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MINI-REVIEW

Probiotic therapy in *Helicobacter pylori* infection: a potential strategy against a serious pathogen?

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Abstract

Helicobacter pylori is a highly prevalent human pathogen responsible for chronic inflammation of the gastric tissues, gastroduodenal ulcers, and cancer. The treatment includes a pair of antibiotics with a proton pump inhibitor PPI. Despite the presence of different treatments, the infection rate is still increasing both in developed and developing states. The challenge of treatment failure is greatly due to the resistance of *H. pylori* to antibiotics and its side effects. Probiotics potential to cure *H. pylori* infection is well-documented. Probiotics combined with conventional treatment regime appear to have great potential in eradicating *H. pylori* infection, therefore, provide an excellent alternative approach to manage *H. pylori* load and its threatening disease outcome. Notably, anti-*H. pylori* activity of probiotics is strain specific,therefore establishing standard guidelines regarding the dose and formulation of individual strain is inevitable. This review is focused on probiotic's antagonism against *H. pylori* summarizing their three main potential aspects: their efficiency (i) as an alternative to *H. pylori* eradication treatment, (ii) as an adjunct to *H. pylori* eradication treatment and (iii) as a vaccine delivery vehicle.

Keywords Antibiotic resistance · Side effects · Alternate therapy · Probiotics mechanism of action · *Helicobacter pylori* · Chronic infection · *Lactococcus lactis* · Vaccine

Introduction

H. pylori resides in more than half of the population on earth (Dunne et al. 2014). They are highly pathogenic when bound to gastric epithelial cells (Hessey et al. 1990). They are Gram negative, helical, flagellated, and microaerophillic organisms, known to cause chronic gastritis, which if uncured eventually may result in duodenal ulcer and gastric cancer (Dunne et al. 2014). *H. pylori* infections have increased prevalence in developing states (Moayyedi and Hunt 2004). High prevalence about 80% or more have been documented in parts of China and some South American and Eastern European states (Roberts et al. 2016; Graham et al. 1991). *H. pylori* has been grouped under class I carcinogen by International Agency for Research on Cancer (Covacci et al. 1999). It is the only bacterium linked with gastric malignancy (IARC 1994), estimated to be the cause of 60% of gastric cancer cases (Parkin 2006). Other than gastric diseases, *H. pylori* is also associated with MALT (mucosa-associated lymphoid tissue lymphoma), vitamin B1 deficiency, iron deficiency, and idiopathic thrombocytopenic purpura (Kuipers 1997). For the prevention of *H. pylori*-associated complications, inhibition of infection is pivotal. Combinations of several treatments are available; triple therapy, including antibiotics and a proton pump inhibitor, is widely used (Toracchio et al. 2000). Increasing incidence of resistant *H. pylori* strains to antibiotics including clarithromycin and metronidazole reduces the effectiveness of triple therapy (Graham 1998). The resistance of *H. pylori* strains differs worldwide, varying from 10 to 90% for metronidazole and 0 to 15% for clarithromycin (Toracchio et al. 2000). Moreover, the adverse effects of antibiotics such as diarrhea, nausea, and vomiting and expensive nature of the treatment have led to the reduced compliance rate of the patients. *H. pylori* infection in childhood may persist through life if not treated (Mcnulty et al. 2012; Arslan et al. 2017). Despite the fact that most infected individuals

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remain asymptomatic, its eradication is important as it may cause chronic gastritis, dyspepsia, and gastroduodenal ulcers (Smith et al. 2014). Considering the declining efficacy of triple therapy due to increasing resistance of *H. pylori* to antibiotics, adverse effect of the antibiotics, patients' non-compliance, and cost of the treatment regime, search for a better and safe alternative approach is critically needed. Probiotics have been extensively explored as an adjunct to antibiotics treatment for *H. pylori* infection (Patel et al. 2014). Different studies have described the therapeutic potential of probiotics to effectively cure several gastric diseases (Goderska et al. 2018; Behnsen et al. 2013; Sarowska et al. 2013).

Probiotics are defined as "living micro-organisms which provide beneficial effect on the host's health when administered in adequate amount" (Ruggiero 2014). There are many microbial species that could potentially function as probiotics, like *Lactobacillus*, *Bifidobacteria*, *Saccharomyces*, *Streptococcus* etc., of which *Lactobacillus* and *Bifidobacteria* are the most commonly studied. Probiotics stabilize the intestinal microflora by inhibiting pathogens, which is mostly attributed to their competitiveness for food and binding sites (Denev 2006), production of antimicrobial substances, and immunomodulation (Isolauri et al. 2001). Beside antagonistic properties of probiotics, their abilities to survive high pH and bile salts and to colonize gastrointestinal surfaces are critical to assign them among the most promising and potential probiotic candidates. These properties have attracted researchers' interest to investigate new strains and gain insight into their beneficial properties (Holzapfel et al. 2001). Numerous studies related to the antagonistic activity of probiotics against *H. pylori* have shown promising results in reducing antibiotic side effects, improving eradication of *H. pylori* infection and reducing cell injury (Lesbros-Pantoflickova et al. 2007; Wilhelm et al. 2011; Patel et al. 2014). Despite the fact that every probiotic strain is not beneficial to improve *H. pylori* eradication treatment, several probiotics appear to mitigate the disease and side effects of the treatment. In an assessment study of *H. pylori* infection after its eradication by conventional therapy in children, 30% of the children were found to be re-infected after 2 years (Magistà et al. 2005); considering this, use of probiotics as an eradication adjunct or as a vaccine delivery tool would be very useful. In the previous literatures, potential of probiotics against *H. pylori* in in vitro, in vivo, and clinical trials has been described without providing much knowledge about their potential as an effective vaccine delivery vehicle. In this review, we have highlighted all the potentialities of probiotics against *H. pylori* from their mechanism of action, preclinical and clinical journey to their use in vaccines with successful examples. Limitations in the above mentioned potentials and suggestions for the future studies have been summarized as well.

