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Review Article

Treating bacteria with bacteria: the role of probiotics in the eradication of Helicobacter pylori

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Abstract: *Helicobacter pylori* (*H. pylori*), with more than 50% global population infection, is an etiology of chronic gastritis and peptic ulcer and a risk factor for gastric malignancies. Due to the increase of *H. pylori*-resistant strains and treatment-related adverse effects, the success rate of eradication therapies has declined to 70%, far below the initial rate of 90%. To improve the eradication rate, researchers have started to look into alternative treatments for *H. pylori*, one of which is probiotics. In this article, we elaborated the mechanisms of action of probiotics against *H. pylori* infection into four aspects: immunomodulation, antimicrobial substances, interfering with adhesion, and mucosal barrier. Although probiotics are varied, we only conducted studies on *Lactobacillus*, *Bifidobacterium*, and yeasts such as *Saccharomyces boulardii* most commonly used in the therapy. The effects of *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces boulardii*as monotherapy or adjuvant therapy combined with antibiotic-PPI for *H. pylori* eradication in children and adults showed diverse outcomes in eradication rate and adverse effects. Extensive studies indicated probiotics plays an important role in *H. pylori* infection. However, many uncertain problems still need to be considered in the clinical application of probiotics.

Keywords: *Helicobacter pylori*, mechanism, *Lactobacillus, Bifidobacterium, Saccharomyces boulardii*, eradication rate, adverse effects

Introduction

Helicobacter pylori (*H. pylori*) are a group of highly prevalent human pathogens infecting more than half of the global population [1]. The prevalence of the bacteria strongly differs between developing and developed countries, where prevalence rate in adults is approximately 60-80% and <40%, respectively. Individuals with a low socioeconomic status, poor sanitary living condition and lower educational level have been associated with a high risk of *H. pylori* infection [2]. Long-term *H. pylori* infection leads to a diverse spectrum of gastrointestinal disorders including chronic gastritis, peptic ulcer, gastric malignancies and gastric mucosa-associated lymphoid tissue lymphoma [3]. Moreover, evidence has been presented linking *H. pylori* to the aetiology of several extragastric diseases, such as unexplained iron-deficiency anaemia, idiopathic thrombocytopenic purpura, and vitamin B_{12} deficiency [4]. Once infection is acquired, spontaneous clearance is relatively rare. Thus, eradication of *H. pylori* is an effective measure to reduce the risk of diseases and, to some extent, provides a feasible method for treatment of diseases.

Triple therapy, consisting of a proton pump inhibitor (PPI), amoxicillin, and clarithromycin or metronidazole, was proposed at the first Maastricht conference in 1996 and has been widely used for twenty years, although an increasing number of data have shown that this combination treatment has lost some efficacy and provides an unsatisfactory result, with the eradication rate only achieving 70%, far lower than the rate at the beginning [5]. The decline of the eradication rate is mainly due to the increase in antibiotic resistance especially of clarithromycin and metronidazole. High incidence of treatment-related adverse effects is another important cause, resulting in the low compliance of patients and, consequently, incomplete therapy. The latest Maastricht V/Florence consensus reportin 2016 recommended the bismuth-containing quadruple therapy as a first-line empirical treatment in areas of high clarithromycin

resistance and an alternative treatment in areas of low clarithromycin resistance. Sequential therapy, concomitant therapy (non-bismuth quadruple therapy), and levofloxacin containing triple therapy were proposed under different situations in the report [4]. Despite these efforts, however, considering increasing antibiotic resistance, frequent adverse effects, vast medical expense and complicated dosing regimens, some patients are disinclined to accept and complete treatment in the clinic.

In light of current unideal therapeutic regimens, researchers have begun to search for new alternative therapies. One potential alternative therapy is probiotics. Probiotics are defined as live microorganism that, when administered in adequate amount, confer a health benefit on the host [6]. A wide variety of probiotics have been found in the current stage and some were used in food, dietary supplements, and drugs. Effect of each probiotic strain is specific and dose-dependent. Additionally, certain strains can imitate commensals playing an important role in the digestive system [7]. Evolving evidences presented probiotics have significant effects in alleviating the symptoms of several diseases, such as acute diarrhea, antibiotic-associated diarrhea, functional gastrointestinal disorders, and inflammatory bowel disease [8]. Much research has been performed with the genera *Lactobacillus*, *Bifidobacterium*, and yeasts such as *Saccharomyces boulardii* (*S. boudlardii*) to explore the interaction between *H. pylori* and probiotics, both *in vivo* and *in vitro*. Albeit some researchers showed no obvious effects of probiotics on *H. pylori* infections, promising results in a large portion of cell experiments, animal studies and human trials have been proven [9-11]. In this review, we introduced the microbiota that commonly interact with *H. pylori* in the stomach, summarized the possible mechanisms of action of probiotics against *H. pylori* infection, and reviewed the outcomes of studies that used probiotics as monotherapy or adjuvant therapy in eradication protocols. In the end, we discussed the challenges and opportunities for probiotics in clinical application.

The human gastric microbiota and *H. pylori*

Previously, the stomach was long-considered sterile, mainly owing to its acid milieu and past limited technologies [9]. Since the discovery of *H. pylori* in 1983, people began to break the inherent thinking and make further efforts to investigate the gastric microbiota. At first, using culture-independent methods of analysis, *Clostridium* sp, *Lactobacillus* sp and *Veillonella* sp were the most represented bacteria of the human stomach under healthy conditions. Notwithstanding, approximately 80% of microbes are not cultivable [12]. To date, in virtue of the recent development of new nucleotide sequencing techniques and advanced bioinformatic tools, the diversity and complexity of the gastric microbiota are obtained further comprehensive research. A diverse community of 128 phylotypes was identified in the stomach by using 16S rDNA sequence analysis, majority of which derive from the phyla *Proteobacteria*, *Firmicutes*, *Actinobacteria*, *Bacteroidetes*, and *Fusobacteria* [13]. Comparing to other parts of the gastrointestinal tract, the microbial load in stomach is lower, whereas an increasing number of studies showed the disruption of gastric microbiota has been associated with different diseases of the stomach, like atrophic gastritis, peptic ulcer and gastric cancer, hence, maintaining these floras in balance is essential to the health of host [14, 15].

Once infected by *H. pylori*, the stomach becomes a reservoir for *H. pylori*. Long term of *H. pylori* infection may change the composition of gastric microbiota. Andersson [16] analyzed the structure of the bacterial community in the stomach of patients of differing *H. pylori* status, which corroborated the finding that the stomach displays a diverse microbiota when *H. pylori* is absent or low in abundance. Another study further showed that positive *H. pylori* status is associated with increased relative abundance of non-*Helicobacter* bacteria from the *Proteobacteria*, *Spirochetes*, and *Acidobacteria* phyla and decreased abundance of *Actinobacteria*, *Bacteroidetes*, and *Firmicutes* [17]. With respect to the study of microbial composition of gastric mucosa from the patients with chronic gastritis, intestinal metaplasia, and gastric cancer, Eun [18] found marked differences that in gastric cancer group, the relative abundance of *Helicobacteraceae* was significantly lower than that of chronic gastritis and intestinal metaplasia, whereas the relative abundance of *Streptococcaceae* was increased.

