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

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

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

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

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

Gastroprotective Mechanisms

*Cirlane Alves Araujo de Lima, Robson Silva de Lima,
Jesica Batista de Souza, Ariel de Souza Graça,
Sara Maria Thomazzi, Josemar Sena Batista
and Charles dos Santos Estevam*

Abstract

Gastric ulcer (GU), a common type of peptic ulcer, results from an imbalance in the action of protective and aggressive agents. Gastroprotective mechanisms are mucus layer, gastric epithelium, gastric blood flow, gastric neurons, mucosal repair capacity, and immune system. Thus, the aim of this chapter was to provide an update on gastroprotective mechanisms. It was carried out through searches in PubMed covering the years 2016–2021 using several keywords. This survey resulted in 428 articles, of which 110 were cited in this chapter. It was reviewed the status of gastroprotective mechanisms and highlighted that mucins can act as a filter; gastric epithelial defenses are composed of the cell barrier, stem cells, and sensors on the mucosal surface; nitric oxide (NO) and hydrogen sulfide (H₂S) act for gastric blood flow homeostasis (GBF); the main effector neurons in the gastric mucosa are cholinergic, nitrergic and VIPergic, and oxytocin can activate neurons; repair of the gastric mucosa requires complex biological responses; the immune system regulates the entry of antigens and pathogens. The main knowledge about gastroprotective mechanisms remains unchanged. However, we conclude that there has been progressing in this area.

Keywords: hydrochloric acid, pepsin, mucus, gastric epithelium, gastric blood flow, gastric neurons, mucosal repair, immune system

1. Introduction

Gastric ulcer (GU) is a common type of peptic ulcer that stands out among different types of ulcers due to the frequency of occurrence in the digestive tract. In addition, it affects approximately 10% of the world's population [1, 2]. Although the number of deaths from GU complications has decreased in recent years, it still seriously affects the patient's quality of life and requires studies in this regard [3]. GU occurs as a gastric mucosal lesion that progresses to the lining of the stomach and becomes chronic and recurrent [4, 5]. In gastric ulcers, different stages of necrosis occur in the glands of the stomach tissue, participating in the formation process, neutrophil infiltration, reduced blood flow, increased oxidative stress and inflammation [6]. These changes are due to the imbalance between protective agents (e.g., production of mucus, bicarbonate, and prostaglandins) and aggressive agents (e.g., secretion of acid and pepsin) caused by different sources. People suffering from stomach ulcers report stomach pains feeling when eating, nausea, vomiting often accompanied by blood, high temperature feeling in the stomach, burning, and bloating.

The main causes of GU includes nonsteroidal anti-inflammatory drugs prolonged use, alcohol intake, smoking, ischemia, delayed gastric emptying [7], chronic inflammation due to exogenous factors, stress (trauma, shock, and burns), *Helicobacter pylori* infection [8, 9] and some dietary habits. When the stomach is exposed to adverse conditions, it tends to increase the production of acid and pepsin and to decrease the production of mucus and other factors that protect the gastric mucosa, which leads to epithelial damage.

The mucosal epithelial damage causes disorganization of the simple columnar epithelium, capillary blood congestion, edema, and necrosis of the gastric mucosa [10]. When the gastric mucosa is injured, there is a continuous secretion of reactive oxygen species (ROS) leading to lipid peroxidation and, consequently, to a decline in the antioxidant defense mechanism [8, 11]. Reactive nitrogen species (RNS) also participate in this process. Both ROS and RNS lead to ulcerative gastritis, stimulate macrophages, and increase the release of inflammatory cytokines [tumor necrosis factor (TNF)- α and interleukin (IL)-6] and nuclear factor kappa B (NF- κ B) signaling [12].

The most used drugs for the treatment of gastric ulcers in the last 5 years are proton pump inhibitors (PPI), histamine H₂ receptor antagonists, and antibiotics eradication of *H. pylori* [13]. However, they cause several adverse effects. PPI can produce hypomagnesemia, cutaneous lupus erythematosus, osteoporosis-related fracture, acute kidney injury, and an increased risk of gastrointestinal infections [14]. Ranitidine can cause cancer in humans due to the presence of impurities containing N-nitrosodimethylamine [15]. Antibiotics, on the other hand, can develop bacterial resistance in users [16].

It is important to highlight that, although therapies with anti-H₂ and PPI are already well established for the treatment of UG, they do not prevent its recurrence and may occur drug interactions in some patients [17, 18]. In view of these unfavorable properties, many researchers have searched for more effective and safer alternative anti-ulcer agents to treat GU that have less or no adverse effects [11, 17, 19].

Therefore, it is necessary to know the gastroprotective mechanisms which are essential to the development of new drugs for the prevention and treatment of GU. In general, gastroprotective mechanisms are mucus layer, gastric epithelium, gastric blood flow, mucosal repair capacity, gastric neurons, and immune system [20–25]. Therefore, the aim of this research was to discuss the gastroprotective mechanisms in the stomach and update the existing knowledge on the subject.

2. Method

This chapter presents an update on gastroprotective mechanisms based on research in PUBMED using the following words—gastroprotective action mechanisms (113 articles); gastric protection against hydrochloric acid and pepsin (4); function of hydrochloric acid and pepsin (31); types of pepsinogen in the stomach (16); function of gastric mucus and bicarbonate (7); gastric mucus and bicarbonate (9); gastric mucus formation (258); gastric sodium bicarbonate (91); defense of the gastric epithelium (43); blood flow gastric defense (15); vascular endothelial growth factor in gastric defense (4); gastric neurons mucosal defense (5); IL-1 β gastric defense (16); stomach interneurons (9). A total of 428 articles were found on the topic researched between the years 2016 to 2021 and, of these, 110 were cited for containing relevant content within the scope of this chapter. The main approach of this update was on the gastroprotective mechanisms related to the prevention and treatment of gastric ulcers.

3. Gastroprotective mechanisms

3.1 Hydrochloric acid and pepsin

Increased production of HCL in the stomach leads to increased conversion of pepsinogen to pepsin. Together, these two substances can cause loss of gastric integrity and constitute harmful agents for the stomach.

The gastric juice is a liquid constituted mainly by HCl, lipase, and pepsin [26]. HCl acts actively in food digestion and is part of the protective barrier against pathogens ingested in food or water [27]. HCl is produced mainly by parietal cells and its secretion is stimulated by gastrin hormone in the gastric antrum G cells in response to food intake. Its secretion is mediated by vagal stimulation and gastrin-releasing peptides [23, 27]. In addition, other endogenous agents also participate in gastric acid secretion, such as histamine released from enterochromaffin cells (paracrine pathway) and acetylcholine from enteric neurons (neurocrine pathway).

Pepsin is the enzyme contained in gastric juice responsible for the digestion of proteins. It is produced by the main cells from the inactive form “pepsinogen” stored in zymogen granules. Under physiological or chemical signals, these granules secrete pepsinogen into the gastric cavity, where is activated into pepsin in the presence of HCl from the gastric juice [24, 28, 29]. The main cells secrete pepsin in its inactive form that prevents the self-digestion of protective proteins in the lining of the gastrointestinal tract. The pepsin activation only occurs in the presence of HCl [27].

There are two types of pepsinogens, type A (with three subtypes A3, A4, and A5) and type C [28, 29]. Other authors refer to pepsinogen as type I and type II. However, type A pepsinogen has characteristics common to type I and, type C to type II. Type I is formed by main gastric cells, whereas type II is formed in the fundic glands in the stomach, pyloric glands, and Brunner’s glands in the duodenum [30]. Type I is reduced in cases of stomach mucosa atrophy below 30 µg/L, and type II can be secreted into the gastric lumen or the circulation, and its concentration in the blood increases in case of gastritis of different origins [31]. In another study, the authors found a relationship between gastric cancer risk and a low level of serum pepsinogen [32]. The diagnosis of atrophic gastritis of the body (AGB) is evaluated by the relationship between the pepsinogen I blood concentration and pepsinogen I versus II proportion (if < 3 means that the patient has AGB), whose values represent the mass of glandulocytes and the main glands in the body region of the stomach [31].

Pepsinogen type A can be used as a diagnostic biomarker for chronic atrophic gastritis and gastric neoplasms [33], and type C pepsinogen as a biomarker for prediction, diagnosis, and prognosis of different types of cancer because it has a broad-spectrum expression characteristic [28].