Helicobacter pylori: pathogenesis

All *H. pylori*-infected individuals are not likely to develop peptic ulcers. *H. pylori* colonize the stomach for years and cause continuous infection, but only minority show symptoms. Right after *H. pylori* colonization to the epithelial tissues of the stomach, the activation of the host's innate and adaptive immune response takes place (Cadamuro et al. 2014). Prolonged existence of chronic inflammation by *H. pylori* may advance to atrophic gastritis, dysplasia, metaplasia, and ultimately gastric carcinoma (Fox and Wang 2007). Studies have shown that genotypic and phenotypic variance in *H. pylori* strains is mainly responsible for different clinical outcomes (Blaser and Berg 2002). *H. pylori* colonization and the successful onset of pathogenesis usually take place in steps, such as survival in low pH, movement towards epithelium mediated by flagella, strong interaction with host cell receptors, and release of several toxins (Kao et al. 2016). Primarily, the infection is developed upon *H. pylori*'s adhesion to the gastric mucosa. The persistent colonization which results in chronic inflammation is facilated by different virulence factors such as the production of urease enzyme and presence of flagella. Urease helps *H. pylori* survival in the low pH of the stomach by generating ammonia (Eaton et al. 1991; Marshall et al. 1990). Urease is composed of four subunits, UreA, UreB, UreC, and UreD. UreB is the strongest immunogen of *H. pylori* (Corthesy-Theulaz et al. 1995) which has been studied widely in the development of anti-*H. pylori* vaccine (Gu et al. 2009; Zeng et al. 2015). *H. pylori* adheres and colonizes the host's epithelial cells by using a number of adhesins including BabA, SabA, HopZ (Odenbreit et al. 2002), AlpA/B (Peck et al. 1999), urease etc. BabA and SabA bind to fucosylated and sialylated blood group antigens. Studies have shown SabA-mediated activation of neutrophils (Unemo et al. 2005). Neutrophils upon activation, either by *H. pylori* soluble factors or as a result of inflammation, further produce ROS which cause epithelial cell DNA damage leading to apoptosis (Bagchi et al. 1996). Urease as an adhesin attaches to MHC class II and CD74 on antigen presenting cells which induce apoptosis of the epithelial cells and stimulate secrection of IL-8 (Fan et al. 2000; Barrera et al. 2005). Thus, attachment of *H. pylori* to the gastric mucosal layer induces inflammation resulting in the mucosal surface injury due to the release of different cytokines and chemokines (Engstrand et al. 1989; Peek Jr et al. 1995). Production of urease enzyme and flagellated structure of *H. pylori* are important virulent factors for successful colonization, which is present in almost all strains. As mentioned above, not all infected individuals develop an ulcer or other complications of *H. pylori*, which is due to variation in virulence of different *H. pylori* strains. Among different virulence factors VacA and CagA, toxin genes are the main virulence factors expressed in specific *H. pylori* strains. CagA is a part of pathogenecity

island (CagPAI). Some of the CagA genes code for T4SS (type IV secretory system) which plays an important role in injecting bacterial components into the host's epithelium leading to the stimulation of macrophages which further triggers the production of IL-8 and INF-γ ultimately disrupt the epithlial barrier (Boonyanugomol et al. 2011). These changes further cause epithelial damage leading to tumor formation. Several studies reported *H. pylori*-mediated over-expression of IL-8 in the host to be significantly linked with stomach cancer (Lee et al. 2013; Macrì et al. 2006). It has been observed that individuals with CagA+ *H. pylori* infection more often develop severe gastric disease and cancer (Kusters et al. 2006). VacA or vacuolating toxins form vacuoles in the host' s epithelial cells and cause disruption in membrane potential. Mitochondrial membrane potential is also disrupted leading to apoptosis (Cover et al. 2003). VacA alter antigen presentation by B cells and inhibit T cell proliferation making it an important virulence factor to establish chronic infection (Cover and Blanke 2005). VacA is present in all *H. pylori* strains, but its pathogenecity depends on it genotypes (Winter et al. 2014). Despite the stimulation of *H. pylori*-mediated immune response, the infection persists which is mainly associated with its potential to evade host's inflammatory response. *H. pylori* avoids TLRs (toll-like receptors) mediated recognition by modulating its LPS and flagellin surface proteins (Cullen et al. 2011). O-antigen on the bacterial outer polysachharide resembles human blood group antigens. This molecular mimicry of *H. pylori* protects it from recognized by the TRLs. Modification of lipid A portion of LPS alters the net charge of its surface resulting in inability of CAMP (cationic antimicrobial peptide) to bind to its surface (Cullen et al. 2011). Besides modulation of LPS, *H. pylori*'s LPS loosely binds to its host's receptor which results in reduced activation of immune cells (Sutton and Chionh 2013). Different studies have also suggested that CagA and VacA virulence genes protect *H. pylori* from phagocytic cells (Ramarao et al. 2000; Zheng and Jones 2003). *H. pylori* also stimulates expansion of regulatory T cell (Treg) which downregulate inflammatory response by actively modulating the differentiation of dendritic cells and T cells (Beswick et al. 2007; Lundgren et al. 2003) (Fig. 1).

How probiotics work against *H. pylori*

Several experimental studies have been able to propose various possible probiotic's antagonistic effect on *H. pylori*, though the precise mechanisms have yet to be uncovered. Probiotic's abilities to compete for binding receptors, modulate immunity, strengthen the mucosal barrier, and co-

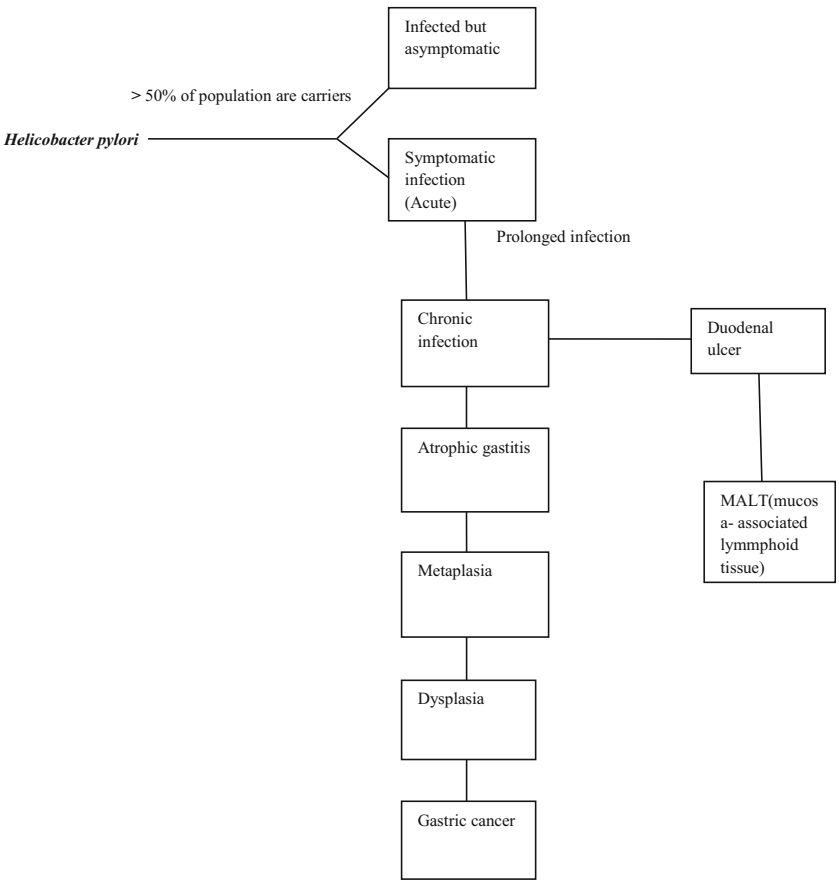

Fig. 1 Overview of possible complications of *H. pylori* infection

aggregate the pathogens are generally attributable to their effectiveness against various pathogens.

