9

New Approaches in Gastritis Treatment

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1. Introduction

Gastritis is an inflammation of the stomach lining, which is fairly common and could have different causes. Many kind of agents may lead the stomach into an inflamed statement; in first place, it could be due to *non-steroidal anti-inflammatory drugs* (NSAID) such as aspirin, ibuprofen, naproxen, etc. (Fig. 1), which are used in different treatments to calm down some specific illness, e.g. rheumatoid arthritis; in second place, inflamation could be due to abrasive compounds (alcohol, acids and others) or unbalanced diets where the stomach is damaged by its own gastric acid; in third place, long-term physical and/or mental stress that result in the production of excessive amounts of stomach acid; in last place, the infection caused by a well-known microorganism, *Helicobacter (H) pylori*. When stomach inflammation is not treated, mainly in the latter case, the illness could end in a gastric ulcer or in the worst case, in gastric cancer.

The signs and symptoms of gastritis depend on how long the problem has existed. If it occurs suddenly is called *acute gastritis*. In acute phase, superficial inflammation of the stomach causes the classic nausea and pain or discomfort in the upper abdomen. If it develops gradually is called *chronic gastritis*, and the symptoms might vary from those of acute, with a dull pain in the upper abdomen and a feeling of fullness and loss of appetite after a few bites of food. However, in some cases, people with chronic gastritis could not feel any of these symptoms. Another type is the *reactive or chemical gastritis,* which is defined as a foveolar elongation, tortuosity, and hypercellularity of the gastric surface epithelium, together with edema, vasodilatation, congestion of gastric lamina propria, and a paucity of inflammatory cells. This type of gastritis has been thought to result from duodenogastric bile reflux or the use of NSAIDs (Voutilainen et. al., 2002).

Clinicians differ on classification of the less common and specific forms of gastritis, particularly since there are so much overlap with *H. pylori* in development of chronic gastritis and its complications. Other types of gastritis that may be diagnosed include: a) *Acute stress gastritis*, the most serious form of gastritis which usually occurs in critical ill patients, such as those in intensive care, where stress erosions may develop suddenly as a result of severe trauma or stress to the stomach lining; b) *Atrophic gastritis,* resulting from chronic gastritis which is leading to atrophy, or decrease in size and wasting away of the gastric lining. Gastric atrophy is the final stage of chronic gastritis and may be a precursor of gastric cancer; c) *Superficial gastritis* is a term often used to describe the initial stages of chronic gastritis; d) *Uncommon specific forms of gastritis* include granulomatous, eosiniphilic and lymphocytic gastritis (Sipponen & Price, 2011).

A recent advance in the histopathology of gastritis is the replacement of the traditional definition of gastric atrophy, "loss of glands", with the new definition of gastric atrophy as the "loss of appropriate glands". By this definition, intestinalized glands represent atrophy when the metaplastic change involves the entire length of the original glandular unit and is considered as metaplastic atrophy. The application of the new definition has resulted in a high level of agreement among gastrointestinal pathologists trained in different cultural contexts. As there is obvious evidence that the severity and the extent of gastric atrophy relate to different risk levels of gastric cancer, an international group of gastroenterologists and pathologists, *Operative Link on Gastritis Assessment* (OLGA), has developed a system of histologically reporting gastritis by combining the semi-quantitative scoring scale of the updated Sydney system (Stolte & Meining, 2001) with the new definition of gastric atrophy. This system expresses the extent of gastric atrophy in terms of gastritis staging (Quach et. al., 2011).

Nowadays, one of the most important cases of gastritis is the infection by *H. pylori* strains. This affection was the attention focus that led to many researchers in the last years to study different branches of the infection process (Chenoll et. al.; 2011; Cui et. al., 2010; Ko et. al., 2010; Wittschier et. al., 2009; Wolle & Malfertheiner, 2007). However, equal important is the gastritis associated to the consumption of NSAIDs since these drugs are widely used to treat some pains. The chronic use of NSAIDs is a common cause of gastroduodenal erosions and peptic ulcers resulting, in many cases, in fatal haemorrhage. Aspirin, a famous NSAID, is thought to cause gastric damage by both, topical irritant effects on the gastric epithelium and systemic effects related to suppression of mucosal prostaglandin synthesis (Fig. 1). Inhibition of prostaglandin synthesis reduces mucosal defenses, including mucus and bicarbonate secretion, blood flow, epithelial cell turnover and repair, and mucosal immunocyte function. NSAIDs can also interfere with the healing of preexisting lesions and cause a fast drop in pH within the mucus cap (Shiotani et. al., 2008). In clinical practice, a prostaglandin E_1 derivative, misoprostol, and anti-acids, including proton pump inhibitors (PPIs) are routinely used for the treatment and prevention of NSAID enteropathy (Peura, 2004). The authors previously reported the usefulness of PPIs for healing the small intestinal mucosal injury in experimental animal models treated with NSAID; however, there are no clinical data on the usefulness of PPIs in such injuries. Some studies indicated the efficacy of misoprostol on NSAID-induced intestinal injuries (Kuroda et. al., 2006) whereas others reported no effectiveness (Davies et. al., 1993).

Among the most conventional drugs employed, PPIs such as omeprazole (OPZ) and its derivates are the most common although most of these drugs produce undesirable side effects and drug interactions (Pali-Schöll et. al., 2010, 2011). OPZ is available over-the-counter and in inexpensive generic formulations. It is promoted as a therapy for a range of disease states, from mild heartburn to aggressive *H. pylori* gastritis (40 mg can suppress over 80% of gastric acid secretion) being also one component of the triple-agent therapy (clarithromycin, amoxicillin, omeprazole) that is commonly used to eradicate *H. pylori* infection (Logan et. al., 1995). However, it is increasingly well-recognized that OPZ may also contribute to gastric gland toxicity, effect demonstrated by Kohler et. al. (2010) in rabbit gastric gland at physiologically relevant doses. Data suggest that thiol oxidation negatively affects intracellular proteins, which are susceptible to this chemical reaction. Authors also evinced that OPZ toxicity can be reversed with Vitamin C, thus providing an explanation for the previously observed benefits of Vitamin C co-administrated with OPZ in *H. pylori* gastritis (Kohler et. al., 2010).

