J Current Biomed Report
ISSN: 2717-1906

2023, Volume 4, Number 4

Research Paper

Evaluation of the efficacy of N-Acetylcysteine combined with standard quadruple therapy versus standard quadruple therapy alone for *Helicobacter pylori* eradication

Farahnaz Joukar[1], Sara Manafi Afkham[1], Afshin Shafaghi[2], Fariborz Mansour-Ghanaei[1*]

1. *Gastrointestinal and Liver Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran*
2. *Department of Internal Medicine, GI Cancer Screening and Prevention Research Center, School of Medicine, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran*

ABSTRACT

Article info:
Received: 14 Sep 2023
Accepted: 21 Nov 2023

Keywords:
Helicobacter pylori
N-acetyl cysteine
Proton pump inhibitor

N-acetyl cysteine (NAC) has recently been proposed as an adjunctive therapy for the eradication of *Helicobacter pylori* infection due to its mucolytic, antioxidant, and antimicrobial properties. This study aimed to evaluate the efficacy of adding NAC to the standard 4-drug regimen consisting of amoxicillin, clarithromycin, pantoprazole, and bismuth subcitrate. In this double-blind, randomized clinical trial, 92 patients with confirmed *H. pylori* infection were randomly assigned to either the intervention group or the control group (46 patients each) using a randomized block design. All patients received a 14-day course of amoxicillin, clarithromycin, pantoprazole, and bismuth subcitrate. The intervention group also received NAC tablets, while the control group received a placebo, matched in dose and schedule. Eradication of *H. pylori* was assessed two weeks after treatment cessation using the urea breath test. *H. pylori* eradication was achieved in 78.3% of patients in the intervention group (95% CI: 66.38–90.21) and 71.7% in the placebo group (95% CI: 59.57–84.49), with no statistically significant difference between groups (p=0.804). The overall eradication rate among all participants was 75% (95% CI: 64.72–85.77). Of the 23 patients who failed treatment, 14 were smokers, and smoking was significantly associated with treatment failure (p<0.0001). Notably, eradication rates among smokers were significantly higher in the NAC group compared to the placebo group (p=0.041). The addition of NAC to standard quadruple therapy did not significantly improve *H. pylori* eradication overall, but its potential benefit in specific subgroups such as smokers suggests the need for further research.

***Corresponding Author(s):**
Fariborz Mansour-Ghanaei, MD, AGAF
Address: *Gastrointestinal and Liver Diseases Research Center, Sardar-Jangle Ave., P.O. Box: 41448-95655, Rasht, Iran*
Tel: +98 13 15535116
E-mail: fmansourghanaei@gmail.com

1. Introduction

Currently, *Helicobacter pylori* eradication therapy typically involves a combination of a proton pump inhibitor (PPI) or bismuth subsalicylate/subcitrate, along with antibiotics such as amoxicillin, clarithromycin, and metronidazole. Among existing regimens, the 3-drug combination of PPI, clarithromycin, and amoxicillin is commonly accepted as the first-line treatment. However, its efficacy is declining, which highlights the urgent need for safer and more effective treatment alternatives [1,2]. *H. pylori* possesses unique adaptations that allow it to thrive in the harsh gastric environment, such as biofilm formation and mucus layer penetration to evade acidity [3–5]. The resulting gastritis is marked by neutrophil infiltration and the release of reactive oxygen species. Studies in humans and animals have shown that antioxidants can reduce gastric inflammation and bacterial load [6–8].

N-acetyl cysteine (NAC), known for its mucolytic and antioxidant properties, has long been used in conditions like cystic fibrosis, chronic bronchitis, acetaminophen toxicity, and contrast-induced nephropathy [9,10]. In vitro, NAC can alter the viscoelastic properties of gastric mucus and exhibits antimicrobial activity [11]. NAC has recently been proposed as an adjunctive therapy for *H. pylori* eradication. However, evidence on its clinical effectiveness remains limited. This study evaluated the efficacy of adding NAC to the 4-drug regimen of amoxicillin, clarithromycin, pantoprazole, and bismuth subcitrate.

