We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



24

Prevention of Gastric Ulcers

Mohamed Morsy and Azza El-Sheikh
Pharmacology Department, Minia University
Egypt

1. Introduction

Upper gastrointestinal tract integrity is dependent upon the delicate balance between naturally occurring protective factors as mucus or prostaglandins and damaging factors as hydrochloric acid present normally in the digestive juices. An imbalance causes peptic ulcer formation and destruction of gastrointestinal tract mucosal lining. Ulcer may develop in the esophagus, stomach, duodenum or other areas of elementary canal. In women, gastric ulcers are more common than duodenal ulcers, while in men the opposite is true.

The ulcer irritates surrounding nerves and causes a considerable amount of pain. Obstruction of the gastrointestinal tract may occur as a result of spasm or edema in the affected area. The ulcer may also cause the erosion of major blood vessels leading to hemorrhage, hematemesis and/or melena. Deep erosion of the wall of the stomach or the intestine may cause perforation and peritonitis, which is a life-threatening condition needing emergency intervention. Duodenal ulcers are almost always benign but stomach ulcers may turn malignant. Although mortality rates of peptic ulcer are low, the high prevalence of the disease, the accompanying pain and its complications are very costly.

The ongoing rapidly expanding research in this field provides evidence suggesting that, with therapeutic and dietetic advances, gastric ulcer may become preventable within the next decade. This could be achieved by strengthening the defense mechanisms of the gastric mucosa and, in parallel, limiting the aggression of predisposing factors causing gastric ulceration. The defenses of the gastric mucosa are incredibly efficient under normal mechanical, thermal or chemical conditions. These defenses can endure insults from food, gastric enzymes and acid secretion. Even trauma caused by a biopsy wound is dealt with and can heal relatively fast, within hours.

However, under certain condition, some risk factors may contribute to mucosal injury and initiation of gastric ulcer, as psychological stress, increased hydrochloric acid secretion, Zollinger Ellison syndrome and family history of gastric ulcer. Conditions associated with increased risk of gastric ulcer include also chronic disorders as liver cirrhosis, chronic obstructive pulmonary disease, renal failure, organ transplantation and rheumatoid arthritis. In addition, severe physical stress as in case of burns, major surgery or head trauma may also contribute as risk factors.

Avoidable risk factors that may predispose to gastric ulcer include smoking, high consumption of alcohol and intake of some medications as non-steroidal anti-inflammatory drugs. Some factors are thought to aggravate already established gastric ulcer, but are no longer considered risk factors predisposing to it, as ingestion of too hot or cold foods or drinks, eating spicy food and intake of caffeine. The key cause of gastric ulcer is now known

to be the infection by a certain gram negative bacterium called Helicobacter pylori. Although the mechanism by which the infection by this bacterium leads to ulcer formation is not yet fully understood, it is believed that infection decreases the normal immunity of the gastrointestinal tract wall, which in turn weakens the mucosa and makes it vulnerable to ulceration under the acidic effect of gastric secretions.

Avoiding risk factors is the first line in prevention of gastric ulcer. Smoking cessation and alcoholic consumption minimization may help in reducing the risk of ulcer formation. In addition, sanitary food and drinking habits to avoid infection with Helicobacter pylori may help in ameliorating the initiation of gastric ulcer and its recurrence. Therapeutic interventions to eradicate Helicobacter pylori can also prevent ulcer formation and its transformation into gastric cancer, one of the major complications of chronic gastric ulcer. Avoiding unnecessary intake of ulcer-inducing over-the-counter medications may help in reducing the prevalence of gastric ulcers.

Active therapeutic measures can aid in preventing gastric ulcers in predisposed groups and in patients with healed gastric ulcer to avoid its recurrence. Such therapeutic interventions may be of natural herbal sources or medicinal drugs. A number of traditional anti-ulcer drugs may be used in prevention as well as in treatment of gastric ulcer. Proton pump inhibitors, histamine H_2 receptor antagonists and mucosal protective agents can thus all be used as protective drugs against initiation of gastric ulcer in predisposed groups as well as prevention of remittent attacks. Recent investigations showed that a number of drugs, other than traditional anti-ulcer medications, can help in prevention of gastric ulcer formation. Herbal compounds can also protect against gastric ulcer and they have the advantage of being safer, cheaper and usually having limited, if any, side effects.

In this chapter, a collection of updated recent information published about gastric ulcer protection is gathered. Information in this chapter can be considered as guidelines for clinical practice to direct medical personnel perception to preferred approaches to prevent gastric ulcer as established by scientifically valid research. Making such information available may also increase public awareness of preventive means of gastric ulcer, which may aid in decreasing the suffering of a large number of populations exposed to the disease worldwide.

2. Avoidance of gastric ulcer risk factors

The best and cheapest method to prevent gastric ulceration is the avoidance of risk factors resulting in the occurrence of the disease. Avoiding Helicobacter pylori infection, alternation of life style and substitution of ulcer-inducing medications with less harmful drugs can thus contribute largely to prevent gastric ulcer disease (Fig. 1). Unfortunately, some risk factors are unavoidable. One of the strongest risk factors for initiation of a gastric ulcer is the presence of prior ulcer disease with history of ulcer complications as previous perforation or hemorrhage.

Zollinger-Ellison Syndrome is another unavoidable cause of gastric ulceration. In this syndrome, tumors producing gastrin hormone (gastrinomas) in the pancreas and duodenum stimulate gastric acid secretion. The large amounts of excess acid produced cause gastro-intestinal ulceration. Ulcers may form in the stomach, duodenum, jejunum or other atypical sites in the elementary tract. The incidence of this disease is less than 1% and men are more affected than women. The syndrome is suspected in patients with ulcers who are not infected with Helicobacter pylori and who have no history of non-steroidal anti-inflammatory drugs use. Diagnosis is confirmed by measurement of serum gastrin hormone

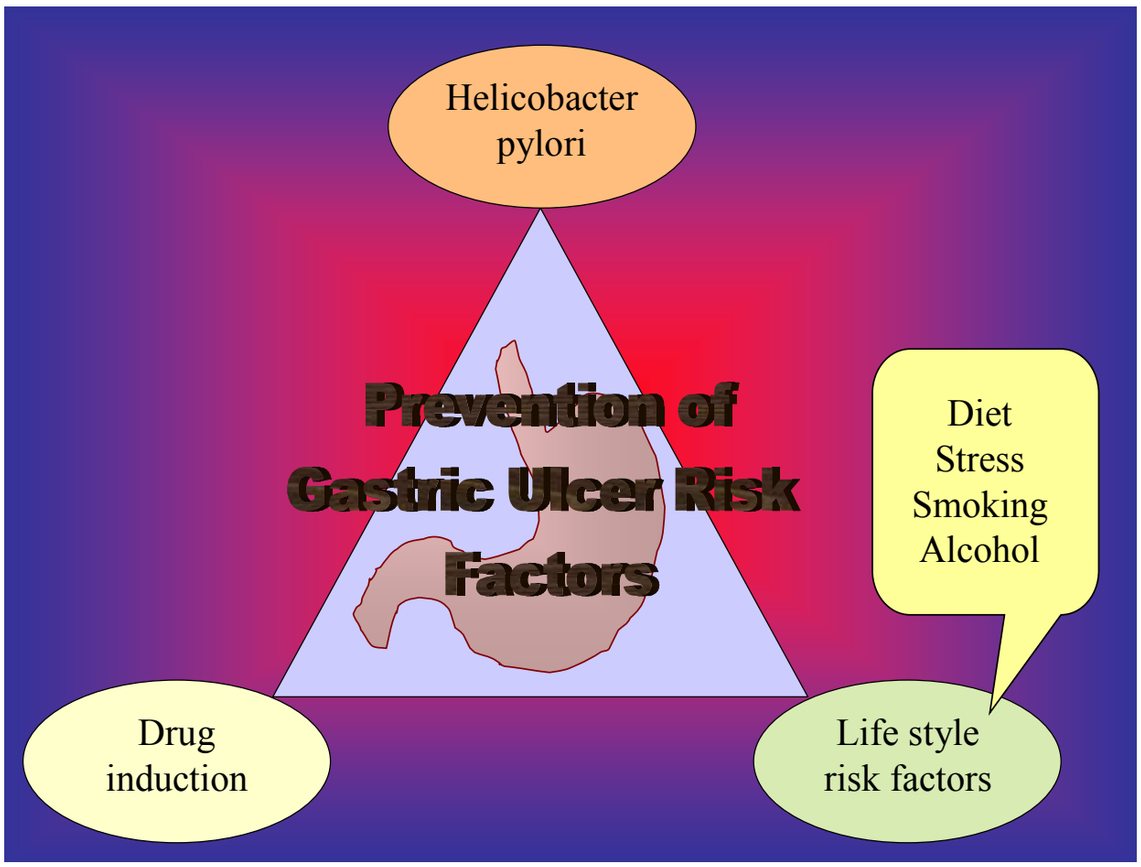


Fig. 1. Methods of prevention of gastric ulcer: Avoiding risk factors as Helicobacter pylori, drug-induced ulcer by medications as non-steroidal anti-inflammatory drugs and performance of life style changes.

levels which is usually very high, reaching above 1000 pg/ml (normal level is < 100 pg/ml). Diarrhea may occur before ulcer symptoms. Gastro-esophageal reflux disease may occur and its complications may include narrowing due to strictures of the esophagus. Ulcers associated with this syndrome are usually persistent and difficult to treat. In the past, removing the stomach was the only option for treatment. Nowadays, treatment includes removing the tumors only and therapeutic suppression of acid secretion.

Other unavoidable factors associated with higher incidence of gastric ulcer include sex, as there is higher prevalence of the disease among women then men. People over age 60 years old are also more prone to gastric ulcer disease. In addition, ethnic backgrounds as African-Americans or Hispanics have 2-fold higher risk in developing gastric ulcer. Furthermore, patients suffering from other diseases as congestive heart failure have higher incidence of having gastric ulcer as well. Type O blood group has also been associated with increased incidence of the disease. Genetics is another unavoidable risk factor of gastric ulcer. Pepsinogen C gene polymorphism, for example, is significantly associated with development of gastric ulcer (Sun et al., 2009). Other relatively rarer predisposing factors to development of gastric ulcer includes Crohn's disease of the stomach, eosinophilic gastritis, systemic mastocytosis, radiation damage and viral infections by cytomegalovirus or herpes simplex (Malfertheiner et al., 2009).

