The efficacy and safety of furazolidone-bismuth quadruple therapy for *Helicobacter pylori* eradication with or without probiotic supplementation

**Nafeh Noorbakhsh¹, Shahriar Nikpour², Mohammad Salehi²**

¹Department of Internal Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
²Department of Internal Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

**ABSTRACT**

**Aim:** In this clinical trial we use furazolidone-bismuth quadruple therapy with or without probiotics for *H.pylori* eradication.

**Background:** Increasing rates of eradication failure in *H.pylori* infection mainly due to antibiotic resistance has led to search for alternative regimens such as using novel antibiotics and/or using probiotic supplementation as conjunctive to the standard eradication regimens.

**Methods:** This double blind clinical trial was performed in gastrointestinal clinic of Loghman Hakim University Hospital, Tehran, Iran. Patients with a positive pathology test for *H.pylori* were enrolled to the study and received a 14 day course of furazolidone 100 mg q.i.d, bismuth 240 mg b.i.d, amoxicillin 1000 mg b.i.d, pantoprazole 40 mg b.i.d plus either probiotic (Familact) b.i.d or placebo b.i.d. Adverse effects and adherence to therapy were evaluated at the end of the treatment course. Eradication was established by *H.pylori* fecal antigen test.

**Results** A total of 200 patients entered the study and were randomly assigned to two groups of placebo and probiotic. There was no significant difference regarding age or gender between placebo and probiotic groups. Adherence to therapy was higher than 90% in total and not significantly different between placebo and probiotic groups. Total eradication rate was 80.5% (n=161). Eradication rate was 84% in probiotic group vs 77% in placebo group (P=0.2). Total rate of adverse effects was 30% in probiotic group vs 62% in placebo group. The most common adverse effects were abdominal pain (15% in probiotic group vs 28% in placebo group, P=0.03) followed by diarrhea (5% in probiotic group vs 12% in placebo group, P=0.1).

**Conclusion:** According to our results, adding probiotic to furazolidone-bismuth quadruple therapy did no increase the eradication rate significantly. However, adverse effects particularly abdominal pain was lower in the probiotic group when compared with placebo.

**Keywords:** *H.pylori*, Furazolidone, Bismuth, Eradication rate, Probiotic.

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**Introduction**

As a very common bacterial infection with a prevalence as high as 80% in developing countries such as Iran, Helicobacter pylori (*H. pylori*) is considered a serious public health issue (1). This pathogen is known to be closely associated with the development of several gastrointestinal disorders including chronic gastritis, peptic ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma (2-5). Being associated with precancerous conditions, the eradication of *H. pylori* infection is recommended by several international guidelines (6-10).

Failure to eradicate *H. pylori* infection has been reportedly increasing during the last decades with failure rates exceeding 20% in some countries (11). The most important factor responsible for increased failure rates is widespread antibiotic resistance resulting from overuse and misuse of antibiotics (12, 13). Several studies from Iran have demonstrated increasing rates of antibiotic resistance in *H. pylori* infection (14-17). To overcome this issue, several alternative strategies have been suggested, such as using novel antibiotics and/or adding probiotics to the standard eradication regimens (17-20).
Probiotics are living microorganisms from bacteria or yeast strains that have shown to be effective in varied gastrointestinal conditions including their effect on *H. pylori* infection (21, 22). According to the literature, the effects of probiotics on *H. pylori* infection are associated with both direct anti-bacterial action as well as a reduction in antibiotic-related adverse effects (23, 24). Despite this beneficial line of evidence for probiotics, there is no consensus on their clinical application in *H. pylori* eradication regimens in the guidelines (25-28).

In the current study, we compare the effect of furazolidone-bismuth quadruple therapy with or without probiotics on *H. pylori* eradication rates, patient adherence rates, and adverse effects.

**Methods**

This double blind randomized clinical trial was performed from September 2019 to September 2020 in Loghman Hakim University Hospital, Tehran, Iran. The study protocol was approved by the Ethics Committee of Shahid Beheshti Medical University with an RCT registry code of IR.SBMU.MSP.REC.1397.682 (https://ethics.research.ac.ir).

Patients older than eighteen years of age who referred to the gastrointestinal clinic of Loghman Hakim University Hospital with chronic dyspepsia and were indicated for upper endoscopy were enrolled in the study. Patients with a history of previous *H. pylori* eradication treatment, antibiotic use within the prior four weeks, and those with severe liver dysfunction, end stage renal disease, severe pulmonary dysfunction, or chronic heart failure, pregnant women, patients with acute peptic ulcer bleeding, and those with G6PD deficiency were excluded.

