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Review

Probiotic strains as adjuvants in *Helicobacter pylori* treatment: A review

*Boyanova, L. Y., Boyanova, L., Yordanov, D. V., Gergova, R. T. and Markovska, R. D.

Department of Medical Microbiology, Medical Faculty, Medical University of Sofia, 2 Zdrave str., 1431 Sofia, Bulgaria

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Abstract

Eradicating *Helicobacter pylori* infection has become increasingly difficult over time, mainly due to rising antibiotic resistance and unsatisfactory patient compliance. Lactobacilli, which taxonomy was revised in 2020 splitting the genus *Lactobacillus* into 24 genera, are frequently used as probiotics. According to the majority of recent studies, probiotics promote faster recovery of antibiotic-associated dysbacteriosis, and significantly reduce the adverse effects of eradication therapy. Some studies revealed a slight increase in *H. pylori* eradication. Other studies, however, showed only a transient *H. pylori* inhibition, suggesting that the period for testing eradication success should be extended from one to at least two months. Since most probiotics are bacteria, they may be inhibited by antibiotics to some extent. Moreover, they can participate in horizontal gene transfer, spreading antibiotic resistance. Therefore, we suggest that probiotic fungi be administered during the eradication therapy, followed by a transition to probiotic lactobacilli afterwards. Lactobacilli temporarily suppress virulent *H. pylori* strains, with bacteriocin production of the strains being an additional advantage. Further evaluation of synergistic or antagonistic effects of probiotic combinations is needed. New probiotics such as *Pediococcus* spp. and *Clostridium butyricum* should also be evaluated.

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Introduction

Helicobacter pylori infects approximately half of the world's population (Yang *et al.*, 2022). It is a Gram-negative bacterium that has been classified by WHO as Class I carcinogen, as it is strongly related to the pathogenesis of both gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma in the stomach (Salar, 2019). The disease-associated evolution of *H. pylori* goes through the following stages: chronic active gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and in some cases, progression to malignancies (Chiang *et al.*, 2022). The eradication of *H. pylori* lowers the risk of gastric cancer (Gao *et al.*, 2022). There exist different treatment regimens, each consisting of at least three medications: usually a proton pump inhibitor (PPI), along with two antibiotics (Safavi *et al.*, 2016). Recently, due to treatment failures and the inability to reach the recommended eradication rate of 90%, quadruple therapies with bismuth have been widely adopted (Graham *et al.*, 2014; Han *et al.*, 2022). Still, none of the regimens have been able to achieve complete success. The aim of the present review was to investigate probiotic strains—on one hand, as adjuvants that may raise eradication rates, and on the other, as agents that can ameliorate antibiotic adverse effects.

Materials and methods

We used the following keywords: '*Helicobacter pylori',* 'probiotic', 'yogurt', 'yoghurt', 'bacteriocins', 'eradication', 'side effects', 'antagonism' in Google Scholar, Scopus, PubMed, and Science Direct electronic databases. We discussed articles in English, most of which have been published over the last five years.

Results

What are probiotics and yoghurt, and how may they interact with H. pylori?

Probiotics (Greek: for life) are defined by WHO as live microorganisms which, when

*Corresponding author.
Email: liliya.boianova@medfac.mu-sofia.bg

administered in appropriate amounts, produce a health benefit to the host (Christie and Andrea, 2021). A probiotic product may contain a single strain or combination of multiple strains.