Mechanism of action of probiotics against *H. pylori* infection

H. pylori infection, in most cases, can persist lifelong in its host in the absence of eradication therapy, because it is capable of adaptations to

Table 1. Immunomodulation mechanism

Author	Probiotic	Type of experiment	Results
Zhou et al [23]	*L. bulgaricus*	Cell (SGC-7901)	IL-8 expression ↓
Yang et al [24]	*L. acidophilus*	Cell (MKN45, AGS)	IL-8 expression ↓
Sunanligano et al [25]	*L. plantarum* B7	Animal (SD rats)	TNF-α, gastric MDA level, epithelial cell apoptosis and gastric inflammation ↓
Yu et al [26]	BIFICO[1]	Animal (C57BL/6 female mice)	TNF-α, IL-6, IL-1β, IL-10, G-CSF and MIP-2 expression ↓

[1]: a mixture of *lactobacillus acidophilus, enterococcus faecalis* and *Bifidobacterium longum*.

colonize the special environment of the stomach [19]. Urease produced by *H. pylori* hydrolyzes urea to ammonia and carbon dioxide, neutralizing the pH, which allows the bacterial survival. The presence of flagella facilitates *H. pylori* penetrating into the mucus layer and reaching the gastric epithelium. As soon as *H. pylori* colonize the gastric epithelium, the host's innate and adaptive immune systems are activated, followed by a series of inflammatory and immunological response [20]. Persistent chronic inflammation induced by *H. pylori* may progress to atrophy, metaplasia, dysplasia, and even gastric cancer, therefore alleviating gastric mucosa inflammation is of great importance for health [21].

Substantial studies have indicated probiotics play an important role in fighting against *H. pylori* infection and in this section; we will elucidate the mechanisms of action of probiotics against *H. pylori* infection into four aspects, namely, immunomodulation, antimicrobial substances, interfering with adhesion, and mucosal barrier.

Immunomodulation mechanism

In the process of *H. pylori* infection, the activation of the immune system can lead to the recruitment of a wide variety of inflammatory cells and mediators, and the activation of nuclear factor-κB (NF-κB) and pro- and anti-inflammatory cytokines [20]. In comparison to the uninfected ones, some cytokines such as TNF-α, IFN-γ, IL-6, IL-7, IL-8, IL-10, IL-17, and IL-18 have generally increased levels in the stomach of *H. pylori*-infected patients (**Table 1**). In addition, the H. *pylori*-specific $CD4^+$ T cells only can be detectable in peripheral blood and gastric mucosa of infected humans [22].

Probiotics have the potential to dampen cytokine reaction triggered by *H. pylori* [9]. Currently extensive studies are focused on the genera *Lactobacillus*. *L. bulgaricus*, when co-cultured with SGC-7901 cells treated with *Helicobacter pylori* Sydney strain 1 lipopolysaccharide (*H. pylori* SS1-LPS), enable the expression of TLR4 to attenuate, and subsequently inhibit the phosphorylation of TAK1 and p38MAPK, prevent the activation of NF-κB, and consequently block IL-8 production [23]. Yang [24] demonstrated that *L. acidophilus* reduced *H. pylori*-induced IL-8 expressions and inflammation through the inactivation of the Smad7 and NF-κB pathways in vitro study. To determined the anti-*H. pylori* property of *L. plantarum* B7, Sunanliganon [25] performed an experiment which researched effects of *L. plantarum* B7 on the serum TNF-α, gastric malondialdehyde (MDA) level, apoptosis, and histopathology in gastric inflammation induced by *H. pylori* in rats, and results indicated that the group receiving *L. plantarum* B7 treatment had a significant decrease in serum TNF-α level compared with *H. pylori*-infected group. Furthermore, *L. plantarum* B7 treatments resulted in a significant improvement in stomach pathology, and decreased gastric MDA level and apoptotic epithelial cells. BIFICO, which contain a mixture of the viable bacteria *Enterococcus faecalis*, *Bifidobacterium longum*, and *L. acidophilus*, were proven to ameliorate *H. pylori*-induced gastritis by inhibiting the inflammatory response in gastric epithelial cells. In this study, BIFICO significantly inhibited *H. pylori*-induced NF-κB and MAPK signaling pathway, and decreased the expression of TNF-α, IL-1β, IL-10, IL-6, G-CSF and MIP-2 [26].

Antimicrobial substances mechanism

Probiotics may inhibit the growth of *H. pylori* by secreting antimicrobial substances. Short chain fatty acids (SCFAs) and bacteriocins are two main types of substances associated with inhibition of *H. pylori*. SCFAs, the final catabolites of energy metabolism, include butyrate, propionate, acetate, and lactic acid [27]. The

Table 2. Antimicrobial substances mechanism

Author	Probiotic strain	Mechanism of inhibition
Bhatia et al [28]	*L. acidophilus*	Lactic acid
Lesbros-Pantoflickova et al [29]	*L. acidophilus LB, L. johnsonii La 1*	Lactic acid
Aiba et al [30]	*L. salivarius*	Lactic acid
Sgouras et al [31]	*L. casei Shitoya*	Lactic acid, suppress the urease activity
Hsieh et al [32]	*L. salivarius* ssp. *salicinius* AP-32	Suppress the urease activity
Lesbros-Pantoflickova et al [29]	*Wissella confusa, L.lactis,* and *Bcillus subtilis*	Bacteriocins
Francavilla et al [34]	*L. reuteri* ATCC 55730	Reuterina
Lorca et al [35]	*L. acidophilus* CRL 639	Autolysins

Table 3. Interfering with adhesion mechanism

Author	Probiotic strain	Mechanism of inhibition
Nam et al [36]	*Weissella confusa* strain PL9001	Compete for adhesion sites
Mukai et al [37]	*L. reueri* strains JCM 1081 and TM 105	Compete for adhesion sites
Sakarya et al [39]	*Saccharomyces boulardii*	Change structure of adhesion sites
Lesbros-Pantoflickova et al [33]	*L. acidophilus LB and L. Johnsonii La1*	Secrete antimicrobial substances

production of relatively large amount of lactic acid by *Lactobacillus* has been implicated as an inhibitory factor by many researchers (**Table 2**). Bhatia [28] first proposed that the inhibitory action of *L. acidophilus* on *H. pylori* is dependent on an extracellular secretory product, probably lactic acid. Furthermore, *L. acidophilus* LB*, L. johnsonii* La 1*, L. salivarius and L. casei* have been demonstrated to exert an inhibitory effect on *H. pylori* by lactic acid production [29, 30]. Some antimicrobial activity, in addition to lactic acid production, could exert effects through inhibiting urease activity, as found in the *L. casei* Shirota and *L. salivarius ssp. salicinius* AP-32 [31, 32].