The mucosal barrier

The epithelium lining the gastrointestinal mucosa acts as a powerful barrier for the pathogens. Intestinal epithelial cells being the primary cell type to encounter the invading pathogens provide the first line of defense against harmful organisms. Upon invasion of pathogens, epithelial cells initiate an innate immune response which stimulates the secretion of chemokines and cytokines that connect the innate and adaptive immune response. Additionally, epithelial cells also produce mucus layer, which further provides protection to the mucosal surfaces from pathogens. Disruption of the mucosal barrier leads to different disease conditions. Probiotics can positively affect the epithelial barrier function which is strain specific (Seth et al. 2008; Karczewski et al. 2010). *H. pylori* damages the gastric mucosa using its virulence factors, like CagA and VacA (Backert et al. 2016). In cases of gastritis caused by *H. pylori*, decreased mucus secretion in a damaged epithelium has been observed (Lesbros-Pantoflickova et al. 2007). Moreover, in a study with human gastric cell line, *H. pylori* suppressed MUCI and MUC5A gene expression (Byrd et al. 2000) and caused disruption of the mucosal barrier, as mucins being high molecular weight glycoproteins are useful for gastric epithelium stability.

Probiotics protect the mucosal barrier from damage by different mechanisms including modification of the expression of mucus and epithelial junction proteins and releasing bioactive molecules to stabilize the barrier, thus preventing its disruption by the pathogens. Different studies demonstrated the increased production of IgA by probiotic strains, which is helpful in strengthening the mucosal barrier against pathogen invasion (Perdigón et al. 2000; Viljanen et al. 2005). As seen in in vitro studies, *L.plantarum* strain 299v and *L.rhamnosus* GG enhance the MUC2 and MUC3 gene expression providing strength to the mucus barrier (Mack et al. 1999). Another study on *H. pylori* gastritis proves increased thickness of mucus layer upon intake of *L. johnsonii* in fermented milk (Pantoflickova et al. 2003). Bergonzelli et al. (2006) reported an efficient binding of recombinant GroEL from *Lactobacillus johnsonii* LA1 to the HT29 cells and hypothsized its potential in pathogens' exclusion.

Competition for adhesion

H. pylori binds to the gastric epithelium in order to colonize and initiate infection. Probiotics ability to prevent *H. pylori* from binding to the epithelial cells usually brought about by different mechanisms such as competing for the adhesion sites or nutrients, causing steric hindrance and secreting antimicrobial substances. Several reports describe the adhesion of probiotics to the specific binding receptors, *L. reuteri* was found to compete for specific binding receptor site asialo-GMI and sulfatide and inhibit *H. pylori* adhesion (Mukai et al. 2002). Another study reports affinity of *S. boulardii* to sialic acid receptor followed by inhibition of *H. pylori* from binding (Sakarya and Gunay 2014). Some *Lactobacilli* strains such as *L. acidophilus* LB (Coconnier et al. 1998) and *L. johnsonii* La1 (Michetti et al. 1999) secrete antimicrobial substances to inhibit attachment of *H. pylori* to the epithelium. Competitive exclusion of *H. pylori* by potential probiotic strains is also evident by several in vitro studies with *L. acidophilus* LB (Coconnier et al. 1998), *L. johnsonii* (Michetti et al. 1999), *L. salivarius* (Kabir et al. 1997), and *W. confusa* (Nam et al. 2002). *W. confusa* strain PL9001 significantly inhibits *H. pylori* from binding to the gastric cell lines (Nam et al. 2002). Some studies provide evidence of reduced *H. pylori* colonization in germ-free mice which were previously colonized by probiotics (Kabir et al. 1997; Johnson-Henry et al. 2004). Anti-adhesion property of probiotics is one of the crucial mechanisms to counteract pathogens from invading the host. It would be interesting to investigate the underlying molecular mechanism of probiotics for their increased affinity towards the binding receptors.

Secretion of antimicrobials

H. pylori survival in the acidic environment of the stomach is mediated by urease production, which increases the pH of the gastric surrounding by converting urea into ammonia and CO_2. Probiotics secrete antimicrobials as a result of fermentation, such as lactic acid, acetic acid, and hydrogen peroxide (Vandenbergh 1993). Lactic acid secreted by probiotic lowers down the surrounding pH making it unfavorable for *H. pylori*'s growth (Aiba et al. 1998; Midolo et al. 1995; Sgouras et al. 2004). Besides lowering the pH, lactic acid was also found to have inhibitory activity against urease (Sgouras et al. 2004). A number of authors have reported the inhibitory action of lactic acid produced by *Lactobacilli* against *H. pylori*, for example, *L. casei* subsp. Rhamnosus and *L. acidophilus* (Midolo et al. 1995; Bhatia et al. 1989).

It is worth noting that not all lactic acid-producing *Lactobacilli* are capable of anti-*Helicobacter pylori* activity, as *L. johnsonii* La10, despite producing lactic acid, does not show inhibition of *H. pylori*, whereas *L. johnsonii* La1 does (Michetti et al. 1999). This also suggests that antagonistic activity of *Lactobacilli* against *H. pylori* is strain specific. Other antimicrobial products have also been reported to have antagonistic effect against *H. pylori*. Culture supernatant of *L. johnsonii* La1 (Michetti et al. 1999) and *L. acidophilus* LB (Coconnier et al. 1998) effectively inhibits *H. pylori* in in vitro as well as in mice. Lorca et al. (2001) described inhibition of *H. pylori*, mediated by autolysin of *L. acidophilus* CRL 639, and suggested that it released after cell lysis. Strong

inhibitory activity against *H. pylori* has been observed by lacticins A164 and BH5 of *L. lactis* subsp. A164 and BH5 (Kim et al. 2003). The exact nature of these antimicrobial substances has not been investigated. Bacteriocins are proteinaceous antimicrobial peptides which have been studied extensively (Cotter et al. 2013). Bacteriocin production by probiotics has been considered as one of their most essential properties (Dobson et al. 2011). Bacteriocin-mediated inhibition of *H. pylori* has been reported by *Bacillus subtilis* (Pinchuk et al. 2001) and *W. confusa* (Nam et al. 2002). Inhibition by *B. subtilis* was shown by animocumacins, grouped under isocoumarin antibiotics (Pinchuk et al. 2001). de Klerk et al. (2016) demonstrated direct action of *L. gasseri* Kx110A1 and *L. brevis* ATCC14869 conditioned medium on *H. pylori* and reported a reduction in SabA gene expression mediated by an unknown effector molecule. The authors suggested the effector molecule to be either an anti-microbial substance or a bacterial surface molecule released into the conditioned medium. Reuterin from *L. reuteri* ATCC 55730 reported to inhibit VacA gene expression of *H. pylori* (Urrutia-Baca et al. 2017).