Lactobacilli are commonly used as probiotics. The *Lactobacillaceae* family was considered to consist of three genera (*Lactobacillus*, *Paralactobacillus*, and *Pediococcus*) up until 2020, when Zheng *et al.* (2020) proposed reclassification of the *Lactobacillus* genus, splitting it into 24 genera. Previously, they used to be grouped together due to their common property of fermenting hexoses. However, gene basis, habitat, and physiological properties have since been taken into consideration (Oberg *et al.*, 2020). In addition, the *Lactobacillaceae* and *Leuconostocaceae* (five genera) families were merged into a single family, *Lactobacillaceae*, which now comprises a total of 31 genera (Qiao *et al.*, 2022). Species commonly used as probiotic strains have undergone name changes, such as *Lacticaseibacillus* (*L. casei* subsp. *casei*, *L. casei* subsp. *rhamnosus*), *Lactiplantibacillus* (*L. plantarum*), and *Limosilactobacillus* (*L. reuteri*), while others, like *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus johnsonii*, and *Lactobacillus acidophilus* have retained the original nomenclature. The term 'lactobacilli' refers to all bacteria that were classified as *Lactobacillus* (Zheng *et al.*, 2020).

Besides lactobacilli, other commonly used probiotics species include *Bifidobacterium* and the fungus *Saccharomyces* (*S. cerevisiae* var. *boulardii*) (Singh *et al.*, 2023).

Prebiotics are defined as substances that favour the viability of probiotic strains. Probiotic and prebiotic combinations are referred to as synbiotics (Yadav *et al.*, 2022).

Probiotics, prebiotics, and synbiotics are widely prescribed for numerous gastrointestinal disorders, including prevention and treatment of antibiotic-associated diarrhoea, which is most commonly caused by *Clostridiodes difficile* (Draper *et al.*, 2017; Maestri *et al.*, 2022).

The term 'Bulgarian yoghurt' denotes a dairy product fermented by *L. delbrueckii* subsp. *bulgaricus* and *Streptococcus salivarius* subsp. *thermophilus* into a final product containing at least 10^7 viable colony-forming units (CFU) per gram (Velikova *et al.*, 2018). *L. bulgaricus* and *S. thermophilus* exhibit a symbiotic relationship in the initial process of fermentation until a large amount of lactic acid accumulates, leading to the inhibition of *S. thermophilus* growth (Aryana and Olson, 2017). Historically, *L. delbrueckii* subsp. *bulgaricus* was first discovered in 1905 by Bulgarian physician Stamen Grigorov, at the time a medical student. Thereafter, it was suggested that the consumption of yoghurt might be the reason behind the longevity of the Bulgarians (Fisberg and Machado, 2015).

The possible mechanisms of interaction between probiotics and *H. pylori* are divided into immunological and non-immunological. Non-immunological mechanisms include the production of antibacterial substances (lactic acid, hydrogen peroxide, short chain fatty acids, and bacteriocins), adhesion competition, and an increase in mucin secretion. Immunological mechanisms include the regulation of cytokines and chemokines, chiefly by inhibiting nuclear factor kappa B (NF-κB), which subsequently leads to the downregulation of the neutrophil-activating cytokine interleukin 8 (IL-8) (Goderska *et al.*, 2018; Wu *et al.*, 2021). The results are summarised in Table 1.

Results on probiotic strains

An *in vivo* randomised placebo-control trial conducted in Iran involved 176 dyspeptic patients with positive stool antigen tests. All participants were administered standard triple therapy for ten days (pantoprazole, amoxicillin, and clarithromycin), along with either a combination of lactobacilli and a *Bifidobacterium* probiotic, or a placebo for four weeks. Six weeks after the intervention, eradication was assessed using a stool antigen test. The probiotic group achieved an eradication rate of 78.4%, compared to 64.8% in the placebo group. However, a six-month follow-up revealed no significant difference in eradication rates between the two groups. Nonetheless, the patients in the probiotic group experienced fewer side effects from antibiotic treatment (Haghdoost *et al.*, 2017).

In an *in vivo* study using a murine model, mice were treated with *L. casei* subsp. *rhamnosus* or *Lactobacillus acidophilus* (*L. acidophilus*), before and for 24 days after inoculation with *H. pylori*. On the 25th day, they were sacrificed. Mice treated with probiotic strains showed a negative rapid urease test, along with a decrease of cyclooxygenase-2 (COX-2), and the inflammatory cytokine tumour necrosis factor alpha (TNF-α) was detected in their gastric mucosa. In addition, authors observed *in vitro* inhibition of IL-8 as well as *H. pylori* CagA translocation and phosphorylation (Chen *et al.*, 2019).

