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Fermented milk product "Narineh" with *Lactobacillus acidophilus* in sequential and classical therapy for *Helicobacter pylori*-associated peptic ulcers

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ABSTRACT

Background: In recent years, there has been a growing dissatisfaction with the classical schemes of the eradication of *Helicobacter pylori* in ulcerative disease among physicians due to frequent failures in eradication therapy, mostly due to antibiotic resistance. It is a known fact that the *Lactobacillus acidophilus* inhibits the growth of *Helicobacter pylori.*

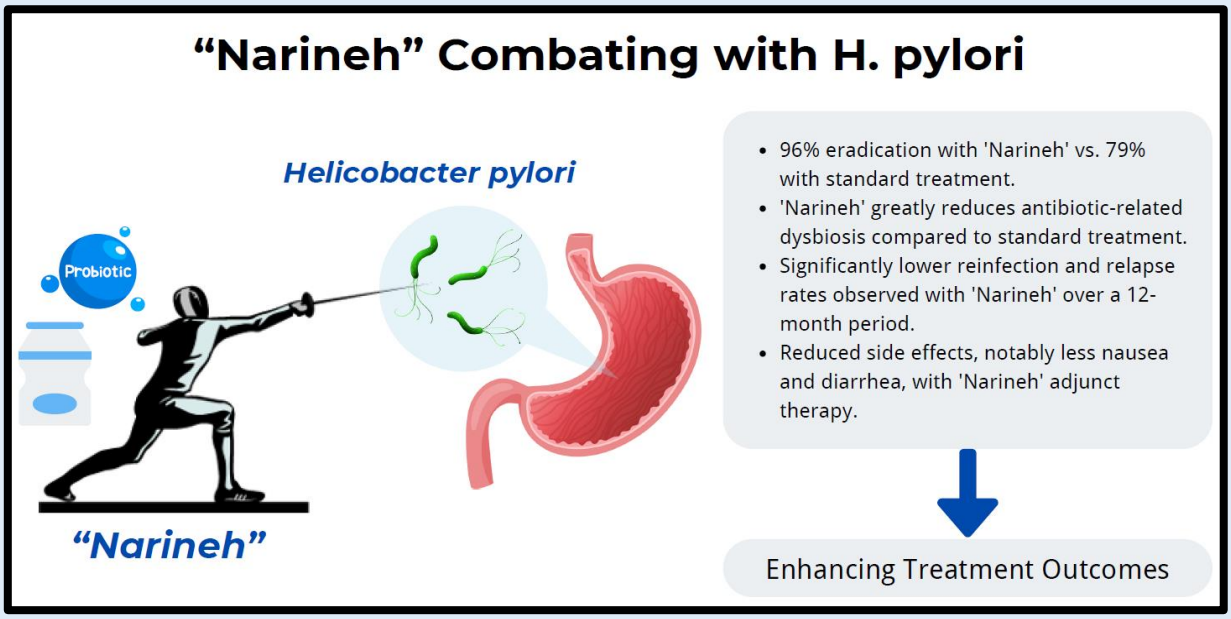
Objective: Our main goal was to investigate the ability of the fermented milk product "Narineh," as a functional food, containing *Lactobacillus acidophilus t*o evaluate the efficiency and incidence of adverse effects in addition to the standard triple scheme of eradication therapy with colloidal bismuth substrate.

Methods: The patients with peptic ulcer were divided into 2 groups: control (42 patients) received traditional treatment regimens, including 7 days proton pump inhibitor (PPI) + amoxicillin (A) and clarithromycin (C) in the standard doses and subsequent 14 day De-nol (colloidal bismuth subcitrate); experimental (44 patients) received in addition to this standard conventional scheme "Narineh" - 200g, containing $2x10^9$ *Lactobacillus acidophilus* one time a day starting from the 8-th day for 4 weeks. The results of the eradication in patients were evaluated after 4 -5 weeks, 6 months, and 12 months after completion of treatment using the C^{13} respiratory urea test (RUT). Repeated endoscopy with histological biopsies was carried out together with RUT in 4-5 weeks after the completion of treatment, and later (6-12 months) for the identification of recurrent ulcer.