SabA and VacA are important virulence factors of *H. pylori*, inhibition of their expression is critically important to regulate inflammation and prevent tumor formation.

Immunomodulation mechanism

H. pylori infection stimulates inflammation, and several inflammatory mediators like cytokines, chemokines etc. are released. Interleukin 8 (IL-8) triggers the secretion of neutrophils and monocytes to the gastric mucosal surfaces. Following this, the dendritic cells and monocytes activate the secretion of TNF-α, IL-1, and IL-6 (Noach et al. 1994). The stimulation of CD 4 + T cells (type 1) by IL-1 and IL-6 produces various cytokines such as IL-4, -5, -6, and IFN-γ (Harris et al. 1996); however, the *H. pylori* infection prevails. Immunomodulation is a well-known characteristic of probiotics. They interact with gastric epithelial cells and reduce the inflammation and gastric activity as a result of secretion of anti-inflammatory cytokines (Wiese et al. 2012). Experimental studies in mice reported a reduction in IgG immunoglobulins specific to *H. pylori* infection after probiotic intake (Aiba et al. 1998; Sgouras et al. 2004). The culture supernatant of *L. acidophilus* strain LB effectively reduces *H. felis* density, urease activity, and cures the inflammation in mice (Coconnier et al. 1998). *L. casei* strain Shirota decreased *H. pylori*-mediated inflammatory response in experimental mice (Sgouras et al. 2004). The strength of probiotics to weaken the *H. pylori* infection and inflammatory response varies from strain to strain. This can be exemplified in a study in which *L. salivarius* significantly reduced inflammation caused by *H. pylori* in gnotobiotic mice as compared to *L. acidophilus* or *L. casei* (Aiba et al. 1998). Lactic acid produced by probiotics has been shown to reduce inflammation by regulating inflammatory cytokines in several animal studies (Coconnier et al. 1998; Murosaki et al. 2000). CagA virulence gene of *H. pylori* has been strongly linked with increased gastric malignancy (Blaser and Berg 2002) which is suggested to be due to CagA-mediated enhanced IL-8 levels in the gastric mucosa (Peek Jr et al. 1995). Some probiotics *L. bulgaricus* (Zhou et al. 2008), *L. acidophilus* (Yang et al. 2012), and *L. salivarius* (Kabir et al. 1997) have been reported to down-regulate IL-8 secretion by *H. pylori*. This characteristic of some probiotic strains would open doors to discover new strategies to manage gastric cancers. Variations in immunomodulation process have been observed in different probiotic strains which may be due to polymorphism in the host's immunity (Noach et al. 1994), which is a complex process to extrapolate. Thus, it is evident from various animal studies that probiotics are significantly effective to reduce the degree of inflammation and outcome of *H. pylori* infection.

Co-aggregation and aggregation

Co-aggregation is the binding of organisms of diverse species, while aggregation or auto aggregation is the attachment of the organisms of similar species (Rickard et al. 2003; Schembri et al. 2001). Exclusion of pathogens binding to the intestinal mucosa as a result of aggregating property of probiotics has been described previously (Tareb et al. 2013). *L. reuteri* DSM17648 significantly co-aggregated with *H. pylori* in in vitro and in vivo studies (Holz et al. 2015). Similarly, *H. pylori* inhibition by *L. gasseri* occurred on account of co-aggregation in vitro (Chen et al. 2010). Studies also reported aggregation of *H. pylori* by *L. johnsonni* La1 (NCC533) recombinant GroEL protein receptor in a specific manner (Bergonzelli et al. 2006). Other probiotic strains are suggested to be investigated for this property.

It is crucial to identify the precise molecular mechanism underlying probiotics action on health and disease conditions. Once identified in vitro efficacy, their potential in physiological conditions is equally important **(**Fig. 2, Table 1**).**

Clinical studies

Numerous clinical studies have been documented to investigate the anti-*H. pylori* activity of probiotics and their potential to ameliorate the antibiotic-associated side effects. (Table 2, Table 3). Different clinical researches with probiotic strain *L. johnsonii* La1 have been described (Felley et al. 2001; Pantoflickova et al. 2003; Ojetti et al. 2012; Michetti et al. 1999). The strain was administered either as a live bacterium added in fermented milk or as a cell-free culture supernatant (Michetti et al. 1999). All results showed a significant