Table 1. Activities of probiotics and yoghurt strains.

No.	Strain	Trial	Human/ animal/ *in vitro*	Country	Co-administration with conventional therapy	Effect	Comment	Reference
				Probiotic strains				
1.	*L. plantarum*	*In vitro*	*In vitro*	China	No	Decrease in adhesion (77.9%), suppression of urease, reduced number of *H. pylori*	Five tested strains; supernatants showed better results – role of bacteriocins and bacteriocin-like substances	Huang *et al.* (2021)
2.	*L. plantarum* (ZDY2013)	*In vitro*	*In vitro*	China	No	Inhibition, anti-adhesive, anti-urease; better results compared to *L. rhamnosus* GG	Higher production of lactic acid by *L. plantarum* ZDY 2013 than *L. rhamnosus*	Zhao *et al.* (2018)
3.	*L. casei* subsp. *rhamnosus* (GG)	*In vitro*	*In vitro*	China	No	Inhibition, anti-adhesive, anti-urease	Lower production of lactic acid than *L. plantarum* ZDY 2013	Zhao *et al.* (2018)
4.	*L. delbrueckii* subsp. *bulgaricus*	*In vitro*	*In vitro*	China	No	Inhibitory zone 25.3 mm, anti-adhesive, anti-IL-8 action	Strong interference with TLR4/IκBα/NF-κB pathway. Food containing it might be adjuvant in treatment	Song *et al.* (2019)
5.	*L. acidophilus*	*In vitro*	*In vitro*	China	No	Inhibitory zone 20.3 mm, anti-adhesive, anti-IL-8 action	Food containing *L. acidophilus* might be adjuvant in treatment	Song *et al.* (2019)
6.	*L. casei* susp. *rhamnosus* (GMNL-74)	*In vivo* *In vitro*	Four mice	Taiwan	No	Negative rapid urease test, decreased COX-2 and TNF alpha, favourable alteration of gut microbiota Growth inhibition, anti-adhesive and anti-invasion action, suppression of IL-8, COX-2, TNF-alpha; inhibited *CagA* translocation and phosphorylation	Probiotic treatment for 24 days. Inoculated with *H. pylori* six times, firstly on 8th day of probiotic administration	Chen *et al.* (2019)

No.	Strain	Trial	Human/ animal/ *in vitro*	Country	Co-administration with conventional therapy	Effect	Comment	Reference
7.	*L. acidophilus* (GMNL-185)	*In vivo* *In vitro*	Five mice	Taiwan	No	Negative rapid urease test, decreased COX-2 and TNF-alpha, favourable alteration of gut microbiota Growth inhibition, anti-adhesive and anti-invasion action, suppression of IL-8, COX-2, TNF-alpha; inhibited *CagA* translocation and phosphorylation	Probiotic treatment for 24 days. Inoculated with *H. pylori* six times, firstly on 8th day of probiotic administration	Chen *et al.* (2019)
8.	*Lactobacilli* + *Bifidobacterium*	*In vivo* randomized placebo-control trial	176 people	Iran	Yes	Less side effects, 13.6% higher eradication rate compared to placebo at 6th week	Probiotic group – 88 patients, placebo groups – 88 patients. At 6th month no difference between two groups	Haghdoost *et al.* (2017)
9.	*L. acidophilus* plus *L. casei* subsp. *rhamnosus*	*In vivo*, double blind, placebo-controlled	40 people	Taiwan	No	No eradication (0%)	Lower delta over baseline value in probiotic group 18.5 *vs* 26	Chen *et al.* (2021)
10	*S. boulardii*	*In vivo*	108 people	Ecuador	Yes	Beneficial effect on gut microbiota including lactobacilli amount	Metagenomics analysis showed lower *Bacteroides* and *Clostridium* levels in probiotic group	Keikha and Kamali (2022)
11.	*Clostridium butyricum*	*In vivo*	105 people	China	Yes	Reduced adverse reactions, fast recovery of microbiota, higher *Bacteroides*:*Firmicutes* ratio	Butyrate was reported as a key factor that keep homeostasis in the guts as well as having anti-bacterial including anti-*H. pylori* action	Chen *et al.* (2018)

