EDITORIAL

DOI: http://dx.doi.org/10.15403/jgld-5172

Oxidative Stress in Gastrointestinal Ulcer Disease: A Gastroenterologist's View

Dusan Popovic[1,2], Marija Stojanovic[1,3], Tomica Milosavljevic[4], Milica Stojkovic-Lalosevic[1,5], Tijana Glisic[1,5], Predrag Savic[1,6], Branka Filipovic[1,2]

1) University of Belgrade, Faculty of Medicine, Belgrade;
2) Department for Gastroenterology and Hepatology, Clinic for Internal Medicine, Dr Dragisa Misovic-Dedinje University Clinical Hospital Center, Belgrade;
3) Richard Burian Institute of Medical Physiology, Belgrade;
4) Euromedik General Hospital, Belgrade;
5) Clinic for Gastroenterohepatology, University Clinical center of Serbia, Belgrade;
6) Clinic for Surgery, Dr Dragisa Misovic-Dedinje University Clinical Hospital Center Belgrade, Serbia

Address for correspondence:
Dusan Popovic, MD, PhD
University of Belgrade, Faculty of Medicine; Department of Gastroenterology and Hepatology, Clinic for Internal Medicine, Dr Dragisa Misovic-Dedinje University Clinical Hospital Center;
Heroja Milana Tepica 1; 11000 Belgrade, Serbia
pduschan@gmail.com

Received: 25.05.2023
Accepted: 23.08.2023

OXIDATIVE STRESS

Oxidative stress is the tissue damage caused by highly reactive molecules, which include: reactive oxygen species (ROS), reactive nitrogen species and reactive sulfur species.

Reactive oxygen species are radicals, molecules or ions that contain partially reduced oxygen. Since there is an unpaired electron in the valence electron shell of oxygen, these are unstable and reactive molecules, which can react with lipids, proteins and nucleic acids and lead to their damage [1].

If they are present in small amounts, ROS can be beneficial for the body because they participate in the process of destroying microorganisms, wound healing and the process of tissue repair [2].

Reactive oxygen species are formed as a result of exposure to various factors (ultraviolent radiation, smoking, infections, ischemia, etc.), but are also produced in numerous metabolic processes in the body [1, 2]. Various cell organelles are a source of ROS, and due to their electron transport chains. These are: mitochondria, nucleus, plasma membrane [nicotinamide dinucleotide phosphate (NADPH) oxidase], endoplasmic reticulum (cytochrome P450), liposomes (myeloperoxidase), peroxisomes (peroxidase, oxidase, catalase) [1]. In addition to organelles, the source of ROS are also enzymes located in the cytoplasm [e.g., xanthine oxidase (XO)] [1]. The two most important enzyme systems that induce intracellular ROS generation are NADPH oxidase and XO. They catalyze the reaction between NADPH, i.e., xanthine or hypoxanthine (for XO) with oxygen, generating superoxide anion [2]. Hydroxyl radical (OH^-), considered the most reactive free radical *in vivo*, is formed in the reaction between O_2^- and H_2O_2 (hydrogen peroxide) in the Fenton reaction.

All the above mentioned indicates that ROS are very reactive compounds that in appropriate situations lead to the cell damage. Therefore, cells have developed a system to avoid the harmful effects of free radicals - the so-called antioxidant protection.

ANTIOXIDANTS

Antioxidants are substances that have the ability to neutralize ROS. They can be classified into endogenous (enzymes) and exogenous (ubiquinones, vitamins, polyphenols and carotenoids) [1].

The most important endogenous antioxidants are [1, 2]: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase, glutathione reductase.

Superoxide dismutase catalyzes the reaction between superoxide radicals and hydrogen, producing H_2O_2 and oxygen [1]. CAT is an enzyme that catalyzes the next reaction in the detoxification of ROS. Catalase leads to decomposition of H_2O_2 into water and oxygen [1].

PATHOGENESYS OF PEPTIC ULCER

The wall of the digestive tube consists of mucosa, submucosa, muscularis propria and serosa/adventitia [1, 3]. Damage to the continuity of the wall of the gastrointestinal tube is categorized into erosions and ulcerations. Erosions are superficial damage to the mucosa, while ulcerations are deeper damages that break through the lamina muscularis mucosae [4].