In a study to assess clinicopathological features of gastric adenocarcinoma of the fundic gland by endoscopy, 90–100% of clinical cases showed positive immunostaining for type I pepsinogen [34]. The honeycomb gastric cancer had negative immunostaining for pepsinogen type I/H⁺/K⁺-ATPase [35]. In another study, the authors reported that type I pepsinogen levels were found to be increased in individuals with gastric cancer and peptic ulcers affected by type I *H. pylori* (which expresses CagA and VacA type proteins) [30]. These authors argue that the different levels of pepsinogen found are probably due to the use of different methods of analysis or population of patients involved and, perhaps, it is uncertain to assess cancer risks and its progression by pepsinogen levels, which require other more accurate tests, such as endoscopy.

3.2 Mucus layer

The mucous epithelium promotes the internal protection of the organs in relation to the external environment (respiratory, digestive, urinary, and reproductive systems) [36]. In the stomach, the mucus-bicarbonate layer has a peculiar role, because it has gelling property and forms a physical barrier against the self-digestion of the epithelium by HCl and pepsin. It covers the mucosal surface and ensures acid neutralization, maintaining the basophilic pH [37–42]. Mucus is a viscoelastic hydrogel with a thickness of ≥ 1 mm formed mostly by mucin molecules produced by goblet cells [43]. It has an antioxidant and protective effect on epithelial surfaces against dehydration, shear stress, and infections [40, 44], and promotes the protection of the gastric mucosa in host defense against pathogens and gastric irritants [45].

The mucus barrier in the stomach is composed of two layers, a very adherent inner layer and a poorly adherent outer layer [46]. This barrier is formed by water ($\leq 90\%$), some salts, carbohydrates, lipids, mucins and lectins [46, 47]. The basic components of mucus are mucin glycoproteins (such as Muc5AC, Muc1, and MUC6) and lectins such as trefoil factor (TFF) 1 and 2 and *Griffonia simplicifolia* II (GSA-II), which bind to MUC6 and stabilize gastric mucus [38, 47–50]. It is noteworthy that mucins are mainly responsible for the viscous character of mucus and TFFs are typical constituents of mucus-secreting epithelia [28, 50, 51]. In gastric neoplasms with differentiation of the oxyntic glands, immature MUC6 is produced from the pyloric gland, with an absence of $\alpha 1,4$ -linked N-acetylglucosamines glycosylation [52], MUC6 positive immunostaining occurs in gastric adenocarcinoma of the fundic gland [34] and MUC5AC/MUC6 positive immunostaining for honeycomb gastric cancer [35].

Mucus can be readily permeable to H^+ and HCO_3^- ions, preventing most HCO_3^- secreted by epithelial cells from mixing with acid, keeping the pH gradient almost neutral [38]. The hypothesis of hydrogen sequestration by mucus is as follows—hydrogen is bound to mucin polymers and the degradation of mucin polymers in the presence of activated pepsin would decrease the capacity of hydrogen sequestration [39], being released in the light of the stomach. On the mucosal surface, the pH gradient is almost neutral due to the retention of HCO_3^- [37, 47]. HCO_3^- is an inorganic alkaline salt that neutralizes excess gastric acidity. The conversion of CO_2 to HCO_3^- is catalyzed by carbonic anhydrase (metalloenzymes) at low pH and by hypoxia in the gastric mucosa [53].

To maintain a balanced pH gradient, HCO_3^- secretion must be in the same order of magnitude as hydrogen secretion according to a model based on the physics of ion transport within the mucosal layer according to the Nernst–Planck Equation [39]. In a neutral environment, mucus forms a tangle of polymers with adequate conformations for the passage of gases and nutrients and constitutes a lubricant against shear stress. Under acidic conditions, mucus constitutes a weak gel with adequate elasticity against gastric acids [41].

Mucins are high molecular weight glycoproteins that can act as a filter to prevent or delay the diffusion of harmful molecules and the entry of pathogens [44, 51]. If mucin production is altered and the mucus layer is damaged, infections such as *H. pylori* can occur [44, 45]. With a greater supply of water, there is a greater separation of mucin chains, as their density formed by interactions between mucins is reduced and may compromise their bactericidal function [41]. In this sense, adequate mucin production and balanced hydration promote the ideal structural condition against pathogen invasion.

Mucosal lining factors are directly involved in normalizing the gastric environment and GU healing [54, 55]. During the process of normalization of the gastric

environment, the production of mucus can be stimulated by nitric oxide (NO) and hydrogen sulfide (H₂S) donors that interact with each other to produce mucus [56].

In ethanol-induced GU experiments, it is observed that in the negative control animals there is a reduction in mucus production, decrease in pH, and increase in gastric acidity [57]. After dissolving the mucus, ethanol inhibits the protective capacity of the mucosa, increases its permeability (allowing transport of large molecules) and leads to the dissolution of lipoproteins in the cell membrane [42, 57].

3.3 Gastric epithelium

The gastric epithelium is formed by a continuous layer of narrow junctions cells with secretory and digestive functions [57, 58]. The main cells that the infectious agent *H. pylori* tries to attach are the gastric epithelial cells [59].

Some of the protective mechanisms of the gastric epithelium include—cell barrier against the entry of toxic or pathogenic agents, stem cells that differentiate into gastric epithelial cells, and sensors located on the mucosal surface capable of detecting microbial antigens, leading to the induction of autonomic mechanisms that result in the effective killing of bacteria [60–62]. One of the proteins responsible for supporting the integrity of the protective barrier is β -catenin, acting as an adherent junction molecule together with E-cadherin [63].

This epithelial barrier is continually renewed by a small population of long-lived dividing stem cells; the renewal period is short, typically ranging from 3 to 10 days depending on your location [64, 65]. The generations of basal stem cells directly neutralize the colonization by pathogens by sensing their approach, promoting the regeneration of clean epithelial cells in the lumen [60].

In addition to the mucosa having cell renewal mechanisms for its own maintenance and secreting hydrochloric acid, pepsin and mucus under normal physiological conditions, it has sensors located on the cell surface that lead to the induction of the invader's death by autonomous effector mechanisms [60]. For example, when gastric epithelial cells become infected by pathogens, they produce factors that recruit immune cells, such as matrix metalloproteinases [66].

3.4 Gastric blood flow

Adequate gastric blood flow (GBF) is a protective factor for the gastric mucosa that has the primary role of maintaining its integrity [25, 56].

Gastric stress-related mucosal disease (SRMD) can lead to ulceration by compromised gastric defenses through gastrointestinal hypoperfusion and, subsequently, ischemia [37]. In order to repair the gastric injury caused by stress, angiotensin (1–7), a metabolite of the renin angiotensin system, NO, H₂S or carbon monoxide (CO) and ghrelin, nesfatin-1 and apelin peptides, participate; together, all these factors promote an increase in gastric microcirculation [67].

Among mediators that induce gastric damage are oxidative stress and inflammation [68]. Ethanol is the main cause of gastric damage in this regard, because it causes damage to vascular endothelial cells of the gastric mucosa, promotes hypoxia by increasing the production of ROS, induces the release of inflammatory mediators, and suppresses the activity of antioxidant enzymes [42, 69, 70], resulting in decreased microcirculation, submucosal edema, and development of hemorrhagic gastritis [45, 70]. Restoration of damaged blood flow in the gastric mucosa by ethanol requires removal of free radicals, pro-inflammatory cytokines, and inhibition of the transcription factor NF- κ B-p65 [70–72].

Aspirin-treated rats have bleeding lesions in the gastric mucosa due to decreased mucus production due to cyclooxygenase blockade, inhibition of endogenous

prostaglandin (PGs) synthesis, and decreased GBF [73–75]. The use of this drug also promotes an increase of almost 50% in the number of neurons that express the pituitary adenylate cyclase-activating polypeptide (PACAP), increasing gastric microcirculation [76]. In this sense, the resumption of the production of prostaglandins, as well as the increase in the endogenous production of CO and H₂S (produced by the enzymes cystathionine- γ -lyase/cystathionine- β -synthase/3-mercaptopyruvate sulfurtransferase or heme oxygenases) [75] and decreased number of PACAP-expressing neurons may contribute to the restoration of injured gastric mucosa and GBF. It is noteworthy that the interaction of NO and H₂S gaso-transmitters is very important for the maintenance of GBF and vascular homeostasis [77], as well as its restoration.

