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Role of Natural Antioxidants in Gastritis

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1. Introduction

Gastritis represents an inflammation of the stomach lining in response to injury. It is either acute or chronic, and has many underlying causes which can be diagnosed and classified histologically where endoscopic appearances such as redness are often misleading. Gastritis is seldom if ever symptomatic, but usually have important clinical sequelae, principally duodenal and gastric ulceration, gastric adenocarcinoma and primary gastric lymphoma (El-Zimaity, 2007; Thirumurthi & Lanza 2010). The three most important causes of gastritis are categorized as Helicobacter pylori infection, prolonged use of aspirin, non-steroidal anti inflammatory drugs (NSAIDs) and autoimmunity (Dohil & Hassall, 2011).

1.1 Acute gastritis

Acute gastritis, is usually a diffuse and intense mucosal alteration, mostly is characterized by a sudden onset of symptoms and rapid resolution after the underlying aetiological mechanisms or agents (either chemical or physical) have been corrected. The patients can present with an acute gastroenteritis-like illness, or other symptoms which may be overshadowed by their general physical condition. Broadly speaking, acute gastritis arises when there is an acute imbalance between mucosal injury and repair mechanisms (Fig. 1) and can be organized in three groups based on the aetiologies: (i) infectious gastritis (ii) secondary to caustic injury; and (iii) ulcero-haemorrhagic (Srivastava & Lauwers, 2007).
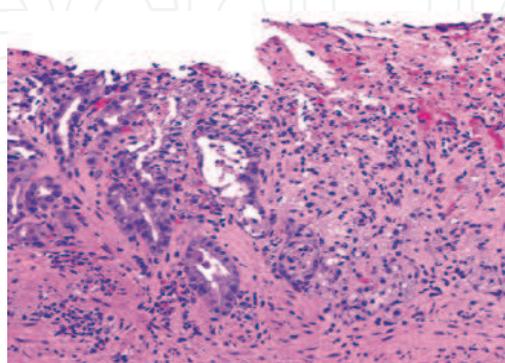

Fig. 1. Acute gastritis. Erosion and complete effacement of the epithelium is observed. The residual glands, on the left, display regenerative changes with basophilic epithelium.

No correlation may be exist between microscopic inflammation (histologic gastritis) and the presence of gastric symptoms (eg, abdominal pain, nausea, vomiting). In fact, most patients with histologic evidence of acute gastritis (inflammation) are asymptomatic. The diagnosis is usually obtained during endoscopy performed for other reasons. Acute gastritis may present with an array of symptoms, the most common being nondescript epigastric discomfort. Other symptoms include nausea, vomiting, loss of appetite, belching, and bloating. Fever, chills may be present. The diagnosis of acute gastritis may be clarified from the patient's history and can be confirmed histologically by biopsy specimens taken at endoscopy. Epidemiologic studies reflect the widespread incidence of gastritis (Ford et al., 2010).

1.1.1 Pathophysiology

Acute gastritis has a number of causes, including certain drugs; alcohol; bile; ischemia; bacterial, viral, and fungal infections; acute stress (shock); radiation; allergy, food poisoning; and direct trauma. The common mechanism of injury is an imbalance between the aggressive and the defensive factors that maintain the integrity of the gastric mucosal lining (mucosa) (Kasper et al., 2006).

Acute erosive gastritis can result from the exposure to a variety of agents or factors, referred to as reactive gastritis. These agents/factors include nonsteroidal anti-inflammatory medications (NSAIDs), alcohol, cocaine, stress, radiation, bile reflux, and ischemia. The gastric mucosa exhibits hemorrhages, erosions, and ulcers. NSAIDs, such as aspirin, ibuprofen, and naproxen, are the most common agents associated with acute erosive gastritis, mostly attributed to therapeutic. Major injury is attributed to reduced prostaglandin synthesis. Prostaglandins are chemicals responsible for maintaining mechanisms that result in the protection of the mucosa from the injurious effects of the gastric acid.

Bacterial infection is another cause of acute gastritis. The corkscrew-shaped bacterium called H. pylori is the most common cause of gastritis. Complications result from a chronic infection rather than from an acute infection. The prevalence of H. pylori in otherwise healthy individuals varies depending on age, socioeconomic class, country of origin where the infection is usually acquired in childhood. In the Western world, the number of people infected with H pylori increases with age. Evidence of H. pylori infection can be found in 20% of individuals younger than 40 years and in 50% of individuals older than 60 years. Transmission is likely from person to person through the oral-fecal route or through the ingestion of contaminated water or food. This is why the prevalence is higher in lower socioeconomic classes and in developing countries. H pylori is associated with 60% of gastric ulcers and 80% of duodenalulcers (Andersen, 2007).

H. pylori gastritis typically starts as an acute gastritis in the antrum, causing intense inflammation, and over time, it may extend to involve the entire gastric mucosa resulting in chronic gastritis. The acute gastritis encountered with H. pylori is usually asymptomatic. The bacterium imbeds itself in the mucous layer, a protective layer that coats the gastric mucosa. It protects itself from the acidity of the stomach through the production of large amounts of urease, an enzyme that catalyzes the breakdown of urea to the alkaline ammonia and carbon dioxide. The alkaline ammonia neutralizes the gastric acid in the immediate vicinity of the bacterium conferring protection. H. pylori also has flagella that enable it to move and help it to penetrate the mucous layer so that it comes into contact with gastric epithelial cells. It also has several adhesions that help it to adhere to these cells. It produces

