wallace, 2005). Since, PGs from COX-1 mediate mucus and bicarbonate secretion and mucosal blood flow, those from COX-2 play a role in regulating epithelial proliferation and leukocyte–endothelial adherence. While, PGs derived from COX-1 appear to downregulate expression, and possibly activity of COX-2. For instance, when COX-2 is acetylated by aspirin, it produces 'aspirin-triggered lipoxin" ATL, which can inhibit leukocyte-endothelial adherence and thereby counteract the pro-adhesive effects of aspirin. That in turn, prevents or reduces the extent of gastric damage that would otherwise be caused by aspirin. In the contrast, when a COX-2 inhibitor is administered together with aspirin, ATL formation is inhibited and much greater levels of gastric damage are seen. Prostaglandins play an important role in mucosal defense by maintaining sulfhydryl groups, which act as oxidative scavengers. The basic aluminum salt of the sulfated disaccharide sucralfate enhances mucosal defense, possibly by providing a protective barrier at the ulcer base, inhibiting the action of pepsin and bile, and blocking the back-diffusion of acid, as well as increasing mucosal prostaglandins. Based on increased understanding of the precise mechanisms of gastric acid secretion at the level of receptors, enzymes, and cytoplasmic signal transduction systems, further possibilities exist for the development of effective antisecretory pharmacotherapy. On the other hand, the gastric mucosal barrier can also be directly damaged by some bacterial toxic enzymes. Bacterial virulence factors such as cag pathogenicity island (cagA), outer inflammatory protein (OipA) and blood-group antigenbinding adhesin (BabA) are associated with strains that cause increased mucosal inflammation (Hong Lu and David Y.Graham, 2006). Immunological processes characterized by mucosal infiltration of neutrophils and lymphocytes, cytokines production and alteration of epithelial permeability also contribute to the pathogenesis of peptic ulcer disease. Nitric oxide production in gastric mucosa as a response to H. pylori infection and its relationship with various cytokines and growth factors are still to be discovered. Although the cytoprotectant role of cytokines and growth factors in this process is not well understood, they have been established in therapeutic investigation in the present era. Acid pump inhibitors and histamine blockers, copper complexes and curcumin along with probiotics should be undertaken as early as possible to Prevnt the occurrence of irreversible gastric damage.

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