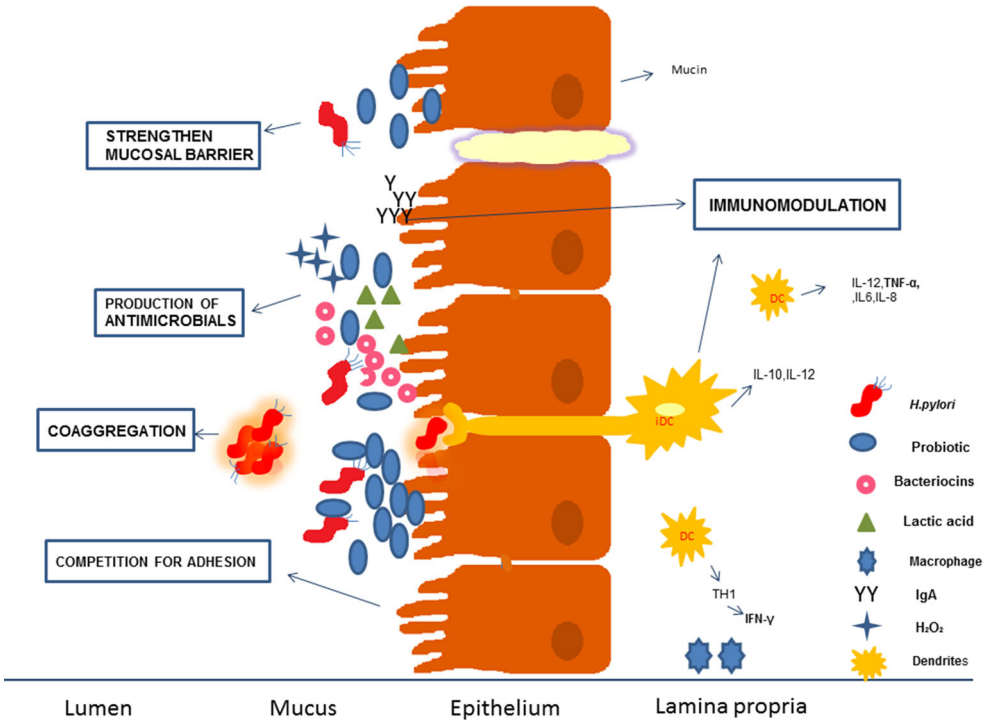

Fig. 2 Mechanisms of antagonism of probiotics against *H. pylori*

reduction in *H. pylori* density. *L. acidophilus* when administered as a cell-free culture supernatant showed anti-urease activity in asymptomatic individuals (Coconnier et al. 1998). In clinical studies, probiotics are generally examined either as an alternative or an adjunct to antibiotics.

Potential of probiotics as an alternative to antibiotics

A double-blind controlled clinical study including 252 asymptomatic children previously tested by C-urea breath test as *H. pylori* positive has been conducted (Cruchet et al. 2003). The children were arranged in groups and administered with live *L. johnsonii* La1, heat-killed *L. johnsonii* La1, live *L. paracsei* ST11, heat-killed *L. paracasei* ST11 daily for a month. At the end of the trial period, only children who received live *L. johnsonii* La1 showed a significant reduction in urease activity as compared to the other groups. Similarly, Wang et al. (2004) demonstrated a decrease in *H. pylori* colonization and gastritis in dyspeptic patients after ingestion of *L. acidophilus* La5 and *B. lactis* Bb12 containing yoghurt. Gotteland et al. (2005) investigated *L. acidophilus* or *S.boulardii* plus inulin effect on *H. pylori*-infected children and also compared the effect as an adjunct to standard triple therapy. Significant decrease in urease activity in inulin group was observed; however, *H. pylori* eradication rate with *L. acidophilus* and inulin group was not significant (6.5% and 12%, respectively) as compared to standard triple therapy (66%). Similarly, Francavilla et al. (2014) administered a daily dose of *L. reuteri* mixture and placebo to the groups of 50 patients each. *L. reuteri* group showed 75% eradication rate whereas 65% of placebo were eradicated. Few patients receiving *L. reuteri* mixture reported side effects as compared to placebo. Different probiotic strains *L. johnsonii* La1 (Gotteland and Cruchet 2003), *L. gasseri* OLL 2716 (Sakamoto et al. 2001), *L. reuteri* ATCC 55730 (Francavilla et al. 2008), and *B. bifidus* BF-1(Miki et al. 2007) as single therapy did not eradicate *H. pylori* in adults rather modulate its colonization. Different level of efficacy is due to different strains of probiotics tested. Further studies are required to address the efficacy of anti-*H. pylori* property of probiotics and evaluation of the specific immune mechanism involved in probiotics immunomodulation is suggested to provide scientific evidence for the clinical benefit of individual probiotic strain (Table 2).

Potential of probiotics as an adjunct to antibiotics

Studies on the effect of probiotics in alleviating the side effects of standard *H. pylori* treatment have been increasing, usually owing to their usefulness in increasing the patient's compliance rate (Goderska et al. 2018). Ojetti et al. (2012) investigated the effect of co-administration of *L. reuteri* ATCC 55730 with antibiotics on *H. pylori*-infected subjects, which significantly increased *H. pylori* eradication rate; additionally, the adverse effects of antibiotics were also reduced. In the same way, Myllyluoma et al. (2005) reported a significant reduction in *H. pylori* load and gastritis after treating the patients with a combination of probiotics as a complement

Table 1 Mechanisms of antagonism of probiotics against *H. pylori*

Probiotic strain	Experiment type	Mechanism of antagonism	Reference
W. confusa strain PL9001	(MKN-45) cells	Compete for binding sites/bacteriocin	Nam et al. (2002)
L. reuteri strains JCM 1081 and TM 105	In vitro	Compete for binding sites	Mukai et al. (2002)
S.boulardii	HuTo 80	Compete for binding sites	Sakarya and Gunay (2014)
L.acidophilus LB	In vitro inhibition (HT-29), Animal (mice)	Compete for binding sites	Coconnier et al. (1998)
L.johnsonii LA1	HT-29 cells	Compete for binding sites	Michetti et al. (1999)
L.salivarius	MKN45 cells and mice	Compete for binding sites	Kabir et al. (1997)
L.rhamnosus R0011 and *L. acidophilus* R0052	Mice (C57BL)	Compete for binding sites	Johnson-Henry et al. (2004)
L. salivarius	In vitro, animal (mice)	Lactic acid	Aiba et al. (1998)
L.acidophilus	In vitro inhibition assay	Lactic acid	Midolo et al. (1995)
L.casei Shirota	In vitro, animal (mice)	Lactic acid, anti-urease activity	Sgouras et al. (2004)
L.acidophilus	In vitro inhibition	Lactic acid	Bhatia et al. (1989)
L. acidophilus CRL 639	In vitro	Autolysin	Lorca et al. (2001)
*L.lactis*BH5	In vitro	Bacteriocin	Kim et al. (2003)
B.subtilis	In vitro	Antimicrobial substance (amicoumacin)	Pinchuk et al. (2001)
L. plantarum 299v and *L. rhamnosus* GG	(HT29)	Increase MUC2 and MUCA3 genes expression and extracelluar secretion of mucin by cell cultures	Mack et al. (1999)
L. johnsonii	Human subjects	Reduction in inflammation, increase mucus thickness	Pantoflickova et al. (2003)
L. johnsonii La1	In vitro (microscope)	Aggregation/adhesion	Bergonzelli et al. (2006)
L. bulgaricus	Cell (SGC-7901)	Decrease in IL-8 Expression	Zhou et al. (2008)
L. acidophilus	Cell (MKN45, AGS)	Decrease in IL-8 expression	Yang et al. (2012)
L.reuteri DSM17648	In vitro/in vivo	Co-aggregation	Holz et al. (2015)
L. rhamnosus GG and *L. gasseri* Chen	In vitro	Co-aggregation	Chen et al. (2010)
L.gasseri Kx110A1 and *L.brevis*ATCC 14869	Invitro, epithelial cell lines AGS (ATCC CRL-1739) and MKN45	Reduced SabA gene expression	de Klerk et al.(2016)
L. reuteri (ATCC 55730)	In vitro, bacteria kill assay, anti microbial activity assay, virulence gene expression assay	Inhibition of vacA gene expression	Urrutia-Baca et al. (2017)