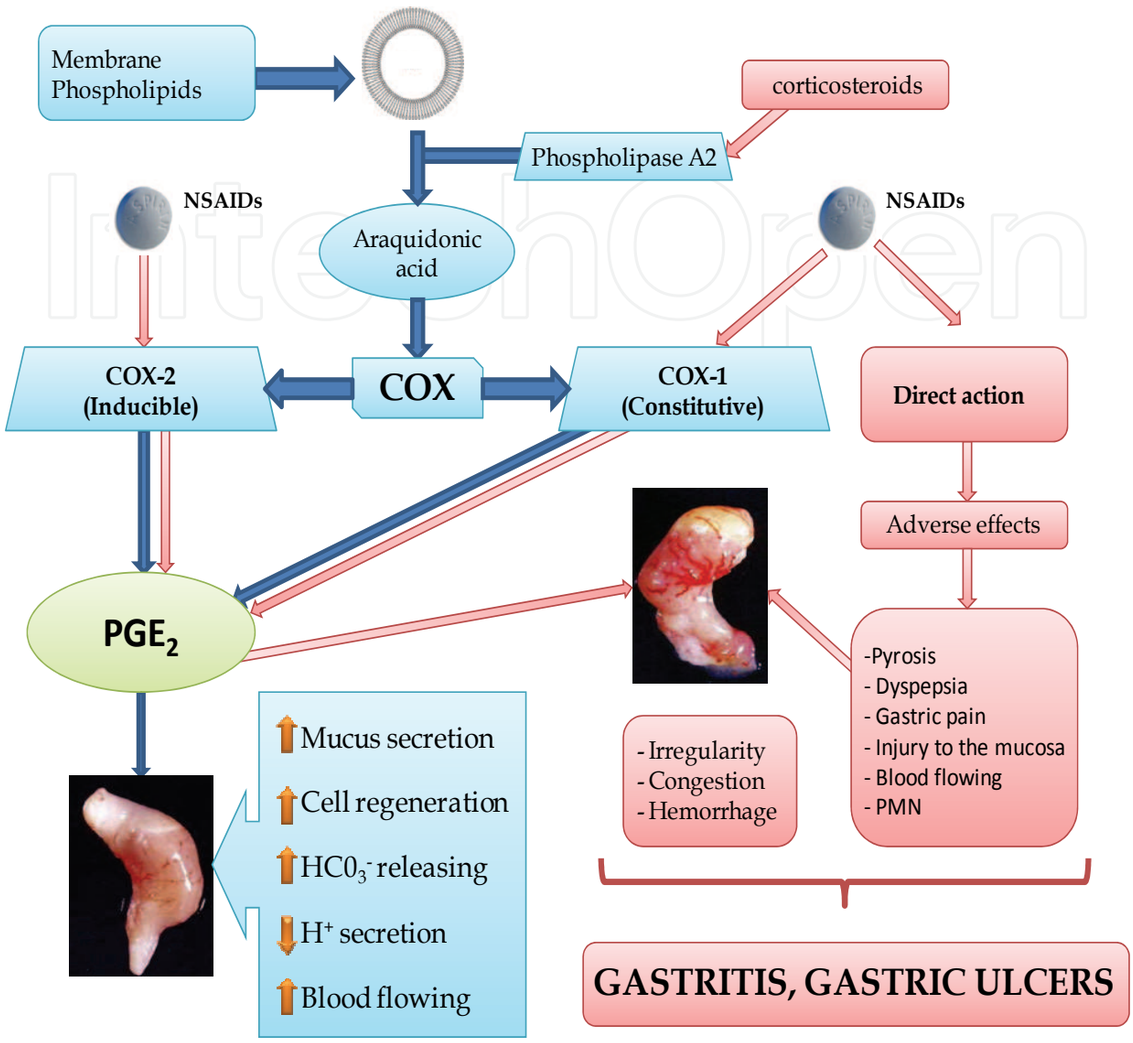

Fig. 1. Deleterious effects of NSAIDs after administration for long periods. Normal levels of PGE_2 helps gastric mucosa in keeping its normal characteristics. The intake of NSAIDs for long periods blocks the PGE_2 generating unbalance in the process and situations of cytotoxicity. These conditions lead gastric mucosa to be unhealthy and to come into gastritis process.

Anti-ulcer drugs are useful co-medications to protect the gastric mucosa from damage due to steroidal and non-steroidal drugs. This is especially relevant during long-term pain and anti-inflammatory therapies, e.g. in management of rheumatoid arthritis or inflammatory bowel disease. Inhibition or neutralization of gastric acid with so-called anti-ulcer drugs is necessary to treat gastritis and peptic ulcers, e.g. drugs such as PPIs, histamine type-2 receptor antagonist, sucralfate, or acid neutralizers like bismuth compounds (co-prescribed to protect the gastric mucosa). The therapy goal is to reach gastric pH levels above 4.5 (Julapalli & Graham, 2005) also for children (Tofil et. al., 2008) or even above 6.0 for treating bleeding

peptic ulcers (Pali-Schöll et. al., 2010). Avoidance of acid is needed to stop autodigestive processes and support mucosal healing in the extreme environment of the gastric lumen.
The success rate of conventional eradication of triple therapy is *ca.* 80% but it is constantly decreasing worldwide, mainly due to *H. pylori* antibiotic resistance (Wolle & Malfertheiner, 2007). In addition to the cost of the treatment, this kind of therapy involves taking too many drugs, which might cause side effects. Before the recognition of *H. pylori* as the main ethiological agent of chronic gastritis and peptic ulcer disease, research studies were focused on the gastroprotective, and/or anti-acid, and/or anti-inflammatory effects of traditional medicinal plants and their mode of action (Borrelli & Izzo, 2000; Castillo-Juarez et. al., 2009). Nowadays, studies of natural products in gastritis therapy have become the main research area around the world. The novel therapies include natural compounds or their derivates co-administered whith conventional drugs. These biological and natural products include beneficial microorganisms and plants.

2. Phytotherapy on gastric diseases

Plant derivates had been employed by population to prevent different kind of diseases for centuries. The knowledge of plant properties was acquired by ancient civilization that passed down from generation to generation until today and it is known as "popular medicine or traditional medicine" (Al-Qura´n, 2009). The number of plants species around the world is infinite and medicinal plants are used to treat different kind of pathologies like infection, internal and external inflammatory process, dermatological, urinary/genital, parasitosis, hemorrhoids, blood pressure, diabetic problems, etc., although the main usage is against gastrointestinal and respiratory problems (Al-Qura´n, 2009; De la Cruz et. al., 2007; Neves et. al., 2009; Rehecho et. al., 2010). The principal way of administration is like beverages, infusion or decoction of different parts of the plants (root, stem, seed, rhizome, bark, leaf, flowers, fruit or mixtures).
The surveys of popular medicine are useful to understanding the application of different plant species, the way of usage, administration and mainly their properties. In some cases, this kind of beverages could be effective against gastric mucosal inflammation (active chronic gastritis, erosive or not) and also against *H. pylori*, thus having antimicrobial activity besides anti-inflammatory effects. *Asteraceae* and *Lamiaceae* families are mainly used as gastroprotector, but at the same time they are also used against other diseases as wound healing, analgesic and anti-inflammatory. Most studies addressed the gastroprotector effect of different plants extracts in experimental models, e.g., gastritis (mucosal inflammation and mucosal infectious model), ulcers and even advanced processes like cancer model (De la Cruz et. al., 2007; Nergard et. al., 2004).
Beverages are known in different cultures as "tea". The *tea* is the extract obtained after maintaining raw plant materials in contact with hot water during certain time (the methodology could change if it is infusion or decoction, where decoction is an aggressive process of extraction). In this extract it is possible to find different compounds like polyphenols, flavonoids (glycosilated or not) and polysaccharides among others, that could interact with the mucosal barrier cells by changing the cell metabolism and modifying the cellular regulation; they could also display anti-*H. pylori* activity (Coşkun et. al., 2004; Formica & Regelson, 1995; Kahraman et. al., 2003; Lengsfeld et. al., 2004). Examples of some medicine plants against gastric disorders are presented in Table 1.