Bacteriocins, proteinaceous molecules synthesized at the ribosomal level, are capable to interfere with the growth of most bacteria, including *H. pylori* [33]. *Wissella confusa*, *L. lactis*, and *Bcillus subtilis* were shown to secrete bacteriocins able to inhibit *H. pylori* growth in vitro [29]. Certain probiotic strain could secrete some special substances with an inhibitory effects on *H. pylori*. Like reuterina, a metabolite produced by *L. reuteri* ATCC 55730, effectively suppressed *H. pylori* infection in humans and reduced *H. pylori* load [34]. *L. acidophilus* CRL 639, in mixed cultures with *H. pylori* after 24 h, showed an autolytic behavior, and *H. pylori* simultaneously decreased, subsequently vanished after 48 h. On the basis of the research, Lorca speculated that after cell lysis, bacteria may release a proteinaceous compound named autolysins suppressing the growth of *H. pylori* [35].

Interfering with adhesion mechanism

Adhesion of *H. pylori* to the gastric epithelium, a crucial step in the *H. pylori* infection, indicates the beginning of *H. pylori* establishing colonization, further interacting with epithelial cells, manipulating the cellular processes and functions, and consequently, influencing outcomes of associated diseases [20]. Probiotics may inhibit adhesion of *H. pylori* through directly competing for adhesion sites, or changing the structure of adhesion sites, resulting in a failure of adhesion. *Like Weissella confusa* strain PL9001 is capable of interfering *H. pylori* colonization by competing for adhesion sites [36]. *L. reueri* strains JCM 1081 and TM 105 show the ability to bind to asialo-GM1 and sulfatide which are putative glycolipid receptor molecules of *H. pylori,* and inhibit binding of *H. pylori* to both glycolipids [37]. Adhesion properties of *H. pylori* to various structures have been described in the past, including evidence for sialic acid-binding [38]. Recently, Sakarya [39] discovered the neuraminidase activity expressed by *S. boulardii* could remove surface α-2,3-linked sialic acid, ligand for the sialic acid-binding *H. pylori* adhesin, which in turn, inhibit *H. pylori* adherence to duodenal epithelial cells (**Table 3**). Certain strainssuch as *L. acidophilus* LB and *L. Johnsonii* La1 can exert

Table 4. Mucosal barrier mechanism

Author	Probiotic strain	Type of experiment	Results
Pantoflickova et al [40]	*L. johnsonii*	Human (*H. pylori* positive adults)	Increase mucus thickness, reduce the degree of gastric inflammation
Mack et al [43]	*L. plantarum* 299v, and *L. rhamnosus* GG	Cell (HT29)	Increase MUC2 and MUCA3 genes expression and extracelluar secretion of mucin by colon cell cultures
Gomi et al [44]	*Bifidobacterium bifidum* BF-1	Animal (rats)	Enhance MUC5AC gene expression

Table 5. Probioticsas a monotherapy

Author	Subjects	Diagnosis	Probiotic strains	Study design	Method	Results
Cruchet et al [45]	252 *H. pylori*-positive, asymptomatic children	^{13}C-UBT	*L. johnsonii* La1, *L. paracasei* ST11	R, DB, PC	Group 1: a product containing live La1 Group 2: heat-killed La1 Group 3: a product containing live ST11 Group 4: heat-killed ST11 Group 5: vehicle	Group 1: A significant difference in Δ DOB (-7.64‰; 95% CI: -14.23 to -1.03‰) Other groups: no differences
Gotteland et al [46]	254 *H. pylori*-positive, a-symptomatic children	^{13}C-UBT	*L. acidophilus* LB, *S. boulardii*	R, O	Group Ab: antibiotic treatment[1] Group Sbl: *S. boulardii* plus inulin Group LB: LB	Group Ab: A moderate but significant difference in Δ DOB (-26.6‰; 95% CI: -33.9 to -19.3‰) Group Sbl: A moderate but significant difference in Δ DOB (-6.3‰; 95% CI: -6.3 to -0.8‰) Group LB: no significant difference in Δ DOB (0.7‰; 95% CI: -5.8 to +7.2‰) Eradication rate: 66% vs. 6.5% vs. 12% (χ^2=51.1, P<0.001)
Boonyaritichaikij et al [47]	440 children (132 *H. pylori*-positive and 308 *H. pylori*-negative)	HpSA	*L. gasseri* OLL2716 (LG21)	SB, PC, DB	Eradication and prevention arms Active group: cheese containing LG21 Placebo group: ordinary cheese	In eradication study: eradication rate: 29.3% vs. 0% (P=0.038) in the prevention study: *H. pylori* infection rate: 4.1% vs. 8.1% (no statistically significant difference)
Francavilla et al [34]	40 *H. pylori*-positive, dyspeptic patients	HpSA, RUT, histopath-ology, ^{13}C-UBT	*L. reuteri* ATCC 55730	DB, PC	Group 1: *L. reuteri* 4 w Group 2: placebo Sequential treatment was administered subsequently	GSRS: a significant decrease in group 1 at 4 w [7.9±4.1 (95% CI: 6.3-9.8) vs. 11.8±8.5 (95% CI: 7.8-15.7); P<0.05] Eradication rate: at 4 w zero No difference in both groups after sequential regimen (88% vs. 82%; P=0.8)
Gotteland et al [48]	12 *H. pylori*-positive, asymptomatic adults	^{13}C-UBT	*L. johnsonii* La1	O	Compare DOB value after 1 and 2 w of ingesting the product	Twice DOB ↓ A significant decrease in DOB after 2 w (27.39‰, 95% CI: 16.24-38.54‰, P=0.043)
Sakamoto et al [49]	31 *H. pylori*-positive adults	serology ^{13}C-UBT	*L. gasseri* OLL2716	O	In the first part: yogurt 8 w In the second phase: yogurt containing LG21 8 w	At 0 w and 9 w: no significant difference in DOB values At 18 w: a significant decrease in DOB values than earlier weeks
Miki et al [50]	80 healthy adults	^{13}C-UBT	*B. bifidum* YIT4007	R, DB, PC	Group 1: BF-1 beverage Group 2: placebo	Group 1: a significant decrease in DOB compared to placebo (P=0.027)
Myllyluoma et al [60]	13 adults (7 *H. pylori*-positive and 6 *H. pylori*-negative)	^{13}C-UBT, histopathology	*L. rhamnosus* GG, *L. rhamnosus* LC705, *Propionibacterium freudenreichii* JS *and B. lactis* Bb12	O	Compare *H. pylori* colonization and the degree of gastric inflammation	DOB value, inflammation activity ↓ (P=0.063)
Wang et al [61]	70 *H. pylori*-positive, asymptomatic adults	^{13}C-UBT, serology	*Lactobacillus*- and *Bifidobacterium*-containing AB-yogurt	PC	Group 1: a bottle of AB-yogurt Group 2: an unfermented milk At the start and 4 w after the end of treatment, specimens of gastric antrum and body were obtained from 14 subjects among the group 1	Group 1: significant differences in the result of ^{13}C-UBT values between 0 w and 4 w, and between 0 w and 8 w (36.2±19.4 compared with 30.1±19.6 and 36.2±29.4 compared with 28.2±15.8, P<0.05) antral biopsies showed *H. pylori* density was reduced (P=0.015)