Results: The treatment with "Narineh" added to the standard regimen significantly reduces the percentage of reinfection and relapse of the disease with a statistical difference (P<0,05). The combination of fermentation milk product "Narineh", containing *Lactobacillus acidophilus* with bismuth subcitrate, doesn't cause a violation of biocenosis of the large intestine, in contrast to the PPI and antibiotics with a statistical difference (P<0,05). In addition, it provides the normalization of gut biocenosis and reduces the frequency of antibiotic-associated diarrhea and other side effects.

Conclusion: The treatment with "Narineh" added to the standard scheme is more effective for eradication of *Helicobacter pylori* infection and significantly reduces the percentage of reinfection and relapse of the disease and lessens the side effects of medications.

Keywords: peptic ulcer, eradication *Helicobacter pylori,* side effects reinfection, fermented milk product "Narineh", *Lactobacillus acidophilus*, functional foods



INTRODUCTION

Recent decades have brought radical changes to the concept of the pathogenesis of peptic ulcer (PU) disease and its treatment, thanks to the discovery of the role of *Helicobacter pylori* (Hp) in the pathogenesis of the disease and development of methods for its diagnosis and eradication [1-5]. Currently, anti-*Helicobacter* therapy, when it is detected, and test-control for eradication of Hp are the standard for the treatment of PU, which is reflected many times in the decisions of international conciliation conferences [6-9]. However, today, due to the increasing resistance of Hp to antibiotics, used in traditional treatment regiments, it is noted there is a tendency to reduce the effectiveness of eradication with traditional first-line drugs and, often, it is necessary to carry out second, third, and sometimes fourth line therapy with reserve antibacterial drugs. [9-12].

In recent years to improve the results of eradication, it has been proposed to increase the dose and lengthen the duration of eradication therapy. However, increasing periods and doses of antibiotic

therapy worsens the tolerability and compliance of therapy and increases the costs of medications.

Numerous data have accumulated proving the anti-*Helicobacter pylori* activity of probiotics containing live bacteria *Lactobacillus acidophilus,* in vitro in laboratory conditions and in vivo in experimental animals [13-17]. There are isolated clinical studies confirming the effectiveness of probiotics for the eradication of Hp in patients with non-ulcer [18-20] and ulcerative dyspepsia [18- 21].

It is a known fact that the biological niche of existence for *Lactobacillus acidophilus* is not only the large and small intestine, but also the antral part of the stomach where it appears as a bacteria-mutualist and inhibits the growth of conditionally pathogenic Hp [22-24]. The antagonistic effect of *Lactobacillus acidophilus* on Hp and other opportunistic bacteria of the gastrointestinal tract is also shown in the work of some other authors [25-28]. It turned out that the degree of eradication when applying monotherapy with probiotics was higher than that with the other anti-*Helicobacter* medicines. [18, 29-30].

For many years, Armenian clinicians have been using the fermented milk product "Narineh", as a functional food, to eliminate the negative effects of antibiotic therapy. This product contains an active biological strain *Er317/402 Lactobacillus acidophilus*.

The above makes it urgent to test new treatment regimens for PU associated with Hp infection with the connection the fermented milk product "Narineh".

AIM OF INVESTIGATION

We set out to evaluate the efficiency and incidence of adverse effects in sequential assignment of fermented milk product "Narineh", containing *Lactobacillus acidophilus*, in addition to the standard conventional triple scheme of eradication therapy with De-Nol (colloidal bismuth subcitrate) in patients with peptic ulcer, associated with Hp, which is a special case of studying the influence of functional foods on disease.

MATERIALS AND METHODS

Materials: The patients with PU were divided into 2 groups: control (42 patients) received traditional treatment regimens, including 7 days proton pomp inhibitor (PPI) + amoxicillin (A) and clarithromycin (C) in the standard doses and subsequent 14 day De-Nol; experimental (44 patients) received in addition to this standard conventional triple scheme fermented milk product "Narineh," 200g, containing $2x10^9$ *Lactobacillus acidophilus* one time a day starting from the 8th day for 4 weeks. The distribution of patients was carried out in such a way that in terms of age, gender, size of the ulcer, localization of the ulcer in the stomach or duodenum, and in ratio of smoking and non-smoking patients, both groups were comparable.