inflammation by activating a number of toxins and enzymes that activate IL-8, which eventually attracts polymorphs and monocytes that cause acute gastritis (Fig. 2) (Das & Paul, 2007).
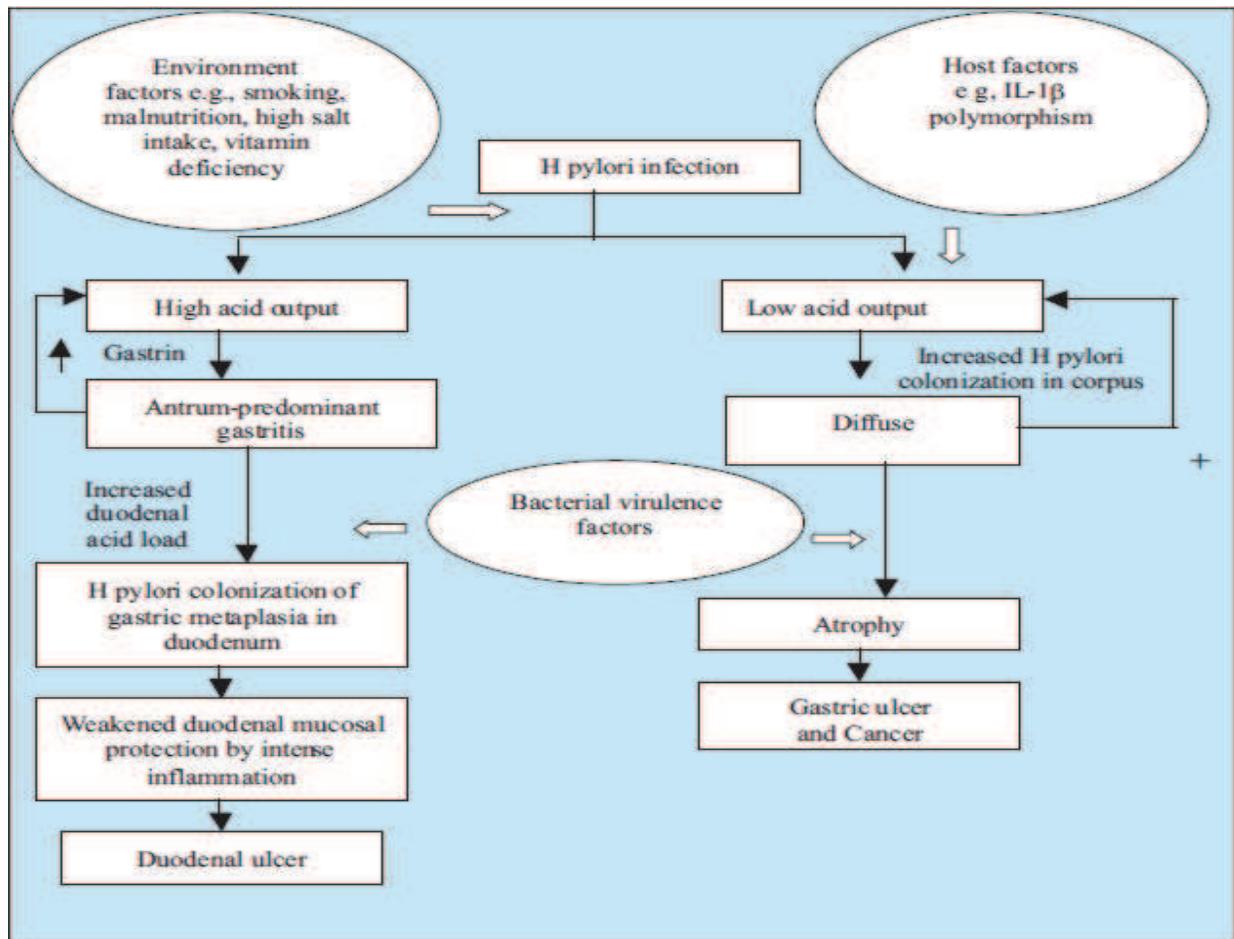

Fig. 2. Proposed interaction between host, environment and H. pylori infection in the development of gastric and doudenal ulcers.

Antigen-presenting cells activate lymphocytes and other mononuclear cells that lead to chronic superficial gastritis. The infection is established within a few weeks after the primary exposure to H. pylori. The intense inflammation can result in the loss of gastric glands responsible for the production of acid and mostly referred to as atrophic gastritis consequently production of gastric acid drops. The virulence genotype of the microbe is an important determinant for the severity of the gastritis of intestinal metaplasia transformation of gastric epithelium which can lead to gastric cancer (Soltermann et al., 2007).

Reactive gastropathy is the second most common diagnosis made on gastric biopsy specimens after H. pylori gastritis. It is now considered to represent a nonspecific response to a variety of other gastric irritants (Owen, 2003).

Tuberculosis is a rare cause of gastritis and generally associated with generally associated pulmonary or disseminated disease (Marshall, 1993) where secondary syphilis of the stomach is a rare cause of gastritis (Chen et al., 2006).

Phlegmonous gastritis is an uncommon form of gastritis (rare) caused by numerous bacterial agents, including streptococci, staphylococci, Proteus species, Clostridium species,

and Escherichia coli. Phlegmonous gastritis usually occurs in individuals who are debilitated. It is associated with a recent large intake of alcohol, a concomitant upper respiratory tract infection, and AIDS. Phlegmonous means a diffuse spreading inflammation of or within connective tissue. In the stomach, it implies infection of the deeper layers of the stomach (submucosa and muscularis).

Viral infections can cause gastritis either localized or diffuse and cytomegalovirus (CMV) is a common viral cause. It is usually encountered in individuals who are immunocompromised, including those with cancer, immunosuppression, transplants, AIDS with a localized or diffuse involvement to the gastric tissuesand AIDS (Bonnet et al., 2001; Sepulveda & Patil, 2008).

Fungal infections that cause gastritis include Candida albicans and histoplasmosis. Gastric phycomycosis is another rare lethal fungal infection. The common predisposing factor is immunosuppression. C albicans rarely involves the gastric mucosa and when isolated in the stomach, the most common locations tend to be within a gastric ulcer or an erosion bed and it is generally of little consequence. Disseminated histoplasmosis can involve the stomach. The usual presenting clinical feature is bleeding from gastric ulcers or erosions on giant gastric folds (Lauwers et al., 2010).

Parasitic infections are rare causes of gastritis. Anisakidosis is caused by a nematode that embeds itself in the gastric mucosa along the greater curvature. Anisakidosis is acquired by eating contaminated sushi and other types of contaminated raw fish. It often causes severe abdominal pain that subsides within a few days and this nematode infection is associated with gastric fold swelling, erosions, and ulcers (Kim et al., 2003).

Ulcero-hemorrhagic gastritis is most commonly seen in patients who are critically ill and it is believed to be secondary to ischemia related to hypotension and shock or to the release of vaso constrictive substances but the etiology is often unknown. The gastric mucosa reveals multiple petechiae, mostly in the fundus and body, or exhibits a diffusely hemorrhagic pattern. The gross pathology may resemble that of NSAID- or other ingestion-induced gastritis except that the location of injury is different. This form of gastritis can be life-threatening if the patient experiences hemorrhaging and may even require emergency gastrectomy (Chamberlain, 1993). Microscopic evidence of acute gastritis can be seen in patients with Crohn disease, though clinical manifestations are rare (occurring in only about 2-7% of patients with Crohn disease). Focally enhancing gastritis is now recognized as a condition seen in both Crohn disease and ulcerative colitis (Xin & Greenson, 2004).