Other endogenous factors that contribute to mucosal recovery, as well as blood flow, will be discussed in the topic of mucosal repair capacity.

3.5 Gastric neurons

The main neurons present in the stomach are gastric interneurons and motor neurons [78].

The vagus nerve is responsible for stimulating the secretion of hydrochloric acid, and one of the first treatments for GU was based on severing this nerve in order to decrease acid production. Gastric neurons act on gastric motility, interact with hormones, regulate HCl and bicarbonate secretion, and induce immune responses [74, 76, 78, 79]. As an example of the interaction with hormones, oxytocin (OT) administered in the ventral tegmental area (VTA) can activate dopamine neurons in the dopamine pathway in the nucleus accumbens through OT receptors and improve the dysfunction caused by stress in the gastric mucosa, reducing the ulcer area, stimulating mucus production, and increasing gastric pH [80].

As part of the mechanism of gastric mucosal integrity, neuropeptides released by afferent C fibers sensitive to capsaicin participate [81].

Human gastric enteric neurons have been identified, mainly in the ganglionic plexus developed between the longitudinal and circular layers of the tunica muscularis called the myenteric plexus [82]. The main neurons identified were—with nonspecific dendritic architecture, cholinergic and nitrergic neurons; cholinergic type I uniaxonal spinous neurons are considered excitatory motor neurons or interneurons in the stomach; type I spinous neurons reactive to (NOS)₊ and vasoactive intestinal peptide (VIP)₊ considered inhibitory motor neurons and/or interneurons; and type II multiaxonal neurons (SOM)₊ co-reactive for somatostatin. However studies are needed to assess the role of these neurons in gastric protection.

Among molecules that participate on the gastric ulcer defense mechanisms we can cite neuronal growth factor (NGF), PACAP, calcitonin gene-related peptide (CGRP) and NO. Reduction of NGF expression in gastric mucosa endothelial cells impairs endothelial cell viability, angiogenesis, and GU healing [74]. There is an increase in the number of PACAP-expressing neurons in the dorsal vagal nucleus in acetylsalicylic acid-induced gastritis, as described above [76], indicating that it is a factor in the neuronal response of inflammation in the stomach, acting to protect the gastric mucosa by reducing the secretion of gastric acid. CGRP and NO have a vasodilating action, probably participate in the mechanism of gastroprotection and increase in GBF in stress-induced damage to the gastric mucosa [81].

It is noteworthy that activation of the gamma-aminobutyric acid (GABA) A receptor of peripheral sensory afferent neurons in the stomach also appears to be involved in gastroprotection [83].

3.6 Ability to repair the mucosa

The integrity of the gastric epithelium depends on the maintenance of redox balance, antioxidant defense, and blood flow [65], as well as a constant renewal by stem cells. In this sense, the treatment of UG requires restoring the balance between cytoprotective agents and aggressive agents, either by reducing or neutralizing the production of gastric acid and/or stimulating gastric cytoprotection [84, 85].

During the healing process, there is a need for complex biological responses such as reduced inflammation, reduced oxidative effect, gastric cell regeneration, cell proliferation, migration, differentiation, gland reconstruction, granulation tissue formation, and neovascularization [3, 7, 86]. These responses are modulated by CO, glutathione peroxidase enzyme (GSH-Px), Cu/Zn superoxide dismutase (SOD), catalase (CAT), PGs, NO, sulfhydryl compounds, epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and the peroxisome proliferator-activator receptor gamma (PPAR- γ) [7, 10, 59, 75, 87–93].

CO is a gas molecule that helps to defend the gastric mucosa due to its vasodilating and antioxidant properties, improves hypoxia, and regulates Nrf-2 expression [75, 90].

The GSH enzyme is the main cellular antioxidant present mainly in the reduced form [67]. SOD and CAT enzymes are also important antioxidants [79]. These three enzymes constitute an important group of defenses against ROS that degrade gastric mucosa components and alter cell metabolism [45, 91]. Despite contributing to injury, ROS can reprogram differential cells together with antioxidant defenses (so that they are successful), as they can up-regulate molecules that stabilize and increase the activity of the cystine/glutamate antiporter, such as CD44v9 [92].

PGs are anti-ulcer agents that protect the barrier of damaged mucosa, increase blood circulation and bicarbonate secretion [67]. Increased production of endogenous PGs may result in increased gastric mucosal resistance against harmful agents, such as ethanol [51]. Particularly, PGs E₂ and I₂ amplify the secretion of bicarbonate and mucus contributing to the balance of gastric pH, maintain the blood flow of the gastric mucosa and coordinate the defense, renewal, and repair of the mucosal epithelial cells [45, 70, 93–95]. In addition, PGE₂ via the EP receptor can inhibit acid secretion and histamine release by parietal cells and enterochromaffin-like cells, respectively [95].

A study demonstrated that NO derived from inducible nitric oxide synthase (NOS) did not influence the healing process of gastric ulcers; on the other hand, the NO produced by the endothelial NOS isoform increased its healing [96]. NO acts as a gastric mucosal protector, activates K_{ATP} channels, modifies blood flow, neutrophil adhesion, and mucus secretion, and aids in wound repair [83, 89, 95]. NO and H₂S are small gaseous molecules that interact with each other, are freely permeable to the plasma membrane, and contribute to stomach homeostasis, integrating the control of mucus production, blood flow, mucosal defense, and gastric motility [77]. Endogenous sulfhydryls are also involved in the protective mechanism of the gastric mucosa [51].

Basic fibroblast growth factor (EGF) is responsible for the accelerated epithelial repair, increased mucus production improving the integrity of the gastric mucosa, and modulates the expression of cells called spasmolytic polypeptide expression metaplasia (SPEM) [2, 94, 97]. It is noteworthy that EGF and PGE participate as defense and repair factors of the gastric mucosa [96].

Vascular endothelial growth factor (VEGF) a functions to promote angiogenesis and protect gastric endothelial cells [74, 98]. Finally, activation of PPAR γ protects against stress-induced gastric ulcer [86].

3.7 Immune system

The innate immune system can recognize molecular patterns associated with common pathogens in microbes and molecular patterns associated with damage through cell damage and the necrosis process through pattern recognition receptors [99].

Antimicrobial peptides form a chemical border between the epithelium and the mucus layer essential in the innate immune response to pathogen infection and are responsible for killing bacteria, fungi, protozoa, and viruses [61, 100]. However, if this chemical defense fails or the pathogen adapts and overcomes both physical and chemical barriers to reach the epithelium, the epithelial cells emit responses to the immune system and the immune system produces specialized defense cells. We can report some of these mechanisms described in the literature—macrophages form one of the first lines of gastric defense against *H. pylori* infection [101]; CD8⁺ T cells are present in the gastric mucosa and can act as a pro-inflammatory [66]; IL-17 and IL-22 are able to inhibit the growth of *H. pylori in vitro* [102]. The interferon 8 regulatory factor circuit (IRF)-8 and interferon γ (IFN)- γ forms an innate immune mechanism in the host's defense against *H. pylori*, which may promote Th1 differentiation, in addition to increasing the inflammatory responses of gastric epithelial cells to eliminate the bacteria [103].

CagA-dependent *H. pylori* infection contributes to activate the mechanistic target of rapamycin complex 1 in gastric epithelial cells; then, there is an increase in pro-inflammatory cytokines TNF- α , IL-1 β and IL-6, CCL7, and CXCL16 chemokines, as well as an increase in the antimicrobial peptide LL37, exerting pro-inflammatory and probactericidal effects, inhibiting *H. pylori* colonization [59].

However, if *H. pylori* resists to these defenses and advances in its colonization, it can lead to ulcer and gastric cancer; which is quite common, since in most cases the infection can last for decades because the immune response has been unable to eliminate the bacteria, and long-term damage can lead to dysplastic changes and malignant transformations [32]. About 17.8% of the different types of cancers in the world are caused by infectious agents, including cancer by *H. pylori* that corresponds to about 5.5% of this total and over 60% of cases of gastric cancer [31]. *H. pylori* has a molecular mimicry between its lipopolysaccharide and the human Le group antigens, Le Type 1 (Lea and Leb) and Type 2 (Lex and Ley), allowing the bacterium to escape the host's immune system response [104]. Its attachment to mucus is mediated by the Lewis^b antigen in MUC5AC and can also be attached to the mucosal epithelium; however, antigens can lead to alterations in the glycosylation sequence in mucins, forming epitopes on oligosaccharide side chains and contributing to aggressiveness and metastasis of gastric cancer [38].