Table 2 Clinical studies on the effect of probiotics as an alternative to *H. pylori* eradication treatment

Probiotic strain	Study design	Patients	Method	Result	Reference
L. acidophilus La1 or *L. paracasei* ST1(Live and Heat killed)	R, DB, PC	326 asymptomatic children	Fermented milk, 10^{10} CFU/day, 4 weeks	Eradication Ne, urease activity ↓ by live La1	Cruchet et al. (2003)
L. acidophilus La5 and *Bifidobacteriumlactis* Bb12	O, C	70 dyspeptic patients	Yoghurt, 10^{10} CFU/day, 4 weeks	ER Ne, urease activity ↓, gastritis and *H. pylori* colonization ↓	Wang et al. (2004)
L. acidophilus LB or *Saccharomyces boulardii* with inulin	O, R	254 asymptomatic children	Daily, LB 1×10^{10} CFU, *S. boulardii* 500 mg + 10 g inulin, 8 weeks	ER ↓, *S. boulardii* with inulin more effective compare to *L. acidophilus* LB	Gotteland et al. (2005)
L. reuteri DSM17938& *L.reuteri* ATCC PTA 6475	R, DB, PC	100 patients	Daily, 2×10^8 CFU 13 weeks	ER ↑, *urease activity* ↓,	Francavilla et al. (2014)
L. johnsonii La1	R, DB, PC	12 asymptomatic patients	Daily10^7 CFU, 2 weeks	ER ↑	Gotteland and Cruchet (2003)
L. gasseri OLL2716	PC	31 asymptomatic adults	Yoghurt, $1.8–2.5 \times 10^9$ CFU/day, 8 weeks	Serum pepsinogen I/II ratio ↑, serum pepsinogen s ↓, urease activity ↓	Sakamoto et al. (2001)
L. reuteri ATCC 55730	R, DB, PC	40 patients	Daily, 10^8 CFU 4 weeks	ER Ne,*urease activity* ↓,	Francavilla et al. (2008)
B. bifidum	R, DB, PC	79 individuals	Beverage BF-1, $10^7$12 weeks	ER ↑,urease activity ↓, PG I level ↓	Miki et al. (2007)

CFU colony forming units, *DB* double blind, *O* open, *PC* placebo controlled, *R* randomized, ↑ = increase, ↓ = decrease, *Ne* no effect, *ER* eradication rate

Table 3 Clinical studies on the effect of probiotic as an adjunct to *H. pylori* eradication treatment

Probiotics	Eradication therapy	Study design	Patients	Method	Result	Reference
L. reuteri	A + esomeprazole + levofl-oxacin 7 days	R	90 individuals	*L. reuteri* 10^8 CFU, 3 weeks	ER ↑ side effects ↓	Ojetti et al. (2012)
LGG + *L. rhamnosus* LC + *Propionibacterium. freudenreichii* + *B. breve*	CT + A + omeprazole	R, DBPC	118 individuals	Milk-based drink, 1×10^9 CFU/mL, twice a day for 4 weeks. followed by once a day for 6 weeks	ER Ne, urease activity ↓, gastritis and *H. pylori* colonization ↓	Myllyluoma et al. (2005)
L. acidophilus	Omeprazole + CT + A 7 days	O,R	234 gastritis patients	3×10^7 CFU, 2 weeks pretreatment OR 2 weeks post-treatment	ER↑ symptoms ↓	Du et al. (2012)
L.reuteri ATCC 55730	A + omeprazole 5 days followed by CT + omeprazole 5 days	DBPC, R	40 dyspeptic children	Capsule, 10^8 CFU, 20 days	ER Ne, side effects ↓	Lionetti et al. (2006)
L.rhamnosus GG	CT + tinidazole	O,R	60 asymptomatic adults	Lyophilized powder, 1.2×10^{10} CFU, 14 days	ER Ne, side effects ↓	Armuzzi et al. (2001)
*L. reuteri*DSM 17938 and *L.reuteri*ATCCPTA 6475	omeprazole + A + CT 14 days	DB,PC,R	70 *H. pylori*-positive, dyspeptic adults	10^8 CFU of all strains, 4 weeks	ER↑ side effects ↓	Emara et al. (2014)
B.animalis, *L. casei*	CT + A + omeprazole 7 days	R	64 children	250 mL yoghurt 10^7 CFU, 1 month	ER Ne	Goldman et al. (2006)
*L.casei rhamnosus*35	Different combinations of standard HP therapy scheme	O	112 patients	1.5×10^8 CFU,	ER Ne, side effects ↓	Uitz et al. (2017)
L.plantarum and *P. acidilactici*	C + A + PPIor C + A + M + PPI 10 days	DB,PC,R	209 patients	1×10^9 CFU, 10 days	ER Ne, side effets Ne	McNicholl et al. (2018)
B. animalis subsp.lactis	A + PPI (7 days) followed byM + C + PPI (7 days)	R,PC	159 patients	7×10^9 CFU, 2 weeks	ER↑, side effects↑	Çekin et al. (2017)

CFU colony forming units, *DB* double blind, *O* open, *PC* placebo controlled, *R* randomized, ↑ = increase, ↓ = decrease, *Ne* no effect, *ER* eradication rate, *CT* clarithromycin, *A* amoxycillin, *PPI* proton pump inhibitor, *M* metronidazole, *L* levofloxacin, *Om* omeprazole

to *H. pylori* treatment. A study by Du et al. (2012) demonstrated improvement in *H. pylori* eradication when *L. acidophilus* was used as a supplement to triple therapy; however, symptoms were not reduced with probiotic alone. No significant eradication was observed upon administration of *L. reuteri* ATCC 55730, though side effects were reduced to some extent (Lionetti et al. 2006). Similar results were observed in a study by Armuzzi et al. (2001) in which *L. rhamnosus* GG was supplemented as a complementary therapy. In view of the potential of probiotics against *H. pylori* infection, researchers have also examined the combination of different species of probiotics complementary to the triple therapy. In a double-blind placebo-controlled study, 66 *H. pylori*-infected children were administered combination of probiotics including *L. rhamnosus*, *L. acidophilus*, *L. bulgaricus*, *L. casei*, *S. thermophilus*, *B. breve*, and *B. infantis* along with triple therapy. A total of 90.09% of the children *supplemented* with probiotics as an adjunct to antibiotic therapy were successfully cured from *H. pylori* infection whereas 69.69% of children in the control group receiving placebo were cured. The significant rise of approximately 20% in eradication rate of the treated group remarkably proves the efficacy of probiotics as an adjunct to *H. pylori* eradication therapy (Ahmad et al. 2013). Emara et al. (2014) demonstrated the administration of a mixture of *L. reuteri* DSM 17938 and *L. reuteri* ATCCPTA 6475 as a complementary therapy. After the treatment, patients were re-examined for the presence of *H. pylori* antigen in stool, and histology of the biopsy specimen was carried out. Increased eradication from *H. pylori* infection was detected with reduced adverse effects of the eradication therapy and improved histology of *H. pylori* as compared to placebo group. Contrastingly, no effect had been observed upon co-ingestion of probiotic containing yoghurt with antibiotic treatment for *H. pylori* infection in children (Goldman et al. 2006) (Table 3).