MEDICINAL PLANTS USED IN GASTRIC DISEASES AROUND THE WORLD							
Family	**Plant species**	**Common name**	**Part used**	**Mode of using**	**Traditional uses**	**Country/ region**	**References**
Acanthaceae	*Dicliptera peruviana* (Lam.) Juss.	Chuncho-chuncho (Q)	Leaves	Infusion	Stomachache	Perú (Canta, Lima)	De la Cruz et. al., 2007
Asteraceae	*Ageratum conyzoides* L.	-	Leaves	Infusion/ Decoction	Purgative, gastric ulcers, wound healing	West Africa, Asia and South America	Shirwaikar et. al., 2003
	Carlina acaulis L.	Caroelina (I)	Roots	Decoction	Stomachache	Italy (Valvestino)	Vitalini et. al., 2009
	Tagetes elliptica Smith	Chinche (S)	Leaves	Decoction	Stomachache, intestinal pain, digestive	Perú (Canta, Lima)	De la Cruz et. al., 2007
	Tagetes filifolia Lag.	Anis Serrano (S)	Aerial parts	Decoction	Stomachache, intestinal pain	Perú (Ancash)	Hammond et. al., 1998
	Vernonia kotschyana Sch.	-	Roots	Decoction, cold macerate	Gastrointestinal disorders, gastritis and gastroduodenal ulcers	Mali	Nergard et. al., 2004
Brassicaceae	*Brassica carinata* A. Braun.	Koza (ET)	Leaves	-	Gastritis	Ethiopia (Sheko)	Giday et. al., 2010
	Brassica nigra (L.) W.D.J.Koch	-	Seeds	-	Stomachache	Ethiopia (Sheko)	Giday et. al., 2010
Celastraceae	*Maytenus ilicifolia* Mart.	Espinheira santa (P)	Leaves	Infusion	Contraceptive, abortifacient, emenagogue, stomach disorders	Argentina, Brazil, Paraguay	Hatsuko Baggio et. al., 2007
Compositae	*Achillea tomentosa* L.	Mifoil (E)	Aerial parts	Infusion	Stomachache	Jordan (Showbak)	Al-Qura'n et. al., 2009
	Croton cajucara Benth	Sacaca (P)	Leaves barks	Infusion	Antiulcerogenic, gastrointestinal disorders	Brazil	Hiruma-Lima et. .al., 2000
Euphorbiaceae	*Jatropha isabelli* Muell.	Yagua rova (G)	Rhi-zome	Infusion/ Decoction	Gastroprotective	Paraguay, Argentina	Pertino et. al., 2007
Geraniaceae	*Geranium molle* L.	Erva de S. Roberto, Bico de pinga amor (P)	Aerial parts, roots	-	Stomach acidity and stomachache, cancer treatment, uterus inflammation	Portugal (Trás-os-Montes)	Neves et. al., 2009
	Pelargonium sidoides DC	Umckaloabo (A)	Roots	-	Antimicrobial effects	Southern Africa	Wittschier et. al., 2007
	Pelargonium roseum (Andrews)	Geranio (S)	Leaves	Infusion/ decoction	Digestive, carminative, gastritis,	Perú (Nor-Yauyos)	Elmann et. al. 2010; Rehecho et. al., 2010

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	W.T.Aiton				amigdalitis, hemorrhagias of the gastro-intestinal tube, others		
Krameriaceae	*Krameria lappacea* (dombey) Burdet et B. Simpson	Ratanya or Ratiñay (Q)	Roots, stems	Decoction	Diarrhea, inflammation, treatment of stomach cancer	Perú (Ancash)	Hammond et. al., 1998; De la Cruz et. al., 2007
Lamiaceae	*Glechoma hederacea* L.	Malvela, redondinha (P)	Aerial parts	-	Cough, stomach pain, gastritis and acidity, diarrhoea, renal problems, others	Portugal (Trás-os-Montes)	Neves et. al., 2009
Lamiaceae	*Melissa officinalis* L.	Cidreira (P)	Aerial parts	-	Intestinal gases and pain, digestion and bile stimulation, stomachache and gastritis, others.	Portugal (Trás-os-Montes)	Neves et. al., 2009
	Mentha piperita L.	Hortelão, Piperita, Pimenta (P); Menta (S)	Green leaves	Infusion	Digestive and antiflatulence to relieve gastritis, dyspepsia and biliar disorders, analgesic, rheuma, others	Portugal (Trás-os-Montes); Perú (Nor-Yauyos)	Neves et. al., 2009; Rehecho et. al., 2010
	Minthostachys mollis (Kunth.) Griseb.	Muña (S)	Leaves	Infusion	Digestive, carminative, emolient ,diuretic, to treat diarrhea, gastritis and colics, others	Perú (Nor-Yauyos)	Rehecho et. al., 2010; Schmidt-Lebuhn, 2008; De la Cruz et. al., 2007
	Marrubium vulgare L.	Mala mujer (S)	Leaves, stems	Infusion	Stomachache	Perú (Canta, Lima)	De la Cruz et. al., 2007
	Ocimun suave Willd	Olomora (A)	Leaves	Oil	Gastric ulcers, anti-cathartic, fever, stomachache	Tropical Asia ; west and east Africa	Tan et. al., 2002
Fabaceae	*Glycyrrhiza glabra* L.	Liquorice (E)	Roots	Syrup	Diuretic, gastric ulcer, expectorant	Mediterranean region, Asia Minor and Middle East	Al-Qura'n et. al., 2009; Wittschier et. al., 2009
Malvaceae	*Althaea rosea* (L.) Cav.	Rose mallow (E); Alteia (P)	Aerial parts, roots	Infusion	Abdominal inflammation, cough, colitis and	Jordan (Showbak); Portugal	Al-Qura'n et. al., 2009; Neves et. al.,