After the gastric injury, there is an increase in the count of circulating neutrophils and a reduction in lymphocytes; the count of these cells or others that are part of the immune system are markers for GU [54, 71]. In a recent study for the development of vaccines against the pathogen *Helicobacter felis*, an infiltration of the antibody Gr-1 in the stomach induced an inflammatory response that led to the formation of CD4⁺ memory T cells (TRM) essential for protection [105].

In gastric injury, inflammatory cytokines IL-1 β , IL-6, IL-8, IL-10, TNF- α , and the transcription factor NF-kB-p65 are present [70, 71, 94, 106, 107]. IL-1 β and TNF- α are increased in ethanol-induced gastric ulcers [57]. IL-1 β is considered a hereditary factor for gastric cancer; and, its reduction together with the reduction of TNF- α contributes to the restoration of the gastric mucosa [57, 99]. IL-6 activates neutrophils, macrophages, and lymphocytes at the site of injury, resulting in oxidative bursts and the formation of cytotoxic metabolites [89, 106].

Activation of the mitogen-activated protein kinase (MAPK) cascade and NF- κ B transcription pathways is critical in several inflammatory and immunomodulatory diseases [108]. TNF- α induces neutrophil infiltration in the gastric epithelium and activation of NF- κ B, increasing its own production, considered the main pro-inflammatory cytokine present during GU [103]. NF- κ B regulates the transcription of IL-1 and IL-6 by activating neutrophils [45]. In addition to the transcription of TNF- α , IL-1, and IL-6, NF- κ B can promote the transcription and expression of more than 100 target genes, which express cytokines and pro-inflammatory enzymes, contributing to tissue inflammation. In this sense, inhibition of NF- κ B is considered the key to reducing gastric ulcer formation [42, 70].

Neutrophils can increase lipid peroxidation, releasing ROS as superoxide and hydrogen peroxide, delaying ulcer healing [91]. ROS secretions activate MAPK signaling in the gastric epithelium, which further activates NF- κ B and Nrf-2, which can suppress the inflammatory response by increasing the antioxidant capacity in the gastric tissue [89]. Corroborating this information, the main antioxidants such as SOD, CAT, HO-1, gamma-glutamylcysteine synthetase, and GSH-Px are regulated by Nrf-2 [109]. Thus, it is noteworthy that Nrf-2 mediated HO-1 induction has cytoprotective, anti-inflammatory, antioxidant, and anti-apoptotic activities providing a therapeutic target against SRMD [107].

IL-10 acts as an anti-inflammatory cytokine, negatively regulating Th1 cell expression, class II MHC antigens, NF- κ B transcription, and costimulatory molecules in macrophages [17]. Therefore, ROS inhibition and immune system improvement are related to the GU healing process [20], as well as the inhibition of the inflammatory cascade and down-regulation of the transcription factor NF- κ B result in the decrease of neutrophils in the gastric tissue.

During wound healing, peptides from the TFF family coordinate the process of cell migration/invasion, angiogenesis, and immune responses [90]. Peptides TFF1, TFF2 and TFF3 are critical for gastric mucosa protection and damage correction [70, 110]. The TFF2 peptide is expressed in the mucus-secreting repair epithelial cell present at the edge of the SPEM ulcer, which coordinates immune cell traffic during repair [93].

Macrophages contribute to ulcer healing, secreting collagenases and elastases to break down damaged tissue and stimulating the release of cytokines, which stimulate chemotaxis, the proliferation of fibroblasts, and smooth muscle cells to build granulation tissue [91].

4. Conclusion

We present a brief summary of the main gastroprotective mechanisms of gastric ulcer. Analyzing such mechanisms is of great importance for advances in the studies of new drugs that aim to attenuate or prevent the actions of aggressive agents in the formation of gastric ulcers. We observed that there was a little scientific advance in relation to gastroprotective mechanisms, among which we can mention: HCO_3^- secretion occurs in the same order of magnitude as H^+ secretion for the maintenance of the gastric buffer system in the absence of food; oxytocin can activate dopaminergic neurons in the ventral tegmental area reducing stress-induced gastric ulcer; the main effector neurons in the gastric mucosa are cholinergic, nitrenergic, and VIPergic; the cagA-dependent *H. pylori* infection that contributes to activating the mechanistic target of rapamycin complex 1 in gastric epithelial cells; infiltration of the Gr-1 antibody in the stomach induces the formation of CD4⁺ TRM cells essential for protection from *H. felis*; and that the main antioxidants SOD, CAT, HO-1, gamma-glutamylcysteine synthetase, and GSH-Px are regulated by Nrf-2.

Acknowledgements

The author wants to thank Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) for the financial support to the research.

Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

The first author thanks her mother Genadir Alves Araujo for helping her with taking care of her 5-year-old son, Pietro Araujo de Lima Pedral, providing her the necessary time to dedicate herself to this research.

Author details

Cirlane Alves Araujo de Lima*, Robson Silva de Lima, Jesica Batista de Souza, Ariel de Souza Graça, Sara Maria Thomazzi, Josemar Sena Batista and Charles dos Santos Estevam
Departamento de Fisiologia, Universidade Federal de Sergipe, Cidade Universitária
Professor José Aloísio de Campos, São Cristóvão, Brasil

*Address all correspondence to: cirlanepink@hotmail.com

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Araruna ME, Silva P, Almeida M, Rêgo R, Dantas R, Albuquerque H, et al. Tablet of *Spondias mombin* L. developed from nebulized extract prevents gastric ulcers in mice via cytoprotective and antisecretory effects. *Molecules*. 2021;**26**(6):1-17. DOI: 10.3390/moléculas26061581
- [2] Wang X-Y, Yin J-Y, Zhao M-M, Liu S-Y, Nie S-P, Xie M-Y. Gastroprotective activity of polysaccharide from *Hericium erinaceus* against ethanol-induced gastric mucosal lesion and pylorus ligation-induced gastric ulcer, and its antioxidant activities. *Carbohydrate Polymers*. 2018;**186**:100-109. DOI: 10.1016/j.carbpol.2018.01.004
- [3] Wang S, Ni Y, Liu J, Yu H, Guo B, Liu E, et al. Protective effects of Weilikang decoction on gastric ulcers and possible mechanisms. *Journal of Natural Medicines*. 2016;**70**:391-403. DOI: 10.1007/s11418-016-0985-1
- [4] Sudi IY, Ahmed MU, Adzu B. *Sphaeranthus senegalensis* DC: Evaluation of chemical constituents, oral safety, gastroprotective activity, and mechanism of action of its hydroethanolic extract. *Journal of Ethnopharmacology*. 2021;**265**:1-12. DOI: 10.1016/j.jep.2020.113597
- [5] Barbosa JAP, Santana MAN, Leite TCC, Oliveira TB, Mota FVB, Bastos IVGA, et al. Gastroprotective effect of ethylacetate extract from *Avicennia schaueriana* Stapf & Leechman and underlying mechanisms. *Biomedicine and Pharmacotherapy*. 2019;**112**:1-10. DOI: 10.1016/j.biopha.2019.01.043
- [6] Sánchez-Mendoza ME, López-Lorenzo Y, Cruz-Antonio L, Cruz-Oseguera A, García-Machorro J, Arrieta J. Gastroprotective effect of juanislamin on ethanol-induced gastric lesions in rats: Role of prostaglandins, nitric oxide and sulfhydryl groups in the mechanism of action. *Molecules*. 2020;**25**(9):1-8. DOI: 10.3390/molecules25092246
- [7] Neto LJJ, Ramos AGB, Sales VS, Souza SDG, Santos ATL, Oliveira LR, et al. Gastroprotective and ulcer healing effects of hydroethanolic extract of leaves of *Caryocar coriaceum*: Mechanisms involved in the gastroprotective activity. *Chemico-Biological Interactions*. 2017;**261**:56-62. DOI: DOI. 10.1016/j.cbi.2016.11.020
- [8] Kwon SC, Kim JH. Gastroprotective effects of irsogladine maleate on ethanol/hydrochloric acid induced gastric ulcers in mice. *Korean Journal of Internal Medicine*. 2021;**36**(1):67-75. DOI: 10.3904/kjim.2018.290
- [9] Lu S, Wu D, Sun G, Geng F, Shen Y, Tan J, et al. Gastroprotective effects of Kangfuxin against water-immersion and restraint stress-induced gastric ulcer in rats: Roles of antioxidation, anti-inflammation, and pro-survival. *Pharmaceutical Biology*. 2019;**57**(1): 770-777. DOI: 10.1080/13880209.2019.168620
- [10] Prazeres LDKT, Aragão TP, Brito AS, Almeida CLF, Silva AD, Paula MMF, et al. Antioxidant and antiulcerogenic activity of the dry extract of pods of *Libidibia férrea* Mart. ex Tul. (Fabaceae). *Oxidative Medicine and Cellular Longevity*. 2019;**2019**:1-23. DOI: 10.1155/2019/1983137
- [11] Zakaria ZA, Balan T, Azemi AK, Omar MH, Mohtarrudin N, Ahmad Z, et al. Mechanism (s) of action underlying the gastroprotective effect of ethyl acetate fraction obtained from the crude methanolic leaves extract of *Muntingia calabura*. *BMC Complementary and Alternative Medicine*. 2016;**16**(78):1-17. DOI: 10.1186/s12906-016-1041-0