Peptic ulcer occurs as a result of an imbalance between aggressive and protective factors (Fig. 1). The gastric mucosa can be attacked by numerous aggressive factors, such as: hydrochloric acid, pepsin, bile salts, various toxins, drugs, ischemia, infectious agents, oxidative stress etc. However, the two most significant factors are nonsteroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* (*H. pylori)* [5-8].

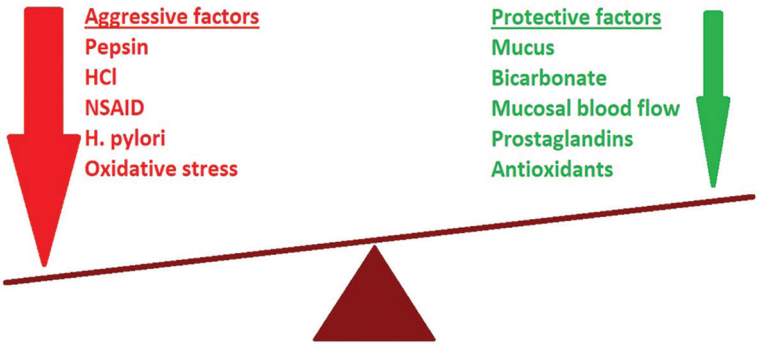

Fig. 1. Pathogenesis of erosions and ulcerations.

Protective factors are primarily localized at the level of the mucosal barrier and include: secretion of mucus, bicarbonate, gastric cell resistance, mucosal blood flow, etc. [9]. Mucus forms a protective layer over the epithelium, protecting it from aggressive factors and, together with bicarbonates, enables an increase in the pH value around the epithelium [9]. Chief cells of the stomach are resistant to low pH, but only on the apical membrane, while the basolateral membrane is very sensitive [9]. Numerous autocides (prostaglandins, nitric oxide, hydrogen sulfide, calcitonin gene-related peptide) also have protective significance [9]. Adequate mucosal blood flow limits the progression of necrosis to the deeper layers of the mucosa [9]. Therefore, all etiological factors that directly or indirectly reduce protective factors can lead to the formation of peptic ulcer.

Oxidative Stress in the Pathogenesis of Peptic Ulcer

The digestive tract is daily exposed to various exogenous and endogenous sources of ROS. The following factors are significant in the pathogenesis of peptic ulcer, from the aspect of oxidative stress [2]: 1) action of exogenous sources of free radicals; 2) NSAIDs; 3) *H. pylori* infection; 4) ethanol intake; 5) ischemia; 6) reduction of endogenous and exogenous antioxidants.

After the formation of ROS, they lead to lipid peroxidation and oxidative damage to proteins and nucleic acids [2].

Lipid peroxidation leads to damage of membrane integrity, damage to its transport characteristics, alter cellular signal transduction and finally damage to cell function [2]. Lipid peroxidation that affects cell membranes, lipoproteins and other molecules leads to the creation of primary highly reactive intermediates, which further breakdown give secondary products of lipid peroxidation [10].

Malondialdehyde (MDA), as a product of lipid peroxidation, can be chemically bound to DNA molecules [11]. This damages the DNA, preventing biochemically complete replication. As a result of oxidative damage to the DNA molecule, the separation and splitting of its chains or hydroxylation of the constitutive bases may occur [11].

All these damages lead to apoptosis or cause disruption of maturation and differentiation of cells, which ultimately leads to inflammation, damage to the epithelium and endothelium, and damage to the digestive tube [2]. A mucosa damaged in this way, is susceptible to further damage under the influence of aggressive factors. In addition to the already listed causes, oxidative stress in the digestive tract can also be provoked by metabolic factors, such as methionine load [12, 13].

Inflammation is a key mechanism of ROS generation and oxidative damage in the development of peptic ulcer. It is mainly caused by NSAIDs use and *H. pylori* infection. In this situation of chronic inflammation, phagocytes are considered the main source of free radicals. Furthermore, stomach inflammation induced by ethanol consumption is linked to overproduction of O_2.