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					gastritis, pleura infection, dental growth and development, others	(Trás-os-Montes)	2009
	Abelmoschus esculentus (L.) Moench.	Okra	Fruits	Fresh fruits	Cholesterol reduction hypoglycemic, gastric irritation	Africa, Asia and America	Lengsfeld et. al., 2004
Papaveraceae	*Papaver rhoeas* L.	Poppy(E)	Leaves, stems	Decoction	Antidysenteric, antispasmodic	Jordan (Showbak)	Al-Qura'n et. al., 2009;
Piperaceae	*Peperomia galioides* HBK var *gladioides*	Congona (Q)	Aerial parts	Crushed/ Juice	Wounds healing, juice is swallowed to treat gastric ulcers	Perú (Ancash)	Hammond et al., 1998
Poaceae	*Cynodon dactylon* L.	Grama (P)	Dried roots	-	Diuretic, depurative, gastric inflammation	Portugal (Trás-os-Montes)	Neves et. al., 2009
Polygalaceae	*Polígala paniculata* Linneau	Barba-de-são-joão,vasso urinha branca or mimosa (P)	Aerial parts	-	Gastrprotector , asthma, bonchitis, stomach pain, diarrhea, anti-inflammatory, anti-spasmodic	Brazilian Atlantic coast	Rocha Lapa et. al., 2007
Punicaceae	*Punica granatum* L.	Pomegranate (E)	Fruits	Fresh fruits	Ulcer, hepatic damage, tonic fever, heart and gastric diseases, others	Europe, Indo-China, South Africa	Ajaikumar et. al., 2005
Rosaceae	*Sarcopetertum spinosum* (L.) Spach.	Thorny burnet (E)	Roots, fruits	Soaking	Renal calculi, antidiabetic, gastric diseases	Jordan (Showbak)	Al-Qura'n et. al., 2009;
Scrophulariaceae	*Calceolaria bicolor* Ruiz & Pav.	Zapatito or globo-globo (S)	Leaves, flowers	Infusion	Stomachache	Perú (Canta, Lima)	De la Cruz et. al., 2007
	Calceolaria lobata Cav.	Globo-globo (S)	Leaves, flowers	Infusion	Stomachache	Perú (Canta, Lima)	De la Cruz et. al., 2007
Solanaceae	*Hyoscyamus aureus* L.	Handbane (E)	Aerial parts	Decoction	Narcotic, hypnotic, stomachache	Jordan (Showbak)	Al-Qura'n et. al., 2009
Verbenaceae	*Lippia siodides* Cham.	-	Aerial parts	Hydro-alcoholic tincture	Wounds, mycoses, stomachache	Northeast Brazil	Barros Monteiro et. al., 2007
	Lippia integrifolia (Gris.) Hieron.	Incayuyo (S)	Aerial parts	Infusion/ Decoction	Dyspepsia, diuretic, cough treatment, indigestion, stomachache	Central and Northwest Argentina	Gorzalczany et. al., 2008

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Vochyslaceae	*Vochysla tucanorum*	Pau-tucano or pau-doce (P)	Leaves, barks	Infusion	Stomach inflammation, asthma, pulmonary congestion	South America	Camargo Gomes et al., 2009
Zingiberaceae	*Amomum subulatum* Roxb. N. O.	Heel kalan, Bari ilaichi (I)	Fruits	Infusion	Stomacheache, digestive, anti-emetic, carminative	India	Jafri et al., 2001

Table 1. Medicinal plants used for treatment gastric disorders according to native population of different areas around the world. The names of the species are given according to the regional language: (Q) *quechua*, an indigenous language from Bolivia, Perú, north-western of Argentina and Chile; (I) Italian; (S) Spanish; (E) English; (ET) Ethiopian; (P) Portuguese; and (G) *Guaraní*, a native language from Paraguay, south-western of Brazil and north-eastern of Argentina.

2.1 Effects of phenolic compounds of medicinal plants on gastritis

Gastritis troubles led to researchers to study the gastric mucosa in different animal model (rat, mouse, pig, rabbit, among others) where mucosal damage was induced by either chemical compounds (aspirin, HCl, ethanol, acetic acid, ibuprofen and more), stress (hypothermia), pylorus ligation or by microbiological agents (*H. pylori)*. These *in vivo* experimental assays are useful to resemble gastric diseases as gastritis or ulcers, and help us to understand the way of action of natural compounds or complex extract of medicinal plants. These compounds acts at different levels, e.g., immune mucosal response, H^+/K^+ pumping block, histamine release from mast cell, mucus wall structure, or prostaglandin (PG), myeloperoxidase (MPO) and nitric oxide (NO) regulation. Results obtained in the framemark of pre-clinical studies may be extrapolated to human cases (Elseweidy et. al., 2008; Hatsuko Baggio et. al., 2007; Wittschier et. al., 2007).

Flavonoids are phenolic compounds widely distributed in a wide variety of edible plants including leafy vegetables, fruits (strawbery, apple, etc.) and beverages (tea, red wine, beer, etc.). They have been reported to exert multiple biological effects, including antiviral, antithrombotic, anti-ischemic, anti-inflammatory, antihistaminic, antioxidant and free-radical scavenging abilities (Kahraman et. al., 2003). The phenolic compounds, widely distributed in plants, are the major compounds associated to human health and beneficial effects on gastritis, ulcer and cancer. The gastroprotective effect seems to be related to increase in endogenous PG, reduction in histamine secretion, scavenging oxygen-derived free radicals and even to gastric mucus stimulation (Rocha Lapa et. al., 2007; Tan et. al., 2002). The importance of such effects is to assure the gastric mucosal integrity by a dynamic balance and homeostasis between epithelial cell renewal and cellular apoptosis. In normal mammalian stomach, gastric mucosal cells have a rapid rate of turnover, being entirely replaced within 3–5 days as the result of rapid proliferation of progenitor cells at the isthmus and rapid cell death at the gastric surface (Park et. al., 2004).

However, treatment of gastric trouble with phenolic compounds is not always beneficial to gastritis condition. On one hand, the main effect is associated to anti-inflammatory response

due to PG and NO inhibition; on the other hand, PG is responsible for the integrity of gastric mucosa through activation of a cascade of mechanisms that include inhibition of gastric acid secretion, stimulation of mucus-bicarbonate secretion and apoptosis, as well as modulation of the blood flow (Atay et. al., 2000) while NO is also involved in regulation of gastric motility, mucus and acid secretion (Uchida et. al., 2001).