No.	Strain	Trial	Human/ animal/ *in vitro*	Country	Co-administration with conventional therapy	Effect	Comment	Reference
12.	*L. reuteri*	Meta-analysis	Six randomised controlled trials involving 378 patients	Review	Yes	8.3% eradication; 29.1% reduction in the side effects of antibiotic therapy	Higher eradication rate in Caucasian race than in Africans and Asians	Yang *et al.* (2021)
13.	Probiotics (general)	Meta-analysis	140 studies involving 20,215 patients	Review	Yes	84.1% eradication *vs* 70.5% for placebo; 14.4% rate of adverse reactions *vs* 30.1% for placebo	Most probiotics were more effective than placebo; combined probiotics were not better than use of a single strain	Wang *et al.* (2017)
14.	Lactobacilli	Meta-analysis	Four studies involving 467 people	Review	Yes	Bismuth-quadruple therapy was more effective as rescue regimen when co-administered with lactobacilli	Eradication rate was assessed through UBT	Karbalaei and Keikha (2021)
15.	Probiotics (general)	Meta-analysis	40 studies involving 8,924 people	Review	Yes	Best combination was probiotic+bismuth quadruple regimen	Lactobacilli were more effective than either *Saccharomyces* or *Bifidobacterium*; multiple strains were more effective	Shi *et al.* (2019)
16.	Probiotics (general)	Pooled-data analysis	11 studies involving 517 people	Review	No	50 out of 403 patients reached eradication (14% mean eradication rate). Reduction of mean value of delta values of UBT by 8.61 *vs* 0.19% for placebo	Lactobacilli 16% eradication rate, multistrain combinations 14%, *Saccharomyces* 12%. 0% eradication in placebo groups (114 patients)	Losurdo *et al.* (2018)
17.	*Pediococcus* spp.	Review	Review	Iran	Yes	Less antibiotic side effects	A promising strain that should be further evaluated	Eslami *et al.* (2019)

No.	Strain	Trial	Human/ animal/ *in vitro*	Country	Co-administration with conventional therapy	Effect	Comment	Reference
				Yoghurt strain				
18.	*L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*, *Bifidobacterium lactis*, and *S. thermophilus*	*In vivo*	46 Mongolian gerbils	Taiwan	No	44% *H. pylori* positive rate in yoghurt group *vs* 100% in negative control group	Best results in long term use group - from infection until sacrifice (48 weeks)	Kuo *et al.* (2013)
19.	*L. delbrueckii* subsp. *bulgaricus* + *Streptococcus thermophilus*	*In vivo*	294 asymptomatic blood donors, 213 of them *H. pylori* positive	Bulgaria	Unknown	Consumption of yoghurt > five days/week was associated with lower CagA seroprevalence	Yoghurt reduced virulence of *H. pylori*	Yordanov *et al.* (2017)
20.	Seven yoghurt strains (three *S. thermophilus* strains, one *L. delbrueckii subsp. bulgaricus* strain, one *L. casei* subsp. *rhamnosus* strain, two *Lacticaseibacillus paracasei* strains)	*In vivo* controlled double-blind randomised	136 people	Germany/ France	Yes	Protective effect on intestinal microbiota, fast recovery of intestinal microbiota	No effect on antibiotic-associated diarrhoea rate	Guillemard *et al.* (2021)
21.	Synbiotic combination of yoghurt+garlic	*In vivo*	13 people	Libya	No	Highest reduction of IgG in yoghurt+garlic group	Yoghurt+garlic resulted better than both triple therapy+yoghurt and triple therapy alone	Nasib *et al.* (2023)
22.	*L. delbrueckii* subsp. *bulgaricus* + *Streptococcus thermophilus*	*In vivo* randomized, double-blind, placebo-controlled	314 hospitalised patients on antibiotic therapy, *H. pylori* infection is not in inclusion criteria	Spain	-	17.6% frequency of diarrhoea *vs* 20.9% in control group	Better results in use of Bulgarian yoghurt than yoghurt enriched with three more species – 23% diarrhoea rate	Velasco *et al.* (2019)