Oxidative Stress Related to NSAIDs

In addition to a direct toxic effect on the gastrointestinal mucosa, NSAIDs also have a harmful effect through the inhibition of cyclooxygenase (COX). There are two isoforms of COX, COX-1 and COX-2 [11]. COX-1 is the constitutive form of the isoenzyme found in tissues and under physiological conditions, while COX-2 is expressed in inflamed tissue [8].

Due to NSAID-induced COX-1 inhibition, the production of prostaglandins E2, I2 and thromboxane A2 is reduced [8,9]. All these eicosanoids are physiologically important, and as a result of their depletion there is a decrease in blood flow through the mucosa, a decrease in the secretion of protective factors, which leads to damage to the mucosa of the digestive tract [9].

In addition to the already mentioned prostaglandin-dependent mechanism of NSAID-induced ulceration, there is another, equally significant mechanism of mucosal damage mediated by NSAIDs, which is the so-called prostaglandin-independent mechanism [14]. The basis of the prostaglandin-independent mechanism is primarily the increased production of ROS as well as the initiation of an inflammatory response. Excessive use of NSAIDs leads to increased accumulation of neutrophilic infiltrate and subsequent release of inflammatory mediators and consequently oxidative tissue damage [14]. Oxidative stress, which is the basis of excessive use of NSAIDs, leads to cell apoptosis through the mitochondrial pathway. Study conducted in rats showed that indomethacin leads to altered morphology and function of mitochondria leading to oxidative stress in this organelle [15].

On the other hand, it should be mentioned that there are cellular protection mechanisms aimed at suppressing the apoptosis pathway in NSAID-induced ulcers, among which the nuclear factor erythroid 2-related factor 2/hemoxygenase-1 (Nrf2/HO-1) signaling pathway is significant. The transcription factor Nrf2 and the enzyme HO-1 play a significant role in the

protection of the gastrointestinal tract through the renewal of the antioxidant protection system [16]. Additionally, HO-1 activity prevents the initiation of an inflammatory response by reducing nuclear factor-kappa B (NF-kB) activation [17].

Oxidative Stress Related to *Helicobacter pylori*

Helicobacter pylori is a microaerophilic, gram-negative bacterium. More than half of the world's population is infected with this microorganism [6]. *H. pylori* causes chronic inflammation and peptic ulcer but can also cause gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma [18, 19]. Helicobacter pylori infection is the cause of about 95% of cases of duodenal ulcer and 70% of gastric ulcer [2].

The virulence factors of the bacterium *H. pylori* play a significant role in the colonization of the gastric mucosa, the maintenance and progression of the chronic inflammation. Flagella, urease and lipopolysaccharide play the most important role in *H. pylori* colonization [18]. *Helicobacter pylori* with urease decomposes urea into CO_2 and ammonium, which acts as a buffer. Since ammonium is a base, it contributes to the alkalinization of stomach acid and provides more favorable microenvironmental conditions for *H. pylori*. When *H. pylori* reaches the gastric mucosal cells, it binds to them using adhesion molecules. The most defined adhesion molecule is blood group antigen binding adhesion (BabA) [13, 19]. After adhesion, the key role is played by exotoxins, cytotoxin-associated gene A (CagA), vacuolized cytotoxin (VacA), etc. [19, 20]. CagA is associated with cell adhesion, tight junction disruption, oxidative stress, inflammation and apoptosis [20]. CagA induces the formation of H_2O_2 in gastric mucosal cells by inducing the enzyme spermine oxidase, which catalyzes the reaction between spermine, oxigen and water, whereby spermidine, 3-aminopropanal and H_2O_2 are formed [20, 21]. VacA is associated with apoptosis. It leads to the formation of acidic vacuoles in the cytoplasm of mucous cells [19]. This cytotoxin primarily leads to mitochondrial damage, through the signaling pathway of β-linked protein, intracellular influx of calcium ions and ROS accumulation [20]. The main virulence factors of *H. pylori* and the pathogenesis of damage to the gastric mucosa caused by this bacterium are shown in Fig. 2.