Methods: The results of the eradication in patients were evaluated after 4-5 weeks, 6 months, and 12 months after completion of treatment using respiratory urea test (RUT) by using C^{13} breath test devices of Fischer ANalysen Instrumente GmbH, FANhp, Germany. Repeated endoscopy with histological biopsies was carried out together with RUT in 4-5 weeks after the completion of treatment, and later (6-12 months) for the identification of recurrent ulcer.

Stepwise biopsy was taken in two pieces from the body, antrum, and duodenum bulb. Histological stains with hematoxylin-eozin, Van-Gieson, and Giemsa were used.

The Bacteriological culture of feces to detect dysbacteriosis and microscopic analysis of stool (scatological study) was carried out before treatment and 5 weeks after the completion of the treatment. X-ray

contrast oral examination of the gastro-intestinal tract was carried out if ulcer penetration was suspected.

An ultrasound examination of the abdominal cavity was performed to exclude concomitant diseases of the liver, biliary tract, pancreas, kidneys, and other organs.

Statistical Analysis: The relative values of the degree of eradication of Hp in different groups were compared with each other using the student's test of significance of differences or the t-test to assess the significance of the difference between the relative indicators [31]. To check the accuracy of reinfection, relapses, and side effects of treatment in different groups, the initial information was compiled in the form of four-field tables. The significance of differences was calculated using the χ^2-test. Using the four-field table, we calculated indicators of relative (RR) and immediate risk (IR) [31]. RR- indicator indicates how many times higher the risk of an event is in the experimental group compared to the control group. IR-indicator is absolute difference in the risk of any event for the experimental and control groups in conditional contingent of 100 people.

RESULTS

After 5-6 weeks since the beginning of the therapy, all the patients (from both groups) were brought into the phase of remission with scarring of the ulcer. However, the degree of eradication Hp was different (Figure 1).

Reinfections and relapses in control (1, 2) and experimental (3, 4) groups (40 and 44 patients respectively) after completion of treatment are shown in Figure 2.

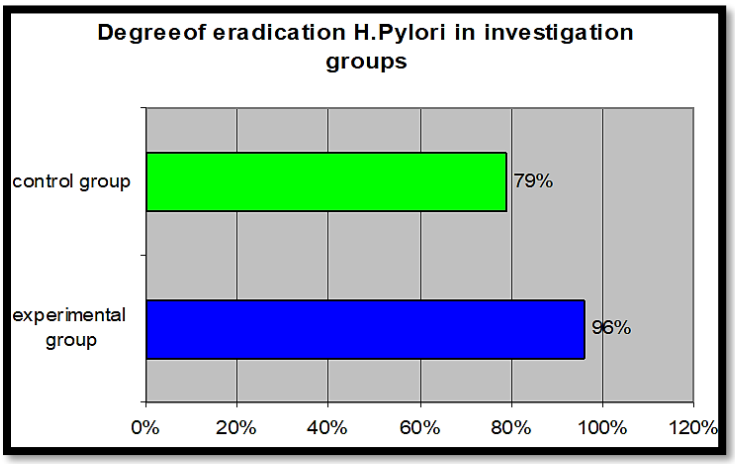


Figure 1. Degree of eradication H. pylori in investigation groups.