2.1 Helicobacter pylori as a risk factor for gastric ulcer

Infection with Helicobacter pylori is the most well-defined risk factor for the development of peptic ulcers. The two Australian scientists who identified Helicobacter pylori as the main cause of stomach ulcers in 1982 were awarded the Nobel Prize in Medicine in 2005 for this discovery. Helicobacter pylori bacteria are found in about 50% of people with gastric ulcer disease. Inflammation of the stomach and stomach ulcers result from the infection by these bacteria, as their corkscrew shape enables them to penetrate the mucus layer of the stomach so that they can attach themselves to the lining. The surfaces of the cells lining the stomach contain a protein, called decay-accelerating factor, which acts as a receptor for the bacterium. Helicobacter pylori can survive in the highly acidic medium of the stomach by producing urease, an enzyme that generates ammonia to neutralize the acid. These bacteria then produce a number of toxins causing inflammation and damage to the stomach, leading to ulcers especially in predisposed individuals. The bacteria also alter certain immune factors that allow them to evade detection by the immune system and cause persistent inflammation. Even if ulcers do not develop, the bacterium is considered to be a major cause of active chronic inflammation in the stomach (gastritis). Helicobacter pylori together with unavoidable risk factors as genetics and concomitant diseases may contribute in gastric ulcer formation and the subsequent metaplasia and dysplasia leading to gastric cancer (Fig. 2). Avoidance of risk factors, therapeutic intervention and some protective herbs can be employed to prevent the initiation of this sequence.

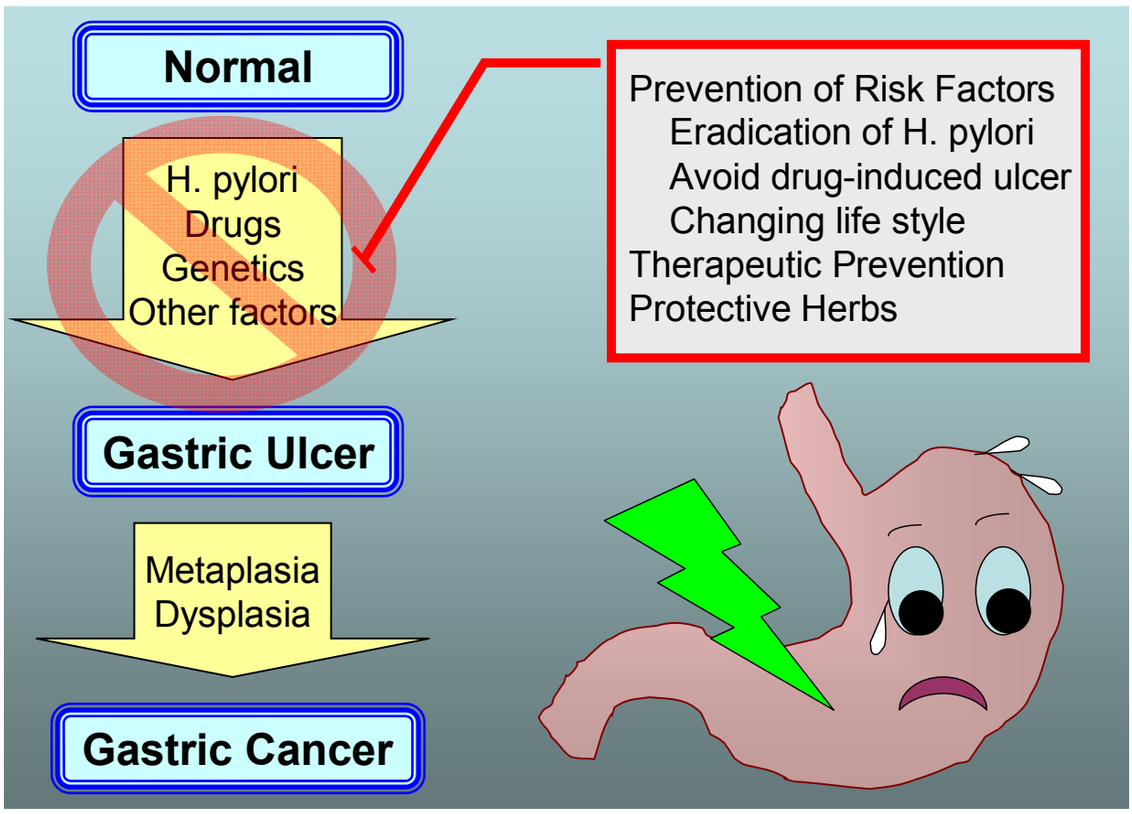


Fig. 2. Prevention of gastric ulcer formation is a step in preventing the development of gastric cancer.

Less than 15% of people infected with Helicobacter pylori develop gastric ulcer. Factors that trigger gastric ulcers in Helicobacter pylori carriers include genetic factors, which explain the higher incidence of development of ulcers in certain ethnicity. Another factor is abnormal immune response, which allows the bacteria to injure the stomach lining. Lifestyle factors as chronic stress, drinking coffee and smoking were long believed to be primary causes of gastric ulcer; it is now thought that they only increase susceptibility to ulcers in some Helicobacter pylori carriers. Interrupted sleep may be another trigger as people who work at night shifts have a significantly higher incidence of ulcers than day workers. Frequent interruption of sleep is thought to weaken the immune system's ability to protect against harmful bacterial substances.

Using certain medications as non-steroidal anti-inflammatory drugs or corticosteroids may contribute to higher infection rates of Helicobacter pylori. Patients with prior gastric ulcer, Zollinger-Ellison syndrome, congenital stomach malformations, malignant diseases such as mastocytosis and basophilic leukemia, head trauma, severe traumatic injuries, burns, radiation, or recently had major surgery are also more prone to Helicobacter pylori infection. Increased risk of Helicobacter pylori infection is seen among people who live in crowded places with unsanitary conditions. Some genetic predispositions for Helicobacter pylori infection cure rate may exist. One example is cytochrome P450-2C19 polymorphism that seems to predict the cure of Helicobacter pylori infection and predisposition to gastric ulcer (Lay and Lin, 2010). Another example is cytokine genes polymorphism that was significantly associated with persistent infection (Abdiev et al., 2010). Polymorphism of multidrug resistance protein 1 also was reported to influence Helicobacter pylori-induced gastric inflammation (Tahara et al., 2011). Such genetic predisposition gives us hope that the infection predisposing to peptic ulcer and gastric cancer may some day be a target for preventive gene therapy in the near future.

Therapeutic interventions to eradicate Helicobacter pylori are needed to prevent ulcer formation and its transformation to gastric cancer, one of the major complications of chronic gastric ulcer. Helicobacter pylori eradication therapy comprises a combination of two or more drugs including antimicrobials, proton pump inhibitors and gastro-protective agents. Several eradication methods were suggested. Dual eradication therapy using proton pump inhibitor with amoxicillin was tried (Graham et al., 2010). Triple eradication therapy employing 2 antimicrobials together with proton pump inhibitor also showed some success, but not enough to be considered first-line treatment. Quadruple Helicobacter pylori eradication was also successfully tried and consisted of 2 antimicrobials, proton pump inhibitor and the gastro-protective agent colloidal bismuth subcitrate (Zheng et al., 2010).

Nowadays, the first line of Helicobacter pylori eradication therapy is a regimen of 7 or 14 days consisting of a proton pump inhibitor as omeprazole (20 mg 12 hourly), in combination with clarithromycin (500 mg 12 hourly) and metronidazole (400 mg 12 hourly). A second regimen that is equally effective is by using omeprazole as previously mentioned, together with less dose of clarithromycin (250 mg 12 hourly) and substituting metronidazole with amoxicillin (1 g 12 hourly). Omeprazole can be replaced with other proton pump inhibitors. Despite that the prevalence of Helicobacter pylori is decreasing in developed countries, as a result of improvements in living standards and hygiene, Helicobacter pylori is still a common cause of gastric ulcer in developing countries. Attempts to develop effective vaccination against this bacterium reached phase I and II clinical trials, and may present effective preventive strategy in preventing gastric ulcer formation and, more importantly, preventing gastric cancer in the future (Majumdar et al., 2011).

2.2 Avoidance of drug-induced gastric ulcers

Patients receiving medications as non-steroidal anti-inflammatory drugs, the anticoagulant drug warfarin, corticosteroids or the anti-osteoporotic drug alendronate may be more prone to gastric ulcer. Non-steroidal anti-inflammatory drugs are valuable therapeutics that act not only as anti-inflammatory, but also as analgesics and antipyretics. They are used in a wide variety of clinical scenarios, including arthritis and other musculoskeletal disorders. Unfortunately, their use has been limited by their gastric ulcer-inducing effects. Nearly 25 % of chronic users of these drugs develop gastric ulcer disease (Lanza et al., 2009).

The rate of non-steroidal anti-inflammatory drugs-induced gastric ulcers is increasing, as more people are taking these drugs regularly as over-the-counter self-therapy. In general, the possibility of gastric ulcer initiation of a non-steroidal anti-inflammatory drug with non-selective cyclooxygenase inhibition actions correlates with its anti-inflammatory activity. Non-steroidal anti-inflammatory drugs with a high analgesic effect at doses with low anti-inflammatory activity, such as ibuprofen, are less ulcerogenic than those that have adequate analgesic effects only at doses with high anti-inflammatory activity, as in case of piroxicam. Ibuprofen appears safer compared to other members of this drug group in part because it is frequently prescribed for short durations in a low dose to control temporary mild painful conditions. However, when full anti-inflammatory doses of ibuprofen are given, the risk of gastric ulceration with ibuprofen is comparable with other non-steroidal anti-inflammatory drugs.

One member of this group is indomethacin, which is a frequently clinically used and is also applied to induce experimental animal model of acute gastric ulcer. Indomethacin induces gastric injury by suppressing the formation of prostaglandins, which control many of the components of mucosal defense system, as they stimulate mucus and bicarbonate secretion, elevate mucosal blood flow, increase the resistance of epithelial cells to injury induced by cytotoxins and suppress the recruitment of leucocytes into the mucosa. Prostaglandins can also inhibit the release of a number of inflammatory mediators, such as tumor necrosis factor-α from macrophages and interleukin-8 from neutrophils. Tumor necrosis factor-α promotes gastric epithelial cell apoptosis and triggers activation of adhesion molecules and leucocyte recruitment, leading to microvascular perturbations. Other mechanisms by which indomethacin induce gastric injury involves gastric hypermotility and the increased production of reactive oxygen species, as well as lipid peroxidation (Morsy et al., 2010).