A very significant feature of *H. pylori* in the pathogenesis of damage to the gastric mucosa mediated by free radicals is its chemotaxic effect on neutrophils [22]. This effect is achieved by the release of chemotaxic factors by the bacteria such as N-formyl-methionyl-leucyl-phenylalanine peptide, which leads to the initiation of an inflammatory response by inducing the release of IL-8 and IL-1β from the gastric mucosa [23]. In the presence of *H. pylori*, neutrophils are attracted to the tissue colonized by the bacteria by chemotaxis. In activated neutrophils, the enzyme myeloperoxidase leads to the formation of a potent oxidant (hypochlorous anion).

Literature data indicate the importance of oxidative stress in the pathogenesis of gastritis caused by *H. pylori*. Namely, studies have shown significantly elevated levels of MDA in the tissue of patients with *H. pylori*, with increased glutathione

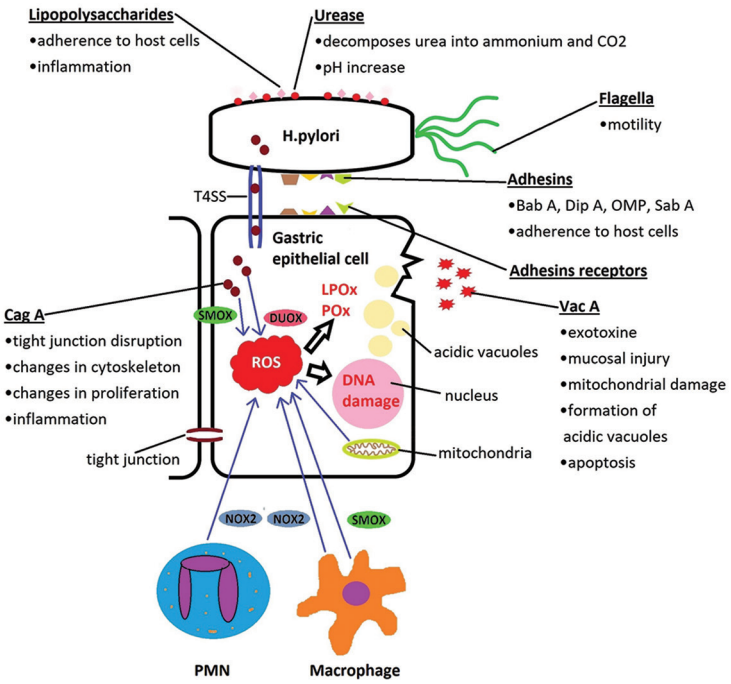

Fig. 2. The main virulence factors of *H. pylori* and the pathogenesis of gastric mucosa damage. T4SS: type 4 secretion system; BabA: blood group antigen binding adhesion; OMP: outer inflammatory protein A; Sab A: sialic acid-binding adhesin; Cag A: cytotoxin-associated gene A; Vac A: vacuolized cytotoxin; ROS: reactive oxygen species; SMOX: spermine oxidase; DUOX: dual oxidase; NOX2: nicotinamide dinucleotide phosphate oxidase 2; DNA: deoxyribonucleic acid; LPOx: lipid peroxidation; POx: protein oxidations; PMN: polymorphonuclear leukocytes.

turnover [24]. This unequivocally indicates oxidative tissue damage, given that MDA is an initiator molecule of lipid damage, and glutathione is considered the most important intracellular antioxidant.

From the perspective of the pathophysiological mechanism of gastric ulcer disease, oxidative stress contributes to the inflammatory response during *H. pylori* infection through numerous redox signaling pathways. One of the mechanisms includes the activation of NF-κB and activator protein 1, under the influence of ROS, which lead to increased production of IL-8 in gastric epithelial cells, promoting an inflammatory response [25].

Although it is possible that during *H. pylori* infection there is an increased activity of the main antioxidant enzymes, as part of the adaptive response, glutathione depletion and oxidative inactivation of peroxidase of the gastric mucosa, which lead to increased lipid peroxidation and damage to cell membranes, which all lead to the progression of ulcer disease [26]. The intracellular antioxidant defense system should prevent and suppress the inflammatory response, but often this is not the case because this system is damaged by *H. pylori* infection [27]. Namely, *H. pylori* possesses γ-glutamyl transpeptidase as a virulence factor that induces apoptosis and enhances the inflammatory response in gastric epithelial cells [27].