Eosinophilic gastritis is often seen in conjunction with eosinophilic gastroenteritis but can be associated with various disorders, including food allergies (eg, cow milk, soy protein), collagen vascular diseases, parasitic infections, gastric cancer, lymphoma, Crohn disease, vasculitis, drug allergies, and H. pylori infections. An eosinophilic infiltrate is seen involving the gastric wall or epithelium (Rothenberg, 2004).

1.2 Chronic gastritis

Chronic gastritis is caused mainly by Helicobacter pylori infection, and nonatrophic gastritis progresses to atrophic gastritis for a long period. It is characterized by the presence of chronic inflammatory infiltrate in the gastric mucosa (Fig. 4). H. pylori-atrophic gastritis is strongly associated with gastric cancers, and its diagnosis is very important. It is diagnosed histologically according to the Updated Sydney System, which is now widely used in the world (Satoh et al., 2008). Chronic gastritis can be classified on the base of the underlying etiologic agent (eg, Helicobacter pylori, bile reflux, nonsteroidal anti-inflammatory drugs

[NSAIDs], autoimmunity, allergic response) and the histopathologic pattern, which may suggest the etiologic agent and clinical course (eg, H pylori –associated multifocal atrophic gastritis). Other classifications are based on the endoscopic appearance of the gastric mucosa (eg, varioliform gastritis) (Rugge & Genta, 2005).

1.2.1 Pathophysiology

The pathophysiology of chronic gastritis complicating a systemic disease, such as hepatic cirrhosis, uremia, or another infection is described in the relevant disease (Boulton et al., 2011). The pathogenesis of the most common forms of gastritis is described as follows.
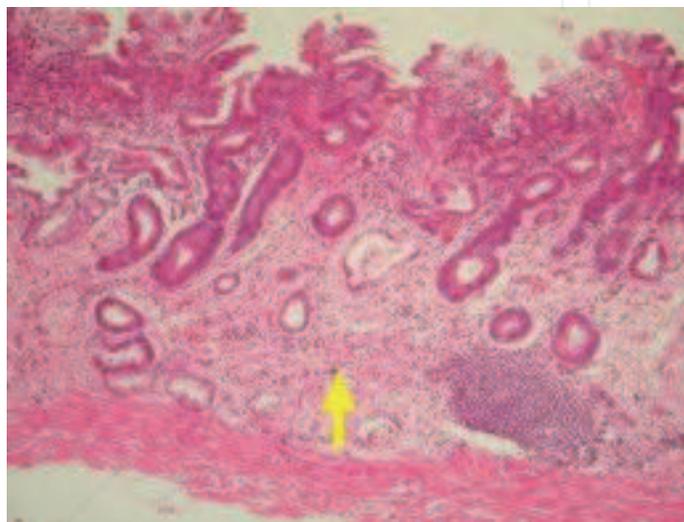

Fig. 3. Chronic gatritis showing inflammation of mucosa linning

The host response to H. pylori and bacterial products is composed of T- and B-cell lymphocytes, denoting chronic gastritis, followed by infiltration of the lamina propria and gastric epithelium by polymorphonuclear leukocytes that eventually phagocytize the bacteria. The presence of polymorphonuclear leukocytes in the gastric mucosa is diagnostic of active gastritis. The interaction of H pylori with the surface mucosa results in the release of proinflammatory cytokine interleukin (IL)-8, which leads to recruitment of polymorphonuclear cells and may begin the entire inflammatory process. Gastric epithelial cells express class II molecules, which may increase the inflammatory response by presenting H pylori antigens, leading to further cytokine release and more inflammation. High levels of cytokines, particularly tumor necrosis factor-a (TNF-α) and multiple interleukins (eg, IL-6, IL-8, IL-10), are detected in the gastric mucosa of patients with H. pylori gastritis (Zalewska-Ziob et al., 2009).

In subsequent or joining such inflammation pattern is an increase in oxidative damage due to high level of ROS and increased apoptosis level in human gastric mucosa (obst et al., 2000; cover et al., 2003). Infection also leads to the expression of inducible nitric oxide synthase (iNOS) in host macrophage and polymorphnuclear leukocytes (Tari et al., 2003). NO produced by these cells infiltrating the gastric mucosa may damage DNA. Interaction between NO and superoxide anion can form peroxinitrite, potent nitrating agent leading to apoptosis in a variety of cell types (yue et al., 2001).

Prostaglandins especially PGE2 in the stomach play an important role in the maintenance of gastric mucosal integrity via several mechanism including regulation of gastric mucosal blood flow, kinetic of epithelial cells, synthesis of mucous, inhibition of gastric acid secretion and referring to its protective potential to gastric mucosa (Takeeda et al., 2004).

Patients having Hpylori infection demonstrate significant gastremia which is mostly attributed to intragastric increase of H pylori inducing corpus atrophy and G cells damage in the antrum part. It may be also depends on alkalinization in G cells environment caused by H pylori urease (walsh et al., 1976; shacter et al., 2002).

Serum pepsinogens (1&11) are higher also and specifically in patient category having IgM positive as compared to others (IgM-ve). This may be attributed to a polypeptides secreted by HP during earlier infection which stimulates chief cells directly and promote pepsinogen synthesis (Takeeda et al., 2004; kist, 1991; Elseweidy et al., 2010 a;b).

This led certain study (Kekki et al., 1991) to consider serum pepsinogen level-as a non endoscopic blood test in the diagnosis of atrophic gastritis, HP eradication and, a screening tool for high risk subjects having atrophic gastritis rather than a test for cancer itself.

Generally known Hp infection is associated with special local and systemic immune response. Early after 18 days of infection IgM response is detectable while IgG, IgA response occurs later after 60 days of infection at which time IgG titers decline. IgG, IgA serology is widely used as an accurate test for the diagnosis of Hp infection but those 2 immunoglobulins remains detectable after eradication of HP and d'not demonstrate the infection status (acute, chronic or previously treated infection). Therefore the use of IgM test would allow for direct screening of the sample and serve as a diagnostic tool for establishing active or recent infection (Alem et al., 2002, Elseweidy et al 2010).