All patients underwent upper endoscopy in which several biopsies were taken and sent for pathology testing. Patients with a positive pathology result for *H. pylori* were referred to the clinic. After they were given a thorough explanation about the importance of eradication therapy and the purpose of the study, informed written consent was obtained from those

![Study methods flow chart](https://ethics.research.ac.ir).
participating in the study. A full medical history was taken, and patients were then randomly assigned to two groups. Each patient received a package containing a 14-day course of furazolidone 100 mg q.i.d., bismuth 240 mg b.i.d., amoxicillin 1000 mg b.i.d., pantoprazole 40 mg b.i.d., plus either Familact b.i.d. or placebo b.i.d. Familact (Zist Takhmir Pharmaceutical Company) is a synbiotic formulation (probiotic plus prebiotic) containing 9 strains of probiotics (i.e. lactobacillus acidophilus, lactobacillus casei, lactobacillus rhamnosus, lactobacillus salivarius, lactobacillus ruteri, bifidobacterium lactis, bifidobacterium langum, bifidobacterium bifidum, and fructooligosaccharide as prebiotic) available as enteric capsules.

All patients were scheduled for a second clinic visit within 14 days and were asked to bring their medication package with them. At this visit, all patients were interviewed about the adverse effects of the treatment, and their adherence to therapy was evaluated by counting the percentage of the medications taken. A patient was considered loyal to therapy if they had consumed equal to or higher than 90% of the medication. All patients gave an H. pylori fecal antigen test at the end of the 14-day treatment course to establish H. pylori eradication. Finally, "per protocol analysis" was performed.

Results

A total of 200 patients with positive gastric pathology results for H. pylori entered the study and were equally and randomly assigned to either the placebo or the probiotic group. Mean patient age was 47.4±13.4 years (age range from 21 to 78 years), and 63% (n=126) of participants were female. There was no significant difference regarding age or gender between the placebo and probiotic groups. Adherence to therapy (consumption of more than 90% of the medications) was higher than 90% in total and not significantly different between the placebo and probiotic groups. Results by age are summarized in Table 1.

Total eradication rate, defined as a negative fecal H. pylori antigen test, was 80.5% (n=161). (Fecal H. pylori antigen test had sensitivity and specificity of 97% and 95%, respectively.) Eradication rate was 84% in the probiotic group and 77% in the placebo group (p=0.2).

Total rate of adverse effects (including abdominal pain, nausea, vomiting, diarrhea, and palpitation) reported by patients was 30% in the probiotic group compared with 62% in the placebo group, but the difference did not reach statistical significance. The most commonly reported adverse effects were abdominal pain (15% in probiotic group, 28% in placebo group; p=0.03) followed by diarrhea (5% in probiotic group, 12% in placebo group; p=0.1). Table 2 compares the major adverse effects reported by patients in the two groups.

| Table 1. | Results of age distribution in study groups |
|----------|-------------------------------------------|
|          | Study Group (number of participants)       |
|          | Probiotic group (n=100)                    |
| Gender   | Mean age (years)                           |
| Male     | 48.24 (n=41)                               |
| Female   | 47.23 (n=59)                               |
|          | St. deviation                              |
| Male     | 13.12                                      |
| Female   | 14.02                                      |
|          | Mean age (years)                           |
| Male     | 47.83 (n=34)                               |
| Female   | 46.94 (n=66)                               |
|          | St. deviation                              |
| Male     | 13.42                                      |
| Female   | 13.32                                      |

| Table 2. | Compares the major adverse effects reported by patients in the two groups |
|----------|-----------------------------------------------------|
|          | Group                           | Total   | Probiotic | Placebo | P-value |
| Abdominal pain | No                 | 157 (78.5%) | 85 (85%) | 72 (72%) | 0.038   |
|               | Yes                | 43 (21.5%)  | 15 (15%)  | 28 (28%)  | 0.214   |
| Nausea          | No                 | 173 (86.5%) | 90 (90%)  | 83 (83%)  | 0.214   |
|                | Yes                | 27 (13.5%)  | 10 (10%)  | 17 (17%)  | 0.121   |
| Vommiting       | No                 | 196 (98)    | 100 (100%)| 96 (96%)  | 0.121   |
|                | Yes                | 4 (2)       | 0         | 4 (4%)    | 0.999   |
| Diarrhea        | No                 | 183 (91.5%) | 95 (95%)  | 88 (88%)  | 0.126   |
|                | Yes                | 17 (8.5%)   | 5 (5%)    | 12 (12%)  |          |
| Palpitation     | No                 | 199 (99.5)  | 100 (100%)| 99 (99%)  |          |
|                | Yes                | 1 (0.5%)    | 0         | 1 (1%)    |          |