O: open; R: randomized; DB: double-blind; SB: single-blind; PC: placebo controlled; RUT: rapid urease test; HpSA: *H. pylori* stool antigens; w: week; d: days; antibiotic treatment[1]: lansoprazole 1 mg/kg, bid, amoxicillin, 50 mg/kg, bid, clarithromycin 15 mg/kg, bid.

their anti-adhesion activity by secreting antimicrobial substances [29].

Mucosal barrier mechanism

Gastric mucosal barrier, consisting of a compact epithelial cell line, a special mucus covering, and foveolar cells, represents a first line of defense pathogenic bacteria. If the barrier is broken, acid will diffuse back into the mucosa where it can cause damage to the stomach. *H. pylori* virulence factors, such as cytotoxin associated gene A (Cag A) and vacuolating cytotoxin (VacA) play a major role in gastric mucosa damage [3]. Mucus, a protective gel-like coat over the surface of the gastric mucosa, protects mucosa from the invasion of bacteria. However, reduced mucus secretion in a damaged or proliferating epithelium is frequently found in *H. pylori* associated gastritis [29]. A research evaluated the effect of *L. johnsonii* intake on *H. pylori* gastritis which found regular ingestion of fermented milk containing *L. johnsonii* has an association with increase of mucus thickness [40]. Mucin, the key viscoelastic component of gastric mucus, is pH dependent, transforming from a viscous solution at neutral pH to a gel in acidic conditions [41]. In the gastric mucosa, MUC1, MUC5AC and MUC6 are three main mucin expression type [42]. *H. pylori*, is known to suppress MUC5AC and MUC1 gene expression in the human gastric cell line [33]. Some probiotic strains are able to regulate mucin expression, strengthening the gastric mucosal barrier, and protect it against the adhesion of *H. pylori.* In vitro studies have shown that *L. plantarum* strain 299v and *L. rhamnosus* GG increased the expression of MUC2 and MUC3 genes and the subsequent extracellular secretion of mucin by colon cell cultures [43]. Gomi [44] indicated that *Bifidobacterium bifidum* BF-1 *B. bifidum* BF-1) has the potential to provide gastric mucosal protection by enhancing MUC5AC gene expression in an acute gastric injury rat model (**Table 4**).

Clinical trials with probiotics in *H. pylori* eradication

In this section, abundant trials and meta-analyses are introduced to provide a comprehensive description, and we will evaluate the effects of probiotics as treatment on *H. pylori*, through single use or in combination with antibiotic-PPI in children and adults in accordance with diverse genera.

Probioticsas a monotherapy in treatment

On account of side effects of antibiotics, single use of probiotics to eradicate *H. pylori* can provide a safer therapy for children, and numerous scholars performed studies on it (**Table 5**). In a double-blind, randomized, controlled clinical trial in Santiago [45], 252 asymptomatic children who were screened as *H. pylori* positive by the ^{13}C-urea breath test (^{13}C-UBT) were distributed into five groups. Each group, by turns, received a product containing live *L. johnsonii* La1, heat-killed *L. Johnsonii* La1, live *L. Paracasei* ST11, heat-killed *L. paracasei* ST11, and a vehicle every day for 4 wk. At the end of the study period, a moderate but significant difference in Δ DOB ($\delta^{13}CO_2$ values above baseline values before and after treatments) was detected in children receiving live *L. johnsonii* La1, whereas no differences were observed in the other groups. Gotteland [46] conducted a similar study, in which he evaluated the effect of *S. boulardii* plus inulin (Sbl) or *L. acidophilus* LB (LB) on *H. pylori* colonization in children, and used standard triple therapy as contrast, demonstrating a moderate but significant decrease in DOB (excess $\delta^{13}CO_2$ values above baseline) values in Sbl group, however, compared with the 66% eradication rate of the standard triple therapy group, the eradication rates of the Sbl and LB groups were extremely low, at about 12% and 6.5%, respectively. Another study used *H. pylori* stool antigen test to detect *H. pylori* and investigated the effects of long-term administration of *L. gasseri* OLL2716 (LG21) strain in the *H. pylori* eradication rate in asymptomatic pre-school children [47]. After regular ingestion of cheese containing LG21 for a year, in eradication study, eradication was found in 24 of 82 subjects (eradication ratio 29.3%; 95% CI: 19.4-39.1%) in the active group, whereas no eradication was observed in the placebo group. In prevention study, rates of *H. pylori* infection were 4.1% and 8.1% in the active and placebo groups, respectively. Above studies indicate that not all probiotics have effective role on treatment of *H. pylori*, such as *L. paracasei* ST11, in addition, certain probiotics may diminish the bacterial load, but are unable to completely eradicate *H. pylori* in children.

Many probiotics, such as *L. johnsonii* La1 [48], *L. gasseri* OLL 2716 [49], *L. reuteri* ATCC 55730

Table 6. Probiotics as adjuvant therapy combined with antibiotics-PPI in *H. pylorieradication*