- [12] Raish M, Shahid M, Jordan YAB, Ansari MA, Alkharfy KM, Ahad A, et al. Gastroprotective effect of sinapic acid on ethanol-induced gastric ulcers in rats: Involvement of Nrf-2/HO-1 and NF- κ B signaling and antiapoptotic role. *Frontiers in Pharmacology*. 2021;12:1-15. DOI: 10.3389/fphar.2021.622815
- [13] Li X-M, Miao Y, Su Q-Y, Yao J-C, Li H-H, Zhang G-M. Gastroprotective effects of arctigenin of *Arctium lappa* L. on a rat model of gastric ulcers. *Biomedical Reports*. 2016;5(5):589-594. DOI: 10.3892/br.2016.770
- [14] Tonchaiyaphum P, Arpornchayanon W, Khonsung P, Chiranthanut N, Pitchakarn P, Kunanusorn P. Gastroprotective activities of ethanol extract of black rice bran (*Oryza sativa* L.) in rats. *Molecules*. 2021;26(13):1-13. DOI: 10.3390/molecules26133812
- [15] European Medicines Agency (EMA). Suspension of Ranitidine Medicines in the EU [Internet]. 2020. Available from: <https://www.ema.europa.eu/en/news/suspension-ranitidine-medicines-eu> [Accessed: August 11, 2021]
- [16] Xie J, Lin Z, Xian Y, Kong S, Lai Z, Ip S, et al. (–) Patchouli alcohol protects against *Helicobacter pylori* urease-induced apoptosis, oxidative stress and inflammatory response in human gastric epithelial cells. *International Immunopharmacology*. 2016;35:43-52. DOI: 10.1016/j.intimp.2016.02.022
- [17] Nascimento RF, Formiga RO, Machado FDF, Sales IRP, Lima GM, Júnior EBA, et al. Rosmarinic acid prevents gastric ulcers via sulfhydryl groups reinforcement, antioxidant and immunomodulatory effects. *Naunyn-Schmiedeberg's Archives of Pharmacology*. 2020;393(12):1-14. DOI: 10.1007/s00210-020-01894-2
- [18] Baiubon P, Kunanusom P, Khonsung P, Chiranthanut N, Panthong A, Rujjanawate C. Gastroprotective activity of the rhizome ethanol extract of *Zingiber simaoense* Y. Y. Qian in rats. *Journal of Ethnopharmacology*. 2016;194:1-15. DOI: 10.1016/j.jep.2016.10.049
- [19] Zakaria ZA, Zainol ASN, Sahmat A, Salleh NI, Hizami A, Mahmood ND, et al. Gastroprotective activity of chloroform extract of *Muntingia calabura* and *Melastoma malabathricum* leaves. *Pharmaceutical Biology*. 2016;54(5):1-15. DOI: 10.3109/13880209.2015.1085580
- [20] Zhenga H, Chen Y, Zhang J, Wang L, Jin Z, Huang H, et al. Evaluation of protective effects of costunolide and dehydrocostuslactone on 2 ethanol-induced gastric ulcer in mice based on multi-pathway regulation. *Chemico-Biological Interactions*. 2016;250:68-77. DOI: 10.1016/j.cbi.2016.03.003
- [21] Karunakaran R, Thabrew MI, Thammitiyagodage GM, Arawwawala LDA. The gastroprotective effect of ethyl acetate fraction of hot water extract of *Trichosanthes cucumerina* Linn and its underlying mechanisms. *BMC Complementary and Alternative Medicine*. 2017;17(312):1-8. DOI: 10.1186/s12906-017-1796-y
- [22] Bobby N, Abbas MA, Lee E-B, Im Z-E, Hsu W, Park S-C. Protective effect of *Pyrus ussuriensis* maxim. Extract against ethanol-induced gastritis in rats. *Antioxidants (Basel)*. 2021;10(3):1-17. DOI: 10.3390/antiox10030439
- [23] Fatima R, Aziz M. Achlorhydria. [Internet]. 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/29939570/> [Accessed: September 8, 2021]
- [24] Heda R, Toro F, Tombazzi CR. Physiology, Pepsin. [Internet] 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/30725690/> [Accessed: September 8, 2021]

- [25] Salaga M, Zatorski H, Zielińska M, Mosinska P, Timmermans JP, Kordek R, Storr M, Fichna J. Highly selective CB2 receptor agonist A836339 has gastroprotective effect on experimentally induced gastric ulcers in mice. *Naunyn-Schmiedeberg's Archives of Pharmacology*. 2017;**390**(10):1015-1027. DOI: 10.1007/s00210-017-1402-3
- [26] Martinsen TC, Fossmark R, Waldum HL. The phylogeny and biological function of gastric juice—Microbiological consequences of removing gastric acid. *International Journal of Molecular Sciences*. 2019;**20**(23):1-22. DOI: 10.3390/ijms20236031
- [27] Prosapio JG, Sankar P, Jialal I. Physiology, Gastrin. [Internet]. 2021. Available from: <https://pubmed.ncbi.nlm.nih.gov/30521243/> [Accessed: October 26, 2021]
- [28] Shen S, Li H, Liu J, Sun L, Yuan Y. The panoramic picture of pepsinogen gene family with pan-cancer. *Cancer Medicine*. 2020;**9**(23):9064-9080. DOI: 10.1002/cam4.3489
- [29] Rao Y-F, Cheng D-N, Xu Y, Ren X, Yang W, Liu G, et al. The controversy of pepsinogen A/Pepsin A in detecting extra-gastroesophageal reflux. *Journal of Voice*. 2021;**21**:1-9. DOI: 10.1016/j.jvoice.2021.04.009
- [30] Yuan L, Zhao J-B, Zhou Y-L, Qi Y-B, Guo Q-Y, Zhang H-H, et al. Type I and type II *Helicobacter pylori* infection status and their impact on gastrin and pepsinogen level in a gastric cancer prevalent area. *World Journal of Gastroenterology*. 2020;**26**(25):3673-3685. DOI: 10.3748/wjg.v26.i25.3673
- [31] Looor A, Dumitrașcu DL. *Helicobacter pylori* infection, gastric cancer and gastropanel. *Romanian Journal of Internal Medicine*. 2016;**54**(3):151-156. DOI: 10.1515/rjim-2016-0025
- [32] Song M, Camargo MC, Weinstein SJ, Best A, Männistö S, Albanes D, et al. Family history of cancer in first-degree relatives and risk of gastric cancer and its precursors in a western population. *Gastric Cancer*. 2018;**21**(5):729-737. DOI: 10.1007/s10120-018-0807-0
- [33] Bang CS, Lee JJ, Baik GH. Diagnostic performance of serum pepsinogen assay for the prediction of atrophic gastritis and gastric neoplasms: Protocol for a systematic review and meta-analysis. *Medicine (Baltimore)*. 2019;**98**(4):1-4. DOI: 10.1097/MD.00000000000014240
- [34] Chiba T, Kato K, Masuda T, Ohara S, Iwama N, Shimada T, et al. Clinicopathological features of gastric adenocarcinoma of the fundic gland (chief cell predominant type) by retrospective and prospective analyses of endoscopic findings. *Digestive Endoscopy*. 2016;**28**(7):722-730. DOI: 10.1111/den.12676
- [35] Yamada A, Kaise M, Inoshita N, Toba T, Nomura K, Kuribayashi Y, et al. Characterization of *Helicobacter pylori*-Naïve early gastric cancers. *Digestion*. 2018;**98**(2):127-134. DOI: 10.1159/000487795
- [36] Khémiri I, Bitri L. Effectiveness of *Opuntia ficus indica* L.inermis seed oil in the protection and the healing of experimentally induced gastric mucosa ulcer. *Oxidative Medicine Cellular Longevity*. 2019;**2019**:1-17. DOI: 10.1155/2019/1568720
- [37] An JM, Kang EA, Han YM, Kim YS, Hon YG, Hah BS, et al. Dietary threonine prevented stress-related mucosal diseases in rats. *Journal of Physiology and Pharmacology*. 2019;**70**:3. DOI: 10.26402/jpp.2019.3.14
- [38] Mall AS, Habte H, Mthembu Y, Peacocke J, Beer C. Mucus and mucins: Do they have a role in the inhibition of the human immunodeficiency virus? *Virology Journal*. 2017;**14**(192):1-14. DOI: 10.1186/s12985-017-0855-9