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Discussion

Considering the high prevalence of *H. pylori* infection and its consequences as well as the increasing rates of antimicrobial resistance in Iran, the reduction in *H. pylori* eradication rates has led to the search for alternative eradication regimens (29-33).

One of these alternative treatments has been the use of novel antibiotics such as furazolidone. Furazolidone is a broad spectrum nitrofuran antimicrobial which was already proven to be effective against *H. pylori*, but its use was limited because of side effects and drug interactions which led to decreased patient adherence (34, 35). Because this antibiotic is locally available, safe, and cost effective in Iran, several studies have focused on determining the optimal effective dosage of it in combination with bismuth in quadruple therapies (36-38). According to a review article by Mohammadi et al. (39), the dosage of 100 mg furazolidone q.i.d. (high dose) in the form of a 14-day bismuth-containing quadruple therapy showed the best cure rate with acceptable side effects.

Accordingly, in the current clinical trial, furazolidone-bismuth quadruple therapy was used for eradication of *H. pylori* and consisted of a 14-day period of furazolidone 100 mg q.i.d., bismuth 240 mg b.i.d., amoxicillin 1000 mg b.i.d., and pantoprazole 40 mg b.i.d. for all patients. The total cure rate was found to be 80.5% with higher than 90% adherence to therapy among patients.

Another alternative suggested for overcoming eradication failure resulting from antimicrobial resistance is the use of probiotic supplementation conjunctive to other standard eradication regimens. Probiotics are bacterial and in some cases yeast species that, when used in particular amounts, can have beneficial health effects in preventing and treating various medical conditions (21, 22, 40). Recent studies have shown a role for probiotic supplementation in the treatment of *H. pylori* infection. While each probiotic has a specific mechanism of action against *H. pylori*, some general mechanisms by which probiotics can contribute to *H. pylori* eradication include strengthening the mucosal barrier, competing for adhesion, secreting antimicrobial compounds, and immunomodulatory actions (41-46).

In addition to their direct beneficial effects against *H. pylori*, probiotics have also been shown to be effective in improving eradication rates by increasing patient compliance because of the reduced adverse effects of antibiotic therapy. This effect is more prominent when using high doses of antibiotics, as in the current study (47-50). Consistently, adding probiotics to furazolidone bismuth quadruple therapy in the current study led to a reduction in adverse effects, particularly abdominal pain.

Despite the evidence supporting the beneficial role of probiotics as adjunctive in *H. pylori* eradication regimens, it is not enough to reach a conclusion on their routine clinical application in anti-*H. pylori* therapies. Several studies have shown that probiotics had no effect on eradication rates, although they could reduce the adverse effects (mainly diarrhea) of antibiotics (51-53). In their recent study, Zagari et al. showed that probiotic supplementation did not improve the efficacy or tolerability of the treatment, regardless of the species of the probiotic (54). Thus, there is still no consensus on the use of probiotics in *H. pylori* treatment guidelines. In the present clinical trial, we compared use of probiotics against a placebo added to 14-day furazolidone bismuth quadruple therapy. The results indicated a reduction in adverse effects and an increase in the eradication rate, although none of them reached statistical significance. While some guidelines suggest adding probiotics to standard anti-*H. pylori* treatments mainly because of their role in decreasing the adverse effects of antibiotics, others do not suggest their routine use, as the supporting studies lack quality (26-28). Moreover, the optimal dosage, duration, and role of specific strains of probiotics are yet to be determined, although there is some evidence that a combination of several strains might be preferred (55). The probiotics used in the present study, Familact (Zist Takhmir Pharmaceutical Company), are available locally in a cost-effective enteric capsule with a symbiotic formulation (probiotic plus prebiotic), and its addition to the standard therapy resulted in a significant decrease in abdominal pain as the most commonly reported adverse effect in this study. In addition, all other adverse effects as well as the total rate of adverse effects were reduced in the probiotic group when compared to the placebo group. The total eradication rate in the current study was 80.5%; although it was
higher in the probiotic group, the difference was not statistically significant.