2. Materials and Methods

2.1 Study design

This randomized, double-blind clinical trial was approved by the International Center for Clinical Trials Registration (IRCT201605201155N24). The study was confirmed by the ethics committee of the Guilan University of Medical Sciences [IR.GUMS.REC.1394.227]. The study included patients presenting with upper dyspepsia who underwent upper endoscopy at a hospital in Rasht, Iran, in 2016 and had confirmed *H. pylori* infection based on both a positive rapid urease test (RUT) and histological examination. Exclusion criteria included: known hypersensitivity to study medications, recent use of bismuth compounds, antibiotics, or PPI, chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, gastrointestinal obstruction, renal failure, gastric cancer, history of gastric surgery, pregnancy, and age under 18 or over 70 years. Eligible patients who met the inclusion criteria were randomly assigned to either the intervention or control group.

2.2 Patients

In the intervention group, patients received 600 mg of NAC every 12 hours, along with a 3-drug regimen consisting of 1000 mg of amoxicillin, 500 mg of clarithromycin, and 20 mg of omeprazole, all administered twice daily with amoxicillin and clarithromycin taken with breakfast and dinner, and omeprazole taken before breakfast and dinner. The control group received the same 3-drug regimen plus a placebo (prepared by Minoo Pharmaceuticals, Iran) instead of NAC. In both groups, the antibiotic regimen was administered for 14 days. Afterward, patients without peptic ulcer continued omeprazole 20 mg once daily for 2 additional weeks, while those with peptic ulcer received omeprazole treatment for an additional 4 to 6 weeks, based on clinical need. Following the completion of the treatment, pantoprazole was discontinued, and two weeks later, a Urethane Breath Test (UBT) was performed to confirm *H. pylori* eradication. Throughout the study period, all patients were monitored for any complications.

2.3 Statistical analysis

The data were analyzed using SPSS version 21. Frequency and percentage were used to describe qualitative variables, while mean and range were used for quantitative variables. Qualitative data were analyzed using the chi-square test or Fisher's exact test, and quantitative variables were analyzed using the t-test to compare means. A P-value of <0.05 was considered statistically significant.

3. Results

A total of 92 patients were enrolled in the study, with 46 patients randomized to the intervention group and 46 patients randomized to the placebo group. The mean age of participants was 43.88±13.19 years, with 69.5% of patients under 50 years of age and 30.5% aged 50 years or older. Of the participants, 38.1% were male and 61.9% were female. The mean age of patients in the intervention group was 42.1±14.26 years, while in the placebo group it was 45.65±11.93 years, with no significant age difference between the two groups (p=0.221). In the placebo group, 34.7% of patients were male and 65.3% were female, while in the intervention group, 41.3% were male and 58.7% were female. No significant difference in gender distribution was observed between the two groups (p=0.445).

A total of 21 patients were smokers, with 11 in the intervention group and 10 in the placebo group (p=0.765). Alcohol consumption was reported by 9 patients, with 4 in the placebo group and 5 in the intervention group (p=0.691). As shown in Table 1, *H. pylori* infection was confirmed in 69 out of 92 patients, with an overall eradication rate of 75% (95% CI: 64.72–85.77). The eradication rate in the intervention group was 78.3% (95% CI: 66.38–90.21), compared to 71.7% in the placebo group (95% CI: 59.57–84.49) (Figure 1). No statistically significant difference in eradication rates was observed between the oral NAC plus 4-drug regimen and the 4-drug regimen alone (p=0.804). Of the 23 patients whose treatment failed, 11 were male and 12 were female, with treatment failure being significantly higher in males (p=0.004). As shown in Table 2, eradication rates in males were significantly higher in the intervention group compared to the placebo group (73.7% *vs.* 62.5%; p=0.010). However, no significant difference was observed between the two groups in female patients (p=0.445).