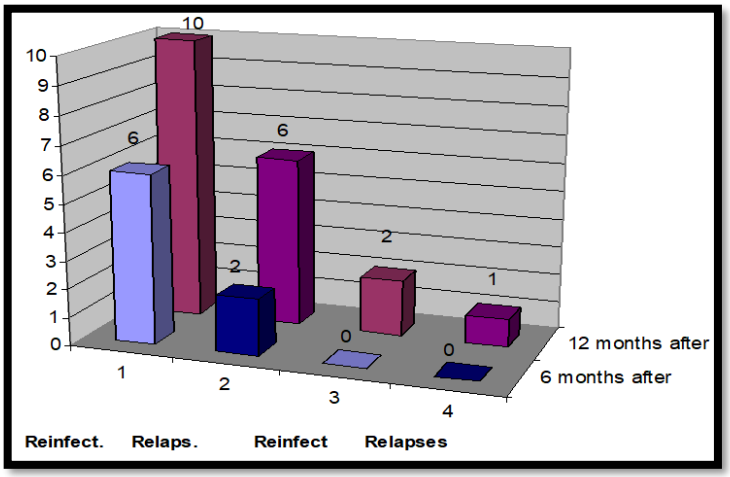


Figure 2. Reinfections and relapses after completion of treatment.

The percentage of by-effects observed during the treatment in two groups are shown in Table 1.

The frequency of side adverse effects on the second (from 8th to 21st day) stage are shown in Figure 3.

The frequency of side adverse effects on the third stage (from 22nd to 35th day) is shown in Figure 4.

The risk of the development of adverse effects in the research groups from the 8th to the 21st day shown in Table 2.

Table 1. The by-effects observed during the treatment.

The terms of observation	Control	Experimental
1-st week The patients received same PPI and antibiotic treatment.	38,1± 7,5 %	39,2 ± 7,2% p_{exp}>0,05
From 8-th to 21-st day Patients in the experimental group received in addition to bismuth fermentation milk product “Narineh” with *Lactobacillus acidophilus.*	45,2 ± 7,7%	25,0 ± 6,5% p_{exp} < 0,05
From 22-th to 35-th Patients in the experimental group received “Narineh” with *Lactobacillus acidophilus,* and those in the control group received nothing.	19,0 ± 6,2%	4,5 ± 3,1% p_{exp} < 0,05

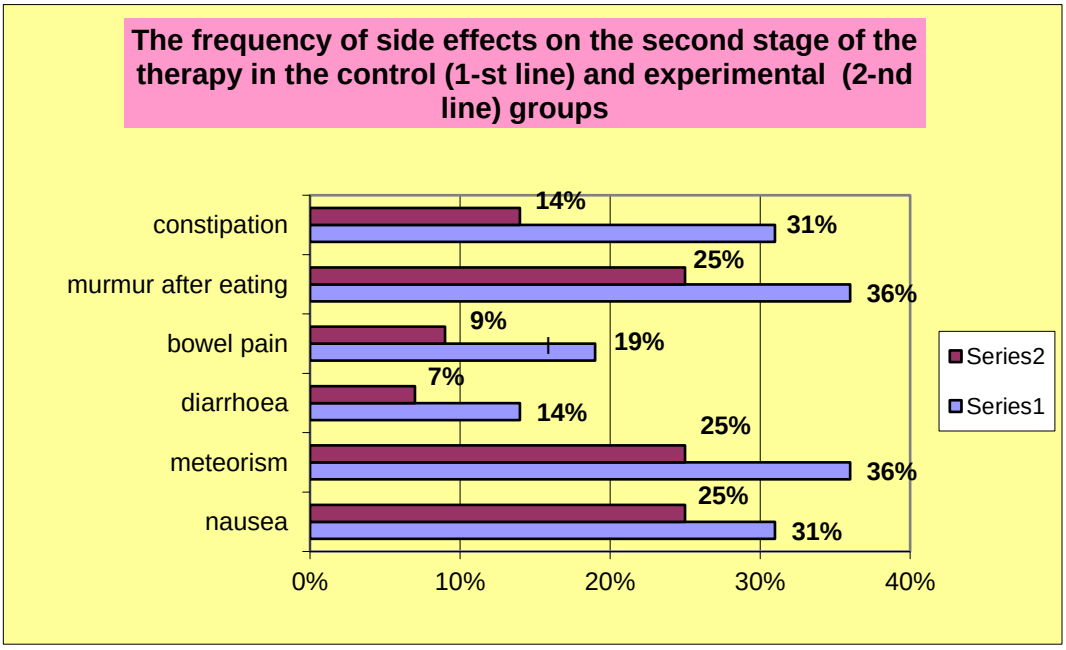


Figure 3. The frequency of side adverse effects from 8th to 21st day.