Author	Study design	Patients	Assessment tools	Probiotics strains	Eradication therapy	Results (probiotics vs. placebo)	
						Eradication rate	Side effects
Du et al [52]	R, O	234 *H. pylori*-positive gastritic adults	RUT, histopath-ology, ^{13}C-UBT/^{14}C-UBT	*L. acidophilus*	Omeprazole 20 mg bid, clarithromycin 500 mg bid, amoxicillin 1000 mg bid	POCA:OCA=79.5%:60.8% P=0.014 OCAP:OCA=79.2%: 60.8% P=0.015	Symptom relieving rate POCA:OCAP:OCA=85.5%:89.2%: 87.2%
Deguchi et al [53]	PC, R	229 *H. pylori*-positive adults	^{13}C-UBT, HpSA	*L. gasseri* OLL2716	Rabeprazole 10 mg bid, amoxicillin 750 mg bid, clar-ithromycin 200 mg bid, 1 w	95/115 (82.6%) vs. 79/114 (69.3%) P=0.018	-
Ojetti et al [54]	PC, R	90 *H. pylori*-positive adults which experienced an unsuccessful anti-*H. pylori* antibiotic treatment	^{13}C-UBT	*L. reuteri* ATCC 55730	Esomeprazole 20 mg bid, levofloxacin 500 mg bid, amoxicillin 1 gr bid, 1w	36/45 (80%) vs. 28/45 (62%) P<0.05	Nausea: 32/45 (66.7%) vs. 45/45 (100%) P<0.001 diarrhea: 10/45 (22.2%) vs. 26/45 (57.7%) P<0.004
Emara et al [55]	DB, PC, R	70 *H. pylori*-positive, dys-peptic adults	HpSA, RUT, Histopath-ology, Question-naire	*L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 6475	Omeprazole 20 mg bid, amoxi-cillin 1000 mg bid, clarithro-mycin 500 mg bid, 2 w	26/35 (74.3%) vs. 23/35 (65.7%) P=0.603	*L. reuteri* group significantly decreased the GSRS scores
Francavilla et al [56]	DB, PC, R	100 *H. pylori*-positive, dyspeptic adults	^{13}C-UBT, RUT, serol-ogy, histopath-olo-gy, question-naire	*L. reuteri* DSM 17938 and *L. reuteri* ATCC PTA 6475	PPI-clarithromycin-amoxicillin (not clear)	33/44 (75%) vs. 29/44 (65.9%) absolute difference: 9.1% (OR: 1.5; 95% CI: 0.6-3.9%)	18/44 (40.9%) vs. 27/43 (62.8%) P<0.04
Dajani et al [59]	O. R	377 *H. pylori*-positive adults and children (group A: stan-dard triple therapy, group B:probiotic concomitant, group C:pre-treatment with probiotic, group D: probiotic concomitant with sequen-tial therapy)	^{14}C-UBT	*B. infantis* 2036	Standard triple therapy: PPI-amoxicillin -clarithromycin or metronidazole 10 d The sequential therapy: PPI-amoxicillin 5 d, PPI-clarithro-mycin-metronidazole 5 d	Group A:B:C:D=68.9%:83%:86%:90.8%	Improvement of clini-cal symptoms group A:B:C:D=28.8%:54%:52.5%:49.8%
Wang et al [62]	PC, R	100 *H. pylori*-positive children	^{13}C-UBT	A mixture of *L.acidophilus*-5 and *B. bifi-dum*-12	PPI 0.6-0.8 mg/kg bid, clarithromycin 10-15 mg/kg bid, amoxicillin 30-50 mg/kg bid, 2 w	36/43 (83.7%) vs. 29/45 (64.4%) P<0.05	5/43 (11.6%) vs. 12/45 (26.7%) P=0.07

O: open; R: randomized; DB: double-blind; PC: placebo controlled; RUT: rapid urease test; *H. pylori: Helicobacter pylori;* HpSA: *H. pylori* stool antigens; w: week; d: days; PPI: proton pump inhibitor; OCA: standard therapy group; POCA: probiotic pre-treated group: OCAP: probiotic post-treated group.

[34], and *B. bifidum* BF-1 [50], show the ability to modulate *H. pylori* colonization instead of eradicating it in adults.

Probiotics as adjuvant therapy combined with antibiotic-PPI in H. pylori eradication

Evaluating the effects of probiotics as adjuvant therapy combined with antibiotic-PPI in clinical trials, needs to consider two main aspects, namely, eradication rates and adverse events (**Table 6**). As the predominant bacteria in human stomach, *Lactobacillus* has been widely studied [51-56]. A study by Zheng [51] broadly examined the efficacy of eradication regimens supplemented with *Lactobacillus*-containing probiotic in a meta-analysis that contained nine randomized, controlled trials. *Lactobacillus*-containing probiotic supplementation potentially elevated *H. pylori* eradication rates by approximately 10%, although side effects were not reduced significantly. In the subgroup analysis, eradication rates significantly increased by 17% in the *Lactobacillus* alone-administered group (RR=1.25; 95% CI=1.13-1.37; NNT=6). *Lactobacillus*-containing probiotics also improved the eradication rates both in adults (RR=1.12; 95% CI=1.04-1.20; NNT=12) and in children (RR=1.25; 95% CI=1.01-1.53; NNT=7). Thus, *Lactobacillus*-containing probiotics were concluded to be effective as adjunct to eradication therapy, although side effects may not decrease. Furthermore, *Lactobacillus* administered alone could distinctly benefit eradication therapy.

L. acidophilus, a microaerophilic species, occurs naturally in the human gastrointestinal tract. Du [52] presented that administration of it could improve *H. pylori* eradication rate whether before or after triple therapy, however, symptom relieving rate has no significant change in probiotic group. In a randomized, controlled clinical research [53], a total of 229 patients were randomized into either 1-week triple therapy or triple therapy plus *L. gasseri*-containing yogurt. In the yogurt-plus-triple therapy groups, the yogurt containing *L. gasseri* OLL2716 was given twice daily for 4 weeks (3 weeks pretreatment and 1 week during eradication therapy). Overall, the eradication rate (ITT/PP) was 69.3/74.5% for the triple-only group, and 82.6/85.6% for the yogurt-plus-triple group (P=0.018/P=0.041). Eradication of primary clarithromycin-resistant strains tended to be higher for the yogurt-plus-triple therapy than the triple-only therapy (38.5 vs. 28.0%, P=0.458). Unfortunately, with respect to the report of adverse reacts were not involved in this research.

Ojetti V [54] found that in *H. pylori*-positive subjects, *L. reuteri* ATCC 55730 supplementation increased the eradication rate while reducing the incidence of the most common side effects associated with antibiotic therapy in a second-line treatment. Recently, the role of a new probiotic preparation (a mixture of *L. reuteri* DSM 17938 and *L. reuteri* ATCCPTA 6475) in *H. pylori* infection was studied by some scholars. Emara MH [55] demonstrated that triple therapy of *H. pylori* supplemented with *L. reuteri* combination increased the eradication rate by 8.6%, improved the GSRS score, reduced the reported side effects, and improved the histological features of *H. pylori* infection as compared with the placebo-supplemented triple therapy. The research of Francavilla R [56] is similar to that of Emara MH, although the former introduced more indexes to assess the influences of *L. reuteri* combination in *H. pylori* infection. In the study, the two groups, both with fifty patients, received *L. reuteri* combination and placebo once daily, respectively. Significantly fewer patients reported side effects in the *L. reuteri* combination as compared with the placebo (40.9% *vs.* 62.8%; P<0.04). Eradication rate was 75% in the *L. reuteri* combination and 65.9% in placebo, such that *L. reuteri* combination increased eradication rate by 9.1% (OR: 1.5). Thus, *L. reuteri* combination, when administered with eradication therapy, a significant reduction in antibiotic-associated side effects and (not significantly) increase of *H. pylori* eradication rate was shown.