Of the 23 patients with treatment failure, 14 were smokers, and treatment failure was significantly higher among smokers (p<0.0001). However, *H. pylori* eradication was significantly higher in smokers in the intervention group compared to the placebo group (p=0.041) (Table 3). Among the 9 patients who consumed alcohol, 6 experienced treatment failure. No significant difference in eradication rates was observed between alcohol users and non-users (p=0.544). Additionally, there was no significant difference between the two groups regarding alcohol consumption (p=0.214) (Table 3). The most common complication observed was heartburn. Treatment side effects are summarized in Table 4.

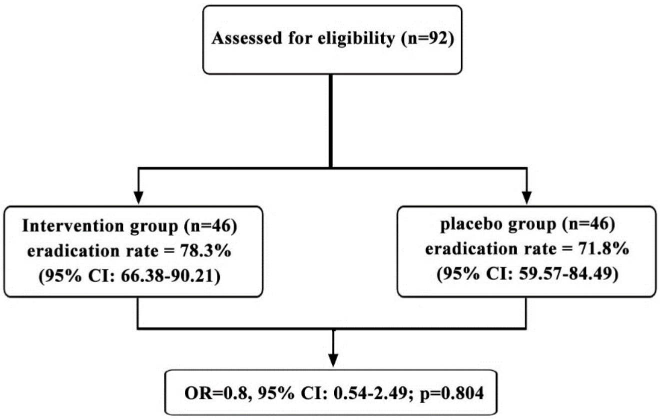

Figure 1. Comparison of treatment responsiveness in the two groups

Table 1. Distribution of efficacy in eradication of *H. pylori* infection in two groups.

Eradication of infection	Placebo group n (%)	Intervention group n (%)	Total n (%)	P value
Treatment failure	13 (28.3)	10 (21.7)	23 (25.0)	
Eradication	33 (71.7)	36 (78.3)	69 (75.0)	0.804
total	46	46	92	

Table 2. Distribution of *H. pylori* infection eradication rate in two groups disaggregated by gender

Gender	Eradication of infection	Placebo group n (%)	Intervention group n (%)	Total n (%)	P value	Total P Value
Male	Treatment failure	6 (37.5)	5 (26.3)	11 (31.4)		
	Eradication	10 (62.5)	14 (73.7)	24 (68.6)	0.01	
	Total	16 (100)	19 (100)	35 (100)		0.004
Female	Treatment failure	7 (23.3)	5 (18.5)	12 (21.1)		
	Eradication	23 (76.7)	22 (81.5)	45 (78.9)	0.457	
	Total	30 (1000	27 (100)	57 (100)		

Table 3. Distribution of *H. pylori* infection eradication rate in two groups disaggregated by alcohol use and smoking

Variables		Placebo group n (%)	Intervention group n (%)	Total n (%)	P value
	Treatment failure	7 (70.0)	7 (63.6)	14 (33.3)	0.041
Smoking	Eradication	3 (30.0)	4 (36.4)	7 (66.7)	
	Total	10 (100)	11 (100)	21 (100)	
	Treatment failure	3 (75.0)	3 (60.0)	6 (66.7)	0.214
Alcohol use	Eradication	1 (25.0)	2 (40.0)	3 (33.3)	
	Total	4 (100)	5 (100)	9 (100)	

Table 4. Frequency of treatment complications in two groups.

Complication	Placebo group (N=46) n (%)	Intervention group (N=46) n (%)	Total n (%)	P value
Headache	6 (13.0)	8 (17.3)		0.507
Nausea and vomiting	3 (6.5)	2 94.3)		0.854
Diarrhea	4 (8.7)	2 (4.3)		0.727
Heartburn	12 (26.1)	13 (28.2)		0.694
Epigastric pain	4 (8.7)	3 (6.5)		0.533
Taste disorder	3 96.5)	4 (8.7)		0.459