Meta-analyses on the available outcomes of clinical trials using probiotics as a therapeutic agent are useful to understand the vitality and drawbacks of the clinical research. Recently, Feng et al. (2017) compared the potential of 17 probiotics as an adjunct to triple therapy versus as a sole therapy and found *L. casei* to be the most potent probiotic used as monotherapy, whereas *L. casei*, *L. plantarum*, *L. acidophilus*, *L. reuteri*, *L. rhamnosus*, *L. salivarius*, *L. sporogenes*, *B. infantis*, *B. longum*, and *S. thermophilus* as a multi-species probiotic combination showed promising result in reducing treatment-related side effects. Zheng et al. (2013) conducted a meta-analysis of 9 RCT (randomized controlled trial) including 1163 patients. They compared the potential of probiotic supplements as an adjunct to triple therapy or sequencial therapy with that of placebo. Upon comparing the outcome of probiotics intervention, they found 78.18% eradication in the treated group and 68.54% eradication in the placebo (control) group, showing approximately 10% increase in the eradication rate of the treated group. However, decrease in the side effect was not significant (31.21% decrease in the treated group vs 34.86% decrease in the control group). In the same study, subgroup analysis of five trials showed significant increase of 17% in eradication rate of the treated group when compared to the control group upon administering *Lactobacillus* species only, whereas only 2.8% eradication was observed when multi-strain probiotics were supplemented. It was concluded that *Lactobacillus* containing probiotic may have enhanced benefits as compared to combination of species of probiotics. In a comprehensive study, Wang et al. (2017) compared the potential of probiotic supplement for *H. pylori* eradication, most probiotics were successful in eradicating the *H. pylori* infection, while single probiotic strain showed improved result as compared to multi strain therapy. Contrastingly, Dang et al. (2014) found a probiotic supplement to be active in *H. pylori* eradication only when the antibiotic treatment failed.

In a recent study co-administeration of *L. casei* rhamnosus (LCR 35) effectively reduced antibiotic side effects but no significant difference in the eradication rate in the tested and control group was observed. The authors suggest that the low difference may be due to the use of better antibiotic regime (Uitz et al. 2017). McNicholl et al. (2018) conducted a controlled double-blind clinical trial with two probiotic strains *L. plantarum* and *Pediococcus acidilactici*, which were previously found effective in vitro in other studies (Kaur et al. 2014; Sunanliganon et al. 2012). No success in the improvement of the side effect and *H. pylori* colonization was observed. This clearly suggests that clinical trials are crucial to evaluate potential of the probiotic strain tested in vitro. *B. animalis* subsp. *lactis* significantly increase the eradication rate with decreased side effects upon its co-administration with conventional antibiotics (Çekin et al. 2017).

The differing results, though apparently indicate probiotics potential against *H. pylori* eradication, may be due to many factors related to deviating experimental design and setup. Thus, consistency in experimental protocol with a defined combination of probiotic supplement would be useful to get accuracy in the outcome.

Vaccine development

Efforts in the development of vaccines against *H. pylori* started soon after its discovery by Marshall. BJ and Warren RM (Marshall and Warren 1984). The gastric cancer due to this notorious bacterium is the main reason of establishing a potent vaccine, as it is the third major cancer causing agent worldwide (IARC 2012). The two main approaches are prophylactic and therapeutic administration of the vaccines. As the infection is usually contracted at an early age (Mitchell et al. 1992), prophylactic immunization of children is crucial. Recently, a phase 3 clinical

trial in China has been reported in which recombinant urease B vaccine successfully immunized 70% of the children (Zeng et al. 2015). This is a breakthrough in the development of potent vaccine prompting further research in this field.

The second approach is a therapeutic vaccine which can be given at any period; however, stimulation of immunosupressive mechanism by *H. pylori* to establish chronic infection is a major challenge. Therapeutic protections in mice have been reported previously in different studies (Doidge et al. 1994; Sutton et al. 2000); hence, its efficacy in human is yet to be achieved.

Probiotics as vaccine delivery system for *H. pylori* infection

With the advancement in the field of genetic engineering, probiotics have emerged as a useful tool to deliver vaccines. Many probiotic organisms are considered GRAS (generally regarded as safe) by the Food and Drug Administration. Owing to their GRAS nature, they are widely used in food industry. *Lactococci* have been suggested as an ideal recombinant vaccine vehicle, mostly due to their potential to induce both acquired and innate immunity in the host. Production of recombinant *H. pylori* antigens like UreB, CagA, NapA etc. have been widely demonstrated in *L. lactis* followed by their efficacy in pre-clinical studies which showed varied outcomes (Gu et al. 2009; Lee et al. 2001; Kim et al. 2009). Previously, in an attempt to develop *H. pylori* vaccine, we have successfully expressed Ure-B antigen in *L. lactis*. The recombinant *L. lactis* produced significant anti-Ure B serum antibody and protected the mice against gastritis (Gu et al. 2009). We detected increase in IgG level, while IgA specific to Ure-B were detected in fresh feces which declined after 38 days. In a similar experiment by Lee et al. (2001), no immunization has been observed, upon administration of recombinant Ure-B *L. lactis* to *H. pyloi* SS1 challenged mice. Interestingly, Ure-B-specific serum IgG were detected. This suggests that presence of both IgG and IgA is important to elicit effective immune response. In order to study surface display expression of *H. pylori* antigens in probiotics, we successfully constructed a recombinat UreBE-SpaxX (Ure B fragment E and fragment Spax of *Staphylococcus aureus*) (Song and Gu 2009). SpaxX is a cell wall anchor of *S. aureus* and its fusion with Ure BE would provide enhanced adjuvant activity. Western blotting of the recombinant *L. lactis* cell wall extract with polyclonal chicken antiserum confirmed its effecacy. *Bacillus subtilis* spores were used to deliver recombinant urease B antigen, which significantly reduced *H. pylori* load (84%) in mice (Zhou et al. 2015). Recently, a vaccine containing recombinant NapA *L. lactis* demonstrated production of protective antibodies in orally administered mice (Peng et al. 2018), reduction in *H. pylori* colonization was observerd though no changes in the *H. pylori*-mediated inflammation occur. Development of multi-epitope vaccine is of increasing interest as it prevents insufficiency of vaccine due to genetic variation of the pathogens. Lv et al. (2014) successfully developed a recombinant *L. lactis* with multi epitope CTB-UE which produced antibody response against *H. pylori* upon oral delivery to mice resulting in significant decrease in *H. pylori* colonization (Fig. 3).