- [39] Lewis OL, Keener JP, Fogelson A. A physics-based model for maintenance of the pH gradient in the gastric mucus layer. *American Journal of Physiology Gastrointestinal and Liver Physiology*. 2017;**313**(6):G599-G612. DOI: 10.1152/ajpgi.00221.2017
- [40] Sidahmed HMA, Vadivelu J, Loke MF, Arbab IA, Abdul B, Sukari MA, et al. Anti-ulcerogenic activity of dentatin from *clausena excavata* Burm.f. against ethanol-induced gastric ulcer in rats: Possible role of mucus and anti-oxidant effect. *Phytomedicine*. 2019;**55**:31-39. DOI: 10.1016/j.phymed.2018.06.036
- [41] Ruiz-Pulido G, Medina D. An overview of gastrointestinal mucus rheology under different pH conditions and introduction to pH-dependent rheological interactions with PLGA and chitosan nanoparticles. *European Journal of Pharmaceutics and Biopharmaceutics*. 2021;**159**:123-136. DOI: 10.1016/j.ejpb.2020.12.013
- [42] Yoo J-H, Lee J-S, Lee Y-S, Ku S, Lee H-J. Protective effect of bovine milk against HCl and ethanol-induced gastric ulcer in mice. *Journal of Dairy Science*. 2018;**101**(5):3758-3770. DOI: 10.3168/jds.2017-13872
- [43] Moura FCS, Perioli L, Pagano C, Vivani R, Ambrogi V, Bresolin TM, et al. Chitosan composite microparticles: A promising gastroadhesive system for taxifolin. *Carbohydrate Polymers*. 2021;**218**:343-354. DOI: 10.1016/j.carbpol.2019.04.075
- [44] Kootala S, Filho L, Srivastava V, Linderberg V, Moussa L, David L, et al. Reinforcing mucus barrier properties with low molar mass chitosans. *Biomacromolecules*. 2018;**19**(3):872-882. DOI: 10.1021/acs.biomac.7b01670
- [45] Bang BW, Dongsun P, Kwon KS, Lee DH, Jang M-J, Park SK, et al. BST-104, a water extract of *Ionicera japonica*, has a gastroprotective effect via antioxidant and anti-inflammatory activities. *Journal of Medicinal Food*. 2019;**22**(2):140-151. DOI: 10.1089/jmf.2018.4231
- [46] Lechanteur A, Neves J, Sarmento B. The role of mucus in cell-based models used to screen mucosal drug delivery. *Advanced Drug Delivery Reviews*. 2018;**124**:50-63. DOI: 10.1016/j.addr.2017.07.019
- [47] Heuer J, Heuer F, Stümer R, Harder S, Schlüter H, Emidio NB, et al. The tumor suppressor TFF1 occurs in different forms and interacts with multiple partners in the human gastric mucus barrier: Indications for diverse protective functions. *International Journal of Molecular Sciences*. 2020;**21**:7. DOI: 10.3390/ijms21072508
- [48] Liu F, Fu J, Bergstrom K, Shan X, McDaniel JM, McGee S, et al. Core 1-derived mucin-type O-glycosylation protects against spontaneous gastritis and gastric cancer. *The Journal of Experimental Medicine*. 2020;**217**(1):1-17. DOI: 10.1084/jem.20182325
- [49] Heuer F, Stümer R, Heuer J, Kalinski T, Lemke A, Meyer F, et al. Different forms of TFF2, a lectin of the human gastric mucus barrier: In vitro binding studies. *International Journal of Molecular Sciences*. 2019;**20**(23):1-13. DOI: 10.3390/ijms20235871
- [50] Hoffmann W. Trefoil factor family (TFF) peptides and their diverse molecular functions in mucus barrier protection and more: Changing the paradigm. *International Journal of Molecular Sciences*. 2020;**21**(12):1-20. DOI: 10.3390/ijms21124535
- [51] Carrillo W, Monteiro KM, Martínez-Maqueda D, Ramos M, Recio I, Carvalho JE. Antiulcerative activity of milk proteins hydrolysates. *Journal of Medicinal Food*. 2018;**21**(4):408-415. DOI: 10.1089/jmf.2017.0087

- [52] Yamada S, Yamanoi K, Sato Y, Nakayama J. Diffuse MIST1 expression and decreased α 1,4-linked N-acetylglucosamine (α GlcNAc) glycosylation on MUC6 are distinct hallmarks for gastric neoplasms showing oxyntic gland differentiation. *Histopathology*. 2020;**77**(3):413-422. DOI: 10.1111/his.14165
- [53] Li T, Liu X, Riederer B, Nikolovska K, Singh A, Mäkelä K, et al. Genetic ablation of carbonic anhydrase IX disrupts gastric barrier function via claudin-18 downregulation and acid backflux. *Acta Physiologica (Oxford, England)*. 2018;**222**(4):1-17. DOI: 10.1111/apha.12923
- [54] Adenivi OS, Emikpe BO, Olaleve SB. Accelerated gastric ulcer healing in thyroxine-treated rats: Roles of gastric acid, mucus, and inflammatory response. *Canadian Journal of Physiology and Pharmacology*. 2018;**96**(6):597-602. DOI: 10.1139/cjpp-2017-0399
- [55] Saremi K, Rad SK, Khalilzadeh M, Hussaini J, Majid NA. In vivo acute toxicity and anti-gastric evaluation of a novel dichloro Schiff base: Bax and HSP70 alteration. *Acta Biochimica Biophysica Sinica (Shanghai)*. 2020;**52**(1):26-37. DOI: 10.1093/abbs/gmz140
- [56] Lucetti LT, Silva RO, Santana APM, Tavares BM, Vale ML, Gomes PGS, Júnior FJBL, Magalhães PJC, Cunha FQ, Ribeiro RA, Medeiros J-VR, Souza HLP. Nitric Oxide and Hydrogen Sulfide Interact When Modulating Gastric Physiological Functions in Rodents. *Digestive Diseases and Sciences*. 2017;**62**(1):93-104. DOI: 10.1007/s10620-016-4377-x
- [57] Monteiro CES, Sousa JAO, Lima LM, Barreiro E, Silva-Leite KES, Carvalho CMM, et al. LASSBio-596 protects gastric mucosa against the development of ethanol-induced gastric lesions in mice. *European Journal of Pharmacology*. 2019;**863**:172662. DOI: 10.1016/j.ejphar.2019.172662
- [58] Qin J, Pei X. Isolation of human gastric epithelial cells from gastric surgical tissue and gastric biopsies for primary culture. *Methods in Molecular Biology*. 2018;**1817**:115-121. DOI: 10.1007/978-1-4939-8600-2_12
- [59] Feng G-J, Chen Y, Li K. *Helicobacter pylori* promote inflammation and host defense through the cagA-dependent activation of mTORC1. *Journal of Cellular Physiology*. 2020;**235**(12):10094-10108. DOI: 10.1002/jcp.29826
- [60] Sigal M, Meyer TF. Coevolution between the human microbiota and the epithelial immune system. *Digestive Diseases*. 2016;**34**(3):190-193. DOI: 10.1159/000443349
- [61] Hartl K, Sigal M. Microbe-driven genotoxicity in gastrointestinal carcinogenesis. *International Journal of Molecular Sciences*. 2020;**21**(20):1-24. DOI: 10.3390/ijms21207439
- [62] Ahluwalia A, Jones MK, Hoa N, Tarnawski AS. Mitochondria in gastric epithelial cells are the key targets for NSAIDs-induced injury and NGF cytoprotection. *Journal of Cellular Biochemistry*. 2019;**120**:1-9. DOI: 10.1002/jcb.28445
- [63] Arita S, Kinoshita Y, Ushida K, Enomoto A, Inagaki-Ohara K. High-fat diet feeding promotes stemness and precancerous changes in murine gastric mucosa mediated by leptin receptor signaling pathway. *Archives Biochemistry and Biophysical*. 2016;**610**:16-24. DOI: 10.1016/j.abb.2016.09.015
- [64] Wizenty J, Tacke F, Sigal M. Responses of gastric epithelial stem cells and their niche to *Helicobacter pylori* infection. *Annals of Translational Medicine*. 2020;**8**(8):568-578. DOI: 10.21037/atm.2020.02.178