UBT: Urea Breath Test.

Huang *et al.* (2021) evaluated *in vitro* activity of five *L. plantarum* strains and their supernatants against *H. pylori*. The strains prevented *H. pylori* adhesion to G-cells, with a mean value of 77.9%. Supernatants performed better than the viable cells in reducing the number of *H. pylori* cells and inhibiting urease activity (by 84.3 - 90.2% at the 6th h).

Other authors compared the anti-*H. pylori* activity of *L. plantarum* and *L. casei* subsp. *rhamnosus* strains. *L. plantarum* demonstrated a superior inhibitory effect (61.4 *vs* 54.8%), as well as greater anti-adhesive activity and anti-urease activity (0.61 *vs* 0.72). A possible reason for that was the higher amount of lactic acid produced by *L. plantarum* (51.1 *vs* 33.1 mmol/L for *L. rhamnosus* GG) (Zhao *et al.*, 2018). Lactic acid increased the permeability of *H. pylori* cell envelope (Westerik *et al.*, 2018).

We also found a number of meta-analyses published in recent years. Some summarised data on the overall effects of antibiotics in controlling *H. pylori* infection, while others focused on particular probiotic strains or group of species, such as lactobacilli.

In one study, the authors compared groups receiving a probiotic strain of *L. reuteri* as an adjuvant treatment with groups receiving only standard therapy. The results showed a non-significant increase in the eradication rate (8.3%) in the probiotic groups, as well as a significant decrease in the side effects of antibiotic therapy (29.1%) (Yang *et al.*, 2021). Wang *et al.* (2017) also observed a slightly higher eradication rate in the probiotic groups compared to the control groups (84.1 *vs* 70.5%), and a significant decrease in antibiotic-related side effects. In addition, the authors found that administering a single strain was as effective as using combined probiotics.

Another meta-analysis compared bismuth quadruple therapy as a stand-alone treatment with therapy supplemented with lactobacilli, reporting eradication rates of 78.8 and 87%, respectively (Karbalaei and Keikha, 2021). Shi's meta-analysis revealed an eradication rate of 81.5% in probiotic groups *vs* 71.6% in control groups, as well as rates of adverse reactions at 18.9 *vs* 39.0%, respectively. The authors concluded that the best combination was the quadruple bismuth regimen plus probiotics, with lactobacilli and multiple strain mixtures yielding the best results (Shi *et al.*, 2019).

Another meta-analysis assessed the eradication rates of probiotic monotherapy using the Urea Breath Test (UBT). Eradication was achieved in 14% of the patients. The use of lactobacilli produced the best results at 16%, followed by 14% for the multi-strain combination, 12% for *S. cerevisiae* var. *boulardii*, and 0% for the placebo. Importantly, the mean reduction of the delta value was estimated at 8.61%, compared to approximately 0 for the placebo (Losurdo *et al.*, 2018). The results from an *in vivo* study conducted in 2021 were contrary. The study compared the effects of *L. acidophilus* plus *L. casei* subsp. *rhamnosus* therapy for four weeks against a placebo. In both groups, ^{13}C-UBT demonstrated lack of eradication (Chen *et al.*, 2021).