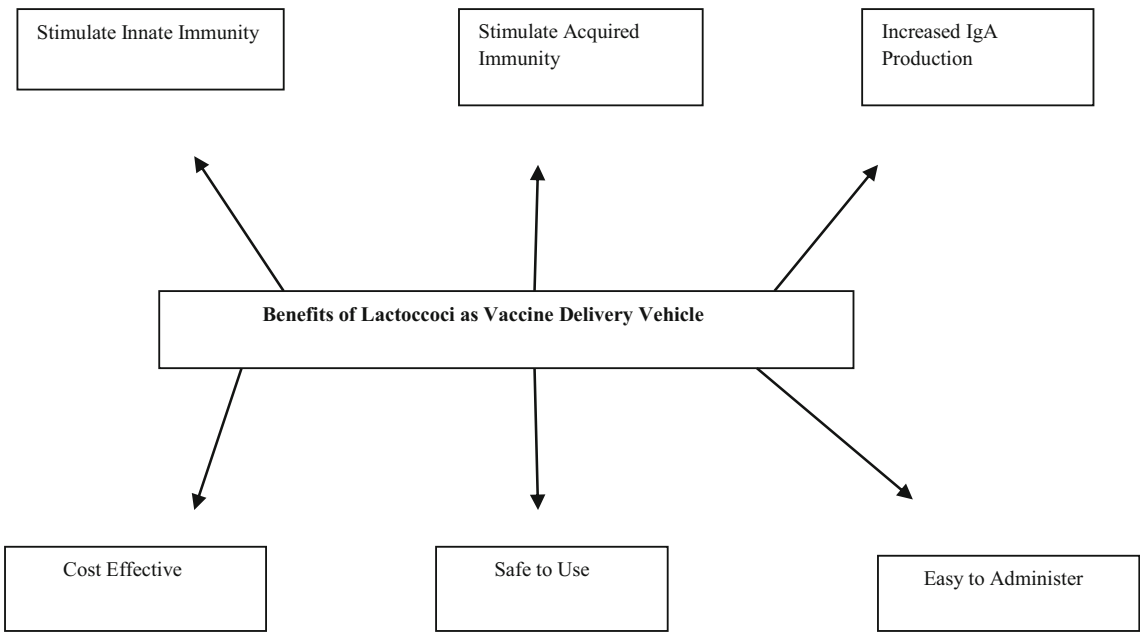

Fig. 3 Benefits of *Lactococci* as vaccine delivery vehicle

Limitations

Studies on the molecular mechanism underlying probiotics antagonizing activities are scarce which leaves a gap in the selection of specific strain to treat *H. pylori* or any other specific pathogen. The studies on probiotics to treat *H. pylori* as a monotherapy are few as compared to the studies on probiotics as an adjunct to antibiotics. To date, a number of clinical trials have been documented which are from different geographical regions and populations of the world. There is lack in the homogeneity in the research design which leads to inconsistent results. Despite a large number of researches in vaccine development, the progress is still lacking. *H. pylori* is infamous to evade host's immune response owing to its ability to release different antigenic components which makes the vaccine ineffective (Phadnis et al. 1996). Another challenge is to provide sterilizing immunity to prevent recurrence (Sutton and Doidge 2003). Due to the above mentioned facts, the investment in this field is also declining, and to date, no vaccine is universally available.

Conclusion

Numerous in vitro, in vivo, and clinical studies have been undertaken thus far, which helped to gain insight into probiotics' role in *H. pylori* treatment. *H. pylori* inhibition could be brought about by different mechanisms of action of probiotics, including immunomodulation, competition for adhesion, secretion of antimicrobial substances, strengthening the mucosal barrier,co-aggregation etc. Diversity in the results for treating *H. pylori* has been observed, this inconsistency may be due to strain specificity of probiotics. Probiotics have shown appealing results in biological experiments; however, minimal studies have been done to determine their impact on human. With respect to various meta-analyses (Feng et al. 2017; Zheng et al. 2013; Wang et al. 2017; Dang et al. 2014), it could be concluded that probiotics significantly improve antibiotic therapy of *H. pylori* infection and also reduce the side effects of the treatment. However, probiotic alone cannot be a sole alternative to treat *H. pylori* disease. Provision of probiotics in conjunction with antibiotic treatment regime or taken as a prophylaxis by the asymptomatic patients can have a potential to eradicate the infection with lessen side effects. The studies on the antagonism of probiotics against *H. pylori* are a milestone in the discovery of a potential probiotic strain. Antibiotic resistance is the biggest challenge for the current eradication treatment options. Patients' non-compliance due to side effects associated with the use of antibiotics further makes the eradication regime to fail. Comprehensive knowledge on the molecular mechanism involved in probiotics antagonizing mechanism will be a breakthrough in understanding and development of an excellent alternative biotherapeutic. In the line of investigational studies to discover new probiotics, it is highly suggested to report complete profile of probiotic tested describing its genus-species, dose, formulation, and molecular mechanism involved, to provide appropriate data for further analysis and help to propose guidelines for strain specific and evidence-based therapy. Uniformity in study design and clinical application of probiotics would be useful for future research. Moreover, studies focused on providing a standardized *H. pylori* eradication treatment plan using probiotics as an adjuvant would be a huge step towards avoiding the excess use of antibiotics and management of this dreadful pathogen. Probiotics efficacy as a tool to deliver anti-*H. pylori* vaccines cannot be overlooked despite the limitation of scarcity in preclinical and clinical trials.

The idea of developing a potent *H. pylori* multi-epitopevaccine is intriguing to overcome the challenge of genotypic and phenotypic variance in *H. pylori*. Insight into the gastric immunology and production of vaccine which provides complete immunity is indeed crucial for successful development of *H. pylori* prophylactics.

Involvement of bioengineering techniques to enhance the efficacy of specific probiotics would be a landmark in the management of *H. pylori* infections. This may shift their status from probiotics to pharmabiotics.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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