S. boulardii, a yeast strain, has been deemed to have a therapeutic potential for many gastrointestinal and extra-intestinal diseases in recent years [57]. Szajewska conducted two systematic reviews with *S. boulardii* as research subject, in 2010 and 2015, respectively [11, 58]. The latest study covered 11 RCTs involving a total of 2200 participants, 330 of which were children. Of the 853 patients in the *S. boulardii* group, 679 (80%, 95% CI=77-82) experienced eradication compared with 608 of the 855 patients (71%; 95% CI=68-74) in the control group (RR=1.11; 95% CI=1.06-1.17). Compared

with the control, *S. boulardii* reduced the risk of overall *H. pylori* therapy-related adverse effects (RR=0.44; 95% CI=0.31-0.64), particularly of diarrhea (RR=0.51; 95% CI=0.42-0.62) and nausea (RR=0.6; 95% CI=0.44-0.83). The addition of *S. boulardii* evidently improved the eradication rate and some of the therapy-related side effects, although it did not achieve the desired level of success [4].

Compared with *Lactobacillus* and *S. boulardii*, fewer studies have been done in recent years on single *Bifidobacterium spp.* as adjuvant therapy in *H. pylori* eradication.

B. infantis, a *Bifidobacterium* strain, inhabits the intestines of both infants and adult which considered beneficial resulting of acid production. Dajani AI [59] evaluated the effect of adding *B. infanti* as adjuvant to common regimens used for *H. pylori* eradication. The clinical study tested three different regimens of *H. pylori* eradication treatment: standard triple therapy with a probiotic added concomitantly (n=100), starting the probiotic for 2 weeks before initiating standard triple therapy along with the probiotic (n=95), and the probiotic given concomitantly to sequential treatment (n=76), and traditional standard triple therapy (n=106) as a control group. The eradication rate of each group was 83%, 90.5%, 90.8%, and 68.9%, respectively. *B. infantis* as an adjuvant to triple and sequential therapies was thus found to be capable of significantly improving the eradication rates.

In regard to the clinical trials of multi-strain probiotics are frequently occur in the literature either as a single use or as adjuvant therapy. In the study of Myllyluoma [60], a probiotic combination including *L. rhamnosus* GG, *L. rhamnosus* LC705, *P. Freudenreichii* JS, and *B. lactis* Bb12 presents the ability to decrease DOB value and exert a beneficial effect on gastric mucosa in *H. pylori* infected patients. *Bifidobacterium* and *Lactobacillus* are generally used together as research subjects, and many studies and meta-analyses demonstrate this combination can decrease *H. pylori* density as montherapy, in addition, effectively reduce eradication rate and incidence of total side effects as adjuvant therapy in children and adults [61-63]. However, not all mixtures were effective in eradicating *H. pylori* and preventing of adverse events, since the role of probiotics may depend on specific combinations [64]

Conclusion

So far, we have a comprehensive understanding of probiotics by numerous in vitro studies, animal model, and human trials. Probiotics may inhibit the infection of *H. pylori* through immunomodulation, producing antimicrobial substances, interfering with adhesion, and enhancing the function of the mucosal barrier. In the treatment of *H. pylori*, probiotics have shown diverse effects depending on certain strains. While *L. paracasei* ST11 has no effect on *H. pylori*, like *L. johnsonii* La1, *L. acidophilus* LB, *L. gasseri* OLL2716, *L. reuteri* ATCC, and *B. bifidum* BF-1 as a montherapy, are capable of diminishing the bacterial load, not eradicating *H. pylori* in adults and children. *L. acidophilus*, *L. gasseri* OLL2716 and *B. infantis,* when combined with antibiotic-PPI as adjuvant therapy, can improve the eradication rate, but not obviously influence the adverse symptoms. *L. reuteri* and *S. boulardii* have the ability to increase eradication rate and reduce adverse effects, however, the eradication rate shows no significant decrease in the mixture of *L. reuteri* strains. Effects of multi-strain probiotics on the treatment depend on specific combination, and not all of them were valid in eradicating *H. pylori.*

Although extensive studies indicates probiotics plays an important role in the *H. pylori* infection, still many uncertain problems are needs to be considered in the clinical application of probiotics, such as the choice of probiotic, safety of certain strain, intake frequency, intake dose, and the time of adding probiotics to the eradication therapy. Moreover, if probiotics are used in combination with antibiotic-PPI, the extra cost may be a limiting factor to its use. Some scholars claim that probiotics are economical as a treatment method; however, more evidence is needed to support this statement. In the past, many researchers have deliberated whether probiotics are effective for the treatment of *H. pylori* infection. Based on unremitting efforts, we are now able to draw preliminary conclusions that certain probiotics are in fact capable of effectively contributing to *H. pylori* eradication in treatments. A discussion

should now be opened on how to use probiotics to their best advantage in preparation for the upcoming era of probiotics.

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Disclosure of conflict of interest

None.

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References

[1] McColl KE. Clinical practice. Helicobacter pylori infection. N Engl J Med 2010; 362: 1597-604.

[2] Eusebi LH, Zagari RM, Bazzoli F. Epidemiology of Helicobacter pylori infection. Helicobacter 2014; 19 Suppl 1: 1-5.

[3] Backert S, Neddermann M, Maubach G, Naumann M. Pathogenesis of Helicobacter pylori infection. Helicobacter 2016; 21 Suppl 1: 19-25.

[4] Malfertheiner P, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M, Selgrad M, Suerbaum S, Sugano K, El-Omar EM; European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection-the Maastricht V/Florence Consensus Report. Gut 2017; 6: 6-30.

[5] Graham DY, Fischbach L. Helicobacter pylori treatment in the era of increasing antibiotic resistance. Gut 2010; 59: 1143-53.

[6] Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, Calder PC, Sanders ME. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 2014; 11: 506-14.

[7] Homan M, Orel R. Are probiotics useful in Helicobacter pylori eradication? World J Gastroenterol 2015; 21: 10644-53.

[8] Sánchez B, Delgado S, Blanco-Míguez A, Lourenço A, Gueimonde M, Margolles A. Probiotics, gut microbiota and their influence on host health and disease. Mol Nutr Food Res 2016; [Epub ahead of print].

[9] Boltin D. Probiotics in Helicobacter pylori-induced peptic ulcer disease. Best Pract Res Clin Gastroenterol 2016; 30: 99-109.

[10] Sheu BS, Cheng HC, Kao AW, Wang ST, Yang YJ, Yang HB, Wu JJ. Pretreatment with Lactobacillus- and Bifidobacterium-containing yogurt can improve the efficacy of quadruple therapy in eradicating residual Helicobacter pylori infection after failed triple therapy. Am J Clin Nutr 2006; 83: 864-9.