Different medicinal plants gave good results in gastric trouble treatments, effects that were related to the anti-inflammatory and antioxidant activity of phenolic compounds. As an example, the ethanol extract of *Ageratum conyzoides* L. (Asteraceae) exhibited DPPH (2,2-diphenyl-1-picrylhydrazyl, and stable radical) scavenging activity and NO generation in a concentration dependent manner, displaying greater gastroprotector effect (at dose levels of 500 and 750 mg/kg) than conventional drugs as misoprostol and famotidine, which are used in gastritis treatment (Shirwaikar et. al., 2003). Flavonoids including quercetin (3,5,7,3',4'-pentahydroxyflavone) and catechins (belonging to the flavan-3-ols group) were identified in *Maytenus ilicifolia* Mart. (Celastraceae) named in Brazil as "espinheira santa"; these compounds are related to antiulcerogenic activity and/or inhibition of gastric acid secretion, both *in vivo* and *in vitro* models. The effective gastric protection of *M. ilicifolia* flavonoid-rich fraction seems to be related to inhibition of gastric acid secretion (cyclooxygenase-prostaglandin system) rather than to glutathione and mucus regulation. The arabinogalactan fraction of this plant proved to be more effective than the flavonoid-rich fraction (Hatsuko Baggio et. al., 2007).

Quercetin is a common flavonoid distributed in a broad variety of vegetables, fruits and beverages as tea, red wine, beer, etc. It is known for its vasoactive properties but it also prevented gastric mucosal ulcers induced in rats by the administration of ethanol. The flavonoid prevented the increase of MPO activity (associated to this experimental model) thus protecting gastric mucosa from the deleterious effects of activated neutrophil infiltration (Kahraman et. al., 2003). Besides, its antioxidant property may reduce the lipid peroxidation and protein carbonyl compounds, increasing the superoxide dismutase activity which may play a role on gastric inflammation (Coskun et. al., 2004; Kahraman et. al., 2003, as cited in Serrano et. al., 1999). A novel natural product isolated from the *Scutellaria baicalensis* Georgi (Lamiaceae) roots (traditionally used against inflammation related diseases) is *Wogonin* (5,7-dihydroxy-8-methoxyflavone) which displayed similar effects of rebamipide (a well-known drug prescribed clinically for the treatment of gastritis and gastric ulcer) in the prevention of alcohol stomach injury (Park et. al., 2004). The target of these compounds would be the araquidonic acid metabolism including suppression of 5-*lipooxigenase* (LOX) and induction of ciclooxigenase-2 (COX-2), thus displaying strong anti-inflammatory activity on alcohol-related gastric disease (Cellotti & Laufer, 2001).

Besides phenolic compounds, terpenes from essential oil (EO) were also tested with outstanding results. Solidagenone is a labdane diterpene synthesized in rhizomes of *Solidago chilensis* Meyen (Asteraceae); it was used to treat symptomatologies related to inflammation. Solidagenone and its derivative solidagen-6β-ol on the HCl/ethanol-induced gastric lesions in mice was assessed at 100 mg/kg, being as active as lansoprazole at 20 mg/kg, but the mode of action remains to be elucidated (Schmeda-Hirschmann et. al., 2002). Oral pre-treatment of mice with EO from *Lippia sidoides* Cham. (Verbenaceae) caused inhibition of gastric lesions but did not stimulate mucus production; similar results were obtained with OPZ. Consequently, the gastroprotective mechanism induced by the *Lippia sidoides* EO would not be related with cytoprotection (Barros Monteiro et. al., 2007). The EO of *Croton*

sonderianus (Muell. Arg), *Amomum sublatum* (Jafri et. al., 2001), *Nigela sativa* (El-Abhar et. al., 2002) and *Croton cajucara* (Hiruma-Lima et. al., 2000) also showed protective activities on gastric mucosa. On the other hand, Anethole, a constituent present in many essential oils and its derivatives 1-hydroxy-1-(4-methoxyphenyl)-propane and 1-hydroxy-1-(4-methoxyphenyl)-2-*m*-chlorobenzoyl-propane seemed to have gastroprotector effect against ethanol-induced gastric lesions without modifying the mucus secretion (Freire et. al., 2005).
OPZ is an effective inhibitor of leukocyte infiltration, over-expression of adhesion molecules, IL-1a, and TNF-α production. When rats received OPZ, the lipid-peroxidation (expressed in terms of malondialdehyde and NO) decreased and pepsinogen secretion is stimulated, so its therapeutic effect could be related to its antioxidant property. On the other hand, authors compare the OPZ with natural compounds as curcuminoids; curcuminoids are isolated from dried roots of turmeric (*Curcuma longa*; Zingiberaceae) and when are administered in rats with induced gastritis the serum NO level tend to decrease compared to control group (without treatment). This effect could be associated to some mechanisms: Reduction of iNOS expression or scavenging of NO molecule. The free radicals scavenging properties of curcuminoids and maintaining cellular glutathione (GSH) stores in glandular stomach are factors acting to inhibit lipid peroxidation. Although curcuminoids significantly decreased serum gastrin level, it failed to stimulate pepsinogen release from chief cells (Elseweidy et. al., 2008).

2.2 Effectiveness of plants glycoside derivate compounds on *H. pylori* infection

Phenolic compounds as flavonoids and their derivates have also antimicrobial effects as it was demonstrated in cases of H. *pylori* infection (Atherton, 2006; Wittschier et. al., 2007, as cited in Warren and Marhall, 1983). Thus, catechins the main component of green tea, may inhibit the *H. pylori* urease (Matsubara et. al., 2003) and also when it is used together with sucralfate in Mongolian gerbils (Takabayashi et. al., 2004). The *green tea* has confirmed its bactericidal and bacteriostatic effects *in vitro* assays while *in vivo* studies demonstrated that its consumption when is taken before infection prevents gastric mucosal inflammation, and when is taken after infection diminishes the magnitude of gastritis. On the other hand, Castillo-Juarez et. al., (2009) studied the anti-*H. pylori* activity of 53 plants used in Mexican traditional medicine for gastrointestinal disorders. On the whole, about 77% of the assayed plants are active, having from moderate to strong antibacterial activity against *H. pylori*. Since some of these medicinal plants are used as condiments or food ingredients (e.g., *Ocimum basiliscum, Persea americana, Lippia berlandieri, Teloxys graveolens*), it seems that a frequent consumption could have a preventive effect in controlling the *H. pylori* population on infected people.
It has been suggested that the best way to prevent *H. pylori* infections is to eliminate the pathogen from its most common habitat, the gastric mucus layer but nowadays research is focused on a new property of some natural compounds, i.e., the anti-*H. pylori* adhesion. The adhesive process of *H. pylori* is based on bacterial adhesins located on its outer cell wall, which are responsible for interaction with mucosal glycoproteins and epithelial mucins; in this way the infection is established. Certain compounds, e.g. polysaccharides, may interact with the bacterial adhesins before adhesin-mucin adhesion avoiding the infection process. Studies on the complex nature of these adhesins are reported by Evans & Evans, (2000), Kusters et. al. (2006), and Wittschier et. al. (2009).
Adhesion to epithelial cells has been recognized as an essential step of the infectious process for virtually all bacterial pathogens and therefore many efforts are aimed to develop anti-