Oxidative stress, in addition to having a harmful effect on the structures of the stomach, also has a harmful effect on *H. pylori*. If it did not have developed defense systems against oxidative stress, *H. pylori* would be destroyed very quickly. The mechanisms that allow *H. pylori* to defend against oxidative stress are: antioxidant enzymes (SOD, CAT and peroxiredoxins), biological reparative systems and inhibitors of oxidant generation [28].

Clinical Features of Ulcer Disease

The clinical presentation of damage to the gastroduodenal mucosa ranges from asymptomatic to very severe symptomatology. Patients may present with abdominal pain, nausea, vomiting and dyspeptic symptoms [9]. About 6% of patients with peptic ulcer disease may have iron deficiency anemia [29]. The most typical symptom of peptic ulcer is pain, but patients with NSAID-induced ulcers do not always have pain, and due to the analgesic effect of NSAIDs [8]. The diagnosis of mucosal damage is confirmed by esophagogastroduodenoscopy (Fig. 3).

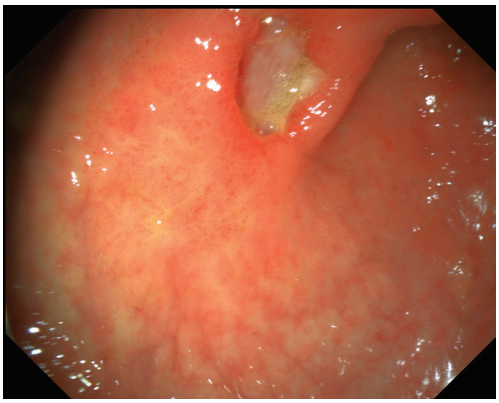

Fig. 3. Endoscopic appearence of gastric ulcer.

THERAPY OF PEPTIC ULCER DISEASE

Conventional Therapy

In the past, antacids and anticholinergics were used to treat peptic ulcer disease, and surgery was often indicated. In the treatment of peptic ulcers, a significant revolution was made by the use of histamine H2-receptor blockers. However, they have been almost completely supplanted by proton pump inhibitors (PPIs), which effectively inhibit gastric acid secretion and lead to healing of peptic ulcers/erosions [5]. If peptic ulcer disease complications occur (bleeding, perforation, penetration, obstruction), endoscopic therapy, interventional radiology or surgery are indicated.

Given that the most common causes of peptic ulcers are *H. pylori* infection and NSAIDs, the key points in therapy and prevention are the eradication of *H. pylori* infection and gastroprotection when using NSAIDs.

Helicobacter pylori Eradication

Eradication of *H. pylori* infection is carried out using PPI and antibiotics. First-line eradication therapy is clarithromycin triple therapy, bismuth quadruple therapy or non-bismuth concomitant quadruple therapy [30]. Adding antioxidants to clarithromycin triple therapy can improve the eradication rate, especially if high-dose vitamins are used as antioxidants [31]. However, this was not confirmed in some earlier meta-analyses [32]. A potential protective treatment with antioxidants on the gastric mucosa after the eradication of *H. pylori* infection can also be considered. Thus, the protective effect of vitamins A, C and E on the gastric mucosa in patients after *H. pylori* eradication has been proposed, most likely due to a reduction in oxidative stress and proinflammatory cytokines level [33].

Misoprostol

Prostanoid depletion is one of the key reasons for damage to the gastroduodenal mucosa due to the use of NSAIDs. Therefore, misoprostol can be used for prevention, but its use is limited due to adverse effects [9]. The main drugs in the prevention of NSAID-induced damage to the gastrointestinal tract are PPIs.