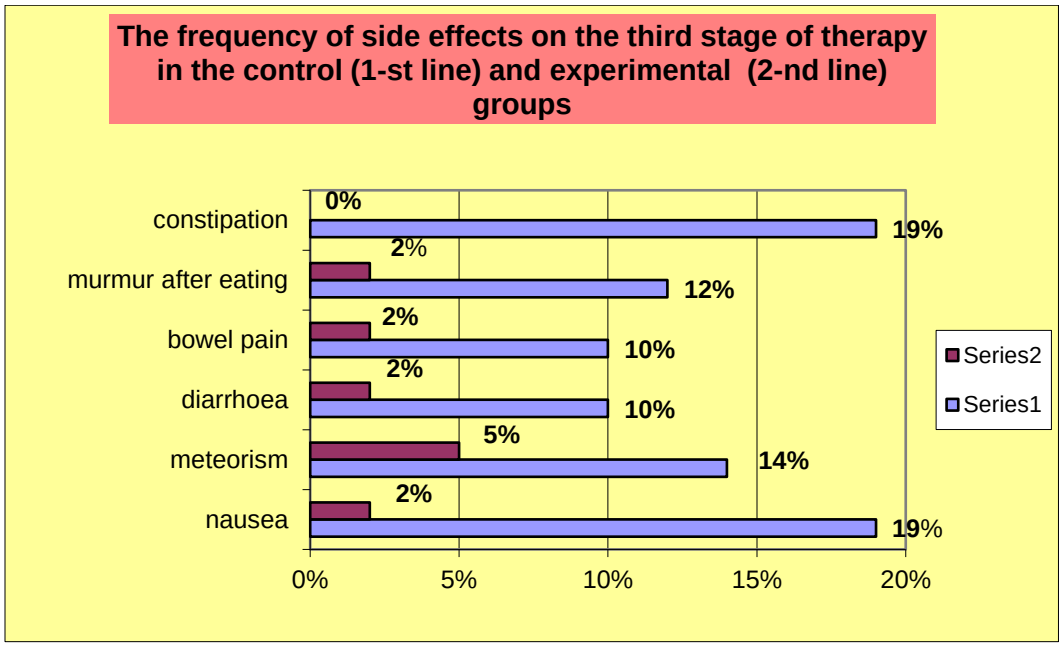


Figure 4. The frequency of side adverse effects from 22nd to 35th day.

Table 2. The risk of the development of adverse effects in the research groups from the 8th to the 21st day

Adverse effects in groups	+ Presence	- Absence	χ2	"p" as compared to the control	Relative risk (RR) and immediate risk (IR)
Control	19	23			
Experimental	11	33	3,9	<0,05	RR =2,5 IR =17

The relative risk (RR) found that the risk of diarrhea side effects in control group was 2,5 (two and half past) times more than in the experimental group.

Thus, the frequency of adverse effects in groups during the first week, when patients in control and experimental group were treated with the same medicines, wasn't different. After the completion of antibiotic therapy, the frequency of diarrhea and other side effects were separate in control and experimental groups. Difference in the frequency of adverse effects in groups became sufficient and reliable.

Studies of changes in the microflora of the large intestine 5 weeks after first line antibiotic eradication showed signs of dysbacteriosis in 18% (14% - latent dysbacteriosis, and 4% - dysbacteriosis clinical) of cases in the experimental group and in 59% (40% and 19%, respectively) of patients in the control group. The absence of dysbacteriosis in the experimental group was twice as frequent.

Frequency of reinfections and relapses in control and experimental groups after completion of treatment was next. In 6 months after treatment in the control group, 6 (15%) patients with reinfection with Hp were revealed, 2 (5%) of which had relapse of disease. In the experimental group, nobody had reinfection or relapses. In 12 months after treatment in the control group, 10 (25%) patients with reinfection with Hp were revealed, 6 (15%) of which had relapses. In the experimental group, 2 (4,5%) patients had reinfection and one (1,3%) had relapse. All the patients with relapses had a positive test

for Hp (the respiratory as well as the histological one). The difference in the frequency of relapses is reliable. The RR of its development in the experimental group is 7 times lower than in the control one, and the IR of the development in the relative virtual group of 100 patients has as much as 12 incidents lesser (Table 3).