Further large-scale clinical trials are required to determine the definite role and optimal dosage, type, and duration of probiotic supplementation in *H. pylori* eradication regimens.

**Conflict of interests**

The authors declare that they have no conflict of interest.

**References**

1. Moayyedi P, Hunt RH. *Helicobacter pylori* public health implications. Helicobacter 2004;9:67–72.

2. Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. Lancet 1991;338:1175–1176.

3. Kuipers EJ. *Helicobacter pylori* and the risk and management of associated diseases: gastritis, ulcer disease, atrophic gastritis and gastric cancer. Aliment Pharmacol Ther 1997;11:71–88.

4. Sipponen P, Hyvärinen H. Role of *Helicobacter pylori* in the pathogenesis of gastritis, peptic ulcer and gastric cancer. Scand J Gastroenterol 1993;196:3–6.

5. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med 2001;345:784–789.

6. Infection with *Helicobacter pylori*. In: IARC monographs on the evaluation of the carcinogenic risks to humans. Vol. 61. Schistosomes, liver flukes and *Helicobacter pylori*. Lyon, France: International Agency for Research on Cancer; 1994. p.177–240.

7. Fock KM, Katelaris P, Sugano K, Ang TL, Hunt R, Talley NJ, et al. Second Asia-Pacific Consensus Guidelines for *Helicobacter pylori* infection. J Gastroenterol Hepatol 2009;24:1587–1600.

8. World Gastroenterology Organisation. World Gastroenterology Organisation Global Guideline: *Helicobacter pylori* in developing countries. J Clin Gastroenterol 2011;45:383–388.

9. Malfertheiner P, Megraud F, O’Morain C, Gisbert J, Kuipers E, Axon A, et al. European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection—the Maastricht V/Florence consensus report. Gut 2017;66:6–30.

10. Sugano K, Tack J, Kuipers EJ, Graham DY, El-Omar EM, Miura S, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. Gut 2015;64:1353–1367.

11. Vitor JMB, Vale FF. Alternative therapies for *Helicobacter pylori*: probiotics and phytomedicine. FEMS Immunol Med Microbiol 2011;63:153–164.

12. De Francesco V, Giorgio F, Hassan C, Manes G, Vannella L, Panella C, et al. Worldwide *H pylori* antibiotic resistance: a systematic review. J Gastrointestin Liver Dis 2010;19:409–414.

13. Di Mario F, Cavallaro LG, Scarpignato C. ‘Rescue’ therapies for the management of *Helicobacter pylori* infection. Dig Dis 2006;24:113–130.

14. Rafeey M, Ghotaslou R, Nikvash S. Primary resistance in Helicobacter pylori isolated in children from Iran. J Infect Chemother 2007;13:291–295.

15. Mohammadi M, Doroud D, Mohajerani N, Massarrat S. *Helicobacter pylori* antibiotic resistance in Iran. World J Gastroenterol 2005;11:6009–6013.

16. Shokrzadeh L, Jafari F, Dabiri H, Baghaei K, et al. Antibiotic susceptibility profile of *Helicobacter pylori* isolated from the dyspepsia patients in Tehran, Iran. Saudi J Gastroenterol 2011;17:261–264.

17. Siavoshi F, Safari F, Doratotaj D, Khatami GR, Fallahi GH, Mirmaseri MM. Antimicrobial resistance of Helicobacter pylori isolates from Iranian adults and children. Arch Iran Med 2006;9:308–314.

18. Goderska K, Agudo Pena S, Alarcón T. *Helicobacter pylori* Treatment: Antibiotics or Probiotics. Appl Microbiol Biotechnol 2018;102:1–7.

19. Yang JC, Lu CW, Lin CJ. Treatment of *Helicobacter Pylori* Infection: Current Status and Future Concepts. World J Gastroenterol 2014;20:5283.

20. Hu Y, Zhu Y, Lu NH. Novel and effective therapeutic regimens for *Helicobacter pylori* in an era of increasing antibiotic resistance. Front Cell Infect Microbiol 2017;7:p.168.

21. Piana M, Morellic L, Strozzib GP, Allesinab S, Barbab M, Deiddab F, et al. Probiotics: from research to consumer. Dig Liver Dis 2006;38:248–255.