adhesion therapy. Sialyllactose (NeuAc[K2-3]Gal[L1-4]Glc), an inhibitor of the sialic acid-specifc adhesin of *H. pylori*, significantly reduced the load of the bacteria in monkeys (Burger et. al., 2000, as cited in Glaser, 1997). Accordingly, it would seem appropriate to target such therapy against *H. pylori* toward its association with the mucus before the pathogen adheres to the underlying epithelial cells and causes disease. However, the bulk production of oligosaccharides specific for the *H. pylori* lectins as anti-adhesion therapeutic agents is still a problem to be solved. As an alternative approach, dietary inhibitors might be the solution for certain infections, e.g. the inhibition of sialic acid-specific adhesion of *H. pylori* to human gastric mucus and to human erythrocytes by cranberry juice (Burger et. al., 2000). Another example is the root extracts of *Pelargonium sidoides* DC (Geraniaceae) a medicinal specie used to treat acute respiratory infections, which contains a polysaccharide fraction, EPs 7630, with anti-adhesive activity against *H. pylori* (Wittschier et. al., 2007). The roots of *Glycyrrhzia glabra* L. contain a raw polysaccharide fraction mainly composed of arabinose, galactose, glucose and glucuronic acid, which interacts with the outer-membrane surface adhesins of *H. pylori* avoiding its adhesion to mucus (Wittschier et. al., 2009). Authors consider this anti-adhesive effect an advantage to prevent re-infection by *H. pylori* after antibiotic eradication therapy.

These beneficial effects lead us to conclude that natural inhibitors of bacterial growth and inflammation may offer alternatives to antibiotic therapy for bacterial eradication and may be used as supplements to conventional eradication therapy in populations at high risk for gastric cancer (Stoicov et. al., 2009).

3. Lactic acid bacteria in gastritis

Lactic acid bacteria (LAB) are a group of *Gram*-positive, non-sporulating bacteria that include species of *Lactobacillus, Leuconostoc, Pediococcus* and *Streptococcus*. Dietary LAB refers to those species and strains that are used in food- and feed-fermentation processes. The term LAB is a group of organisms that are defined by their ability to produce a common end product, lactic acid, from the fermentation of sugar. LABs have limited biosynthetic abilities, and require pre-formed amino acids, B vitamins, purines, pyrimidines and, usually, a sugar as a carbon and energy source. LABs occupy a range of niches, including milk, plant surfaces and the oral cavity, gastrointestinal tract and vagina of vertebrates. Since ancient times, dietary LABs have been used to ferment a range of raw materials such as milk, which is used to produce cheese (species of *Lactococcus*) and yoghurts (species of *Streptococcus* and *Lactobacillus*). Consumed for centuries, LABs have a long and safe association with humans and their food (Wells & Mercenier, 2008).

Probiotic foods containing LAB have been proposed as a natural alternative to improve the general health status, preventing various gastrointestinal disorders such as gastric ulcers and inflammation related to *H. pylori* infection, gastrointestinal infections (Lebeer et. al., 2010) or antibiotic-associated diarrhea (Chen et. al., 2009; Gill & Guarner, 2004; Penner et. al., 2005) providing beneficial effects to the host by modulating immune functions, e.g. systemic cytokine production (Borchers et. al., 2009).

Different LAB species were tested in gastritis models mainly in treatment of *H. pylori* infection. Some reports suggested that certain species of exogenous lactobacilli have inhibitory effects on gastric infection (Cui et. al., 2010; Ryan et. al., 2008), e.g., *Lactobacillus (L.) reuteri* ATCC 55730 displayed ability to colonize the gastrointestinal tract and at the same time, to generate an inmune response when it was administered to human volunteers.

After administration, *L. reuteri* was detected by fluorescence in situ hybridization (FISH) in stomach and duodenum in some volunteers. According to these results it was suggested that stimulation of T-helper cells in human ileum could be a central mechanism of symbiosis for improving the health of the host gut (Valeur et. al., 2004). Similar results were obtained with a commercial product (Lacidofil®) containing *L. acidophilus* R0052 and *L. rhamnosus* R0011 (Johnson-Henry et. al., 2004). The probiotic mixture exhibits bactericidal activity in a dose-dependent manner by altering normal *H. pylori* morphology and thereby inhibiting its growth. Authors (Johnson-Henry et. al. 2004) suggested that probiotics are an attractive option for counteracting the effects caused by *H. pylori* infection for many reasons: LABs are able to resist acid and bile, to transiently remain under the harsh stomach conditions, and to competitively exclude pathogenic bacteria. *In vitro* studies showed that certain LAB strains and their cell-free cultures are able to inhibit or kill *H. pylori* (Michetti et. al., 1999; Sgouras et. al., 2005) as well as to reduce urease activity in the human gastric epithelial cells (AGS) by exclusion effect (Lin et. al., 2011). Likely, Ko et. al. (2010) evinced that *L. casei* ATCC 393-loaded chitosan microspheres inhibited *H. pylori* growth in *in vitro* assays.

B. bifidum CECT 7366 is also a promising microorganism against *H. pylori* infection. Results from *in vitro* and *in vivo* models (BALB/c mice) indicated that the strain partially relieves damage of gastric tissues caused by the pathogen and also decreases the *H. pylori* pathogenicity ratio (Chenoll et al., 2011).