4. Discussion

Over the past decade, the potential of adding a mucolytic drug as an adjunct to the standard *H. pylori* treatment regimen has garnered significant interest among researchers [12]. Some studies suggest that this adjunctive treatment can effectively aid in eradicating H. pylori, while others propose that its effectiveness may depend on specific factors, such as smoking status, gender, age, or race. Additionally, some studies have found no significant benefit from the treatment [13,14]. This present study found that, while NAC supplementation resulted in a higher eradication rate, the difference was not statistically significant. However, NAC did improve eradication rates in smokers and men

A study conducted in Iran by Karbasi et al. found that *H. pylori* infection was eradicated in 70% of patients receiving an NAC treatment regimen, compared to 60.7% in those who did not receive NAC. Although the NAC group showed a higher eradication rate, this difference was not statistically significant, similar to the findings in our study [15].

In a study by Yoon et al. in Korea, the addition of NAC to the *H. pylori* treatment regimen increased the eradication rate to 80.5% in the NAC group, compared to 70% in the placebo group. However, this difference was also not statistically significant, aligning with our study's results [16]. Additionally, a study by Emami et al. in Isfahan, Iran, involving 121 patients, concluded that the addition of NAC to a three-drug regimen did not significantly impact the eradication of *H. pylori* [17].

On the contrary, Hamidian et al. reported that in patients who received NAC alongside a three-drug regimen containing amoxicillin, clarithromycin, and omeprazole, the *H. pylori* eradication rate was 72.9%, compared to 60.9% in those who did not receive NAC. Their study demonstrated that adding NAC to this regimen significantly increased the eradication rate [18]. A study by Fontes et al. reported that the effectiveness and safety of adding NAC to *H. pylori* treatment remain uncertain due to inconsistent findings, study heterogeneity, and limited evidence on adverse events [19]. Oxidative stress is thought to play a key role in *H. pylori*-induced mucosal damage. *H. pylori* infection triggers the infiltration and activation of neutrophils and macrophages in the gastric mucosa without directly invading the mucus layer [8,20].

This immune response leads to the production of inflammatory mediators, including reactive oxygen species (ROS) and reactive nitrogen species (RNS), resulting in oxidative stress within the gastric tissue [21]. NAC is an antioxidant that generates glutathione and also acts as an inhibitor of hydroxyl radicals and hydrogen peroxide (H_2O_2). Studies have shown that NAC exerts both direct and indirect antioxidant effects [22,23].

Animal studies have shown that NAC reduces the thickness of the gastric mucosa and alters its physicochemical properties. The mucosal layer, composed primarily of glycoproteins, is responsible for the viscosity and elasticity of the mucus, providing lubrication, protection, and a barrier between epithelial cells and gastric contents [18,24].

While this layer offers essential benefits such as nutrient support and defense against stomach acid and enzymes, it may also serve as a refuge for bacteria like *H. pylori*, allowing them to evade the harsh gastric environment [25]. *H. pylori* initially stimulates increased mucin production and upregulates mucin gene expression. Reduced mucus viscosity has been associated with a higher rate of *H. pylori* eradication [26]. The use of a mucolytic agent enhances the eradication of *H. pylori* [27]. The mucolytic properties of NAC appear to inhibit *H. pylori* growth by reducing the hydrophobicity and thickness of the mucus layer [18].

Based on the results of this study, treatment failure was higher in smokers compared to non-smokers, and also higher in men, who represented the majority of smokers. However, in the intervention group, the addition of NAC to the standard quadruple therapy significantly improved the eradication rate among smokers. Several mechanisms have been proposed to explain the relationship between smoking and the failure of *H. pylori* eradication therapy. The most significant factor contributing to treatment failure in smokers is non-compliance with the prescribed regimen [28]. Some studies have reported that pentagastrin, which stimulates gastric acid secretion, is significantly higher in long-term smokers compared to non-smokers. As a result, smokers have a more acidic gastric environment [29]. Cigarette smoking also increases oxidative stress and reduces antioxidant capacity [30,31].

NAC can reduce the oxidative effects on stomach mucus and the inflammatory response, mitigating the impact of cigarette-induced oxidation, thereby enhancing the eradication of *H. pylori* infection in smokers [32,33].