22. Gupta V, Garg R. Probiotics. Indian J Med Microbiol 2009;27:202-9.

23. De Brito BB, Da Silva FAF, Soares AS, Pereira VA, Cordeiro Santos ML, Sampaio MM, et al. Pathogenesis and clinical management of Helicobacter pylori gastric infection. World J Gastroenterol 2019;25:5578–89.

24. Losurdo G, Cubisino R, Barone M, Principi M, Leandro G, Ierardi E, et al. Probiotic monotherapy and *Helicobacter pylori* eradication: a systematic review with pooled-data analysis. World J Gastroenterol 2018;24:139–49.

25. Ierardi E, Giorgio F, Losurdo G, Di Leo A, Principi M. How antibiotic resistances could change *Helicobacter pylori* treatment: A matter of geography? World J Gastroenterol 2013;19:8168–8180.

26. Malfertheiner P, Megraud F, O’Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, et al. Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report. Gut 2017;66:6–30.
27. Zagari RM, Romano M, Ojetti V, Stockbrugger R, Gullini S, Annibale B, et al. Guidelines for the management of *Helicobacter pylori* infection in Italy: The III Working Group Consensus Report 2015. Dig Liver Dis 2015;47:903–912.

28. Fallone CA, Chiba N, van Zanten SV, Fischbach L, Gisbert JP, Hunt RH, et al. The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults. Gastroenterology 2016;151:51–69.e14.

29. Fakheri H, Bari Z, Aarabi M, Malekzadeh R. *Helicobacter pylori* eradication in West Asia: a review. World J Gastroenterol 2014;20:10355–10367.

30. Farshad S, Alborzi A, Japoni A, Ranjbar R, Hosseini Asl K, Badiie P, et al. Antimicrobial susceptibility of *Helicobacter pylori* strains isolated from patients in Shiraz, Southern Iran. World J Gastroenterol 2010;16:5746–5751.

31. Khadem F, Faghi F, Pourina F, Esfahani BN, Moghim SH, Fazeli H, et al. Resistance pattern of *Helicobacter pylori* strains to clarithromycin, metronidazole, and amoxicillin in Isfahan, Iran. J Res Med Sci 2013;18:1056–1060.

32. Milani M, Ghotaslou R, Akhi MT, Nahaei MR, Hasani A, Somi MH, et al. The status of antimicrobial resistance of *Helicobacter pylori* in Eastern Azerbaijan, Iran: comparative study according to demographics. J Infect Chemother 2012;18:848–852.

33. Malekzadeh R, Mohamadnejad M, Siavoshi F, Massarrat S. Treatment of *Helicobacter pylori* infection in Iran: low efficacy of recommended western regimens. Arch Iranian Med 2004;7:1–8.

34. Lu H, Zhang W, Graham DY. Bismuth-containing quadruple therapy for *Helicobacter pylori*: lessons from China. Eur J Gastroenterol Hepatol 2013;25:1134–1140.

35. Liang X, Xu X, Zheng Q, Zhang W, Sun Q, Liu W, et al. Efficacy of bismuth-containing quadruple therapies for clarithromycin-, metronidazole-, and fluorquinolone-resistant *Helicobacter pylori* infections in a prospective study. Clin Gastroenterol Hepatol 2013;11:802–807.

36. Safaralizadeh R, Siavoshi F, Malekzadeh R, Akbari MR, Derakhshian MH, Sohrabi MR, et al. Antimicrobial effectiveness of furazolidone against metronidazole-resistant strains of *Helicobacter pylori*. East Mediterr Health J 2006;12:286–293.

37. Daghaghzadeh H, Emani MH, Karimi S, Raeisi M. One-week versus two-week furazolidone-based quadruple therapy as the first-line treatment for *Helicobacter pylori* infection in Iran. J Gastroenterol Hepatol 2007;22:1399–1403.

38. Roghani HS, Massarrat S, Shirekhoda M, Botorab Z. Effect of different doses of furazolidone with amoxicillin and omeprazole on eradication of *Helicobacter pylori*. J Gastroenterol Hepatol 2003;18:778–782.

39. Mohammadi M, Attaran B, Malekzadeh R, Graham DY. Furazolidone, an underutilized drug for *H. pylori* eradication: lessons from Iran. Dig Dis Sci 2017;62:1890–1896.

40. Papastergiou V, Georgopoulos S, Karatapanis S. Treatment of *Helicobacter pylori* infection: meeting the challenge of antimicrobial resistance. World J Gastroenterol 2014;20:9898–9911.