The inclusion of probiotics in a conventional therapy (triple therapy: antibiotics and PPI) for *H. pylori* eradication was also evaluated (Kim et. al., 2008). *H. pylori*-infected patients were administered with yogurt (*Will* yogurt) containing *L. acidophilus* HY2177, *L. casei* HY2743, *Bifidobacterium longum* HY8001 and *Streptococcus thermophilus* B1; at the same time, they were treated according to the triple therapy. As a conclusion, the addition of yogurt did not reduce the side-effects of the therapy but increased the *H. pylori* eradication rate. Similar results had been reported using fermented milks with *L. acidophilus* and *L. casei* (M.J. Park et. al., 2001). Recently, Shirasawa et. al. (2010) evinced that the probiotic strain *B. bifidum* BF-1 is able to suppress IL-8 induction by *H. pylori* through inhibition of the genes related to the NF-κB signaling pathways. Other LAB strains were also effective against *H. pylori* in gastritis cases, e.g., *L. johnsonii* La1 displayed a pronounced anti-inflammatory effect on *H. pylori*-associated neutrophilic and lymphocytic infiltration in animal model by reducing pro-inflammatory chemokine levels in the gastric mucosa during the early stages of infection (Sgouras et. al., 2005). The markers for gastric inflammation such as prostaglandin I/II ratio (Sakamoto et. al., 2001) or ornithine decarboxylase activity (Linsalata et. al., 2004) also decreased in patients treated with probiotics, effects that persisted for several weeks after cessation of the treatment. Likely, Cui et. al. (2010) demonstrated that *L. fermenti* (CCTCC M 206110) and *L. acidophilus* LC, isolated from gastric biopsy materials of patients, could alleviate the gastric inflammation in *H. pylori*-infected BALB/c mice after oral administration. These results would indicate that specific lactobacilli strains may colonize the gastric mucosa, which may be related to their capacity to survive and develop in acidic environments (Cats et. al., 2003; Cui et. al., 2010; Gotteland & Cruchet, 2003; Mater et. al., 2005; Mozzi et. al., 2009; Valeur et. al., 2004; Wang et. al., 2004).

The effect of LAB on acute gastric lesions induced by chemical agents in experimental models was also reported. The administration of probiotic lactobacilli as *L. gasseri* OLL2716, *L. casei* GG, *L. paracasei* subsp. *paracasei* NTU 101 and *L. plantarum* NTU 102 to rats inhibits the gastric mucosa injury in HCl/ethanol-induced ulcer and pyloric ligation models (Lam et. al., 2007; Liu et. al., 2009; Uchida & Kurakazu, 2004).

Researchs on the functional properties of metabolites produced in food by LAB during fermentation such as exopolysaccharides (EPS) increased in recent years by assigning to biopolymers potential beneficial effects on human health. These effects include prebiotic effects (Dal Bello et. al., 2001; Korakli et. al., 2002; Salazar et. al., 2009), hypocholesterolemic effect (Pigeon et. al., 2002) and immunomodulatory and anti-tumor activity (Chabot et. al., 2001; Kitazawa et. al., 1998;) as well as other immune functions such as proliferation of T-lymphocytes (Forsén et. al., 1987), activation of macrophages and induction of cytokine production (Kitazawa et. al., 1991, 1996). The EPS could remain attached to the cell wall (capsular EPS) or be excreted into the environment in the form of slime or ropy EPS and its structure may vary depending, mainly, on the strain (van Hijum et. al., 2006). LABs produce two different kinds of EPS by using distinct biosynthetic pathways. The homo-polysaccharide (HoPS) are synthesized by extracellular glycansucrases and contain only one type of sugar (generally glucose) and the hetero-polysaccharide (HePS) that are assembled by cell wall-bound glycosyl-transferases from intracellular sugar nucleotide precursors, which may be constituted by 3 to 8 different monosaccharides (de Vuyst et. al., 2001). There are many EPS-producing LABs, e.g., *L. acidophilus, L. sakei, L. delb.* subsp. *bulgaricus, L. helveticus, L. paracasei, L. pentosus, L. plantarum, L., rhamnosus, L. reuteri, L. casei, Leuconostoc mesenteroides* and *Streptococcus thermophilus* although it is a strain-dependent property (Mozzi et. al., 2006; Ruas-Madiedo et. al., 2002).

It is known that the EPS of LAB have many functional properties; they have effect on the mucosal immune system, could avoid the *H. pylori* adhesion to the mucus layer, and could make the mucus layer stronger, among others. Despite these beneficial properties, there are few studies in the literature concerning the protection of gastric epithelium by EPS-producing LAB or the role they could play in the gastric injury. Ruas-Madiedo et. al. (2006) suggested that the biopolymers are involved in the mechanism of competitive exclusion of probiotics through adherence to the mucus and Nagaoka et. al. (1994) reported anti-ulcer effects of the cell wall polysaccharide of bifidobacteria, lactobacilli and streptococci strains, which were attributed to the high rhamnose content of the polymers (> 60%).

Rodríguez et al. (2009, 2010) reported the first evidences on the beneficial effects of both the EPS-producing LAB strains and the biopolymer on gastritis experimental animal models using acetyl salicylic acid (ASA) as gastritis inductor. Authors demonstrated the gastroprotector effect of fermented milk with the EPS-producing strain *S. thermophilus* CRL 1190 on superficial chronic gastritis in BALB/c mice as preventive and therapeutic treatment. Other EPS-producing strains *S. thermophilus* CRL 804 and CRL 638, and *L. casei* CRL 87 were also evaluated *in vivo* assays but with unsuccessful results. The biopolymers had different physical-chemical properties: *S. thermophilus* CRL 1190 produced a high molecular mass EPS (1500 kDa) composed of D-glucose and D-galactose; *S. thermophilus* CRL 638, a high EPS (1200 kDa) composed of D-glucose, D-galactose and N-acetilglucosamine; *S. thermophilus* CRL 804 produced a low EPS (95 kDa) composed of D-galactose and L-rhamnose, and at last, *L. casei* CRL 87 produced a low EPS (800 kDa) composed of D-glucose, D-galactose and L-rhamnose. The strains CRL 1190 and CRL 87 also produced capsular polysaccharide in addition to the slime EPS in milk and was able to form ropy milk cultures similar to CRL 638, while the strain CRL 804 was negative for both the capsular and ropy phenotypes (Mozzi et. al., 2006).

The fermented milk with *S. thermophilus* CRL 1190 (FM-1190) as well as the EPS (EPS-1190) suspended in milk (but not in water) was the only one effective in both the therapeutic and preventive treatment of chronic gastritis in animal models. Results obtained were similar to

that of OPZ but with the advantage of not having side effects. The FM-1190 also activated the synthesis of mucin, which in turn led to an increase in the thickness of the mucus layer and in the amount of mucus of the body and antrum that were decreased after ASA administration. The recovery of the gastric defensive systems and the mucus-bicarbonate layer in animals fed FM-1190 favored the recovery of the damaged gastric mucosa. These evidences support previous reports obtained in rats with acute gastric damage which were fed with probiotic lactobacilli (Nam et. al., 2005; Lam et. al., 2007).