Accordingly many authors concluded that diagnosis of atrophic gastritis using test panel of seum gastrin 17, pepsinogen 1, HP antibodies were in good agreement with endoscopic and biopsy findings, considering such panel a non endoscopic diagnostic and screening tool (vaananen et al., 2003).
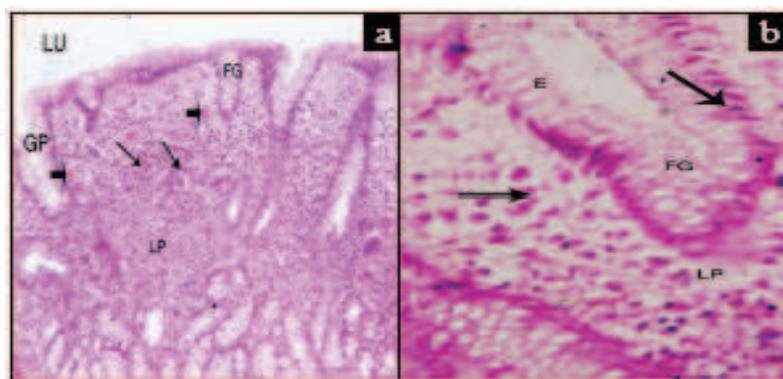

Fig. 4. Histological section of human fundic gland of patient suffering from gastritis with anti H. pylori IgM positive group showing (a) x100 irregular short fundic gland (FG), wide gastric pit (GP), multiple inflammatory cells (arrows) and blood vessels (double arrows) filling lamina propria (LP), (b) x400 showing irregular simple columnar epithelium (E), small pyknotic nuclei (arrows) of cells lyning fundic gland (FG) and multiple inflammatory cells (double arrows) filling lamina propria (LP) (Elseweidy et al., 2010 a).

2. Natural products used in treating gastritis

Phenolic compounds, which include tannins and flavonoids, are apparently related to the interesting anti-inflammatory, woundhealing, antioxidant and antiulcerogenic properties to several medicinal plants (Moleiro et al., 2009).

Tannins are potent scavengers of peroxyl radicals and can also interact with mucus proteins, improving their cytoprotective effect by forming a protein lining over the gastrointestinal mucosa (Okuda, 2005; Moleiro et al., 2009).

Fresh fruit and vegetables have been reported to exert multiple biological effects on the mucosa of the gastrointestinal tract due to their antioxidant contents (La Vecchia & Tavani, 1998). In particular, a diet rich in vegetable is associated with a lower incidence of gastric tumours (Roukos et al., 2003).

Apart from their action as radical scavengers, phenolic compounds also have several indirect effects; they can inhibit lipoxygenase (Laughton et al., 1991), reduce platelet aggregation (Ferro-Luzzi & Ghiselli, 1993) and reduce the bioavailability of food carcinogens (Stavric, 1994). Certain flavonoids or compounds with flavonoid-like properties have antiulcer activity and can prevent gastric mucosal lining lesions brought about by a number of ulcerogens (Alarcon de la Lastra et al., 2002).

Certain polyphenolics can exert a preventive action on gastric injury in rats. Research topics her have focussed on the antiulcer activity of polyphenol from grape seed (Saito et al., 1998), cacao liquor (Osakabe et al., 1998), curcuminoids and Black seed oil (Elseweidy et al., 2008) or from Opuntia ficus indica (Galati et al., 2003). This activity was mainly explained by the strong antioxidant power and/or by some other factors, such as strong protein-binding capacity (Saito et al., 1998), modulation of leukocyte function (Osakabe et al., 1998), mucus production and restoration (Galati et al., 2003). It is believed that the antioxidant activity of polyphenols is an important factor to combat the potential of free radicals.

2.1 Morinda citrifolia aqueous fruit extract

Morinda citrifolia L. (Rubiaceae), commonly known worldwide as "Noni" or so called in Thai as "Yor" is regularly consumed as food, additionally as medicinal plants used in primary health care. The decoction or infusion of roasted mature unripe fruits is recommended to relieve the symptoms of nausea and vomiting, if it is not too severe. According to the claimed efficacies in Thai traditional textbooks, the fruit is also used for treatment of various gastrointestinal disorders as a carminative, appetite stimulant, and reliever of gum diseases, heartburn or stomachache. Nevertheless, experimental studies demonstrated the preventive activity of an ethyl acetate extract of the fruit against acute gastric lesions induced by ethanol, aspirin and pyloric ligation; and acute duodenal ulcer induced by cysteamine in rats (Muralidharan & Srikanth, 2009). This extract was claimed to exhibit potent antioxidant properties and the active components are thought to be non-polar lignans (Kamiya et al., 2004). Previous studies of the effect of an aqueous fruit extract on gastrointestinal motility reported controversial results with increase (Chuthaputti et al., 1996) and delay (Pu et al., 2004) gastric emptying action.

It has been claimed also that aqueous extract have anti-inflammatory (McKoy et al., 2002) and antioxidative activities (Ikeda et al., 2009) in several in vitro test systems. Among a number of major components identified in the aqueous fruit juice, scopoletin, a coumarin derivative, as one of the main compounds that has known pharmacological activities especially an ability to control the serotonin level in the body (Levand and Larson, 1979),

together with anti-inflammatory (Deng et al., 2007; Moon et al., 2007) and antioxidative activities (Ikeda et al., 2009). Scopoletin is also recommended as a marker constituent for the quality control and pharmacokinetic study of Noni products (Samoylenko et al., 2006).

This aqueous fruit extract as well as its biomarker: scopoletin, may be beneficial as a potential preventive and therapeutic agent for gastro-esophageal inflammation. This is mainly through its antisecretory and prokinetic activities including its ability to enhance the mucosal defensive mechanisms. Their efficacy was compared with a standard potent antisecretory proton pump inhibitor (lansoprazole) and referring to its stronger prokinetic efficacy in accelerating gastric emptying and intestinal transit in rats. These observed beneficial effects of AFE may be accounted for by one of its major active biological components scopoletin (Mahattanadul et al., 2011).

2.2 Quercetin-3-O-β-D-glucuronopyranoside (QGC), isolated from Rumex Aquaticus herb

It is well known that flavonoids which have anti-inflammatory, antioxidant, antiallergic, hepatoprotective, antithrombotic, antiviral, and anticarcinogenic activities. As reported before the anti-inflammatory activities of flavonoids demonstrate their candidacy as therapeutic agents (Lewis, 1989). The flavonoids are typical phenolic compounds that act as potent metal chelators, antioxidants and free radical scavengers, which modulate intracellular signaling caused by upstream binding partners, such as, regulatory kinases and receptors (Williams et al., 2004a).