41. Collado MC, Gonzalez A, Gonzalez R, Hernandez M, Ferrus MA, Sanz Y. Antimicrobial peptides are among the antagonistic metabolites produced by bifidobacterium against *Helicobacter pylori*. Int J Antimicrob Agents 2005;25:385–91.

42. Aiba Y, Suzuki N, Kabir AM, Takagi A, Koga Y. Lactic acid-mediated suppression of *Helicobacter pylori* by the oral administration of *Lactobacillus salivarius* as a probiotic in a gnotobiotic murine model. Am J Gastroenterol 1998;93:2097–2101.

43. Michetti P, Dorta G, Wiesel PH, Brassart D, Verdu E, Felley C, et al. Effect of whey-based culture supernatant of *Lactobacillus acidophilus* (johnsonnii) LAl on *Helicobacter pylori* infection in humans. Digestion 1999;60:203–209.

44. Nam H, Ha M, Bae O, Lee Y. Effect of Weissella confusa strain pI9001 on the adherence and growth of Helicobacter pylori. Appl Environ Microbiol 2002;68:4642–4645.

45. Hwang SW, Kim N, Kim JM, Huh CS, Ahn YT, Park SH, et al. Probiotic suppression of the *H. pylori*-induced responses by conjugated linoleic acids in a gastric epithelial cell line. Prostaglandins Leukot Essent Fatty Acids 2012;86:225–231.

46. Mack DR, Ahrne S, Hyde L, Wei S, Hollingsworth MA. Extracellular MUC3 mucin secretion follows adherence of lactobacillus strains to intestinal epithelial cells in vitro. Gut 2003;52:827–833.

47. Zhu XY, Liu F. Probiotics as an adjuvant treatment in *Helicobacter pylori* eradication therapy. J Dig Dis 2017;18:95–202.

48. Dang Y, Reinhardt JD, Zhou X, Zhang G. The effect of probiotics supplementation on *Helicobacter pylori* eradication rates and side effects during eradication therapy: A meta-analysis. PLoS One 2014;9:e111030.

49. Lv Z, Wang B, Zhou X, Wang F, Xie Y, Zheng H, et al. Efficacy and safety of probiotics as adjuvant agents for *Helicobacter pylori* infection: A meta-analysis. Exp Ther Med 2015;9:707–716.

50. Lu M, Yu S, Deng J, Yan Q, Yang CH, Xia G, et al. Efficacy of probiotic supplementation therapy for *Helicobacter pylori* eradication: a meta-analysis of randomized controlled trials. PLoS One 2016;11:e0163743.

51. Cremonini F, Di Caro S, Covino M, Armuzzi A, Gabrielli M, Santarelli L, et al. Effect of different probiotic preparations on anti-helicobacter pylori therapy-related side effects: a parallel group, triple blind, placebo-controlled study. Am J Gastroenterol 2002;97:2744–2749.

52. Cindoruk M, Erkan G, Karakan T, Dursun A, Unal S. Efficacy and safety of *Saccharomyces boulardii* in the 14-day triple anti-Helicobacter pylori therapy: a prospective randomized placebo-controlled double-blind study. Helicobacter 2007;12:309–316.

53. Hurduc V, Plesca D, Dragomir D, Sajin M, Vandenplas Y. A randomized, open trial evaluating the effect of *Saccharomyces boulardii* on the eradication rate of...
Helicobacter pylori infection in children. Acta Paediatr 2009;98:127–131.

54. Zagari RM, Romiti A, Ierardi E, Gravina AG, Panarese A, Grande G, et al. The “three-in-one” formulation of bismuth quadruple therapy for Helicobacter pylori eradication with or without probiotics supplementation: Efficacy and safety in daily clinical practice. Helicobacter 2018;23:e12502.

55. McFarland LV, Huang Y, Wang L, Malfertheiner P. Systematic review and meta-analysis: Multi-strain probiotics as adjunct therapy for Helicobacter pylori eradication and prevention of adverse events. United European Gastroenterol J 2016;4:546-56.

56. Wu D, Cao M, Zhou J, Yan Sh, Peng J, Yu Zh, et al. Lactobacillus casei T1 from kurut against Helicobacter pylori-induced inflammation and the gut microbial disorder. J Funct Foods 2021;85:104611.

57. Westerik N, Reid G, Sybesma W, Kort R. The Probiotic Lactobacillus rhamnosus for Alleviation of Helicobacter pylori-Associated Gastric Pathology in East Africa. Front Microbiol 2018;9:1873.