A potential future application of probiotics is their use as an oral vaccine against *H. pylori* through genetic engineering carrying *H. pylori* antigens. The oral administration of such a recombinant strain (*Lactococcus lactis*) might elicit IgG and IgA responses (Keikha and Karbalaei, 2021).

Chinese researchers compared the effects of seven probiotic strains using an agar-well diffusion method. *L. delbrueckii* subsp. *bulgaricus* and *L. acidophilus* yielded the best results, with inhibitory zone diameters of 25.3 and 20.3 mm, respectively. The authors concluded that *L. delbrueckii* subsp. *bulgaricus* interacted strongly with the toll-like receptor-4/NFKB inhibitor-α/ nuclear factor κB (TLR4/IκBα/NF-κB), signalling a pathway resulting in IL-8 inhibition, a major neutrophil activator. The authors suggested that foods containing these species, such as yoghurt, could be promising preventive agents as well as adjuvant therapeutics for the infection (Song *et al.*, 2019).

We also found a number of *in vivo* trials that examined the effect of yoghurt on *H. pylori* infection, as well as its impact on microbiota during antibiotic treatment.

Results on effects of yoghurt strains

A study evaluated anti-*H. pylori* IgG and anti-*cagA* IgG in asymptomatic blood donors using ELISA. Authors found an inverse association between the frequency of Bulgarian yoghurt consumption and the presence of anti-*cagA* IgG. Among those who consumed yoghurt at least five days a week, 40.4% had *cagA* positive strains, compared to 47.6% among those that did not consume it (Yordanov *et al.*, 2017).

A randomised control trial revealed the effect of yoghurt supplementation on gut microbiota during anti-*H. pylori* treatment with triple therapy (pantoprazole, clarithromycin, and amoxicillin for 14 days) (Guillemard *et al.*, 2021). The treatment group received yoghurt with seven strains (three *S. thermophilus* strains, one *L. delbrueckii* subsp. *bulgaricus* strain, one *L. casei* subsp. *rhamnosus* strain, and two *Lacticaseibacillus paracasei* strains) twice daily for 28 days, while the control group received lactose-free acidified milk, containing phosphoric acid and carboxymethyl cellulose. Intestinal microbiota was assessed through flow cytometry and 16S rRNA sequencing at baseline, during treatment and up to 28 days after cessation of triple therapy. Fermented milk intake did not affect the incidence of diarrhoea, nor its duration. However, the treatment group experienced faster normalisation of their intestinal microbiota (Guillemard *et al.*, 2021).

Nasib *et al.* (2023) reported a beneficial effect on IgG levels following the administration of a combination of yoghurt and garlic, which served as a prebiotic. The combination appeared to be more effective than both triple therapy and triple therapy + yoghurt. In our view, the small sample size (only 13 patients) was a significant limitation of that study. However, the trial demonstrated that the combination of the natural probiotic and the natural prebiotic was highly efficient.

Another *in vivo* study examined the effect of yoghurt on the occurrence of diarrhoea in hospitalised patients on antibiotic treatment. The first group of patients received traditional yoghurt (*S. thermophilus* and *L. delbrueckii* subsp. *bulgaricus*), the second group received yoghurt supplemented with *L. acidophilus*, *Bifidobacterium*, and *L. casei*, and the control group did not receive any yoghurt. The frequency of diarrhoea was lowest in the traditional yoghurt group, at 17.6% (Velasco *et al.*, 2019).

The effect of yoghurt on *H. pylori* infection was also assessed in an animal model using Mongolian gerbils. The animals had been infected with a *cagA/vacA*-positive *H. pylori* strain for four weeks. They were then split into two groups, one receiving yoghurt (*L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*, *Bifidobacterium lactis*, and *S. thermophilus*) mixed with water. The group that was fed fermented milk from inoculation until sacrifice (48 weeks) had the lowest *H. pylori* positivity (44%), highest level of IL-10, and lowest level of TNF-alpha, while the negative control group, which did not receive yoghurt, remained 100% infected (Kuo *et al.*, 2013).