Such flavonoid is a natural flavone with various bioactivities and was found to be highly efficient to scavenge free radicals in cell-free systems (Rice-Evans et al., 1996), as compared to traditional antioxidants like vitamin C and E (Geetha et al., 2005). Gerritsen et al., (1995) found that flavonoids, especially an apigenin, blocked the cytokine-induced expressions of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin on human endothelial cells.

Regarding gastric secretion, the oral administration of QGC reduced gastric content significantly, dose-dependently, and prevented the development of reflux esophagitis. These results suggest that QGC has inhibitory effects on reflux esophagitis and gastritis in rats. Furthermore, in feline esophageal epithelial cells, QGC was found to have a protective effect on ethanol induced cell damage by inhibiting ROS generation, activation downstream of ERK (Min et al., 2009), and downstream signal transduction induced by interleukin-1 beta (Lee et al., 2009a).

2.3 The aqueous decoction of mango flowers (Mangifera indica L.)

Mangifera indica L. (Anacardiaceae) is a large tree that grows in tropical and subtropical regions. The Caribbean population used aqueous decoction from M. indica flowers for the treatment of gastritis and gastric ulcer. Phytochemical research from different parts of M. indica has demonstrated the presence of phenolics, triterpenes, flavonoids, phytosterols and polyphenols (Selles et al., 2002; Singh et al., 2004).

Garrido et al., (2004) reported the antinociceptive and anti-inflammatory activities of Vimang®, an aqueous extract obtained from M. indica. They attributed these activities to their inhibitory influence on the prostaglandin synthesis through arachidonic acid metabolism additionally production of reactive oxygen species. Tordera et al., (1994) demonstrated the influence of several anti-inflammatory flavonoids present in M. indica on mast cell degranulation and arachidonic acid release in rats.

M. indica is also described as an antioxidant agent (Sanchez et al., 2003). Oxygen-derived free radicals have been postulated to play an important role in the pathogenesis of acute gastric mucosal injuries such as those induced by stress (Hariganesh & Prathiba, 2000), ethanol (Salim, 1990) and NSAIDs (Pihan et al., 1987) and scavenging of these radicals can stimulate the healing process. This was illustrated before in experimental model induced by acetic acid and attributed mainly to their high content of flavonoids (Naito et al., 1995).

2.4 Abarema cochliacarpos

Several medicinal plants including species of the Brazilian Cerrado biome as well as plants of the "Caatinga" biome contain phenolic compounds like tannins and flavonoids that have anti-inflammatory, antioxidant and antiulcerogenic properties (Almeida et al., 2005; Moleiro et al., 2009).

Catechins (flavan-3-ols) such as catechin, epicatechin, epigallocatechin, epicatechin gallate and epigallocatechin gallate, are particularly abundant in the bark of the species of Mimosaceae family (Santos et al., 2002). These compounds has anti-inflammatory and anti cholesterolemic effects additionally protective agent against cytotoxicity owing to their antioxidant properties (Williams et al., 2004b).

Araujo et al. (2008) studied plants with elevated levels of phenolic compounds within specific groups of plants for further therapeutic applications. They concluded that Caatinga medicinal plants, which are known and/or used for their wound-healing or anti-inflammatory properties, tend to have high tannin contents. Moreover, these compounds appear markedly elevated in some species, such as Abarema cochliacarpos, that are intensively used by the local communities (Monteiro et al., 2006).

Abarema cochliacarpos is a plant native to Brazil, occurring mainly in the Atlantic Forest and in the Caatinga biomes. It is a tree species of the legume family Mimosaceae (International Union for Conservation of Nature "IUCN", 2009), which is popularly known as "barbatimao". In this community, the decoction of the bark is utilized to wash external ulcers while its tincture, (bark immersed in white wine) "cachaca", or ingested form is used against inflammation and gastric ulcers, among other uses (Silva et al., 2006). Other authors also observed similar applications in different traditional communities (Agra et al., 2008).

As to pharmacologic effects, the hydroalcoholic extract from the bark of Abarema cochliacarpos showed antimicrobial activity. Both crude aqueous and methanol extracts also showed antinociceptive effects (Silva et al., 2009). Butanolic fraction of the methanolic extract was tested recently in a model of acute experimental trinitrobenzene sulfonic acid (TNBS)-induced colitis and showed anti-inflammatory effects (Silva et al., 2010a).

It has been suggested that Abarema cochliacarpos (Gomes) Barneby & Grimes extracts exerts gastroprotective effects and wound healing properties in the ethanol-induced ulcer model. The safety and efficacy in the healing of gastric ulcers is based on its ability to activate the expression of COX-2, vascular-endothelial growth factor (VEGF) and stimulate proliferative factors like HSP-70 that re-establish the gastric mucosa integrity (Silva et al., 2010b).

2.5 Apple polyphenol extracts

Eberhardt and colleagues (2000) illustrated the antiproliferative effect of apple extract in vitro using tumor cells and attributed such effect to the presence of phytochemicals (phenolic acids and flavonoids) other than ascorbic acid. Therefore, dietary antioxidants play a crucial role in the maintenance of gastric homeostasis by counteracting the potentially

mucosal damage exerted by ROS. This may explain the role of dietary antioxidants as scavenger of oxygen, nitrogen free radicals and breaking lipid peroxisdation reactions. Phenolic compounds are one of the major classes of dietary antioxidants and apple phenolic compounds represent 22 percent of such total (Le Marchand et al., 2000).

In vitro and in vivo studies demonstrated the protective effect of apple juice regarding gastric mucosa of rat. This was markedly observed in gastric injury model induced by aspirin and independently of its inhibition to gastric acid. Therefore it might be of therapeutic benefit in prophylaxis of aspirin- related gastropathy (D' argenio et al., 2008). Accordingly a diet rich in apple antioxidants might exert a beneficial effect in gastric diseases associated with generation of reactive oxygen species (Graziani et al., 2005).

2.6 Foeniculum vulgare (Fennel)

Foeniculum vulgare (FVE) is a well-known umbelliferous plant. For centuries, FVE fruits have been used as traditional herbal medicine in Europe and China. It is native to southern Europe and the Mediterranean area. The seeds of this plant have been used to regulate menstruation, alleviate the symptoms of female climacteric syndrome, and increase libido (Albert-Puleo, 1980). FVE also possesses emnenagague, galactagogue and antispasmodic properties additionally in folk remedies for treatment of dysmenorrheal, also as diuretic and wound dressing in Turkish traditional medicine (Savino et al., 2005).