Non-conventional Therapy

Antioxidants

Given that oxidative stress is of great importance in the development of peptic ulcer disease, the effect of antioxidants in its healing was investigated. Flavonoids have shown a significant effect in the healing of peptic ulcers, *in vitro*, so they are promising in this indication [34]. Flavonoids have shown a protective effect in NSAID-induced ulcerations, due to their antioxidant, anti-inflammatory and anti-apoptotic effects [35, 36]. Also, dietary polyphenols can be an effective and safe therapy for peptic ulcer disease [37, 38]. Sulforaphane contributes to the protection of the gastrointestinal mucosa from the harmful effects of NSAIDs and *H. pylori* infection [39]. Also, the effects of exogenous 8-hydroxydeoxyguanosine in the regulation of gastritis induced by oxidative stress were demonstrated, as this molecule blocks the gastric inflammatory cascade. Based on these effects, exogenous 8-hydroxydeoxyguanosine can be considered

an anti-inflammatory and antioxidant mediator of gastritis and gastritis-based carcinogenesis [40].

CONCLUSIONS

Observed from the aspect of oxidative stress, the basis of peptic ulcer disease is the balance between the harmful effects of free radicals and the antioxidant defense system. Since oxidative stress is recognized as one of the basic mechanisms in the pathophysiological process of gastrointestinal ulcer disease, it is justified to consider the use of antioxidants in order to prevent an advanced form of inflammation and more intense mucosal damage.

There are literature data that show the beneficial effects of the use of antioxidants in the protection of the gastrointestinal mucosa, but additional research in this area is definitely required.

Although PPIs are available, which are effective drugs in the treatment of peptic ulcer disease, further research in this area is necessary. We believe that future research should be directed in two directions, towards the treatment of peptic ulcer disease and its prevention. In treatment, it is necessary to further develop more effective drugs for gastrointestinal ulcers/erosions. In prevention, further research is necessary in the development of a vaccine against *H. pylori*, the use of more effective and tolerable eradication protocols and the use of adequate probiotics. There is no doubt that research into the use of antioxidants in the prevention and treatment of peptic ulcer disease will remain relevant.

Conflicts of interest: None to declare.

Authors' contribution: D.P. and M.S. made a significant contribution to the conception of the manuscript and wrote the draft. D.P., M.S., T.M., M.S.L., T.G., P.S. and B.F. conducted the research, analyzed the data, critically revised the draft and approved the final version of the manuscript.