However, this study has some limitations. It was conducted at a single center with a relatively small sample size, which may affect the generalizability and statistical power. Patient adherence was not objectively verified, and factors such as antibiotic resistance or lifestyle habits were not assessed, which could have influenced the eradication outcomes. Future research with larger, multicenter trials is recommended to confirm these findings. Evaluating antibiotic resistance patterns, treatment adherence, and lifestyle factors may help improve H. pylori eradication strategies. While the addition of NAC to the standard 4-drug regimen (amoxicillin, clarithromycin, bismuth, and pantoprazole) resulted in a higher eradication rate of *H. pylori* infection, this difference was not statistically significant. However, the eradication rate in smokers significantly improved in the intervention group with the inclusion of NAC, suggesting potential benefits for this subgroup.

Acknowledgments

We thank all subjects for participating in this study and the Guilan University of Medical Science, Rasht, Iran for supporting this study. The current study is derived from Sara Manafi Afkham's Specialty thesis in Internal Medicine (Code: 812).

Authors' contributions

Data collection: FMGH, FJ, ASH, SMA. Survey execution: FMGH, FJ, SMA, Writing of text and revisions: ASH, SMA, FJ. Statistical analysis: FJ.

All authors have read and approved the final manuscript.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical declarations

This randomized, double-blind clinical trial was approved by the International Center for Clinical Trials Registration (IRCT201605201155N24). The study design was confirmed by the ethics committee of the Guilan University of Medical Sciences [IR.GUMS.REC.1394.227].

Informed consent obtained from all of the participants by signing a form in a written format. In cases where the research participants are unable to sign a form, because of a language barrier, then oral or verbal consent have been obtained and documented in the presence of a witness. In the case of adults with cognitive decline, a parent and/or legal guardian/family or an appropriate representative gave informed consent to participate on their behalf.

Financial support

Self-funded.