Physicians prescribing these drugs face two problems; one problem is identification of high-risk patients and the second is selection of appropriate strategies to prevent gastric ulcer. Risk factors of these drugs-induced gastric ulcers include older age, concomitant use of anticoagulants, corticosteroids, other non-steroidal anti-inflammatory drugs including low-dose aspirin, and chronic debilitating disorders, especially cardiovascular diseases. Helicobacter pylori infection increases the risk of this drugs-induced gastric ulcer. Eradication of Helicobacter pylori infection, if present, in patients requiring long-term therapy by these drugs is recommended.

Patients who require long-term non-steroidal anti-inflammatory drug therapy can reduce their risk of inducing ulcers by concomitantly taking conventional anti-ulcer therapy. Proton pump inhibitors and/or histamine H_2 receptor antagonists can significantly reduce these drug-induced gastric ulcers. The synthetic prostaglandin E_1 analog, misoprostol, is also very effective in preventing the development of gastric ulcers in patients taking these medications. Unfortunately, its use is limited by its gastrointestinal adverse effects.

Avoiding unnecessary intake of ulcer-inducing over-the-counter medications may help in reducing the prevalence of gastric ulcers. When it is mandatory to use such therapeutics, their replacement with less irritating drugs may reduce ulcer formation. Non-steroidal anti-inflammatory drugs which are selective cyclooxygenase-2 inhibitors show similar anti-inflammatory, analgesic and antipyretic efficacy compared to non-selective inhibitors. However, these selective drugs are associated with lower incidence of gastric ulcers. Unfortunately, there use is limited due to their association with myocardial infarction and thrombosis. Unexpectedly, experiments using cyclooxygenase-1 knockout mice showed that these animals do not develop gastric ulceration at higher rate and have some reduced inflammatory response.

Some studies tried to find a safer replacement for non-steroidal anti-inflammatory drugs as regards their gastric ulcerogenic effect. In one study, a safer anti-inflammatory drug as regards its gastric toxicity was developed (Shoman et al., 2009). A number of nitric oxide donating pyrazoline derivatives were synthesized and they showed equivalent anti-inflammatory effect to the anti-inflammatory drug indomethacin, with significantly less development of gastric ulceration. Other similar trials have been made by other investigators, for example testing the effect of cyclodextrin combination with non-steroidal anti-inflammatory drugs on gastric ulcer formation which resulted in gastro-protective effect (Alsarra et al., 2010).

2.3 Life style risk factors

Several studies implied that modulating life style factors as dietary factors, controlling stress, reducing smoking and alcohol intake may directly prevent the initiation of gastric ulcers, especially in predisposed people. Some even suggested certain physical exercises to reduce the risk of ulcer formation or recurrence. Such exercises were seen to directly improve psychological and cardiovascular conditions and thus may be indirectly related to decreasing gastric ulcer development.

2.3.1 Diet

Diet rich in fibers may decrease the risk of developing gastric ulcers by about 50%. Fiber found in fruits and vegetables is particularly protective, as vitamin A contained in many of these foods may increase the benefit. Milk, previously thought to aid in decreasing ulcer symptoms, actually encourages the production of acid in the stomach, although moderate amounts (2-3 cups/day) appear to do no harm. However, yogurt may protect against gastric ulcer, as it contains probiotics. Coffee (caffeinated and decaffeinated), soft drinks and fruit juices with citric acid increase stomach acid production. Although no studies have proven that any of these drinks contribute to ulcers, consuming more than 3 cups of coffee per day may increase susceptibility to Helicobacter pylori infection (University of Maryland Medical Center website).

Studies conducted on spices and peppers have yielded conflicting results. In general, these substances should be used moderately, and should be avoided if they irritate the stomach. Some studies suggest that high amounts of garlic may have some protective properties against stomach cancer, although a recent study concluded that garlic offered no benefits against Helicobacter pylori and, in large amounts, can cause considerable gastrointestinal distress. Studies have shown that phenolic compounds in virgin olive oil may be effective against Helicobacter pylori infection. Although no vitamins have been shown to protect

against Helicobacter pylori-induced ulcers, Helicobacter pylori appears to impair the absorption of vitamin C, which may play a role in the higher risk of stomach cancer.

2.3.2 Psychological factors: stress

As a body response to stress, many diseases may develop. There is debate as to whether psychological stress can influence the development of gastric ulcers. Some studies still suggest that stress may predispose a person to ulcers or prevent existing ulcers from healing. Some even believe that the relationship between stress and ulcers is so strong that people with ulcers should be treated for psychological conditions. Stress causes the digestive tract to slow down and more gastric acid is allowed to accumulate in the stomach. Increased stomach acidity may predispose to or aggravate an already present ulcer. Stress can also cause change in appetite, leading to over-eating or lack of appetite. Overeating causes the stomach to produce more acid while lack of appetite will subject the stomach mucosa to the acid produced in an empty stomach. Although psychological stress is no longer considered a direct cause of ulcers, it surely can delay the healing and aggravate already existing gastric ulcers. Physical stress, however, is definitely a risk factor for developing gastric ulcers, as in patients with injuries such as severe burns or patients undergoing major surgeries.

2.3.3 Smoking

Cigarette smoking appears to be a risk factor for the development and recurrence of gastric ulcer. The incidence of gastric ulcer is higher among smokers than non-smokers. Compared with non-smokers, people who smoke cigarettes are twice as likely to develop gastric ulcer. Smoking may lead to initiation of ulceration, slow ulcer healing and an increased risk of gastric ulcer recurrence. Smoking may have an inconsistent effect on gastric acid secretion; however it reduces prostaglandin and bicarbonate production, reduces mucosal blood flow, interferes with the action of histamine H_2 receptor antagonists and accelerates gastric emptying of liquids. Cessation of smoking or reducing it is usually associated with the prompt relief of already existing gastric ulcer symptoms.

2.3.4 Excess alcohol intake

Alcohol increases the production of acid in the stomach, which may irritate an existing ulcer. Alcohol also relaxes the lower esophageal sphincter, allowing stomach contents to reflux back up into the esophagus, increasing the discomfort associated with gastric ulcer. Patients suffering of gastric ulcer should, thus, avoid taking alcohol. People predisposed to gastric ulcer may dilute alcoholic beverages to reduce their concentration, restrict the number of drinks to one or two a day, replace red wine with white wine of less toxic content, or better, have drinks which are non-alcoholic.

3. Endogenous protection against gastric ulcer

Astonishingly, despite of the presence of one or more risk factors as smoking, alcohol intake, non-steroidal anti-inflammatory drugs consumption and/or Helicobacter pylori infection, some people still do not develop gastric ulcer. For example, non-steroidal anti-inflammatory drugs induce clinically significant gastric ulceration in 17% of patients receiving these drugs. This is due to the strong natural endogenous gastric cyto-protection that spares the vast

majority of patients at risk. Gastric mucosal barrier together with endogenous mediators comprise a strong defense mechanism against gastric ulceration. Understanding these naturally occurring defense mechanisms is crucial to try to enhance them to prevent gastric damage and ulceration in more vulnerable patients.

3.1 Physiological gastric mucosal barrier

The gastric mucosal barrier is considered the main defense system against gastric ulcer formation. Several luminal factors contribute to this barrier (Fig. 3). These factors include secretion of bicarbonates, mucus, phospholipids and immunoglobulins. The gastric epithelial barrier also represents part of the defense system that is remarkably resistant to acids or irritants and has the capability of rapid repair. The mucosal microcirculation, together with sensory innervations, harmonically defends the mucosal barrier. Sensing acidic diffusion into the gastric mucosa results in neural system-mediated induced endogenous mediator release and hormonal responses leading to increase in mucosal blood flow, which is a critical step in preventing damage and facilitating repair of gastric mucosa. The mucosal immune system represents another gastric mucosal protective method. Mast cells and macrophage generate immune signals of inflammatory response that contributes to prevention of gastric damage.

3.1.1 Luminal gastric protection

The mucus-bicarbonate-phospholipid barrier comprises the first line of mucosal defense mechanism. This barrier is formed of mucus, bicarbonate and phospholipids. Mucus presents a layer that contains secreted bicarbonate and surfactant phospholipids. Mucus that acts as a physical barrier against luminal digestive enzymes, bicarbonate that maintains an almost neutral pH at the epithelial surface, together with phospholipids of high hydrophobic properties can naturally protect against mucosal damage. Disruption of this mucus-bicarbonate-phospholipid barrier by ulcerogenic substances, as bile salts or non-steroidal anti-inflammatory drugs causes elevated diffusion of acid into the mucosa and mucosal damage (Allen and Flemstrom, 2005). Helicobacter pylori release phospholipase enzymes and ammonium ions that can reduce the strength of this single and only barrier existing between the epithelium and the lumen. Other protective mechanisms may then interfere to protect against this bacterial induced injury.

3.1.2 Gastric epithelial barrier

Mucosal surface is formed of a continuous layer of surface epithelial cells that secrete components of the mucus barrier as well as endogenous protective mediators as prostaglandins, heat shock proteins and cathelicidins (see below; section 3.2). These surface epithelial cells form a physical barrier preventing back-diffusion of gastric acid and digestive enzymes. Basolateral membrane of epithelial parietal cells, that secrete hydrochloric acid in high concentrations into the lumen of the stomach, contains transporters responsible for maintaining intracellular homeostasis. These transporters efflux large amounts of bicarbonate to prevent cell alkalinization. The effluxed bicarbonate, known as alkaline tide, is an integral constituent of mucus-bicarbonate barrier (Tulassay and Herszenyi, 2010). Continuous and rapid cell renewal enhances the resistance of epithelial barrier to damage. Mucosal progenitor cells in gastric epithelium promote cell renewal by continuously replacing surface cells that undergo apoptosis. Proliferation of progenitor cells is controlled by endogenous growth factors' mediators.