- [65] Cherkas A, Zarkovic N. 4-hydroxynonenal in redox homeostasis of gastrointestinal mucosa: Implications for the stomach in health and diseases. *Antioxidants* (Basel). 2018;7(9):1-14. DOI: 10.3390/antiox7090118
- [66] Lv Y-P, Cheng P, Zhang J-Y, Mao F-Y, Teng Y-S, Liu Y-G, et al. *Helicobacter pylori*-induced matrix metalloproteinase-10 promotes gastric bacterial colonization and gastritis. *Science Advances*. 2019;5(4):1-14. DOI: 10.1126/sciadv.aau6547
- [67] Brzozowski T, Magierowska K, Magierowski M, Ptak-Belwska A, Pajdo R, Kwiecien S, et al. Recent advances in the gastric mucosal protection against stress-induced gastric lesions. Importance of renin-angiotensin vasoactive metabolites, gaseous mediators and appetite peptides. *Current Pharmaceutical Design*. 2017;23(27):3910-3922. DOI: 10.2174/1381612823666170220160222
- [68] Saadaoui N, Weslati A, Barkaoui T, Khemiri I, Gadacha W, Souli A, et al. Gastroprotective effect of leaf extract of two varieties grapevine (*Vitis vinifera* L.) native wild and cultivar grown in North of Tunisia against the oxidative stress induced by ethanol in rats. *Biomarkers*. 2020;25(1):48-61. DOI: 10.1080/1354750X.2019.1691266
- [69] Chen H, Olatunji OJ, Zhou Y. Anti-oxidative, anti-secretory and anti-inflammatory activities of the extract from the root bark of *Lycium chinense* (Cortex Lycii) against gastric ulcer in mice. *Journal of Natural Medicines*. 2016;70(3):610-619. DOI: 10.1007/s11418-016-0984-2
- [70] Yu L, Li R, Liu W, Zhou Y, Li Y, Qin Y, et al. Protective effects of wheat peptides against ethanol-induced gastric mucosal lesions in rats: Vasodilation and anti-inflammation. *Nutrients*. 2020;12(8):1-13. DOI: 10.3390/nu12082355
- [71] Araújo ERD, Guerra GCB, Araújo DFS, Araújo AA, Fernandes JM, Júnior RFA, et al. Gastroprotective and antioxidant activity of *Kalanchoe brasiliensis* and *Kalanchoe pinnata* leaf juices against indomethacin and ethanol-induced gastric lesions in rats. *International Journal of Molecular Science*. 2018;19(5):1-25. DOI: 10.3390/ijms19051265
- [72] Yang HJ, Kim MJ, Kwon DY, Kang ES, Kang S, Park S. Gastroprotective actions of *Taraxacum coreanum* Nakai water extracts in ethanol-induced rat models of acute and chronic gastritis. *Journal of Ethnopharmacology*. 2017;208:84-93. DOI: 10.1016/j.jep.2017.06.045
- [73] Hernández C, Barrachina MD, Vallecillo-Hernández J, Álvarez Á, Ortiz-Masiá D, Cosín-Roger J, et al. Aspirin-induced gastrointestinal damage is associated with an inhibition of epithelial cell autophagy. *Journal of Gastroenterology*. 2016;51(7):691-701. DOI: 10.1007/s00535-015-1137-1
- [74] Tarnawski AS, Ahluwalia A. Increased susceptibility of aging gastric mucosa to injury and delayed healing: Clinical implications. *World Journal of Gastroenterology*. 2018;24(42):4721-4727. DOI: 10.3748/wjg.v24.i42.4721
- [75] Magierowski M, Magierowska K, Hubalewska M, Adamski J, Bakalarz D, Sliwowski Z, et al. Interaction between endogenous carbon monoxide and hydrogen sulfide in the mechanism of gastroprotection against acute aspirin-induced gastric damage. *Pharmacological Research*. 2016;114:235-250. DOI: 10.1016/j.phrs.2016.11.001
- [76] Reglodi D, Liles A, Oppert B, Schafer E, Tamas A, Horcath G. Presence and effects of pituitary adenylate cyclase activating polypeptide under physiological and pathological conditions in the stomach. *Frontiers Endocrinology (Lausanne)*.

2018;**9**(90):1-12. DOI: 10.3389/fendo.2018.00090

[77] Lucetti LT, Silva RO, Santana APM, Tavares BM, Vale ML, Gomes PGS, et al. Nitric oxide and hydrogen sulfide interact when modulating gastric physiological functions in rodents. *Digestive Diseases and Sciences*. 2017;**62**(1):93-104. DOI: 10.1007/s10620-016-4377-x

[78] Furness JB. Integrated neural and endocrine control of gastrointestinal function. *Advances in Experimental Medicine and Biology*. 2016;**891**:159-173. DOI: 10.1007/978-3-319-27592-5_16

[79] Gillis RA, Dezfuli G, Bellusci L, Vicini S, Sahibzada. Brainstem neuronal circuitries controlling gastric tonic and phasic contractions: A review. *Cellular and Molecular Neurobiology*. DOI: 10.1007/s10571-021-01084-5

[80] Xiaogian HL, Zhang X, Wang Q, Luan X, Sun X, Guo F, et al. Regulation of stress-induced gastric ulcers via central oxytocin and a potential mechanism through the VTA-NAc dopamine pathway. *Neurogastroenterology and Motility*. 2019;**31**(9): 1-14. DOI: 10.1111/nmo.13655

[81] Czekaj R, Majka J, Ptak-Belowska A, Szlachcic A, Targosz A, Magierowska K, et al. Role of curcumin in protection of gastric mucosa against stress-induced gastric mucosal damage. Involvement of hypoacidity, vasoactive mediators and sensory neuropeptides. *Journal of Physiology and Pharmacology*. 2016;**67**(2):261-275

[82] Anetsberger D, Kürten S, Jabari S, Brehmer A. Morphological and immunohistochemical characterization of human intrinsic gastric neurons. *Cells, Tissues, Organs*. 2018;**206**(4-5):183-195. DOI: 10.1159/000500566

[83] Viana AFSC, Silva FV, Fernandes HB, Oliveira IS, Braga MA,

Nunes PIG, et al. Gastroprotective effect of (–) myrtenol against ethanol-induced acute gastric lesions: Possible mechanisms. *Journal of Pharmacy and Pharmacology*. 2016;**68**(8):1085-1092. DOI: 10.1111/jphp.12583

[84] Júnior EBA, Formiga RO, Serafim CAL, Araruna MEC, Pessoa MLS, Vasconcelos RC, et al. Estragole prevents gastric ulcers via cytoprotective, antioxidant and immunoregulatory mechanisms in animal models. *Biomedicine and Pharmacotherapy*. 2020;**130**:1-15. DOI: 10.1016/j.biopha.2020.110578

[85] Arunachalam K, Damazo AS, Pavan E, Oliveira DM, Figueiredo FF, Machado MT, et al. *Cochlospermum regium* (Mart. ex Schrank) Pilg.: Evaluation of chemical profile, gastroprotective activity and mechanism of action of hydroethanolic extract of its xylopodium in acute and chronic experimental models. *Journal of Ethnopharmacology*. 2019;**233**:101-114. DOI: 10.1016/j.jep.2019.01.002