References

1. Graham DY, Lee SY. How to effectively use bismuth quadruple therapy: the good, the bad, and the ugly. Gastroenterology Clinics of North America. 2015;44(3):537. DOI: 10.1016/j.gtc.2015.05.003 PMID: 26314667
2. Vieira RR, Fontes LE, Pacheco RL, Fernandes MA, Malta PP, Riera R. Proton pump inhibitor-and clarithromycin-based triple therapies for Helicobacter pylori eradication. The Cochrane Database of Systematic Reviews. 2020;2020(9):CD013734. DOI: 10.1002/14651858.CD013734
3. Gupta N, Kumar A, Verma VK. Strategies adopted by gastric pathogen Helicobacter pylori for a mature biofilm formation: Antimicrobial peptides as a visionary treatment. Microbiological Research. 2023;273:127417. DOI: 10.1016/j.micres.2023.127417
4. Sharndama HC, Mba IE. Helicobacter pylori: an up-to-date overview on the virulence and pathogenesis mechanisms. Brazilian Journal of Microbiology. 2022;53(1):33-50. DOI: 10.1007/s42770-021-00675-0
5. Kao CY, Sheu BS, Wu JJ. Helicobacter pylori infection: An overview of bacterial virulence factors and pathogenesis. Biomedical journal. 2016;39(1):14-23. DOI: 10.1016/j.bj.2015.06.002
6. Bhattacharyya A, Chattopadhyay R, Mitra S, Crowe SE. Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. Physiological reviews. 2014;94(2):329-54. DOI: 10.1152/physrev.00040.2012 PMID: 24692350
7. Zhang S, Shen Y, Liu H, Zhu D, Fang J, Pan H, Liu W. Inflammatory microenvironment in gastric premalignant lesions: implication and application. Front Immunol. 2023;14:1297101. DOI: 10.3389/fimmu.2023.1297101 PMID: 38035066
8. Sah DK, Arjunan A, Lee B, Jung YD. Reactive Oxygen Species and *H. pylori* Infection: A Comprehensive Review of Their Roles in Gastric Cancer Development. Antioxidants (Basel). 2023;12(9):1712. DOI: 10.3390/antiox12091712 PMID: 37760015
9. Tieu S, Charchoglyan A, Paulsen L, Wagter-Lesperance LC, Shandilya UK, Bridle BW, Mallard BA, Karrow NA. N-Acetylcysteine and Its Immunomodulatory Properties in Humans and Domesticated Animals. Antioxidants (Basel). 2023;12(10):1867. DOI: 10.3390/antiox12101867 PMID: 37891946
10. Schwalfenberg GK. N-Acetylcysteine: A Review of Clinical Usefulness (an Old Drug with New Tricks). J Nutr Metab. 2021;2021:9949453. DOI: 10.1155/2021/9949453. PMID: 34221501
11. Meziu E, Shehu K, Koch M, Schneider M, Kraegeloh A. Impact of mucus modulation by N-acetylcysteine on nanoparticle toxicity. International Journal of Pharmaceutics: X. 2023;6:100212. DOI: 10.1016/j.ijpx.2023.100212
12. Dascălu RI, Bolocan A, Păduaru DN, Constantinescu A, Mitache MM, Stoica AD, Andronic O. Multidrug resistance in Helicobacter pylori infection. Frontiers in Microbiology. 2023;14:1128497. DOI:10.3389/fmicb.2023.1128497
13. White B, Winte M, DeSipio J, Phadtare S. Clinical factors implicated in antibiotic resistance in Helicobacter pylori patients. Microorganisms. 202;10(2):322. DOI: 10.3390/microorganisms10020322
14. Cardos IA, Zaha DC, Sindhu RK, Cavalu S. Revisiting therapeutic strategies for H. pylori treatment in the context of antibiotic resistance: focus on alternative and complementary therapies. Molecules. 2021;26(19):6078. DOI: 10.3390/molecules26196078
15. Karbasi A, Hosseini H, Shohrati M, Amini M, Najafian B. Effect of oral N-acetyl cysteine on eradication of Helicobacter pylori in patients with dyspepsia. Minerva Gastroenterologica e Dietologica. 2013;59(1):107-12. PMID: 23478248
16. Yoon H, Lee DH, Jang ES, Kim J, Shin CM, Park YS, Hwang JH, Kim JW, Jeong SH, Kim N. Effects of N-acetylcysteine on first-line sequential therapy for Helicobacter pylori infection: a randomized controlled pilot trial. Gut and liver. 2015;10(4):520. DOI: 10.5009/gnl15048 PMID: 26347514
17. Emami MH, Zobeiri M, Rahimi H, Arjomandi F, Daghagzadeh H, Adibi P, Hashemi J. N-acetyl cysteine as an adjunct to standard anti-Helicobacter pylori eradication regimen in patients with dyspepsia: A prospective randomized, open-label trial. Advanced Biomedical Research. 2014;3(1):189. DOI: 10.4103/2277-9175.140403 PMID: 25298958
18. Hamidian SM, Aletaha NS, Taslimi R, Montazeri M. An Additive Effect of Oral N-Acetyl Cysteine on Eradication of Helicobacter pylori. J Pathog. 2015;2015:540271. DOI: 10.1155/2015/540271 PMID: 26421191
19. Fontes LES, Martimbianco ALC, Zanin C, Riera R. N-acetylcysteine as an adjuvant therapy for Helicobacter pylori eradication. Cochrane Database Syst Rev. 2019 ;2(2):CD012357. DOI: 10.1002/14651858.CD012357.pub2 PMID: 30746681