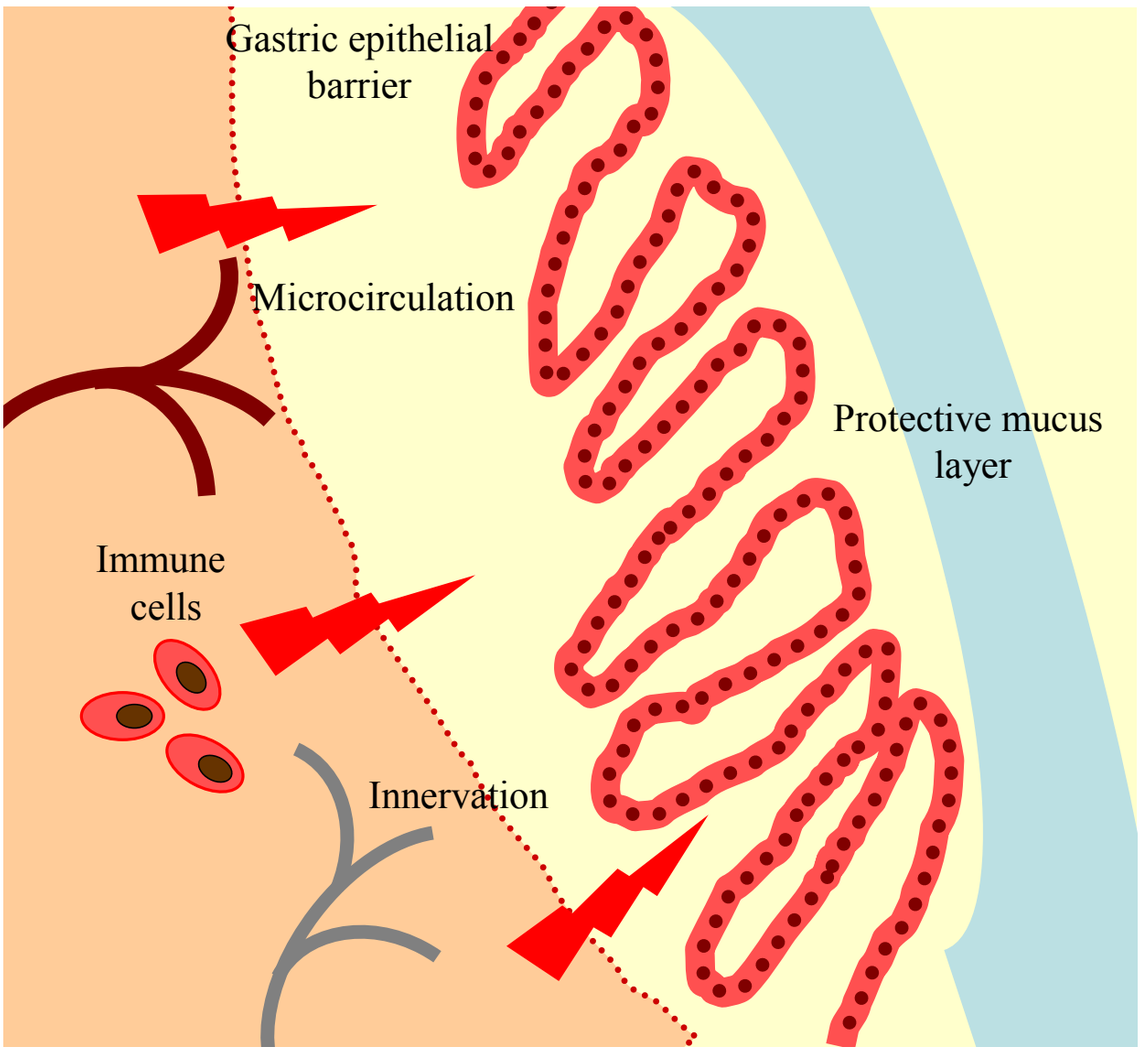


Fig. 3. Physiological gastric mucosal barrier. It is composed mainly of protective luminal mucus layer, gastric epithelial barrier, immune cells, gastric microcirculation and sensory gastric innervation.

3.1.3 Mucosal microcirculation

Mucosal ischemia triggers gastric ulcer by inducing tissue necrosis, free radical formation and cessation of nutrient transport, all resulting from vascular and microvascular injury such as thrombi, constriction or other occlusions. Mucosal blood flow thus provides gastric lining with adequate vascular perfusion that prevents epithelial damage from progressing to necrosis of deeper layers of the mucosa. Increase in mucosal blood flow occurs as a response to gastric mucosal exposure to an irritant or when acid back-diffusion occurs. Potent vasodilators such as nitric oxide and prostaglandin I_2 generated by endothelial cells protect the gastric mucosa against injury and damaging action of vasoconstrictors such as leukotriene C_4, thromboxane A_2 and endothelin. These potent vasodilators prevent platelet and leucocyte adherence to endothelial cells, maintain the integrity of the gastric epithelium and the mucus barrier and protect the gastrointestinal tract by inhibiting gastric acid

secretion from parietal cells. Endogenous mediators that affect mucosal microcirculation as nitric oxide and hydrogen sulfide are further discussed below (section 3.2).

3.1.4 Gastric sensory innervation

Gastric mucosal defense is also regulated by the central nervous system innervation. Gastric mucosa and submucosal vessels are innervated by primary afferent sensory neurons. When gastric mucosa gets exposed to damage by gastric acid or other irritating chemicals, afferent neurons are activated and directly start controlling the tone of the submucosal arterioles, which regulate mucosal blood flow. When sensory afferent nerves of the superficial mucosa detect gastric acid, they respond by releasing neurotransmitters as substance P and calcitonin gene-related peptide. These mediators cause relaxation of smooth muscle surrounding gastric mucosal arterioles, resulting in an elevation of mucosal blood flow. In addition, vagal activation increase mucus secretion, while nervous response to stress control central corticotropin-releasing factor signaling pathways. Furthermore, the transient receptor potential vanilloid 1 agonists are effective in protecting gastric mucosa against various experimentally induced ulcer models (Morsy and Fouad, 2008).

3.1.5 Mucosal immune system

The mucosal immune system is a key factor of mucosal defense against exogenous and endogenous irritants. Impairment of this immune system can lead to mucosal injury and to impairment of endogenous cyto-protective repair mechanisms. The mucosal immune system is coordinated by innate and adaptive immune response regulated by several mediators released from immuno-regulating cells. Neutrophils and macrophages infiltrate into the gastric mucosa as a response to Helicobacter pylori infection. These cells release lysosomal enzymes, leukotrienes and reactive oxygen species which impairs mucosal defense and drives the immunopathogenetic process of ulcerogenesis. T and B lymphocytes activated by bacterial antigens and pro-inflammatory cytokines regulate the local and systemic immune response with release of further cytokines and antibodies. The type of T-cell response can change the outcome of this infection, as more mucosal damage results from T-helper predominant response, whereas a high regulatory T-cell response with interleukin-10 release confers gastric ulcer protection (Malfertheiner et al., 2009).

3.2 Endogenous gastro-protective mediators

Some endogenous mediators can work through cyto-protective mechanisms reducing gastrointestinal injury induced by topical irritants, thus preventing the initial steps of gastric inflammation. These endogenous mediators may be inhibited by causative risk factors, leading to gastric ulceration and thus provide a mechanism through which these risk factor contribute in gastric damage. On the other hand, therapeutic modulation of endogenous gastric mediators can provide a target to improve gastric protection against ulceration.

3.2.1 Mediators of cyclooxygenase pathway: prostaglandins and lipoxins

Prostaglandins are fatty acids produced from arachidonic acid via cyclooxygenase enzyme. It is known that suppression of prostaglandin synthesis is a major mechanism of action of aspirin and other non-steroidal anti-inflammatory drugs, which is probably one of the mechanisms by which these drugs cause gastric ulcers. Prostaglandins modulate a number of components of mucosal defense as they stimulate mucus and bicarbonate secretion,

promote mucosal blood flow, increase the resistance of epithelial cells to cytotoxins-induced injury and suppress the recruitment of leukocytes into gastric mucosa. Prostaglandins can also down regulate the release of a number of other inflammatory mediators that may contribute to the generation of gastric ulcer (Martin and Wallace, 2006). Prostaglandin E receptors have a prominent role in mucosal protection and gastric ulcer healing (Takeuchi, 2010). Prostaglandin E_2 has been shown to be a potent inhibitor of tumor necrosis factor-α and interleukin-1 release from macrophages and of leukotriene B4 and interleukin-8 release from neutrophils.

Lipoxins are the resultant of consequent conversion of arachidonic acid by cyclooxygenase-2 and 5-lipoxygenase enzymes. Lipoxin-A_4 is an endogenous mediator contributing to resolution of the inflammatory state and, thus, has an important role in mucosal defense. Lipoxin A_4 protects the stomach from aspirin-induced damage via suppressing leukocyte adherence within gastric micro-circulation. In addition, Lipoxin A_4 can inhibit inflammatory pain processing and regulate trans-epithelial electrical resistance. Antagonism of Lipoxin A_4 receptor can significantly exacerbate gastric ulcer (Lim et al., 2009).

3.2.2 Nitric oxide

Oxidization of arginine by nitric oxide synthase yields the volatile gas nitric oxide, which has numerous physiologic properties including regulation of inflammation. Nitric oxide is an important factor in modulating gastrointestinal mucosal defense mechanisms. Some of nitric oxide actions overlaps with that of prostaglandins, as it modulate the activity of mucosal immunocytes and reduce leukocytic endothelial adhesion. In addition, it modulates mucosal blood flow and reduces epithelial permeability, resulting in enhanced mucosal resistance to ulceration. Nitric oxide also prevents adherence of leukocytes to the vascular endothelium. This gaseous mediator has a role also in modulating gastric mucus and bicarbonate secretion. Suppression of nitric oxide synthesis renders the gastric mucosa more susceptible to injury, while administration of nitric oxide donors can protect the stomach from injury. Agents that release nitric oxide in small amounts over a prolonged period have been shown to greatly reduce inflammation and to accelerate ulcerative healing (Martin and Wallace, 2006).

Some studies showed that dietary nitrate and pretreatment with nitric oxide donor protected against drug-induced gastric ulcer. Furthermore, the use of nitric oxide-donating agents concomitantly with non-steroidal anti-inflammatory drugs as aspirin also resulted in reduced risk for gastric ulceration and bleeding. This lead to the development of cyclo-oxygenase inhibiting/nitric oxide donating drugs, in which nitric oxide is chemically linked to a non-steroidal anti-inflammatory drug, which showed effective anti-inflammatory capabilities together with less gastric injury. Examples of such drugs include nitric oxide-flurbiprofen, nitric oxide-ketoprofen, nitric oxide-diclofenac and nitric oxide-naproxen. These drugs are suitable therapeutic options for patients with diseases requiring long-term non-steroidal anti-inflammatory drugs therapy (Lanas, 2008).

Despite all evidence that nitric oxide contribute in mediating mucosal defense under normal conditions, under different circumstances, as in case of already inflamed mucosa, it is suggested that nitric oxide may contribute to tissue injury. In this case, nitric oxide reacts with superoxide anion, produced by activated neutrophils, to form peroxynitrite, which is another potent oxidant. Peroxynitrite is known to produce widespread gastrointestinal injury and inflammation. Although the role of nitric oxide is still controversial, most studies suggest a net protective effect of this molecule in the gastrointestinal tract.