[86] Elshazly SM, Motteleb DMAE, Ibrahim I, A.A.E-H. Hesperidin protects against stress induced gastric ulcer through regulation of peroxisome proliferator activator receptor gamma in diabetic rats. *Chemico-Biological Interactions*. 2018;**291**(153-161). DOI: 10.1016/j.cbi.2018.06.027

[87] Bueno G, Rico SLC, Périco LL, Ohara R, Rodrigues VP, Emílio-Silva MT, et al. The essential oil from *Baccharis trimera* (Less.) DC improves gastric ulcer healing in rats through modulation of VEGF and MMP-2 activity. *Journal of Ethnopharmacology*. 2021;**271**(1-9). DOI: 10.1016/j.jep.2021.113832

[88] Magierowski M, Hubalewska-Mazgaj M, Magierowska K, Wojcik D, Sliwowski Z, Kwiecien S, et al. Nitric oxide, afferent sensory nerves, and antioxidative enzymes in the

mechanism of protection mediated by tricarbonyldichlororuthenium (II) dimer and sodium hydrosulfide against aspirin-induced gastric damage. *Journal of Gastroenterology*. 2018;**53**(1):52-63. DOI: 10.1007/s00535-017-1323-4

[89] Liu J, Lin H, Yuan L, Wang D, Wang C, Sun J, et al. Protective effects of anwulignan against HCl/ethanol-induced acute gastric ulcer in mice. *Evidence-Based Complementary and Alternative Medicine*. 2021;**2021**(2021):1-14. DOI: 10.1155/2021/9998982. eCollection

[90] Kwiecien S, Magierowka K, Magierowski M, Surmiak M, Hubalewska M, Paido R, et al. Role of sensory afferent nerves, lipid peroxidation and antioxidative enzymes in the carbon monoxide-induced gastroprotection against stress ulcerogenesis. *Journal of Physiology and Pharmacology*. 2016;**67**(5):717-729

[91] Adeniyi OS, Makinde OV, Friday ET, Olaleve SB. Effects of quinine on gastric ulcer healing in Wistar rats. *Journal of Complementary and Integrative Medicine*. 2017;**14**(4):1-11. DOI: 10.1515/jcim-2016-0132

[92] Meyer AR, Engevik AC, Willet S, Williams JA, Zou Y, Massion PP, et al. Cystine/glutamate antiporter (xCT) is required for chief cell plasticity after gastric injury. *Cellular and Molecular Gastroenterology and Hepatology*. 2019;**8**(3):379-405. DOI: 10.1016/j.jcmgh.2019.04.015

[93] Balogun ME, Besong EE, Obimma N, Mbamalu OS, Diobissie FSA. Protective roles of *Vigna subterranea* (Bambara nut) in rats with aspirin-induced gastric mucosal injury. *Journal of Integrative Medicine*. 2018;**16**:342-349. DOI: 10.1016/j.joim.2018.07.004

[94] Chen W, Wu D, Jin Y, Li Q, Liu Y, Qiao X, et al. Pre-protective effect of polysaccharides purified from *Hericium*

erinaceus against ethanol-induced gastric mucosal injury in rats. *International Journal of Biological Macromolecules*. 2020;**159**:948-956. DOI: 10.1016/j.ijbiomac.2020.05.163

[95] Moawad H, Awdan SAE, Sallam NA, El-Eraky W, Alkhawlan MA. Gastroprotective effect of cilostazol against ethanol- and pylorus ligation-induced gastric lesions in rats. *Naunyn-Schmiedeberg's Archives of Pharmacology*. 2019;**392**(12):1605-1616. DOI: 10.1007/s00210-019-01699-y

[96] Lebda MA, El-Far AH, Noreldin AE, Elewa YHA, Jaouni SKA, Mousa AS. Protective effects of miswak (*Salvadora persica*) against experimentally induced gastric ulcers in rats. *Oxidate Medicine and Cellular Longevity*. 2018;**2018**:1-14. DOI: 10.1155/2018/6703296

[97] Teal E, Dua-Awereh M, Hirshorn ST, Zavros Y. Role of metaplasia during gastric regeneration. *American Journal Physiology Cell Physiology*. 2020;**319**(6):C947-C954. DOI: 10.1152/ajpcell.00415.2019

[98] Cuzziol CI, Castanhole-Nunes MMU, Pavarino EC, Goloni-Bertollo EM. MicroRNAs as regulators of VEGFA and NFE2L2 in câncer. *Gene*. 2020;**759**:1-19. DOI: 10.1016/j.gene.2020.144994

[99] Cao X, Xu J. Insights into inflammasome and its research advances in câncer. *Tumori Journal*. 2019;**105**(6):456-464. DOI: 10.1177/03008916198680007

[100] Padra M, Benktander J, Robinson K, Lindén SK. Carbohydrate-dependent and antimicrobial peptide defence mechanisms against *Helicobacter pylori* infections. *Current Topics in Microbiology and Immunology*. 2019;**421**:179-207. DOI: 10.1007/978-3-030-15138-6_8

[101] Latour YL, Gobert AP, Wilson KT. The role of polyamines in the regulation

of macrophage polarization and function. *Amino Acids*. 2020;**52**(2):151-160. DOI: 10.1007/s00726-019-02719-0

[102] Dixon BREA, Radin JN, Piazuolo MB, Contreras DC, Algood HMS. IL-17a and IL-22 induce expression of antimicrobials in gastrointestinal epithelial cells and may contribute to epithelial cell defense against *Helicobacter pylori*. *PLoS One*. 2016;**11**(2):1-19. DOI: 10.1371/journal.pone.0148514

[103] Yan M, Wang H, Sun J, Liao W, Li P, Zhu Y, et al. Cutting edge: Expression of IRF8 in gastric epithelial cells confers protective innate immunity against *Helicobacter pylori* infection. *The Journal of Immunology*. 2016;**196**(5):1999-2003. DOI: 10.4049/jimmunol.1500766

[104] Fagoonee S, Pellicano R. *Helicobacter pylori*: Molecular basis for colonization and survival in gastric environment and resistance to antibiotics. A short review. *Infectious Disease (Lond)*. 2019;**51**(6):399-408. DOI: 10.1080/23744235.2019.1588472

[105] Hu C, Liu W, Xu N, Huang A, Zhang Z, Fan M, et al. Silk fibroin hydrogel as mucosal vaccine carrier: Induction of gastric CD4⁺TRM cells mediated by inflammatory response induces optimal immune protection against *Helicobacter felis*. *Emerging and Infections*. 2020;**9**(1):2289-2302. DOI: 10.1080/22221751.2020.1830719

[106] Souza MC, Vieira AJ, Beserra FP, Pellizzon CH, Nóbrega RH, Rozza AL. Gastroprotective effect of limonene in rats: Influence on oxidative stress, inflammation and gene expression. *Phytomedicine*. 2019;**53**:37-42. DOI: 10.1016/j.phymed.2018.09.027

[107] An JM, Kim E, Lee HJ, Park MH, Son DJ, Hahm KB. Dolichos lablab L. extracts as pharmanutrient for stress-related mucosal disease in rat stomach.

Journal of Clinical Biochemistry Nutrition. 2020;**67**(1):89-101. DOI: 10.3164/jcbn.20-11

[108] Zhang C, Gao F, Gan S, He Y, Chen Z, Liu X, et al. Chemical characterization and gastroprotective effect of an isolated polysaccharide fraction from *Bletilla striata* against ethanol-induced acute gastric ulcer. *Food and Chemical Toxicology*. 2019;**131**:1-37. DOI: 10.1016/j.fct.2019.05.047

[109] Wu Y, Chen H, Zou Y, Yi R, Um J, Zhao X. *Lactobacillus plantarum* HFY09 alleviates alcohol-induced gastric ulcers in mice via an anti-oxidative mechanism. *Journal of Food Biochemistry*. 2021;**45**(5):1-9. DOI: 10.1111/jfbc.13726

[110] He H, Feng M, Xu H, Li X, He Y, Qin H, et al. Total triterpenoids from the fruits of *Chaenomeles speciosa* exerted gastroprotective activities on indomethacin-induced gastric damage via modulating microRNA-423-5p-mediated TFF/NAG-1 and apoptotic pathways. *Food and Function*. 2020;**11**(1):662-679. DOI: 10.1039/c9fo02322d