It contains 1%-3% of a volatile oil, which is composed of 50%-85% of anethole and about 20% of d-fenchone (Dadalioglu & Evrendilek, 2004). Other compunds present in FVE are d-a-pinene, d-a-phellandrene, dipentene, methyl chavicol, feniculun, anisaldehyde, and anisic acid (Mimica-Dukic et al., 2003).

Previous studies proved that anethole possesses significant antioxidant, anti-inflammatory and ulcer healing activity in experimental models (Freire et al., 2005). Additionally, flavonoids, sterols, tannins and coumarins of some plants are also known to possess antiulcer activity (Khalil, 2006). Therefore, the presence of flavonoids content and other bioactive compounds in FVE may be beneficial in ulcer therapy. Its gastro protective effect has been also observed before in certain gastric mucosal lesion induced by ethanol, attributed mostly to its antioxidant activity and reduction of lipid peroxidation cascade.

Therefore it may be a new alternative for clinical management of gastric ulcer diseases and/or an antioxidant against oxidative stress (Birdane et al., 2007).

2.7 Flavonoids isolated from Piper carpunya Ruiz & Pav

The leaves of Piper carpunya Ruiz & Pav. (syn Piper lenticellosum C.D.C.) (Piperaceae), known with the popular name of "guaviduca" in Ecuador are widely used in folk medicine in tropical and subtropical countries of South America, as an anti-inflammatory, anti-ulcer, anti-diarrheal and anti-parasitical remedy as well as an ailment for skin irritations. The antiinflammatory activity has been confirmed in rat models like the carrageenan-induced paw edema and the results obtained can support its use in the traditional medicine of Ecuador (De las Heras et al., 1998). Recently, this plant has been shown to protect against gastric ulcers induced by non-steroidal anti-inflammatory drugs (NSAID) in rats (Trabadela et al., 2009).

Numerous plant remedies have shown to be active against Helicobacter pylori infection, such as the oil extract of Chamomilla recutita (Shikov et al., 2008), the ethanolic extract of Cuminum cyminum L., Propolis (Nostro et al., 2005) as well as the methanolic extract of

Alchornea triplinervia (Spreng.) Mull. Arg., which exhibited anti-secretory, anti-Helicobacter pylori and gastroprotective effects (Lima et al., 2008).

Several mechanisms of action have been proposed to illustrate its anti-inflammatory effects. This may be explained through other properties such as anti-oxidant activity, inhibition of eicosanoid generating enzymes or as modulator for proinflammatory molecules. Recent studies have also shown that some flavonoids are modulators of proinflammatory gene expression (Garcia-Lafuente et al., 2009). Gastro protective activity of flavonoids may be through reducing gastric acid secretion and inhibition of gastric H+, K+-ATPase. One example is Baccharis illinita D.C., which is also used in folk medicine, and whose anti-secretory activity is attributable to the flavonoid luteolin (Freitas et al., 2008).

Furthermore, some flavonoids have also demonstrated inhibitory effects on Helicobacter pylori growth and vacuolation. Helicobacter pylori induces gastric epithelial cell apoptosis via secreted mediators such as the VacA cytotoxin and lipopolysacccharides which damage epithelial acid-secreting parietal cells (Neu et al., 2002). Several flavonoids have inhibitory influence on the apoptotic signaling induced by Helicobacter pylori VacA toxin (Xiao et al., 2007). Antimicrobial compounds from plants may inhibit bacterial growth by different mechanisms and could therefore be useful in case of resistance state to antibiotics. In this way, Castillo-Juarez et al., (2007) found that the petroleum ether fraction from Amphipterygium adstringens (Schltdl.) Standl. had significant anti-microbial activity against Helicobacter pylori. From this fraction, the authors isolated a mixture of anacardic acids and three known triterpenes: masticadienonic acid, 3-alpha-hydroxymasticadienonic acid, 3-epi-oleanolic as well as the sterol ß-sitosterol.

Previous study suggested that the flavonoids (vitexin, isovitexin, rhamnopyranosylvitexin and isoembigenin), nervogenic acid and geranylbenzoate isolated from the ethanolic extract of Piper carpunya may contribute to the anti-myeloperoxidase activity, as well as to their anti-Helicobacter pylori effect. These flavonoids may also be responsible for the important inhibition of H+, K+-ATPase pathway, additionally the obtained phytosterols and phytol could be involved in these gastroprotective activities (Quilez et al., 2010).

2.8 Quassia amara

Quassia is a plant that grows typically in the American tropical regions (from Mexico to the Brazilian Amazona) below 500 m altitude, especially in the Caribbean side of Central America and the Pacific coast of Costa Rica and Panama. The plant prefers very humid environments, but it can be found in the dry forest next to a riverbank (López and Pérez, 2008).

Quassia amara L. is one of the most mentioned plants in ethnomedicine for the treatment of malaria, mainly in Surinam, Guyana and French Guyana, where tea cups are carved from the wood and the addition of hot water forms an infusion in them (Odonnea et al., 2007). There only exist a few studies on the gastrointestinal, digestive and secretagogue activity of Quassia amara L. extracts. The results point to an increase of bile secretion with a standardized extract, inhibition of ulcer induction with crude extracts, accompanied by a slight decrease in pH and peptic activity of gastric juice additionally an enhancement of cytoprotective factors like gastric mucus (Toma et al., 2002).

The biological activity of Quassia amara L. has been attributed mainly to its high content of quassinoids. These metabolites are oxygenated triterpenes derived from euphol and are exclusive to the Simaroubaceae family. The most important quassinoids in Quassia amara L. are quassin and neoquassin. Quassin is one of the most bitter substances known, it

represents 0.1% of the dried weight of wood and bark, and it is present in larger quantities when the plant is grown in the shade (Guo et al., 2005).

Quassia amara L. bark standardized extracts, Lipro® and Ligas®, which were standardized to its quassinoid content, showed an important anti-ulcerogenic and gastroprotective potential in acute ulcer induction models. Their effect was related to an increase in gastric barrier mucus and non protein sulfhydril groups (Garcia-Barrantes & Badilla, 2011). Gastric barrier mucus is an important factor in gastroprotection (Kaunitz, 1999). Animals treated with Ligas® showed substantial mucus production. Prostaglandins I2, E2 and F2 are some of the main stimuli for the production of gastric and duodenal mucus (Dharmani et al., 2005). The increase in mucus could be a signal of the role of prostaglandins in the anti-ulcerogenic properties of the extracts.