Discussion

Does this indicate a possible transitory inhibition, rather than eradication?

Results from the Iranian *in vivo* trial (Haghdoost *et al.*, 2017) revealed only a transient *H. pylori* inhibition. These findings raise the question of the optimal post-treatment period for control testing. Current recommendations suggest waiting for at least four weeks (Tonkic *et al.*, 2018), but it may be beneficial to extend the period to six weeks or two months.

Reduced rate of adverse reactions caused by antibiotic and PPIs

The data show that probiotics are appropriate adjuvants to conventional therapy as they reduce the side effects of antibiotic therapy. This is a significant advantage as it can increase patients' compliance. Antibiotic treatment can affect gut microbiota in various ways, depending on the specific agent(s) used and duration of treatment, leading to changes that may persist for up to two years (Kesavelu and Jog, 2023).

Keikha and Kamali (2022) examined the protective role of *S. boulardii* on normal microbiota using metagenomic analysis. They reported a higher relative abundance and greater quantities of both lactobacilli and *Bifidobacterium* in the group that received triple therapy + *S. boulardii*, compared to that on triple therapy alone (Keikha and Kamali, 2022).

Chinese authors Chen *et al.* (2018) evaluated the effect of a 14-day quadruple therapy (bismuth, pantoplazole, amoxicillin, and furazolidone) on gut microbiota, performing microbiome analysis at the metagenomic level using 16s RNA sequencing on faecal samples. The authors stressed the importance of both a decreased *Bacteroidetes* (*Bacteroides*):*Firmicutes* ratio and a reduced amount of butyrate-producing bacteria. Butyrate was identified as a major energy source for gut epithelial cells, and a contributor to the mucosal barrier, thereby helping to maintain homeostasis. The authors reported that co-administration with *Clostridium butyricum* was beneficial for maintaining the equilibrium of intestinal bacteria. In addition, it was

thought to exhibit anti-*H. pylori* action by destroying its envelope (Chen *et al.,* 2018; Zhang *et al.,* 2020). Some authors have indicated that butyrate acid has stronger antimicrobial activity than lactic acid (Zhang *et al.*, 2020).

Moreover, changes in the microbiome during *H. pylori* treatment are not only attributable to antibiotics but may also be caused by PPIs. The latter may alter the microbiota throughout the entire gastrointestinal tract due to changes in pH (Bruno *et al.*, 2019).

In addition, probiotics protect against *C. difficile* (Mills *et al.,* 2018), a potent dangerous infectious agent that sometimes causes severe diarrhoea or pseudomembranous colitis, particularly in association with broad-spectrum antimicrobial chemotherapy and the use of PPIs (Tawam *et al.*, 2021).

Eradication rate

The results indicated that co-administration of conventional therapy with a probiotic increased the eradication rate; however, it did not, unfortunately, reach statistical significance. The specifics of anti-*H. pylori* treatment and the expected results should be clearly explained to patients by their treating physicians. Unsuccessful eradication, in combination with the prevalence of unreliable information in the public domain, may lead to reluctance regarding further testing and treatment of this potentially hazardous infection.

Probiotic strains as possible donors of resistance genes?

There is evidence that probiotic strains can acquire resistance to antibiotics, and subsequently become a source of resistance genes for pathogens through horizontal transfer of plasmids or transposons (Gueimonde *et al.*, 2013; Merenstein *et al.*, 2023). Recently, Zaman *et al.* (2023) provided evidence for the *in vitro* transfer of resistance genes during the co-cultivation of *Lactobacillus* spp. and *Escherichia coli*. The reported genes included *qnrS* (a gene associated with plasmid-mediated quinolone resistance), *CTX-M-1* (an extended-spectrum beta-lactamase), and *tetA* (a gene encoding a tetracycline efflux pump). Therefore, we suggest the administration of a non-pathogenic yeast strain, such as *S. cerevisiae* var. *boulardii*, as a good option during antibiotic treatment, since yeasts are unaffected by antibiotics and thus, they cannot acquire resistance. After the cessation of antibiotic treatment, a transition to bacterial probiotic strain(s) can be considered.