3.2.3 Hydrogen sulfide

Hydrogen sulfide is another gaseous mediator generated endogenously that causes vasodilatation, decreases adhesion of leukocyte to vascular endothelium, inhibits non-steroidal anti-inflammatory drugs-induced gastric mucosal injury and inhibit tumor necrosis factor-α expression (Tulassay and Herszenyi, 2010). The enzymes responsible for hydrogen sulfide generation in the gastric mucosa are cystathionine β-synthase and cystathionine γ-lyase.

Despite the protective role of this gas against mucosal injury, it suspected that hydrogen sulphide may contribute to the pro-inflammatory actions in Helicobacter pylori infection. Nevertheless, with non-steroidal anti-inflammatory drugs, hydrogen sulfide provide gastric protection by inducing up-regulation of anti-inflammatory and cyto-protective genes, including hemeoxygenase-1, vascular endothelial growth factor, insulin-like growth factor receptor and several genes associated with the transforming growth factor-β receptor signaling pathway (Lim et al., 2009).

A number of therapeutic possibilities combining hydrogen sulfide with non-steroidal anti-inflammatory drugs are considered in early stages of development. This new class of combination is based on that non-steroidal anti-inflammatory drugs reduce hydrogen sulphide production in gastric mucosa, which may contribute to these drugs' inducing mechanisms of gastric ulcer. In return, sodium hydrogen sulfide prevents the reduction of mucosal blood flow induced by non-steroidal anti-inflammatory drugs. Furthermore, this gaseous mediator reduces non-steroidal anti-inflammatory drugs-induced leukocyte adhesion to vascular endothelial cell. The combination causes reversal of the increased expression of tumor necrosis factor-α and improvement prostaglandin E_2 synthesis impaired by non-steroidal anti-inflammatory drugs (Lim et al., 2009).

3.2.4 Cytokines

Cytokines are important in mucosal defense and play a pivotal role in the regulation of the mucosal immune system. Interleukin-1β and tumor necrosis factor-α release comprise the early inflammatory systemic response to inflammation or infection. Various types of cells produce interleukin-1β, including monocytes, macrophages, neutrophils, endothelial cells and fibroblasts. Interleukin-1β increases the resistance of gastric mucosa to injury and reduces the severity of ulcerative damage. This is through its action as a potent inhibitor of gastric acid secretion, stimulator of prostaglandins and nitric oxide release and inhibitor of ulcer-promoting mediators as platelet-activating factor from mast cells (Tulassay and Herszenyi, 2010). Tumor necrosis factor-α is another key cytokine that contribute in producing gastric mucosal injury. Still, by stimulating cell proliferation, tumor necrosis factor-α may also promote mucosal repair after damage associated with Helicobacter pylori infection and the use of non-steroidal anti-inflammatory drugs. Tumor necrosis factor-α reverses gastric mucosal injury via stimulation of epithelial cell proliferation.

3.2.5 Proteinase-activated receptors

Proteinase-activated-2 receptors are expressed throughout the gastrointestinal tract, especially in the epithelial cells and sensory afferent neurons. In the stomach, the activation of these receptors triggers mucus secretion and reduces the extent of stomach endothelial damage induced by non-steroidal anti-inflammatory drugs. This may be through modulating sensory afferent nerves and regulating the release of vascular endothelial

growth factor from platelets, which affect new blood vessel angiogenesis that promote ulcer healing (Yoshida and Yoshikawa, 2008).

3.2.6 Proteolytic enzymes

Proteolytic enzymes have important functions in gastric ulcer prevention and healing. It has been shown that impaired fibrinolysis occurs due to alteration of the proteolytic enzymes formed through tissue-type plasminogen activator-inhibitor system. Intramucosal proteases; as cathepsins, are also involved in protection against gastric ulcer initiation and promotion of healing. Cathepsins act as antimicrobial peptides expressed by the gastric epithelium preventing bacterial colonization and accelerate ulcer healing. The proteolytic enzymes urokinase-type plasminogen activator and plasminogen activator-inhibitor type-1 are involved in angiogenesis process, and thus has a direct role in cell proliferation, inflammation and ulcer healing. Matrix metalloproteases are involved in extracellular matrix reconstitution and tissue remodeling and thus may have an impact in gastric ulcer healing (Tomita et al., 2009). Secretory leucocyte protease inhibitor exerts antimicrobial and anti-inflammatory effects. Its expression is induced during inflammation. However, the expression is significantly decreased during Helicobacter pylori-mediated gastritis. This is due to local down-regulation of this proteolytic enzyme in gastric mucosa in response to Helicobacter pylori infection (Tulassay and Herszenyi, 2010).

3.2.7 Heat shock proteins

Heat shock proteins are important mediators of cellular homeostasis during normal cell growth. They also promote cell survival during various cellular stresses, as they are generated by gastric epithelial cells in response to oxidative stress, cytotoxicity and high temperature. Heat shock proteins generated play an important role in cellular recovery. This is done through acting on enzymes related to cyto-protection, gastric inflammation and gastric ulcer healing. Heat shock proteins act by refolding these partially damaged functional enzymes or increasing delivery of their precursor proteins to important organelles such as mitochondria and endoplasmic reticulum. This results in improvement of mucosal defense, protection against gastric ulcer and promotion of healing of existing damage (Choi et al., 2009).

3.2.8 Growth factors

Growth factors are considered a pivotal stimulus for cell proliferation, division, migration and re-epithelization. Cell proliferation and repair of injured gastric mucosal epithelium are controlled by a number of these growth factors activated as a response to tissue injury. Growth factors such as epidermal growth factor, hepatocyte growth factor, platelet derived growth factor and basic fibroblast growth factor activate epithelial cell migration and proliferation and accelerate ulcer healing by binding to their specific receptors on the cell surface, triggering a number of intracellular signaling events that result in cell migration and proliferation.

In the stomach, epidermal growth factor triggers mitogenic response and is important for epithelial cell proliferation, migration, re-epithelization and reconstruction of gastric glands. Vascular endothelial growth factor is important for angiogenesis, vascular remodeling and mucosal regeneration. Transforming growth factor-α protects against gastric mucosal injury and promotes wound healing. Receptors for epidermal and transforming growth factors are

expressed in gastric progenitor cells and are trans-activated by gastrin and prostaglandin E_2 that trigger cell proliferation and repair of gastric mucosa (Tulassay and Herszenyi, 2010). These growth factors are mainly derived from platelets, macrophages and injured tissue. Ulceration also triggers induction of genes encoding these growth factors in cells lining mucosa of the ulcer margin. These locally produced growth factors activate epithelial cell migration and proliferation via actions on autocrine and/or paracrine systems.

3.2.9 Peroxisome proliferation-activated receptor

Peroxisome proliferation-activated receptors (α, β and γ) are members of the nuclear response family of transcription factors. These receptors are expressed in the gastrointestinal tract, liver, skeletal muscle, heart, adipose tissue, breast and skin. Stimulation of peroxisome proliferation-activated receptors plays an important role in the mechanism of non-steroidal anti-inflammatory drugs action. Peroxisome proliferation-activated receptors cause subsequent inhibition of nuclear factor-κB and other transcription factors. These receptors regulate transcription of target genes involved in lipid and lipoprotein metabolism, glucose homeostasis and cell differentiation. In addition, peroxisome proliferation-activated receptors inhibit the activation of certain inflammatory response genes. Thus, activation of peroxisome proliferation-activated receptors during non-steroidal anti-inflammatory drugs administration blocks the production of inflammatory response markers, such endothelin-1, vascular cell adhesion molecule-1 in endothelial cells and tissue factors as matrix metalloproteinase-3 and tumor necrosis factor-α in macrophages. These anti-inflammatory actions are mediated by inhibition of pro-inflammatory transcription pathways as nuclear factor-κB, activator protein-1 and nuclear factor of activated T cells (Lim et al., 2009).

3.2.10 Neuropeptides

Several neuropeptides as cholecystokinin, gastrin 17, bombesin, corticotrophin-releasing factor, peptide YY and intragastric peptone are involved in gastro-protection. Ghrelin is also a neuropeptide associated with gastro-protective effects with important effects on energy homeostasis and gastrointestinal motility. Ghrelin is effective against ethanol-induced gastric ulcers. This protective effect is dependent on cyclooxygenase-1-derived prostaglandin E_2. Ghrelin mediates its gastro-protective effects also via stimulation of nitric oxide production and calcitonin gene related peptide release from sensory afferent nerves, enhancing gastric mucosal blood flow. Orexins are another family of neuropeptides having gastro-protective role, especially orexin-A. Orexin-A prevents mucosal injury and gastric ulceration through several mechanism including increasing gastric blood flow, elevating luminal nitric oxide, reducing lipid peroxidation, generating prostaglandin E_2 and enhancing vagal and sensory nerve activity (Nayeb-Hashemi and Kaunitz, 2009).

3.2.11 Hemeoxygenase-1 enzyme

Hemeoxygenase-1 is the rate-limiting enzyme of heme catabolism that catalyzes the breakdown of heme into carbon monoxide, iron and biliverdin. Hemeoxygenase isoform 1 is a phase II drug detoxifying enzyme. It is highly inducible as a response to stress, as oxidative stressors, ultraviolet irradiation, inflammatory cytokines, heavy metals and non-steroidal anti-inflammatory drugs. Up-regulation of hemeoxygenase-1 infers anti-apoptotic resistance to the cells due to potent antioxidant effect of bilirubin, biliverdin and carbon

monoxide formed. Hemeoxygenase was shown to protect gastric mucosal cells against non-steroidal anti-inflammatory drugs (Aburaya et al., 2006).

4. Therapeutic interventions in prevention of gastric ulcer

Several therapeutic interventions may aid in preventing gastric ulcer. Enhancement of normal physical barriers and physiological protective factors can aid in prevention of gastric ulcer. Some endogenous gastro-protective factors (see above) may be enhanced to decrease the risk of gastric ulcer formation. Conventional medications used in treatment of gastric ulcer can also be used in prevention as well, especially in predisposed people. Several investigations also tested drugs not conventionally used in treatment of gastric ulcer for having possible ulcerogenic protective effects. The main aim of most of these studies is to decide which drug to preferentially use in treating conditions presenting concomitantly with high risk of development gastric ulcer.

4.1 Prevention of gastric ulcer by conventional anti-ulcer drugs

Most anti-ulcer drugs target gastric acid secretion and mucosal defense mechanisms (Table 1). Successful classes in treating gastric ulcer include Helicobacter pylori eradication therapy, prostaglandin analogs, cyto-protective drugs, histamine H_2 receptor antagonist and proton pump inhibitor groups. In terms of acid inhibition, proton pump inhibitors possess higher acid inhibitory potency. Histamine H_2 receptor antagonists have, thus, been gradually replaced with the more potent class of acid inhibitory drugs, the proton pump inhibitors. Current ulcer therapy consists of Helicobacter pylori eradication in Helicobacter pylori-positive gastric ulcer and proton pump inhibitors for healing and preventing peptic ulcers induced by drugs.