20. Han L, Shu X, Wang J. Helicobacter pylori-mediated oxidative stress and gastric diseases: a review. Frontiers in microbiology. 2022;13:811258. DOI: 10.3389/fmicb.2022.811258
21. Butcher LD, den Hartog G, Ernst PB, Crowe SE. Oxidative Stress Resulting From *Helicobacter pylori* Infection Contributes to Gastric Carcinogenesis. Cell Mol Gastroenterol Hepatol. 2017;3(3):316-322. DOI: 10.1016/j.jcmgh.2017.02.002 PMID: 28462373
22. Pedre B, Barayeu U, Ezeriņa D, Dick TP. The mechanism of action of N-acetylcysteine (NAC): The emerging role of H2S and sulfane sulfur species. Pharmacology & therapeutics. 2021;228:107916. DOI: 10.1016/j.pharmthera.2021.107916
23. Tenório MCDS, Graciliano NG, Moura FA, Oliveira ACM, Goulart MOF. *N*-Acetylcysteine (NAC): Impacts on Human Health. Antioxidants (Basel). 2021;10(6):967. DOI: 10.3390/antiox10060967 PMID: 34208683
24. Miyazaki K, Sasaki A, Mizuuchi H. Advances in the Evaluation of Gastrointestinal Absorption Considering the Mucus Layer. Pharmaceutics. 2023 Nov 30;15(12):2714. DOI: 10.3390/pharmaceutics15122714 PMID: 38140055
25. Gupta A, Shetty S, Mutalik S, Chandrashekar H R, K N, Mathew EM, Jha A, Mishra B, Rajpurohit S, Ravi G, Saha M, Moorkoth S. Treatment of *H. pylori* infection and gastric ulcer: Need for novel Pharmaceutical formulation. Heliyon. 2023;9(10):e20406. DOI: 10.1016/j.heliyon.2023.e20406 PMID: 37810864
26. Navabi N, Johansson ME, Raghavan S, Lindén SK. Helicobacter pylori infection impairs the mucin production rate and turnover in the murine gastric mucosa. Infect Immun. 2013;81(3):829-37. DOI: 10.1128/IAI.01000-12 PMID: 23275091
27. Yoon H, Lee DH. Mucolytics as Adjuvant Agent to Improve Helicobacter pylori Eradication Rate: Still Long and Winding Road to Positive Results. Gut Liver. 2015;9(3):257-8. DOI: 10.5009/gnl15117 PMID: 25918255
28. Yu J, Yang P, Qin X, Li C, Lv Y, Wang X. Impact of smoking on the eradication of Helicobacter pylori. Helicobacter. 2022;27(1):e12860. DOI: 10.1111/hel.12860 PMID: 34708484
29. Berkowitz L, Schultz BM, Salazar GA, Pardo-Roa C, Sebastián VP, Álvarez-Lobos MM, Bueno SM. Impact of Cigarette Smoking on the Gastrointestinal Tract Inflammation: Opposing Effects in Crohn's Disease and Ulcerative Colitis. Front Immunol. 2018;9:74. DOI: 10.3389/fimmu.2018.00074 PMID: 29441064
30. Ahmadkhaniha R, Yousefian F, Rastkari N. Impact of smoking on oxidant/antioxidant status and oxidative stress index levels in serum of the university students. J Environ Health Sci Eng. 2021;19(1):1043-1046. DOI: 10.1007/s40201-021-00669-y PMID: 34150292
31. Seo YS, Park JM, Kim JH, Lee MY. Cigarette Smoke-Induced Reactive Oxygen Species Formation: A Concise Review. Antioxidants (Basel). 2023;12(9):1732. DOI: 10.3390/antiox12091732 PMID: 37760035
32. Kamceva G, Arsova-Sarafinovska Z, Ruskovska T, Zdravkovska M, Kamceva-Panova L, Stikova E. Cigarette Smoking and Oxidative Stress in Patients with Coronary Artery Disease. Open Access Maced J Med Sci. 2016;4(4):636-640. DOI: 10.3889/oamjms.2016.117 PMID: 28028404
33. Gurbuz AK, Ozel AM, Ozturk R, Yildirim S, Yazgan Y, Demirturk L. Effect of N-acetyl cysteine on Helicobacter pylori. South Med J. 2005;98(11):1095-7. DOI: 10.1097/01.smj.0000182486.39913.da PMID: 16351030