Bacteriocins and bacteriocin-like substances

In some cases, the supernatant is more effective than the live microorganisms (Huang *et al.,* 2021). The reason may be the bacteriocins and bacteriocin-like inhibitory substances released by certain probiotic strains. This aligns with the view of some researchers that the production of bacteriocin-like inhibitory substances can be a major advantage of a probiotic strain (Boyanova *et al.*, 2017).

Single strain or multiple species probiotic?

Another fundamental question is whether to prescribe one probiotic strain or a combination of multiple species. The data on this topic are controversial. It is possible that antagonistic effects may occur between different strains, resulting in a lack of additive benefits. Therefore, the compound effect of probiotic combinations should be further evaluated in more studies.

Yoghurt as functional food

Data on the preventative effects of yoghurt against *H. pylori* infection indicates that regular consumption by children can protect them from acquiring the infection, which is most often contracted in early childhood and commonly transmitted from mother to child (Li *et al.*, 2024). In addition, yoghurt intake seems to attenuate the virulence of *H. pylori* (Yordanov *et al.*, 2017).

New approaches

Other probiotic species not mentioned earlier may also be beneficial against *H. pylori* infection. For instance, Eslami *et al.* (2019) suggested that *Pediococcus* spp. may be effective against *H. pylori* infection in a mouse model due to pediocin production. Therefore, both *in vitro* and *in vivo* testing of variable strains should continue as a future direction. Another relatively new approach involves encapsulating probiotics with nanocarriers, such as alginate, to keep the beneficial bacteria viable (Silva *et al.*, 2020).

Rare complications of probiotic intake

Probiotics have to be applied with caution in severely immunocompromised patients. Finnish authors reported 20 cases of probiotic-associated

fungemia in patients who had received *S. cerevisiae* var. *boulardii* across five university hospitals between 2009 and 2018. The authors identified severe immunosuppression, permanent catheterisation, terminal illness, and compromised gastrointestinal integrity as the main risk factors (Rannikko *et al.*, 2021). Kullar *et al.* (2023) summarised 25 cases of bacteraemia caused by lactobacilli (*L. rhamnosus* GG, *L. paracasei*, and *L. plantarum*), in which the strains were genetically identical as those administered orally to the patients. All 25 patients successfully recovered after antibiotic treatment. Authors highlighted the presence of a central venous catheter as a serious risk factor, as it can be contaminated through air or contact with medical staff's hands, providing direct entry into the bloodstream.

Recent data have indicated certain risks associated with the consumption of refined inulin, which is commonly used as prebiotic. According to Tian *et al.* (2023), inulin may induce large bowel inflammation, and promote carcinogenesis.

Conclusion

Both probiotics and yoghurt exhibit positive effects on *H. pylori* infection. Administering probiotics can slightly increase the eradication rate, as well as help relieve the side effects of antimicrobial therapy. Yoghurt has some protective properties against infection, and reduces the virulence of *H. pylori*. However, neither probiotics nor yoghurt can be used as standalone treatments. The data we summarised herein suggest that the probiotic preparations can offer benefits in controlling *H. pylori* infection and standard strain(s), with particular doses and treatment durations may become a part of therapeutic protocols. Therefore, further studies, including clinical trials, are needed to examine the properties of different probiotic strains, such as their production of various active molecules, and to determine the most appropriate doses and dosage forms. New probiotic strains and technologies, such as nanocoating, hold promise for advancing treatment options.

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