2.9 Gardenia jasminoides Ellis ethanol extract

Gardenia jasminoides Ellis (GJE), has been used in traditional oriental medicine for the treatment of jaundice, fever, hypertension, and ulcers of a skin (Tseng et al., 1995). It has been reported that the crude extract of GJE fruit has biological and pharmacological activities. In the phytochemical studies of GJE, genipin, chlorogenic acid, rutin, and ursolic acid were detected in GJE extracts (He et al., 2006). Genipin is an aglycone derived from an iridoid glycoside called geniposide present in fruit of GJE, and is an excellent natural cross-linker for proteins, collagen, gelatin, and chitosan cross-linking. It has been also used for pharmaceutical purposes, such as choleretic action for liver diseases control, and the relief of type 2 diabetes symptoms. Ursolic acid is a pentacyclic triterpene acid, used in cosmetics (Shishodia et al., 2003), and as inhibitor for various types of cancer cells by inhibiting the STAT3 activation pathway (Pathak et al., 2007) and human fibrosarcoma cells by reducing the expression of matrix metalloproteinase-9 by the glucocorticoid receptor.

Gastric cancer is the second commonest cause of death from malignant disease worldwide (Neugut et al., 1996). Antioxidant compounds, such as vitamin C and E, have a key role for prevention and termination of development of gastric cancer (Block, 1991). It has been recognized that chronic infections of the gastric mucosa by Helicobater pylori (H. pylori) plays a pivotal role in gastric carcinogenesis. Such infection usually causes acute and chronic inflammation cell infiltrate, leading to an increase of reactive oxygen species (ROS), which are highly reactive compounds. The latter may combine with DNA in a number of potentially genotoxic ways, subsequently accumulated in H. pylori gastritis. Therefore it may be possible to prevent carcinogenesis through reduction of ROS damage to cellular constituents, especially DNA, additionally the eradication of H. pylori can lead to a reduction in ROS activity in the gastric mucosa (Drake et al., 1998).

Lee et al., (2009b) in confirm indicated that the ethanolic extracts of GJE exerted protective activities against potential gastritic diseases like gastritis and gastric cancer. This action might be due to antioxidant activity, anti-H. pylori activity of ursolic acid and genipin that counteract free radicals exerting anti-ulcer activity.

2.10 Curcumin

Curcumin, the polyphenolic yellowish pigment of the rhizome Curcuma longa Linn, is known to possess anti-inflammatory, antioxidant, wound-healing, and antiallergic activities (Das& Das, 2002). Several investigators have also reported the antiulcerogenic activity of the ethanolic extract of the rhizome of C. longa in acute gastric mucosal lesion (Rafatullah et.,

1990), but not in chronic ulcer models. More recently, it has been considered that curcumin exerts a variety of pharmacological actions through inhibition of inducible nitric oxide synthase (iNOS) as well as its potential as radical scavenger (Elseweidy et al., 2008) Thus, the previously proposed mechanisms for antiulcerogenic effect of curcumin (Yano et al., 2000), such as inhibitory effect on gastric secretion, cytoprotection, antioxidant activity and inhibition of mast-cell degranulation, need to be evaluated again.

Curcumin, exerted its preventive effect on gastric lesion formation, although it possesses anti-inflammatory activity resulting from a blockade of all branches of the arachidonic acid pathway (Ammon et al., 1993). This effect is consistent with the findings reported by several authors that the inhibition of prostaglandins synthesis is unlikely to be the mechanism responsible for the inflammatory ulceration formation. Curcumin therefore may exert this through its antioxidant activity and its inhibition of nuclear factor kappa B activation which up-regulates many genes involved in inflammation and immunity, including its potent suppressive effect on mast-cell degranulation (Jobin et al., 1999). Although there is a potential increase of gastric acid secretion with a high dose of curcumin, gastric acid secretion has been found to play little role in the pathogenesis of this model (Ohta et al., 1999).

Apparent healing – promoting effect of curcumin was also observed in gastric ulcer model, induced by acetic acid with an enhancement of mucosal layer regeneration. This effect was not seen in a dose-related fashion, presumably through some curative mechanisms differently modified by curcumin dosage. Accordingly, it is conceivable that the effect of curcumin occurs at least partly through its inhibition of the cytokine-mediated inflammatory mechanism, suppression of iNOS activity and antioxidant activity as mentioned above. In addition, the curative properties and ulcer healing might result from the elevation of epidermal growth factor and transforming growth factor-beta-1, as shown in acceleration of cutaneous wound healing in rats, guinea pigs and mice (Sidhu et al., 1998). Another study attributed such preventive and curative effects of curcumin to an increase in the mucosal defensive mechanism through its antioxidant property, increase in mucin secretion and inhibition of NO or cytokine-mediated inflammation (Mahattanadul et al., 2006).

2.11 Artichoke leaf extract

Artichoke (Cynara Scolymus L.) is a plant that is widely grown in Mediterranean countries, including southern France and California in the United States. In general, the dried extract consisting of leaves and not flowering heads of artichoke has been eluted with water in European countries and the main components are caffeoylquinic acid derivatives (cynarin and chlorogenic acid), flavonoids (luteolin and apigenin) and bitters (cynaropicrin) (Joy & Haber, 2007). Artichoke leaf extract has been used for hepatoprotective and cholesterol reducing (Aktay et al., 2000) purposes. Based on in vitro (Perez-Garcia et al., 2000) and in vivo (Speroni et al., 2003) studies, it is believed that artichoke leaf extract is very effective as an antioxidant and its leaf extract contains cynaropicrin and chlorogenic acid as the main components. It is currently used in Germany and Switzerland as a remedy for indigestion. And its better compounds such as cynariopicrin as inflammatory agents due to its inhibitory influence on inflammatory mediators (Holtmann et al., 2003).

Previous results indicated that artichoke leaf extract is effective against acute hemorrhagic gastritis and its beneficial effect is due to that of cynaropicrin. The gastric mucus-increasing

action of artichoke leaf extract may be, at least in part, related to the anti-gastritic action of the extract (Ishida et al., 2010).

2.12 Pear (Pyrus communis L.) procyanidins

Some European pear (Pyrus communis L.) cultivars have been reported to contain significant amounts of polyphenols, such as chlorogenic acid, flavan-3-ols and arbutin. procyanidins are reported to have many beneficial properties, such as potent antioxidant activity (Zhu et al., 2002), free radical scavenging activity (Arteel & Sies, 1999), antiinflammatory activity and anti-influenza viral activity (Hamauzu et al., 2005).