Proton pump inhibitors selectively block the H^+/K^+ ATPase of the parietal cells. These proton pump inhibitors are the most popular group of drugs used in Helicobacter pylori eradication regimens (see before; section 2.1). Misoprostol, a prostaglandin analog, has been the most widely used but its application is limited by abdominal side-effects as abdominal cramps and diarrhea. Sucralfate and bismuth salts improve mucosal repair. Sucralfate also acts by reducing acid secretion and suppressing Helicobacter pylori infection. Bismuth salts, having mild anti-Helicobacter pylori activity, are used in treatment of gastric ulcer therapy in combination with antibiotics (Malfertheiner et al., 2009).

All of these drugs have been used successfully to treat gastric ulcers and prevent remittent attacks. Nevertheless, their efficiency in prevention of gastric ulcers in individual predisposed groups is still controversial. Histamine H_2 receptor antagonist is one example, as their standard dosage succeeded only in reducing the risk of duodenal ulcer, but not gastric ulcer induced by non-steroidal anti-inflammatory drugs. The benefit from histamine H_2 receptor antagonists was limited to preventing the risk of ulcers induced by Helicobacter pylori infection (Chan and Graham, 2004). Contrarily, in another study, histamine H_2 receptor antagonists were effective for prevention of low dose aspirin-induced ulcers and showed similar potency as proton pump inhibitors (Nakashima et al., 2009). Another example is the use of cyto-protective drugs (as in Table 1) for prevention of gastric ulcer, whose efficacy is still controversial.

Using these conventional anti-ulcer drugs in prevention of gastric ulceration is, thus, dependent on the type of predisposing risk factor. Risk factors used in assessment are old age, presence of cardiovascular diseases, use of high dose or multiple non-steroidal anti-

inflammatory drugs, concomitant use of low-dose aspirin and other anti-platelet drugs, corticosteroids or warfarin. When one or two of these factors are present, presenting a moderate risk, an anti-secretory agent or misoprostol may be used. If three or more risk factors are combined, presenting a high risk, switching from non-selective, to selective cyclooxygenase inhibitors is recommended. In addition, misoprostol can be used for prevention of aspirin- or warfarin-induced gastric ulcers. In very high risk patients, who have been subjected to previous ulcer complications, avoidance of non-steroidal anti-inflammatory drugs and intake of proton pump inhibitor and/or misoprostol is recommended.

Drug group	Examples	Mechanism of action
Helicobacter pylori eradication therapy	Proton pump inhibitor with two antibiotics	Treatment of Helicobacter pylori infection and prevention of ulcer formation
Proton pump inhibitors	Omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole	Most potent acid inhibition
Histamine H_2 receptor antagonists	Cimetidine, ranitidine, famotidine, nizatidine, roxatidine, lafutidine	Less potent acid inhibition
Prostaglandin analogs	Misoprostol	Weak acid inhibition and increase mucosal resistance
Cyto-protective drugs	Rebamipide, azulensulfonate, teprenone, polaprezinc, sofalcone, alginate sodium	Very weak effect in cyto-protection and enhancement of natural defense mechanisms
Bismuth salts	Subcitrate, subsalicylate	Weak antibacterial effect and increase mucosal prostaglandin synthesis

Table 1. Drugs used in prevention and treatment of gastric ulcer and their main mechanism(s) of action.

4.2 Non-conventional gastro-protective drugs

A number of drugs, other than traditional anti-ulcer medications, were investigated and showed an effect in prevention of gastric ulcer formation. Stress causing hypertension may concomitantly predispose to gastric ulcer. The effect of antihypertensive drugs, namely angiotensin II T_1 receptor blocker; telmisartan, was investigated for its effect as gastro-protective agent. The results showed that telmisartan and candesartan can prevent gastric ulcer formation, with higher potency of telmisartan than candesartan. Telmisartan's protection of gastric mucosa from non-steroidal anti-inflammatory drugs-induced ulceration is possibly through its anti-oxidant action and may also be ascribed, at least in part, to its peroxisome proliferator-activated receptor γ agonistic properties (Morsy et al., 2009).

Gastric ulcer is also commonly seen concurrently in type 2 diabetic patients. Moreover, peptic ulcers related to the diabetic state are more severe and are often associated with complications. The possible gastro-protective effects of insulin sensitizers

thiazolidinediones; rosiglitazone and metformin were tested. Both drugs have the ability to ameliorate oxidative stress and inflammation, rendering them attractive candidates for the prevention of gastric ulcer in patients with type 2 diabetes. Both rosiglitazone and metformin prevented indomethacin-induced gastric ulcer in diabetic rats. Their gastro-protective effects were probably due to anti-secretory actions, enhanced mucosal protection and anti-oxidant activity. This was reflected on their ability to increase mucin concentrations and gastric mucosal nitric oxide levels. In addition, rosiglitazone increased gastric juice pH, providing superior gastro-protection to metformin (Morsy et al., 2010).

Other investigations tested the effect of another anti-diabetic drug; pioglitazone as a gastro-protective drug. Pioglitazone has an agonist of peroxisome proliferator-activated receptor γ and exerted strong effect in both preventing the formation of gastric ulcers and healing of already existing ones. This gastric ulcer preventing/healing effect of pioglitazone is, at least in part, mediated by endogenous nitric oxide. Astonishingly, under diabetic conditions, pioglitazone gastro-protective effect decreased. The attenuation of pioglitazone action is possibly due to reduction in nitric oxide, angiogenesis and increased expression and release of pro-inflammatory cytokines under diabetic conditions (Konturek et al., 2010).

Organoselenium compounds were tested in naproxen- and Helicobacter pylori-induced gastric ulcers and showed not only gastro-protective and ulcer healing effects, but also they possessed antibacterial effect against Helicobacter pylori (Santhosh et al., 2010). When tested on indomethacin-induced gastric ulcer in mice, melatonin demonstrated gastro-protective effects via having angiogenic properties through up-regulation of matrix metalloproteinase-2; an important regulator of angiogenesis (Ganguly et al., 2010).

5. Gastric protection by herbs

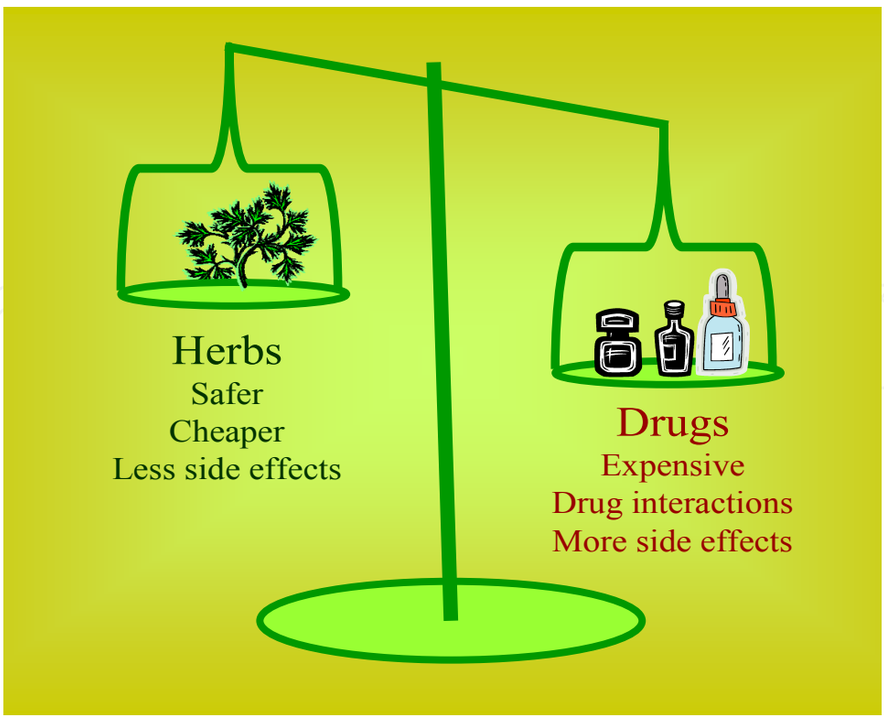


Fig. 4. Herbs, unlike traditional drugs are natural, safer, cheaper and with less side effects.

The need for more effective and cheaper management and prevention of gastric ulcer has attracted an increasing interest for herbal products because of their effectiveness, less side effects and relatively low costs (Fig. 4). For long, some herbal tea constituents and food additives have been known for their gastro-protective effects. For example, liquorice has been used as gastro-protective agent. Eugenol, a compound extracted from clove oil, has also protective effect against the formation of indomethacin-induced gastric ulcer. This effect was mediated by its anti-oxidant activity, decreasing acid-pepsin secretion and increasing mucus production (Morsy and Fouad, 2008).

Similarly, curcumin demonstrated protective effect against gastric ulcer via inhibiting gastric acid secretion, relieving oxidative stress and ameliorating apoptosis. A number of Chinese naturally occurring phytochemicals were reported to have gastro-protective action with potent anti-Helicobacter pylori effects (Li et al., 2005). Lysophosphatidic acid, which is a component of soybean lecithin and antyu-san, has a protective effect against gastric ulcer induction in an animal model, suggesting that daily intake of lysophosphatidic acid-rich foods or Chinese medicines may be beneficial for prevention of gastric ulcer in humans (Adachi et al., 2011). In the ongoing search for bioactive natural products of herbal origin that have ulcer protective activity, crude plant extracts and plant-derived compounds are tried in different experimental models.

5.1 Herbal extracts

Several studies on the gastro-protective effect of crude plant extracts have been undertaken. Although the pathogenesis of gastric ulcer is multi-factorial, secretion of gastric acid is still recognized as a central component of this disease; therefore the main therapeutic target is the control of this secretion using the anti-secretory drugs. On the other hand, many plant extracts, which significantly decrease the ulcer index in experimental animals, have no clinical effects owing to their deficient anti-secretory activity. Accordingly, a large number of studies have been addressing the relationship between plant extracts and their anti-secretory activity on animal experimental models.

We conducted a PubMed search to identify the most relevant articles to these crude plant extracts and focused on those related to the anti-secretory properties, published between January 2010 and December 2010. The number of articles retrieved in a search with such tight limitations reflected the increased scientific interest in using plant extracts in prevention and treatment of gastric ulcer. These natural herbal extracts that has gastro-protective effect include methanol extract of Abarema cochliacarpos bark, a plant that mainly grows in Brazil (da Silva et al., 2010). Another herb, celery (Apium graveolens), which is widely used as food additive worldwide, was also tested, and ethanol extracts of it showed anti-secretory properties (Al-Howiriny et al., 2010).