Table 3. Relative risk (RR) and immediate risk (IR) of development of relapses in the groups of patients in 12 months after the therapy.

Relapse (Rl) / Groups	+ Presence Rl	- Absence Rl	χ2	"p" as compared to the control	Relative risk (RR) and immediate risk (IR)
Control	6	36			
Experimental	1	43	4,15	<0,05	7/ 12

DISCUSSION

The data we obtained confirm the belief that relapses of PU are associated with and always coincide with reinfection of Hp. In our material, Hp reinfection was often several months ahead of the exacerbation of PU. Dissatisfaction with existing standard eradication regimens in recent years dictates the need to search for new treatment regimens to obtain higher eradication rates after 1st line therapy [9]. Several approaches are proposed: lengthen the duration of therapy; increase the dose of antibacterial drugs; increase the number of antibacterial drugs ("concomitant" regiment); prescribe sequentially first some, then other antibacterial drugs ("sequential" regiment); use new, more effective anti-*Helicobacter* drugs. The first three approaches are limited by the increase in side effects and low patient compliance, so we are against such approaches, although they are supported by some authors [32]. In addition, it has been shown that with the extension of classical triple therapy with PPI, amoxicillin, and clarithromycin from 7 to 14 days, the degree of eradication increases not by 10-12%, as was previously thought, but by 4-5% [33-34]. Regine of sequential administration of anti-*Helicobacter* drugs, "sequential" regime, in recent years, has many supporters in Italy and Canada [35-39]. The "concomitant" regiment includes 4 medications, including PPI and three antibacterial drugs in generally accepted dosages. This is more effective compared to a "sequential" course, however, there are more side effects and lower patient compliance with this treatment [40]. We believe that if you select drugs with anti-*Helicobacter* action in the "sequential" course, so that the effectiveness is not inferior to the course with a "concomitant" regimen, you can achieve fewer side effects from taking the drugs and increase patient compliance with this course of treatment.

In recent years, in literature one can more often find works of bismuth subcitrate preparations as a component of the 1st line, including the advisability therapy, which is reflected in the decisions of international conciliation conferences [7-8]. The advantage of bismuth subcitrate compared to other anti-*Helicobacter* drugs is that Hp resistance does not develop to it. At the same time, it acts on bacteria located deep in the gastric pits, including its cocci forms. In addition, bismuth subcitrate does not cause intestinal dysbiosis, since, unlike antibiotics, it does not suppress normal microflora, and the opposite helps to normalize it [41-44].

In various years, one can find isolated works in the literature that indicate the need to supplement classical

antibacterial therapy in eradication regimens with probiotics containing *Lactobacillus acidophilus* in order to increase the degree of eradication and reduce the incidence of side effects [45-48]. It is also shown that *Lactobacillus acidophilus* had an inhibitory effect on Hp in peptic ulcer patients and also in vitro. In this study, HP was isolated from gastric biopsy specimens of fifteen peptic ulcer patients (eleven patients with gastric ulcer and four patients with duodenal ulcer). Inhibition clear halo zone of HP around the colonies of *Lactobacillus acidophilus* under microaerophilic conditions for 72 hours was interpreted as the inhibitory effect on Hp and was observed in 13/15 patients (86.67%) [49]. It is known that the other probiotics (mainly *Lactobacillus, Saccharomyces boulardii,* and *Bacillus clausii*) have been shown to reduce the side effects of HP eradication therapy, such as diarrhea and abdominal pain, and improve the eradication rates [50-55]. However, this opinion was reflected only in the recommendations of the latest international conciliation conference [9]. The use of multi-strain probiotics as an adjunct therapy for *H. pylori* eradication has been increasingly discussed in recent years [47]. In addition, the positive effect of probiotics on the course of non-infectious PU has been established [56]. This once again confirms the importance of using probiotics in the treatment of PU. Today, the optimal strains and dosages of probiotics have yet to be established, and further research is needed to determine the most effective probiotic regimen strains and dosages.