REFERENCES

1. Vona R, Pallotta L, Cappelletti M, Severi C, Matarrese P. The Impact of Oxidative Stress in Human Pathology: Focus on Gastrointestinal Disorders. Antioxidants (Basel) 2021;10:201. doi:10.3390/antiox10020201
2. Bhattacharyya A, Chattopadhyay R, Mitra S, Crowe SE. Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. Physiol Rev 2014;94:329-354. doi:10.1152/physrev.00040.2012
3. Milosavljevic T, Popovic D, Zec S, Krstic M, Mijac D. Accuracy and Pitfalls in the Assessment of Early Gastrointestinal Lesions. Dig Dis 2019;37:364-373. doi:10.1159/000495849
4. Popović D. Gastroenterološki pristup krvarenju iz digestivnog trakta. Belgrade: Medicinski fakultet Univerziteta u Beogradu CIBID; 2022.
5. Kavitt RT, Lipowska AM, Anyane-Yeboa A, Gralnek IM. Diagnosis and Treatment of Peptic Ulcer Disease. Am J Med 2019;132:447-456. doi:10.1016/j.amjmed.2018.12.009
6. Öztekin M, Yılmaz B, Ağagündüz D, Capasso R. Overview of Helicobacter pylori Infection: Clinical Features, Treatment, and Nutritional Aspects. Diseases 2021;9:66. doi:10.3390/diseases9040066
7. Melcarne L, García-Iglesias P, Calvet X. Management of NSAID-associated peptic ulcer disease. Expert Rev Gastroenterol Hepatol 2016;10:723-733. doi:10.1586/17474124.2016.1142872
8. Krstic M, Popovic D, Milosavljevic T. Side-effects of nonsteroid antiinflamatory drugs and low-dose aspirin on upper-gastrointestinal tract. Acta Clinica 2018;18:25-32.
9. Wallace JL. Prostaglandins, NSAIDs, and gastric mucosal protection: why doesn't the stomach digest itself? Physiol Rev 2008;88:1547-65. doi: 10.1152/physrev.00004.2008
10. Leonarduzzi G, Chiarpotto E, Biasi F, Poli G. 4-Hydroxynonenal and cholesterol oxidation products in atherosclerosis. Mol Nutr Food Res 2005;49:1044-1049. doi:10.1002/mnfr.200500090
11. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007;39:44-84. doi:10.1016/j.biocel.2006.07.001
12. Stojanović M, Todorović D, Šćepanović L, et al. Subchronic methionine load induces oxidative stress and provokes biochemical and histological changes in the rat liver tissue. Mol Cell Biochem 2018;448:43-50. doi:10.1007/s11010-018-3311-2
13. Stojanović M, Šćepanović L, Todorović D, et al. Suppression of methionine-induced colon injury of young rats by cysteine and N-acetyl-L-cysteine. Mol Cell Biochem 2018;440:53-64. doi:10.1007/s11010-017-3155-1
14. Wallace JL, Keenan CM, Granger DN. Gastric ulceration induced by nonsteroidal anti-inflammatory drugs is a neutrophil-dependent process. Am J Physiol 1990;259:G462-G467. doi:10.1152/ajpgi.1990.259.3.G462
15. Maity P, Bindu S, Dey S, et al. Indomethacin, a non-steroidal anti-inflammatory drug, develops gastropathy by inducing reactive oxygen species-mediated mitochondrial pathology and associated apoptosis in gastric mucosa: a novel role of mitochondrial aconitase oxidation. J Biol Chem 2009;284:3058-3068. doi:10.1074/jbc.M805329200
16. Yanaka A. Role of NRF2 in protection of the gastrointestinal tract against oxidative stress. J Clin Biochem Nutr 2018;63:18-25. doi:10.3164/jcbn.17-139
17. Raish M, Shahid M, Bin Jardan YA, et al. Gastroprotective Effect of Sinapic Acid on Ethanol-Induced Gastric Ulcers in Rats: Involvement of Nrf2/HO-1 and NF-κB Signaling and Antiapoptotic Role. Front Pharmacol 2021;12:622815. doi:10.3389/fphar.2021.622815
18. Suerbaum S, Michetti P. Helicobacter pylori infection. N Engl J Med 2002;347:1175-1186. doi:10.1056/NEJMra020542
19. de Brito BB, da Silva FAF, Soares AS, et al. Pathogenesis and clinical management of Helicobacter pylori gastric infection. World J Gastroenterol 2019;25:5578-5589. doi:10.3748/wjg.v25.i37.5578
20. Han L, Shu X, Wang J. Helicobacter pylori-Mediated Oxidative Stress and Gastric Diseases: A Review. Front Microbiol 2022;13:811258. doi:10.3389/fmicb.2022.811258
21. Cervelli M, Amendola R, Polticelli F, Mariottini P. Spermine oxidase: ten years after. Amino Acids 2012;42:441-450. doi:10.1007/s00726-011-1014-z
22. Mai UE, Perez-Perez GI, Allen JB, Wahl SM, Blaser MJ, Smith PD. Surface proteins from Helicobacter pylori exhibit chemotactic activity for human leukocytes and are present in gastric mucosa. J Exp Med 1992;175:517-525. doi:10.1084/jem.175.2.517
23. Sommer F, Bäckhed F. The gut microbiota engages different signaling pathways to induce Duox2 expression in the ileum and colon epithelium. Mucosal Immunol 2015;8:372-379. doi:10.1038/mi.2014.74