Extracts of herbs that mainly grow and are widely used in India were tested for their gastro-protective effects as aqueous extract of Pedalium murex leaves (Banji et al., 2010), methanol extract of Hedyotis puberula (Joseph et al., 2010), methanol extract of Punica granatum (Alam et al., 2010), aqueous extract of Myrtus communis (common myrtle) berries (Sumbul et al., 2010), extracts of Cinnamomum tamala leaves (Eswaran et al., 2010) and extracts of Xylocarpus granatum fruit (Lakshmi et al., 2010). Roxb (Ailanthus excelsa bark) (Melanchauski et al., 2010) and camelthorn (Alhagi maurorum) (Shaker et al., 2010) that are widely used in Egypt also showed gastro-protection against ulcers. Hot water extract of Trichosanthes cucumerina Linn that is mainly used in Sri Lanka also showed similar effects (Arawwawala et al., 2010).

5.2 Pure compounds

Purified compounds may have the privilege of specifying the exact compound that is exerting gastro-protective effects. Unlike total herbal extract, pure compounds may lack the presence of several combined components that may contradict each other's action or add an undesired adverse effect.

5.2.1 Flavonoids

Flavonoids represent a highly diverse class of secondary metabolites that constitute the largest and most important group of polyphenolic compounds in plants. The pleiotropic actions of natural compounds are important for developing new drugs for multifactorial diseases. This is particularly true with regards to flavonoids as they display several pharmacological properties in the gastro-protective area, acting as anti-secretory, cyto-protective and antioxidant agents. Besides their action as gastro-protective, flavonoids also can be alternatives for suppression or modulation of gastric ulcers associated with Helicobacter pylori. Flavonoid fraction extracted from Mouriri pusa leaves, a plant from Brazilian cerrado also known as manapuçá or jaboticaba do mato which is commonly used in the treatment of gastrointestinal disturbs in its native region, shows beneficial effects in prevention and reversal of gastric ulcer (Vasconcelos et al., 2010).

Quercetin has an anti-secretory mechanism of action. It has antihistaminic properties, therefore, decreases histamine levels, as well as preventing the release of histamine from gastric mast cells and inhibiting the gastric H^+/K^+ proton pump, diminishing acid gastric secretion. On the other hand, the gastro-protective effects of chalcones involve increasing the mucosal blood flow, stimulating the synthesis of mucus in the gastric mucosa and increasing prostaglandin levels. Nevertheless, the most important mechanism of action responsible for the anti-ulcer activity of flavonoids is their antioxidant properties, seen in garcinol, rutin and quercetin, which involve free radical scavenging, transition metal ions chelation, inhibition of oxidizing enzymes, increase of proteic and nonproteic antioxidants and reduction of lipid peroxidation. In addition, sofalcone (a chalcone) and quercetin (flavonol) have anti-Helicobacter pylori activity (Mota et al., 2009).

5.2.2 Alkaloids

Alkaloids represent a diverse group of low molecular weight nitrogen-containing secondary metabolites that have gastro-protective activity. For examples, the isoquinoline alkaloid isolated from Coptidis rhizome, coptisine; the quinolizidine alkaloid isolated from Sophora flavescens, matrine which decreases the acid secretion and inhibits the gastric motility; the piperidine alkaloid piperine, which protects the stomach against ulceration by decreasing the volume of gastric juice, gastric acidity and pepsin-A activity; the phenylakylamide alkaloid capsaicin, which inhibits the acid secretion, stimulates the alkali/mucus secretions and mainly increases the gastric mucosal blood flow; the steroidal alkaloid pachysandrine A obtained from Pachysandra terminalis; and the indole alkaloid nigakinone found in Picrasma quassioides, which decreases gastric acid/pepsin secretions and protects the mucous membrane (de Sousa et al., 2008).

5.2.3 Terpenoids

Terpenoids are a large and diverse class of naturally-occurring organic chemicals similar to terpenes. Gastro-protective terpenoids have been isolated from several plants, including

sesquiterpenes from Artemisa douglasiana, triterpenes from Fabiana imbricate and carbenoxolone from Glycyrrhiza glabra. Most of the work on the gastro-protective activity has been focused on the clerodane diterpenes from Croton cajucara. Other diterpenes with anti-ulcerogenic effect include cordatin from Aparisthmium cordatum and trichorabdal A from Rabdosia trichocarpa (Schmeda-Hirschmann and Yesilada, 2005).

6. Conclusion

Gastric ulcer is a multi-factorial disease that has become a real socio-economic burden and opposes a great challenge in its treatment. Prevention is better than cure, as they say. Usage of medications designed for treatment of gastric ulcer as a means for its prevention is faced by several drawbacks; as limited effectiveness of these drugs in ulcer prevention, numerous side effects of available anti-ulcer drugs and the cost of gastric ulcer medications. Consequently, separate line of research has been devoted to investigate preventive measures of gastric ulcer. Despite of the size of investigations done on this subject, prevention of gastric ulcer is still a challenge especially in predisposed groups. Herbal compounds can provide an alternative preventive means for gastric ulcer as they are safer, cheaper and usually having limited, if any, side effects. For reaching the optimal remedy that can prevent gastric ulcer formation, more investigations are definitely still needed.

7. References

Abdiev, S.; Ahn, K.S.; Khadjibaev, A.; Malikov, Y.; Bahramov, S.; Rakhimov, B.; Sakamoto, J.; Kodera, Y.; Nakao, A. & Hamajima, N. (2010) Helicobacter pylori infection and cytokine gene polymorphisms in Uzbeks. *Nagoya J. Med. Sci.*, vol. 72, p.p. 167-172.

Aburaya, M.; Tanaka, K.; Hoshino, T.; Tsutsumi, S.; Suzuki, K.; Makise, M.; Akagi, R. & Mizushima, T. (2006). Heme oxygenase-1 protects gastric mucosal cells against non-steroidal anti-inflammatory drugs. *J. Biol. Chem.*, vol. 281, p.p. 33422-33432.

Adachi, M.; Horiuchi, G.; Ikematsu, N.; Tanaka, T.; Terao, J.; Satouchi, K. & Tokumura, A. (2011) Intragastrically Administered Lysophosphatidic Acids Protect Against Gastric Ulcer in Rats Under Water-Immersion Restraint Stress. *Dig. Dis. Sci.* [Epub ahead of print-PMID: 21298479].

Al-Howiriny, T.; Alsheikh, A.; Alqasoumi, S.; Al-Yahya, M.; ElTahir, K. & Rafatullah, S. (2010). Gastric antiulcer, antisecretory and cytoprotective properties of celery (Apium graveolens) in rats. *Pharm. Biol.*, vol. 48, p.p. 786-793.

Alam, M.S.; Alam, M.A.; Ahmad, S.; Najmi, A.K.; Asif, M. & Jahangir, T. (2010) Protective effects of Punica granatum in experimentally-induced gastric ulcers. *Toxicol. Mech. Methods*, vol. 20, p.p. 572-578.

Allen, A. & Flemstrom, G. (2005) Gastroduodenal mucus bicarbonate barrier: protection against acid and pepsin. *Am. J. Physiol Cell Physiol*, vol. 288, p.p. C1-19.

Alsarra, I.A.; Ahmed, M.O.; Alanazi, F.K.; Eltahir, K.E.; Alsheikh, A.M. & Neau, S.H. (2010). Influence of cyclodextrin complexation with NSAIDs on NSAID/cold stress-induced gastric ulceration in rats. *Int. J. Med. Sci.*, vol. 7, p.p. 232-239.

Arawwawala, M.; Thabrew, I.; Arambewela, L. & Handunnetti, S. (2010). Anti-inflammatory activity of Trichosanthes cucumerina Linn. in rats. *J. Ethnopharmacol.*, vol. 131, p.p. 538-543.

Banji, D.; Singh, J. & Banji, O.J. (2010). Scrutinizing the aqueous extract of leaves of pedalium murex for the antiulcer activity in rats. *Pak. J. Pharm. Sci.*, vol. 23, p.p. 295-299.

Chan, F.K. & Graham, D.Y. (2004). Review article: prevention of non-steroidal anti-inflammatory drug gastrointestinal complications--review and recommendations based on risk assessment. *Aliment. Pharmacol. Ther.*, vol. 19, p.p. 1051-1061.

Choi, S.R.; Lee, S.A.; Kim, Y.J.; Ok, C.Y.; Lee, H.J. & Hahm, K.B. (2009). Role of heat shock proteins in gastric inflammation and ulcer healing. *J. Physiol Pharmacol.*, vol. 60, Suppl. 7, p.p. 5-17.

da Silva, M.S.; de Almeida, A.C.; de Faria, F.M.; Luiz-Ferreira, A.; da Silva, M.A.; Vilegas, W.; Pellizzon, C.H. & Brito, A.R. (2010). Abarema cochliacarpos: gastroprotective and ulcer-healing activities. *J. Ethnopharmacol.*, vol. 132, p.p. 134-142.

de Sousa, F.H.; Leite, J.A.; Barbosa-Filho, J.M.; de Athayde-Filho, P.F.; de Oliveira Chaves, M.C.; Moura, M.D.; Ferreira, A.L.; de Almeida, A.B.; Souza-Brito, A.R.; de Fatima Formiga M.D. & Batista, L.M. (2008). Gastric and duodenal antiulcer activity of alkaloids: a review. *Molecules*, vol. 13, p.p. 3198-3223.

Eswaran, M.B.; Surendran, S.; Vijayakumar, M.; Ojha, S.K.; Rawat, A.K. & Rao, C. (2010). Gastroprotective activity of Cinnamomum tamala leaves on experimental gastric ulcers in rats. *J. Ethnopharmacol.*, vol. 128, p.p. 537-540.

Ganguly, K.; Sharma, A.V.; Reiter, R.J. & Swarnakar, S. (2010). Melatonin Promotes Angiogenesis During Protection and Healing of Indomethacin-Induced Gastric Ulcer: Role of Matrix Metaloproteinase-2. *J. Pineal Res.,* vol 49, p.p.130-140.

Graham, D.Y.; Javed, S.U.; Keihanian, S.; Abudayyeh, S. & Opekun, A.R. (2010). Dual proton pump inhibitor plus amoxicillin as an empiric anti-H. pylori therapy: studies from the United States. *J. Gastroenterol.*, vol. 45, p.p. 816-820.