It was in view of the above that we decided to study the effectiveness of the treatment regimen we had developed, where we combined the rational of classical standards with a new regimen of sequential therapy: after the course of two classical anti-*Helicobacter* drugs, the subsequent course with the bismuth subcitrate drug with the probiotic “Narineh” containing the *Lactobacillus acidophilus -Er317/402*. An effective form of probiotic administration is a fermented milk product – liquid “Narineh.” In this form, the bacterial cells of the probiotic are covered with a layer of denatured milk casein, which protects the bacteria from the inactivating effect of gastric juice. This form of probiotic can effectively carry out the treatment process directly in the stomach, providing contact interactions between *Lactobacillus acidophilus* and *Helicobacter pylori.* In fact, we adhered to the basic principle of standard therapy, according to which anti-*Helicobacter* interaction must be ensured by least two drugs. Therefore, we combined bismuth subcitrate with the probiotic containing *Lactobacillus acidophilus*, taking into the fact that the anti-*Helicobacter* activity of each of these drugs is not inferior in effectiveness to the action of antibiotics taken separately from the classical anti-*Helicobacter* regimen [22, 18]. In addition, when we chose this combination, we also proceeded from the fact that both drugs do not cause disruption of the normal intestinal bacterial flora, unlike antibiotics [57-58]. Short-term antibiotic exposure has been shown to be associated with alterations in gut microbiota and antibiotic resistance genes (ARGs) in the human gut [59].

The use of fermented milk product "Narineh" containing *Lactobacillus acidophilus* displays a special case of the impact of functional foods on disease. The Functional Food Center defines functional foods as “natural or processed foods that contain biologically active compounds, which, in defined, effective, non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers, to promote optimal health and reduce the risk of chronic/viral diseases and manage their symptoms” [60]. The Functional Food Center’s step-by-step process outlines the development process of creating functional food products [61]. Fermented milk product “Narineh” satisfies several necessary requirements for consideration as a functional food. Alternative antimicrobial remedies, such as propolis, have already been explored as functional ingredients against Gram-

negative bacteria [62-63]. Likewise, probiotics in the eradication of *Helicobacter pylori*, a Gram-negative bacterium, can be investigated for their functional therapeutic approach. The goal of "Narineh" is to aid in the eradication of *H. pylori*. "Narineh" serves as an effective food vehicle, providing a suitable medium for delivering probiotics to the gastrointestinal tract. *Lactobacilli* plays a crucial role in the intestinal tract, including regulation of the intestinal flora and inflammation [64-66]. Probiotics [including those present in "Narineh"] produce bioactive compounds that actively compete with pathogens [67], actively working to help restore the intestinal microbial environment against disease. The quantum and tempus theories of functional food science establish the dosage and duration at which a bioactive compound is effective by preventing or managing symptoms of a disease [68]. The dosage in this study (200g containing 2 x 10^9 *Lactobacillus acidophilus* once a day for 4 weeks) was effective in the treatment of *H. pylori* in patients without creating adverse effects. Significant findings have already been made in identifying the specific pathways and mechanisms of *Lactobacillus acidophilus*, supported by preclinical and clinical trials. It is crucial to note, however, that epidemiological and after-market research in populations is necessary to further classify "Narineh" as a fully established functional food product. Specifically, steps 16 and 17 from the Functional Food Center's step-by-step development process specify that to receive the optimal level of functional food product classification (level A), they must first undergo epidemiological studies followed by continuous after-market research [61]. In the future, researchers must focus on these remaining steps for the establishment of "Narineh" as a functional food product.