The fermented milk FM-1190 and the EPS-1190 were able to modulate the gastric inflammatory response at the immune system level (decrease in the number of cells producing pro-inflammatory cytokines, INF-γ and TNF-α, and increase in the number of cells producing regulatory cytokines, such as IL-10). These promising results, however, can not be ascribed to all EPS-producing LABs because of the complexity of the phenomenon. The fermented milk with the strain *S. thermophillus* CRL 804 which produced an EPS formed by rhamnose and galactose did not display any anti-gastritis effect in contrast to the results obtained by Nagaoka et. al. (1994) with cell wall polysaccharides containing rhamnose. In contrast to the FM-1190, the fermented milk with *S. thermophilus* CRL 638 generated a great stomach inflammation in animal model, without gastritis induction, after 7d of feeding.

Studies of scanning electronic microscopy (SEM) confirmed a greater secretion of gastric mucus after oral administration of FM-1190; they also put in evidence the presence of the strain CRL 1190 in the stomach at least 15 days after finishing the administration of the fermented milk. These confirmed previous reports concerning the ability of *S. thermophilus* strains to survive the passage through the gastrointestinal tract and to exert the beneficial effects on various gastrointestinal disorders (Brigidi et. al., 2003; Delorme, 2008; Guarner et. al., 2005; Mater et. al., 2005; Vinderola & Reinheimer, 2003). Studies performed in *in vitro* gastric system evinced a partially degradation of the EPS-1190 when subjected to this harsh conditions (Mozzi et. al., 2009). From results from *in vivo* and *in vitro* studies, it is assumed that the biopolymer may still exert its beneficial properties in the stomach even partially degraded.

Several studies reported that high molecular mass-polysaccharides of different sources (herbs, marine microalgae and fungi) have anti-ulcer, anti-inflammatory or inmuno-stimulatory effects related to anti-secretory activity of acid and pepsin, inmuno-stimulation, stimulation of gastric mucus, increase in gastric prostaglandin levels and partially suppression of TNF-α genes (Gao et. al., 2002, 2004; Yamada, 1995; Yim et. al., 2005). However, the beneficial effects can not be only attributed to the size of the polymer. The different effect obtained with the strains CRL 1190, CRL 804 and CRL 638 evinced that the phenomenon is strongly strain-dependent and complex.

Whey proteins as α-lactalbumin would also have gastroprotector effect (Matsumoto et. al., 2001; Rosaneli et. al., 2004; Ushida et. al., 2003, 2007); so, the interaction of EPS-producing LAB or the EPS with milk proteins may be a key factor in gastroprotection. Studies on the interaction between EPS and milk proteins is complex since EPS are gradually produced during fermentation, and the characteristics of the proteins such as charge and hydrophobicity may change during fermentation and consequently the interaction between them. The EPSs bind water and increase the moisture in the non-fat portion, interfere with protein-protein interactions reducing the rigidity of the protein network, and increase the viscosity of the serum phase (Hassan, 2008). Similar research was carried out by Ayala-Hernandez et. al. (2008) who studied the interaction between milk proteins and the EPS produced by *Lactococcus lactis* ssp. *cremoris* using SEM techniques. They observed that EPS

molecules clearly interact not only with caseins but also with whey proteins and play an active role in the formation of the aggregates.
Considering these statements, it is assumed that in fermented milks, e.g., FM-1190, the LAB strains and the EPS together with the milk and whey proteins perform a stable three-dimensional complex network, which is attached to the gastric mucosa preferably to the mucus layer, when it is administered to animals. Thus, the EPS could interact with the mucosal tissue exerting an inmunomodulador effect, thus avoiding inflammation and or making the mucus barrier stronger, which could also affect *H. pylori* adhesion. The mode of action of probiotic LAB strains and their EPS in gastritis has not yet been completely elucidated.

4. Conclusion

Gastritis is the most common illness associated to the stomach, and it is the beginning of different complication that led to ulcers and, in the worst case, gastric cancer. The disease is due to different causes as an imbalanced diet, intake of aggressive agents, or stress process (related to neurological condition) which is very common nowadays due to the population rhythm of life. However, the most aggressive case is due to *H. pylori* infection. Allopathic treatment of gastritis includes different conventional drugs acting as inhibitors of the proton pump and of the acid gastric production, thus helping the stomach to balance the acid condition when there is an inflammation, infection or injury. The increase in gastric pH is a necessary condition to stop autodigestive processes and support mucosal healing in the extreme environment of the gastric lumen; this effect is mainly required in the treatment of peptic ulcer. Other drugs are also used, which exert different effects on the gastric mucosa tissue to alleviate the inflamed condition, e.g., by stimulation of the mucus synthesis, inhibition of the stomach motility, or by displaying anti-*H. pylori* effects, among other properties. The disadvantages of employing these drugs for long periods, such as ranitidine, OPZ and derivates, and antibiotics in the case of *H. pylori* infection, is that many of them could have side effects.
Medicinal plants and their effect in different kind of diseases, on the basis of ancient knowledge and supported by scientific evidences, emerge as an alternative therapy to cure or prevent gastric disorders. The beneficial effects are mainly related to anti-inflammatory activity and the ability to maintain a balance in the mucus barrier and mucosal renovation. Phenolic compounds, polysaccharides and derivates in different combinations are mainly involved in gastric protection, effect associated in some cases to modulation of the immune system (cytokine regulation) and mucus stimulation.
Probiotic lactic acid bacteria and probiotic foods, which beneficial effects on the gut health are strongly supported by scientific evidences, also appear as a novel and promising bio-alternative for gastritis treatment. Recent evidences indicate that some exopolysaccharide (EPS)-producing lactic acid bacteria are able to regulate and to revert the gastritis process prompted by NSAIDs, a property that is mainly related to the EPS produced by specific strains. The biopolymers could also interact with *H. pylori* and inhibit its adhesion to mucus barrier thus avoiding the infection process. The mode of action of probiotics and their EPS, which involves modulation of the immune system, increase in gastric pH, and stimulation of mucus production, among other cascade reactions, is under study.
Considering the beneficial effects of these bio-treatments in gastritis processes, it would be advisable to include them as adjunct in conventional treatments programs to reduce the side effect derived from the intake of drugs during long periods.

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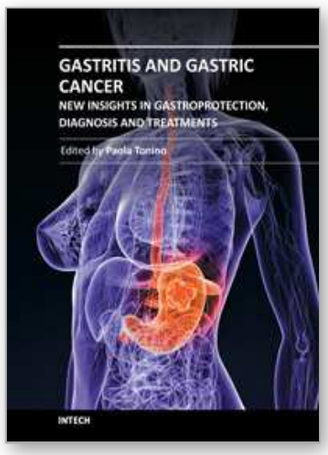

Gastritis and Gastric Cancer - New Insights in Gastroprotection, Diagnosis and Treatments

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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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