[11] Szajewska H, Horvath A, Piwowarczyk A. Meta-analysis: the effects of Saccharomyces boulardii supplementation on Helicobacter pylori eradication rates and side effects during treatment. Aliment Pharmacol Ther 2010; 32: 1069-79.

[12] Ianiro G, Molina-Infante J, Gasbarrini A. Gastric Microbiota. Helicobacter 2015; 20 Suppl 1: 68-71.

[13] Bik EM, Eckburg PB, Gill SR, Nelson KE, Purdom EA, Francois F, Perez-Perez G, Blaser MJ, Relman DA. Molecular analysis of the bacterial microbiota in the human stomach. Proc Natl Acad Sci U S A 2006; 103: 732-7.

[14] Aviles-Jimenez F, Vazquez-Jimenez F, Medrano-Guzman R, Mantilla A, Torres J. Stomach microbiota composition varies between patients with non-atrophic gastritis and patients with intestinal type of gastric cancer. Sci Rep 2014; 4: 4202.

[15] Abreu MT, Peek RM Jr. Gastrointestinal malignancy and the microbiome. Gastroenterology 2014; 146: 1534-1546.

[16] Andersson AF, Lindberg M, Jakobsson H, Bäckhed F, Nyrén P, Engstrand L. Comparative analysis of human gut microbiota by barcoded pyrosequencing. PLoS One 2008; 3: e2836.

[17] Maldonado-Contreras A, Goldfarb KC, Godoy-Vitorino F, Karaoz U, Contreras M, Blaser MJ, Brodie EL, Dominguez-Bello MG. Structure of the human gastric bacterial community in relation to Helicobacter pylori status. ISME J 2011; 5: 574-9.

[18] Eun CS, Kim BK, Han DS, Kim SY, Kim KM, Choi BY, Song KS, Kim YS, Kim JF. Differences in gastric mucosal microbiota profiling in patients with chronic gastritis, intestinal metaplasia, and gastric cancer using pyrosequencing methods. Helicobacter 2014; 19: 407-16.

[19] De Flora S, Bonanni P. The prevention of infection-associated cancers. Carcinogenesis 2011; 32: 787-795.

[20] Cadamuro AC, Rossi AF, Maniezzo NM, Silva AE. Helicobacter pylori infection: Host immune response, implications on gene expression

and microRNAs. World J Gastroenterol 2014; 20: 1424-1437.
[21] Fox JG, Wang TC. Inflammation, atrophy, and gastric cancer. J Clin Invest 2007; 117: 60-9.
[22] Razavi A, Bagheri N, Azadegan-Dehkordi F, Shirzad M, Rahimian G, Rafieian-Kopaei M, Shirzad H. Comparative Immune Response in Children and Adults with H. pylori Infection J Immunol Res 2015; 2015: 315957.
[23] Zhou C, Ma FZ, Deng XJ, Yuan H, Ma HS. Lactobacilli inhibit interleukin-8 production induced by Helicobacter pylori lipopolysaccharide-activated Toll-like receptor 4. World J Gastroenterol 2008; 14: 5090-5.
[24] Yang YJ, Chuang CC, Yang HB, Lu CC, Sheu BS. Lactobacillus acidophilus ameliorates H. pylori-induced gastric inflammation by inactivating the Smad7 and NFκB pathways. BMC Microbiol 2012; 12: 38.
[25] Sunanliganon C, Thong-Ngam D, Tumwasorn S, Klaikeaw N. Lactobacillus plantarum B7 inhibits Helicobacter pylori growth and attenuates gastric inflammation. World J Gastroenterol 2012; 18: 2472-80.
[26] Yu HJ, Liu W, Chang Z, Shen H, He LJ, Wang SS, Liu L, Jiang YY, Xu GT, An MM, Zhang JD. Probiotic BIFICO cocktail ameliorates Helicobacter pylori induced gastritis. World J Gastroenterol 2015; 21: 6561-71.
[27] Gotteland M, Brunser O, Cruchet S. Systematic review: are probiotics useful in controlling gastric colonization by Helicobacter pylori? Aliment Pharmacol Ther 2006; 23: 1077-86.
[28] Bhatia SJ, Kochar N, Abraham P, Nair NG, Mehta AP. Lactobacillus acidophilus inhibits growth of Campylobacter pylori in vitro. J Clin Microbiol 1989; 27: 2328-30.
[29] Lesbros-Pantoflickova D, Corthésy-Theulaz I, Blum AL. Helicobacter pylori and probiotics. J Nutr 2007; 137 Suppl 2: 812S-8S.
[30] 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: 2097-101.
[31] Sgouras D, Maragkoudakis P, Petraki K, Martinez-Gonzalez B, Eriotou E, Michopoulos S, Kalantzopoulos G, Tsakalidou E, Mentis A. In vitro and in vivo inhibition of Helicobacter pylori by Lactobacillus casei strain Shirota. Appl Environ Microbiol 2004; 70: 518-26.
[32] Hsieh PS, Tsai YC, Chen YC, Teh SF, Ou CM, King VA. Eradication of Helicobacter pylori infection by the probioticstrains Lactobacillus johnsonii MH-68 and L. salivariusssp. salicinius AP-32. Helicobacter 2012; 17: 466-77.
[33] Pessione E. Lactic acid bacteria contribution to gut microbiota complexity: lightsand shadows. Front Cell Infect Microbiol 2012; 2: 86.
[34] Francavilla R, Lionetti E, Castellaneta SP, Magistà AM, Maurogiovanni G, Bucci N, De Canio A, Indrio F, Cavallo L, Ierardi E, Miniello VL. Inhibition of Helicobacter pylori infection in humans by Lactobacillus reuteri ATCC 55730 and effect on eradication therapy: a pilot study. Helicobacter 2008; 13: 127-34.
[35] Lorca GL, Wadström T, Valdez GF, Ljungh A. Lactobacillus acidophilus autolysins inhibit Helicobacter pylori in vitro. Curr Microbiol 2001; 42: 39-44.
[36] Nam H, Ha M, Bae O, Lee Y. Effect of Weissella confusa strain PL9001 on the adherence and growth of Helicobacter pylori. Appl Environ Microbiol 2002; 68: 4642-5.
[37] Mukai T, Asasaka T, Sato E, Mori K, Matsumoto M, Ohori H. Inhibition of binding of Helicobacter pylori to the glycolipid receptors by probiotic Lactobacillus reuteri. FEMS Immunol Med Microbiol 2002; 32: 105-10.
[38] Hirmo S, Kelm S, Schauer R, Nilsson B, Wadström T. Adhesion of Helicobacter pylori strains to α-2,3-linked sialic acids. Glycoconj J 1996; 13: 1005-11.
[39] Sakarya S, Gunay N. Saccharomyces boulardii expresses neuraminidase activity selective for α-2,3-linked sialic acid that decreases Helicobacter pylori adhesion to host cells. APMIS 2014; 122: 941-50.
[40] Pantoflickova D, Corthesy-Theulaz I, Dorta G, Stolte M, Isler P, Rochat F, Enslen M, Blum AL. Favourable effect of regular intake of fermented milk containing Lactobacillus johnsonii on Helicobacter pylori associated gastritis. Aliment Pharmacol Ther 2003; 18: 805-813.
[41] Celli JP, Turner BS, Afdhal NH, Keates S, Ghiran I, Kelly CP, Ewoldt RH, McKinley GH, So P, Erramilli S, Bansil R. Helicobacter pylori moves through mucus by reducing mucin viscoelasticity. Proc Natl Acad Sci U S A 2009; 106: 14321-6
[42] Niv Y. Helicobacter pylori and gastric mucin expression: A systematic review and meta-analysis. World J Gastroenterol 2015; 21: 9430-6.
[43] 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: 827-33.
[44] Gomi A, Harima-Mizusawa N, Shibahara-Sone H, Kano M, Miyazaki K, Ishikawa F. Effect of Bifidobacterium bifidum BF-1 on gastric protection and mucin production in an acute gastric injury rat model. J Dairy Sci 2013; 96: 832-7.
[45] Cruchet S, Obregon MC, Salazar G, Diaz E, Gotteland M. Effect of the ingestion of a dietary product containing Lactobacillus johnsonii La1 on Helicobacter pylori colonization in children. Nutrition 2003; 19: 716-21.