The attenuation of the gut microbiota through bioactive compounds has emerged as a promising avenue. Such interventions have been explored in literature in the context of metabolic syndrome and mental disorders. Probiotics play a crucial role in the bidirectional communication between the gut and the brain, often referred to as the gut-brain axis, influencing not only metabolic health and mental illnesses but also immune responses [69-70]. The multifaceted role of probiotics, especially in eradication regimens for *H. pylori*, underscores their beneficial nature due to their capacity to modulate the gut microbiota, promote immune responses, and more. In addition, other literature has identified the antioxidative properties of amaranth oil, which is a compound utilized for its benefits in the liver. Similar to *Lactobacillus acidophilus* serving as an antioxidant in the gastrointestinal tract, amaranth oil may contribute to antioxidative processes within the liver, an accessory organ of the digestive tract, highlighting its potential role in gastrointestinal health [71]. Continued research is necessary to establish standardized guidelines for probiotic usage in *H. pylori*-associated conditions, ensuring their optimal application and effectiveness in gastrointestinal health.

In the available literature, we did not find similar studies where the effectiveness of such a combination of drugs bismuth subcitrate and a probiotic containing the *Lactobacillus acidophilus* was studied. In some existing literature, such as those addressing abdominal bloating, there is valuable insight into the role of other probiotics with colloidal bismuth subcitrate in addressing intestinal-related issues. In one study, patients with functional abdominal bloating receiving probiotics showed a significantly lower frequency of abdominal bloating compared to other groups after 2 weeks (P= 0.006). At 4 and 8 weeks, both probiotic and bismuth subcitrate groups exhibited reduced bloating frequency compared to placebo (P= 0.001 and P= 0.037, respectively) [72]. These results further emphasize the potential benefits of both probiotics and bismuth subcitrate in addressing intestinal issues. This also indicates their potential in mitigating the side effects associated with classic antibacterial therapy eradication methods.

Results of our research allowed us to come to the following conclusion.

CONCLUSION

The use of fermented milk product "Narineh" containing *Lactobacillus acidophilus* in food added to the standard scheme antibiotic eradication with sequential De-Nol therapy in patients with peptic ulcer, associated with *Helicobacter pylori* infection, is more effective for eradication of *H. Pylori* infection and significantly reduces the percentage of reinfection and relapse of the disease, which is a special case of the impact of functional foods on disease.

The combination of fermentation milk product "Narineh," containing *Lactobacillus acidophilus* with bismuth subcitrate, doesn't cause a violation of biocenosis of the large intestine, in contrast to the PPI and antibiotics. In addition, it provides the normalization of gut biocenosis and reduces frequency of antibiotic-associated diarrhea and other side effects.

The Novelty of This work: Considering the challenges posed by antibiotic resistance in traditional *Helicobacter pylori* eradication therapies, our study takes a novel approach into the standard conventional triple scheme of eradication therapy. Previous research has highlighted the anti-*Helicobacter pylori* activity of probiotics, including *Lactobacillus acidophilus*. Our study aims to assess the efficiency and incidence of adverse effects in a sequential treatment regimen, presenting a distinct perspective on the utilization of functional foods in the management of peptic ulcer disease associated with Hp infection. Our findings underscore the potential of incorporating "Narineh" into conventional therapy as a well-tolerated and effective strategy for enhancing *Helicobacter pylori* eradication, minimizing adverse effects, and reducing the risk of relapse in patients.

List of Abbreviations: PPI, proton pomp inhibitor; A, amoxicillin, C, clarithromycin; RUT, respiratory urea test; PU, peptic ulcer; Hp, *Helicobacter pylori*; RR- relative risk; IR – immediate risk; RL, relapse.

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: Gagik Yeganyan (GY) and Mkrtich Avakyan (MA) discussed the idea about the additional use of probiotic containing *Lactobacillus acidophilus* to the classical antibacterial therapy in eradication regimens in order to increase the degree of eradication and reduce the incidence of side effects. GY and MA participated in data collection. GA participated in the analysis of the results, drawing of the graphs, and editing and finalizing the manuscript for submission. MA contributed to the study design, the selection of the patients participating in the study, and supervised the project. Emma Yeganyan (EY) participated in the histological and histochemical study of biopsy samples of the gastric mucosa and duodenum taken through gastroduodenoscopy and contributed to writing the abstract and introduction. Tori Trachtenberg (TT) did article improvement and editing, Jiawei (Vivian) Zhou (JZ) provided graphical abstract and formatted the final copy to editorial.

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