It has been shown that procyanidins extracted from pear (Winter Nelis) fruit had a very high mean degree of polymerization (mDP), indicating that these compounds may interact with mucosa proteins. Accordingly the mechanism of mucosa protection by pear procyanidins may be both physical and chemical. By binding strongly to the mucosa, procyanidins build a protective layer against injury, reducing leukocyte migration, and then exerting its local antioxidant protection against free radicals (Hamauzu et al., 2007).

2.13 Sesame lignan sesamol

Sesamol (3,4-methylenedioxyphenol), the lignan of sesame oil, is a potent antioxidant and anti-inflammatory agent in various oxidative systems, including endotoxin and iron intoxication (Hsu et al., 2007). Recent study has confirmed its effect in gastric haemorrhage model and mucosal ulcer induced in rats by aspirin. Sesamol her significantly reduced gastric mucosal lipid peroxidation, nitric oxide production, gastric mucosal proinflammatory cytokines (tumor necrosis factor-a and interleukin 1-ß levels), and the activity of gastric mucosal myeloperoxidase. This was attributed to an inhibition of neutrophil infiltration, subsequent gastric mucosal inflammation and oxidative stress in rats (Hsu et al., 2009a). It seems likely that sesamol protective influence on gastric mucosal injury may be at least partially through an inhibition of mucosal reactive nitrogen species and subsequent lipid peroxidation.

Inhibition of neutrophils activation and their infiltration into gastric mucosa may be sesamol's anti-inflammatory and antioxidative mechanism. Neutrophil activation and infiltration are crucial in the pathogenesis of NSAID-induced gastric inflammation and oxidative stress (Souza et al., 2008). Activating neutrophils results in the expression of proinflammatory genes and the overproduction of proinflammatory mediators, including TNF-α and IL-1ß, which initiates an inflammatory response (Jaeschke & Hasegawa, 2006). Overproduction of proinflammatory mediators can upregulate nitric oxide production leading to an increase of reactive nitrogen species, lipid peroxidation, and cell damage (Hayes and McLellan, 1999). Similar effect for Sesamol was also observed in the gastric mucosa of aspirin-treated rats preventing inturn gastric injury. This may be attributed to certain combination between sesamol and aspirin, inhibiting inturn neutrophil infiltration, mucosal inflammation and oxidative stress (Hsu et al., 2009a).

Daily consumption of sesame or sesame oil may be beneficial in protecting against gastric mucosal damage induced by long-term use of NSAID. Sesame lignan sesamol is one of the important antioxidative components in sesame in addition to some other antioxidants such as sesamin, sesamolin, and gamma-tocopheral (Tokusoglu et al., 2003). All of them could attenuate NSAID initiated gastric mucosal oxidative stress. Therefore, we suggested that daily consumption of sesame or sesame oil could protect against NSAID-induced gastric mucosal damage. However, more investigations will be needed to confirm this.

Also, pretreatment of sesame oil, significantly decreased acidified ethanol-induced mucosal ulcer formation and luminal hemorrhage. Sesame oil her reduced mucosal lipid peroxidation, as well as glutathione and nitric oxide production in experimental rats model attenuating in turn oxidative stress and gastric mucosal injury (Hsu et al., 2009b).

3. Conclusion

Gastritis represents an inflammation of the stomach lining in response to injury.It is either acute or chronic and has many underlying causes ,however the most important of them are Helicobacter pylori (HP) infection, Autoimmunity additionally prolonged uptake of certain drugs ,specifically aspirin and nonsteroidal antiinfilammatory drugs (NSAIDs).The common mechanism of an injury is an imbalance between the aggressive and defensive factors that maintain the integrity of the gastric lining (mucosa). In subsequent or joining such inflammation pattern an increase in oxidative damage due to high level of reactive oxygen species (ROS) , higher gastrin, pepsinogen, expression of inducible nitric oxide synthase (iNOS) leading to corpus atrophy and G cells damage. Interaction of NO and can form peroxynitrite, leading finally to apoptosis in a variety of cell types.
Tannins and flavonoids (phenolic compounds) are commonly found in several medicinal plants. Certain therapeutic properties mainly anti-inflammatory, wound healing, antioxidant and anti ulcerogenic are mostly attributed to these plant constituents.
Tannins are potent scavengers of per oxi radicals and can interact with mucus proteins, improving their cytoprotective effect by forming a protein lining over the gastrointestinal mucosa, additionally involved in wounds treatment. Fresh fruits and vegetables have been reported to exert multiple biological effects on the mucosa of gastrointestinal tract due to their antioxidants content. Certain flavonoids or compounds with flavonoid-like properties have antiulcer activity, prevent gastric mucosal lesions brought about by a number of ulcerogens. This had been illustrated before on polyphenol from grape seed, aqueous fruit extract of morinda citrifolia, Quarcetin, apple extract, curcumin, black seed oil, quassin, artichoke and others. It is conceivable that some of these plant constituents exerted their effects through the inhibition of cytokine-mediated inflammatory mechanism, suppression of iNOS, antioxidant activities and healing of the produced ulcer.

4. Acknowledgment

5. References

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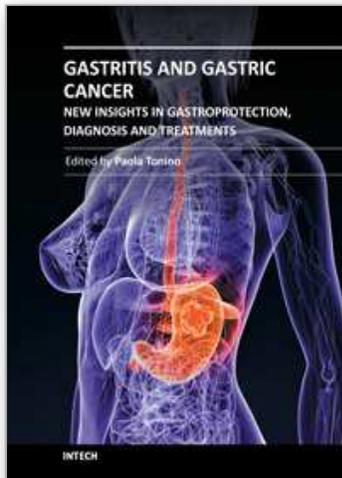
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This book is a comprehensive overview of invited contributions on Helicobacter pylori infection in gastritis and gastric carcinogenesis. The first part of the book covers topics related to the pathophysiology of gastric mucosal defense system and gastritis including the gastroprotective function of the mucus, the capsaicin-sensitive afferent nerves and the oxidative stress pathway involved in inflammation, apoptosis and autophagy in H. pylori related gastritis. The next chapters deal with molecular pathogenesis and treatment, which consider the role of neuroendocrine cells in gastric disease, DNA methylation in H. pylori infection, the role of antioxidants and phytotherapy in gastric disease. The final part presents the effects of cancer risk factors associated with H. pylori infection. These chapters discuss the serum pepsinogen test, K-ras mutations, cell kinetics, and H. pylori lipopolysaccharide, as well as the roles of several bacterial genes (cagA, cagT, vacA and dupA) as virulence factors in gastric cancer, and the gastrokine-1 protein in cancer progression.

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