[46] Gotteland M, Poliak L, Cruchet S, Brunser O. Effect of regular ingestion of Saccharomyces boulardii plus inulin or Lactobacillus acidophilus LB in children colonized by Helicobacter pylori. Acta Paediatr 2005; 94: 1747-51.

[47] Boonyaritichaikij S, Kuwabara K, Nagano J, Kobayashi K, Koga Y. Long-term administration of probiotics to asymptomatic pre-school children for either the eradication or the prevention of Helicobacter pylori infection. Helicobacter 2009; 14: 202-7.

[48] Gotteland M, Cruchet S. Suppressive effect of frequent ingestion of Lactobacillus johnsonii La1 on Helicobacter pylori colonization in asymptomatic volunteers. J Antimicrob Chemother 2003; 51: 1317-9.

[49] Sakamoto I, Igarashi M, Kimura K, Takagi A, Miwa T, Koga Y. Suppressive effect of Lactobacillus gasseri OLL 2716 (LG21) on Helicobacter pylori infection in humans. J Antimicrob Chemother 2001; 47: 709-10.

[50] Miki K, Urita Y, Ishikawa F, Iino T, Shibahara-Sone H, Akahoshi R, Mizusawa S, Nose A, Nozaki D, Hirano K, Nonaka C, Yokokura T. Effect of Bifidobacterium bifidum fermented milk on Helicobacter pylori and serum pepsinogen levels in humans. J Dairy Sci 2007; 90: 2630-40.

[51] Zheng X, Lyu L, Mei Z. Lactobacillus-containing probiotic supplementation increases Helicobacter pylori eradication rate: evidence from a meta-analysis. Rev Esp Enferm Dig 2013; 105: 445-53.

[52] Du YQ, Su T, Fan JG, Lu YX, Zheng P, Li XH, Guo CY, Xu P, Gong YF, Li ZS. Adjuvant probiotics improve the eradication effect of triple therapy for Helicobacter pylori infection. World J Gastroenterol 2012; 18: 6302-7.

[53] Deguchi R, Nakaminami H, Rimbara E, Noguchi N, Sasatsu M, Suzuki T, Matsushima M, Koike J, Igarashi M, Ozawa H, Fukuda R, Takagi A. Effect of pretreatment with Lactobacillus gasseri OLL2716 on first-line Helicobacter pylori eradication therapy. J Gastroenterol Hepatol 2012; 27: 888-92.

[54] Ojetti V, Bruno G, Ainora ME, Gigante G, Rizzo G, Roccarina D, Gasbarrini A. Impact of Lactobacillus reuteri Supplementation on Anti-Helicobacter pylori Levofloxacin-Based Second-Line Therapy. Gastroenterol Res Pract 2012; 2012: 740381.

[55] Emara MH, Mohamed SY, Abdel-Aziz HR. Lactobacillus reuteri in management of Helicobacter pylori infection in dyspeptic patients: a double-blind placebo-controlled randomized clinical trial. Therap Adv Gastroenterol 2014; 7: 4-13.

[56] Francavilla R, Polimeno L, Demichina A, Maurogiovanni G, Principi B, Scaccianoce G, Ierardi E, Russo F, Riezzo G, Di Leo A, Cavallo L, Francavilla A, Versalovic J. Lactobacillus reuteri strain combination in Helicobacter pylori infection: a randomized, double-blind, placebo-controlled study. J Clin Gastroenterol 2014; 48: 407-13.

[57] Ianiro G, Bruno G, Lopetuso L, Beghella FB, Laterza L, D'Aversa F, Gigante G, Cammarota G, Gasbarrini A. Role of yeasts in healthy and impaired gut microbiota: the gut mycome. Curr Pharm Des 2014; 20: 4565-9.

[58] Szajewska H, Horvath A, Kołodziej M. Systematic review with meta-analysis: Saccharomyces boulardii supplementation and eradication of Helicobacter pylori infection. Aliment Pharmacol Ther 2015; 41: 1237-45.

[59] Dajani AI, Abu Hammour AM, Yang DH, Chung PC, Nounou MA, Yuan KY, Zakaria MA, Schi HS. Do probiotics improve eradication response to Helicobacter pylori on standard triple or sequential therapy? Saudi J Gastroenterol 2013; 19: 113-120.

[60] Myllyluoma E, Kajander K, Mikkola H, Kyrönpalo S, Rasmussen M, Kankuri E, Sipponen P, Vapaatalo H, Korpela R. Probiotic intervention decreases serum gastrin-17 in Helicobacter pylori infection. Dig Liver Dis 2007; 39: 516-23.

[61] Wang KY, Li SN, Liu CS, Perng DS, Su YC, Wu DC, Jan CM, Lai CH, Wang TN, Wang WM. Effects of ingesting Lactobacillus- and Bifidobacterium-containing yogurt in subjects with colonized Helicobacter pylori. Am J Clin Nutr 2004; 80: 737-41.

[62] Wang YH, Huang Y. Effect of Lactobacillus acidophilus and Bifidobacterium bifidum supplementation to standard triple therapy on Helicobacter pylori eradication and dynamic changes in intestinal flora. World J Microbiol Biotechnol 2014; 30: 847-53.

[63] Wang ZH, Gao QY, Fang JY. Meta-analysis of the efficacy and safety of Lactobacillus-containing and Bifidobacterium-containing probiotic compound preparation in Helicobacter pylori eradication therapy. J Clin Gastroenterol 2013; 47: 25-32

[64] 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: 546-561.