24. Farinati F, Cardin R, Libera GD, et al. Determinants for the development of chronic atrophic gastritis and intestinal metaplasia in the stomach. Eur J Cancer Prev 1995;4:181-186. doi:10.1097/00008469-199504000-00009
25. O'Hara AM, Bhattacharyya A, Mifflin RC, et al. Interleukin-8 induction by Helicobacter pylori in gastric epithelial cells is dependent on apurinic/apyrimidinic endonuclease-1/redox factor-1. J Immunol 2006;177:7990-7999. doi:10.4049/jimmunol.177.11.7990
26. Drake IM, Mapstone NP, Schorah CJ, et al. Reactive oxygen species activity and lipid peroxidation in Helicobacter pylori associated gastritis: relation to gastric mucosal ascorbic acid concentrations and effect of H pylori eradication. Gut 1998;42:768-771. doi:10.1136/gut.42.6.768
27. Gong M, Ling SS, Lui SY, Yeoh KG, Ho B. Helicobacter pylori gamma-glutamyl transpeptidase is a pathogenic factor in the development of peptic ulcer disease. Gastroenterology 2010;139:564-573. doi:10.1053/j.gastro.2010.03.050
28. Stent A, Every AL, Sutton P. Helicobacter pylori defense against oxidative attack. Am J Physiol Gastrointest Liver Physiol 2012;302:G579- G587. doi:10.1152/ajpgi.00495.2011
29. Popovic D, Zec S, Rankovic I, Glisic T, Milovanovic T. Upper and lower gastrointestinal endoscopy in patients with iron deficiency anemia. Srp Arh Celok Lek 2020;148:31-36. doi:10.2298/SARH190325088P
30. Malfertheiner P, Megraud F, Rokkas T, et al; European Helicobacter and Microbiota Study group. Management of Helicobacter pylori infection: the Maastricht VI/Florence consensus report. Gut 2022;71:1724-1762. doi:10.1136/gutjnl-2022-327745
31. Yang-Ou YB, Hu Y, Zhu Y, Lu NH. The effect of antioxidants on Helicobacter pylori eradication: A systematic review with meta-analysis. Helicobacter 2018;23:e12535. doi:10.1111/hel.12535
32. Li G, Li L, Yu C, Chen L. Effect of vitamins C and E supplementation on Helicobacter pylori eradication: a meta-analysis. Br J Nutr 2011;106:1632-1637. doi:10.1017/S0007114511003813
33. Nabavi-Rad A, Azizi M, Jamshidizadeh S, et al. The Effects of Vitamins and Micronutrients on Helicobacter pylori Pathogenicity, Survival, and Eradication: A Crosstalk between Micronutrients and Immune System. J Immunol Res 2022;2022:4713684. doi:10.1155/2022/4713684
34. Zhang W, Lian Y, Li Q, et al. Preventative and Therapeutic Potential of Flavonoids in Peptic Ulcers. Molecules 2020;25:4626. doi:10.3390/molecules25204626
35. El-Demerdash AA, Menze ET, Esmat A, Tadros MG, Elsherbiny DA. Protective and therapeutic effects of the flavonoid "pinocembrin" in indomethacin-induced acute gastric ulcer in rats: impact of anti-oxidant, anti-inflammatory, and anti-apoptotic mechanisms. Naunyn Schmiedebergs Arch Pharmacol 2021;394:1411-1424. doi:10.1007/s00210-021-02067-5
36. Serafim C, Araruna ME, Júnior EA, Diniz M, Hiruma-Lima C, Batista L. A Review of the Role of Flavonoids in Peptic Ulcer (2010-2020). Molecules 2020;25:5431. doi:10.3390/molecules25225431
37. Chiu HF, Venkatakrishnan K, Golovinskaia O, Wang CK. Gastroprotective Effects of Polyphenols against Various Gastro-Intestinal Disorders: A Mini-Review with Special Focus on Clinical Evidence. Molecules 2021;26:2090. doi:10.3390/molecules26072090
38. Farzaei MH, Abdollahi M, Rahimi R. Role of dietary polyphenols in the management of peptic ulcer. World J Gastroenterol 2015;21:6499-6517. doi:10.3748/wjg.v21.i21.6499
39. Yanaka A. Role of Sulforaphane in Protection of Gastrointestinal Tract Against H. pylori and NSAID-Induced Oxidative Stress. Curr Pharm Des 2017;23:4066-4075. doi:10.2174/1381612823666170207103943
40. Ock CY, Hong KS, Choi KS, et al. A novel approach for stress-induced gastritis based on paradoxical anti-oxidative and anti-inflammatory action of exogenous 8-hydroxydeoxyguanosine. Biochem Pharmacol 2011;81:111-122. doi:10.1016/j.bcp.2010.08.023