Joseph, J.M.; Sowndhararajan, K. & Manian, S. (2010), Protective effects of methanolic extract of Hedyotis puberula (G. Don) R. Br. ex Arn. against experimentally induced gastric ulcers in rat. *J. Ethnopharmacol.*, vol. 131, p.p. 216-219.

Konturek, P.C.; Brzozowski, T.; Burnat, G.; Szlachcic, A.; Koziel, J.; Kwiecien, S.; Konturek, S.J. & Harsch, I.A. (2010). Gastric ulcer healing and stress-lesion preventive properties of pioglitazone are attenuated in diabetic rats. *J. Physiol Pharmacol.*, vol. 61, p.p. 429-436.

Lakshmi, V.; Singh, N.; Shrivastva, S.; Mishra, S.K.; Dharmani, P.; Mishra, V. & Palit, G. (2010). Gedunin and photogedunin of Xylocarpus granatum show significant anti-secretory effects and protect the gastric mucosa of peptic ulcer in rats. *Phytomedicine,* vol. 17, p.p. 569-574.

Lanas, A. (2008). Role of nitric oxide in the gastrointestinal tract. *Arthritis Res. Ther.,* vol. 10, Suppl. 2, p.p. S4.

Lanza, F.L.; Chan, F.K. & Quigley, E.M. (2009). Guidelines for prevention of NSAID-related ulcer complications. *Am. J. Gastroenterol.*, vol. 104, p.p. 728-738.

Lay, C.S. & Lin, C.J. (2010). Correlation of CYP2C19 genetic polymorphisms with helicobacter pylori eradication in patients with cirrhosis and peptic ulcer. *J. Chin Med. Assoc.*, vol. 73, p.p. 188-193.

Li, Y.; Xu, C.; Zhang, Q.; Liu, J.Y. & Tan, R.X. (2005). In vitro anti-Helicobacter pylori action of 30 Chinese herbal medicines used to treat ulcer diseases. *J. Ethnopharmacol.*, vol. 98, p.p. 329-333.

Lim, Y.J.; Lee, J.S.; Ku, Y.S. & Hahm, K.B. (2009). Rescue strategies against non-steroidal anti-inflammatory drug-induced gastroduodenal damage. *J. Gastroenterol. Hepatol.,* vol. 24, p.p. 1169-1178.

Majumdar, D.; Bebb, J. & Atherton, J. (2011). Helicobacter pylori infection and peptic ulcers. *Medicine*, vol. 39, p.p. 154-161.

Malfertheiner, P.; Chan, F.K. & McColl, K.E. (2009). Peptic ulcer disease. *Lancet*, vol. 374, p.p. 1449-1461.

Martin, G.R. & Wallace, J.L. (2006). Gastrointestinal inflammation: a central component of mucosal defense and repair. *Exp. Biol. Med. (Maywood),* vol. 231, p.p. 130-137.

Melanchauski, L.S.; Broto, A.P.; Moraes, T.M.; Nasser, A.L.; Said, A.; Hawas, U.W.; Rashed, K.; Vilegas, W. & Hiruma-Lima, C.A. (2010). Gastroprotective and antisecretory effects of Ailanthus excelsa (Roxb). *J. Nat. Med.*, vol. 64, p.p. 109-113.

Morsy, M.; Ashour, O.; Amin, E. & Rofaeil, R. (2009). Gastroprotective effects of telmisartan on experimentally-induced gastric ulcers in rats. *Pharmazie,* vol. 64, p.p. 590-594.

Morsy, M.A.; Ashour, O.M.; Fouad, A.A. & Abdel-Gaber, S.A. (2010). Gastroprotective effects of the insulin sensitizers rosiglitazone and metformin against indomethacin-induced gastric ulcers in Type 2 diabetic rats. *Clin. Exp. Pharmacol. Physiol*, vol. 37, p.p. 173-177.

Morsy, M.A. & Fouad, A.A. (2008). Mechanisms of gastroprotective effect of eugenol in indomethacin-induced ulcer in rats. *Phytother. Res.*, vol. 22, p.p. 1361-1366.

Mota, K.S.; Dias, G.E.; Pinto, M.E.; Luiz-Ferreira, A.; Souza-Brito, A.R.; Hiruma-Lima, C.A.; Barbosa-Filho, J.M. & Batista, L.M. (2009). Flavonoids with gastroprotective activity. *Molecules.*, vol. 14, p.p. 979-1012.

Nakashima, S.; Ota, S.; Arai, S.; Yoshino, K.; Inao, M.; Ishikawa, K.; Nakayama, N.; Imai, Y.; Nagoshi, S. & Mochida, S. (2009). Usefulness of anti-ulcer drugs for the prevention and treatment of peptic ulcers induced by low doses of aspirin. *World J. Gastroenterol.*, vol. 15, p.p. 727-731.

Nayeb-Hashemi, H. & Kaunitz, J.D. (2009). Gastroduodenal mucosal defense. *Curr. Opin. Gastroenterol.*, vol. 25, p.p. 537-543.

Santhosh, K.B.; Tiwari, S.K.; Saikant, R.; Manoj, G.; Kunwar, A.; Sivaram, G.; Abid, Z.; Ahmad, A.; Priyadarsini, K.I. & Khan, A.A. (2010). Antibacterial and Ulcer Healing Effects of Organoselenium Compounds in Naproxen Induced and Helicobacter Pylori Infected Wistar Rat Model. *J. Trace Elem. Med. Biol.,* vol 24, p.p. 263-270.

Schmeda-Hirschmann, G. & Yesilada, E. (2005). Traditional medicine and gastroprotective crude drugs. *J. Ethnopharmacol.*, vol. 100, p.p. 61-66.

Shaker, E.; Mahmoud, H. & Mnaa, S. (2010). Anti-inflammatory and anti-ulcer activity of the extract from Alhagi maurorum (camelthorn). *Food Chem. Toxicol.*, vol. 48, p.p. 2785-2790.

Shoman, M.E.; Abdel-Aziz, M.; Aly, O.M.; Farag, H.H. & Morsy, M.A. (2009). Synthesis and investigation of anti-inflammatory activity and gastric ulcerogenicity of novel nitric oxide-donating pyrazoline derivatives. *Eur. J. Med. Chem.*, vol. 44, p.p. 3068-3076.

Sumbul, S.; Ahmad, M.A.; Asif, M.; Saud, I. & Akhtar, M. (2010). Evaluation of Myrtus communis Linn. berries (common myrtle) in experimental ulcer models in rats. *Hum. Exp. Toxicol.*, vol. 29, p.p. 935-944.

Sun, L.P.; Guo, X.L.; Zhang, Y.; Chen, W.; Bai, X.L.; Liu, J. & Yuan, Y. (2009). Impact of pepsinogen C polymorphism on individual susceptibility to gastric cancer and its

precancerous conditions in a Northeast Chinese population. *J. Cancer Res. Clin. Oncol*., vol. 135, p.p. 1033-1039.

Tahara, T.; Shibata, T.; Yamashita, H.; Hirata, I. & Arisawa, T. (2011). Influence of MDR1 polymorphism on H. pylori-related chronic gastritis. *Dig. Dis. Sci*., vol. 56, p.p. 103-108.

Takeuchi, K. (2010). Prostaglandin EP receptors and their roles in mucosal protection and ulcer healing in the gastrointestinal tract. *Adv. Clin. Chem*., vol. 51, p.p. 121-144.

Tomita, M.; Ando, T.; Minami, M.; Watanabe, O.; Ishiguro, K.; Hasegawa, M.; Miyake, N.; Kondo, S.; Kato, T.; Miyahara, R.; Ohmiya, N.; Niwa, Y. & Goto, H. (2009). Potential role for matrix metalloproteinase-3 in gastric ulcer healing. *Digestion,* vol. 79, p.p. 23-29.

Tulassay, Z. & Herszenyi, L. (2010). Gastric mucosal defense and cytoprotection. *Best. Pract. Res. Clin. Gastroenterol*., vol. 24, p.p. 99-108.

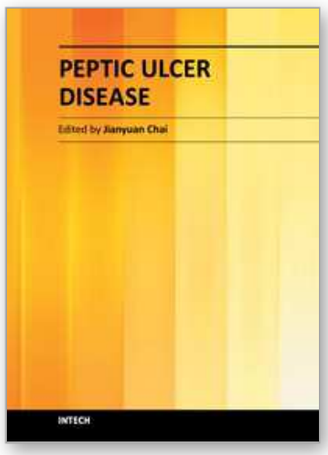
University of Maryland Medical Center website. Accessed on 22 February, 2011. Available at http://www.umm.edu/patiented/articles/peptic_ulcers_000019.htm

Vasconcelos, P.C.; Andreo, M.A.; Vilegas, W.; Hiruma-Lima, C.A. & Pellizzon, C.H. (2010). Effect of Mouriri pusa tannins and flavonoids on prevention and treatment against experimental gastric ulcer. *J. Ethnopharmacol*., vol. 131, p.p. 146-153.

Yoshida, N. & Yoshikawa, T. (2008). Basic and translational research on proteinase-activated receptors: implication of proteinase/proteinase-activated receptor in gastrointestinal inflammation. *J. Pharmacol. Sci*., vol. 108, p.p. 415-421.

Zheng, Q.; Chen, W.J.; Lu, H.; Sun, Q.J. & Xiao, S.D. (2010). Comparison of the efficacy of triple versus quadruple therapy on the eradication of Helicobacter pylori and antibiotic resistance. *J. Dig. Dis*., vol. 11, p.p. 313-318.

IntechOpen



Peptic Ulcer Disease

Edited by Dr. Jianyuan Chai

ISBN 978-953-307-976-9

Hard cover, 482 pages

Publisher InTech

Published online 04, November, 2011

Published in print edition November, 2011

Peptic ulcer disease is one of the most common chronic infections in human population. Despite centuries of study, it still troubles a lot of people, especially in the third world countries, and it can lead to other more serious complications such as cancers or even to death sometimes. This book is a snapshot of the current view of peptic ulcer disease. It includes 5 sections and 25 chapters contributed by researchers from 15 countries spread out in Africa, Asia, Europe, North America and South America. It covers the causes of the disease, epidemiology, pathophysiology, molecular-cellular mechanisms, clinical care, and alternative medicine. Each chapter provides a unique view. The book is not only for professionals, but also suitable for regular readers at all levels.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Mohamed Morsy and Azza El-Sheikh (2011). Prevention of Gastric Ulcers, Peptic Ulcer Disease, Dr. Jianyuan Chai (Ed.), ISBN: 978-953-307-976-9, InTech, Available from: http://www.intechopen.com/books/peptic-ulcer-disease/prevention-of-gastric-ulcers

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen