Research Article ISSN 2835-6276

American Journal of Medical and Clinical Research & Reviews

Limosilactobacillus reuteri DSMZ17648 in Helicobacter pylori infection: clinical information and mechanisms

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Received: 19 April 2024; Accepted: 24 April 2024; Published: 30 April 2024

Citation: José Angel Marañón. Limosilactobacillus reuteri DSMZ17648 in Helicobacter pylori infection: clinical information and mechanisms. AJMCRR 2024; 3(4): 1-11.

ABSTRACT

Objectives: *Helicobacter pylori is a ubiquitous organism that is present in about 50% of the global population. Chronic infection with Helicobacter pylori causes atrophic and even metaplastic changes in the stomach, and it has a known association with peptic ulcer diseases. Due to the increasing issue of antimicrobial resistance, the effectiveness of current first-line treatments for Helicobacter pylori is diminishing, resulting in decreased eradication rates. Limosilactobacillus reuteri spray-dried strain DSMZ17648 (Pylopass™) constitutes a promising therapeutic approach to enhance bacterial eradication, consequently reducing the risk of developing associated diseases.*

Methods: *the literature in this review was found by searching in databases including PubMed, clinicaltrials.gov and Google Scholar.*

Results: *clinical evidence has shown that Limosilactobacillus reuteri DSMZ17648 reduces H. pylori load in the stomach in both adults and children, improves gastrointestinal symptoms, minimizes antibiotic side effects, and decreases inflammation and atrophy of the gastric mucosa. Long-term intervention with Limosilactobacillus reuteri DSMZ17648 had a similar eradication rate to standard triple therapy, and supplementation has been found to increase the eradication rates of antibiotic therapy.*

Conclusion: *Limosilactobacillus reuteri DSMZ17648 represents a novel therapeutic approach that opens a new path to the use of postbiotics against H. pylori, contributing indirectly to the fight against antibiotic resistances. The spray-drying technology makes Lactobacillus reuteri DSMZ17648 easy to preserve and transport, establishing a potential solution for treating H. pylori infections in developing countries, where antibiotic resistance rates are the highest worldwide.*

KEYWORDS: Helicobacter pylori, ulcer disease, gastritis, antimicrobial resistance, probiotics, postbiotics, Lactobacillus reuteri.

Introduction

Helicobacter pylori (H. pylori) is a microaerophilic, spiral-shaped, gram-negative bacterium that infects the epithelial lining of the stomach. It was identified by Barry J. Marshall and J. Robert Warren in 19831 as a cause of peptic ulcer disease, leading to the development of novel treatment strategies based on antibiotics. The human host serves as the primary reservoir for H. pylori.[2]

Typically, the acquisition of the bacteria occurs during childhood and may persist for several years without any noticeable symptom.[3] Transmission occurs most commonly via person-to-person contact, but there is also a possible association between water used for consumption and H. pylori infection.[4] The primary mode of person-to-person transmission is through the fecal-oral route. Nevertheless, H. pylori DNA has been detected in the saliva and dental plaque, which introduces the possibility of oral-oral transmission.[5]

H. pylori is associated with gastric ulcers, duodenal ulcers and chronic gastritis in both adults and children.[2] Furthermore, the World Health Organization has classified H. pylori as a Group 1 carcinogen. Chronic infection may lead to non-cardia gastric adenocarcinoma and low-grade B-cell gastric mucosa-associated lymphoid tissue (MALT) lymphoma.[6]

The majority of people infected with H. pylori remain asymptomatic and it has never been demonstrated that upper gastrointestinal symptoms are more frequent in patients infected with H. pylori.[6] Additionally, H. pylori may be associated with other comorbidities, such as iron deficiency anemia or immune thrombocytopenic purpura.[7,8]

Moreover, emerging evidence suggests that H. pylori may play a key role in other several extragastric diseases[9], including:

- Neurological diseases (Alzheimer's and Parkinson diseases, multiple sclerosis, or Guillain-Barré syndrome);
- Respiratory diseases, such as COPD or lung cancer;
- Circulatory diseases, including atherosclerosis or hypertension;
- Other diseases such as autoimmune thyroid diseases, hyperemesis gravidarum, inflammatory bowel disease, or gastroesophageal reflux disease.

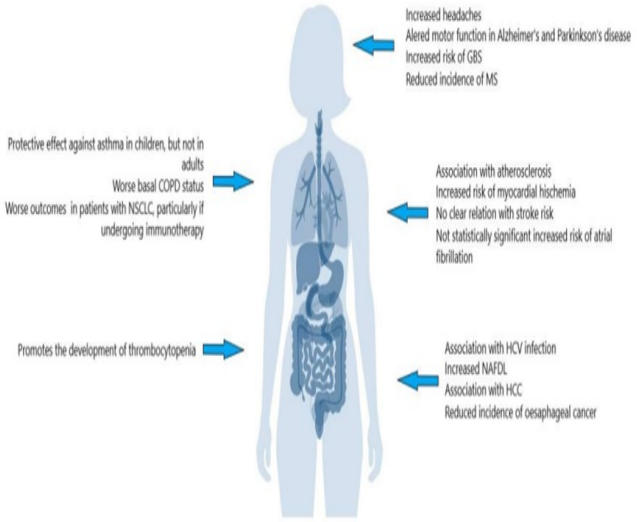

Figure 1. Extra gastric manifestations of H. pylori by Candelli et al, 2023[10].

The global prevalence of H. pylori is estimated to be approximately 50%, exhibiting substantial variation among regions and differences linked to countries' development[11], socioeconomic status and lifestyle. The highest prevalence is observed in Africa (79%), Latin America (63%) and Asia (55%).[11] In contrast, the lowest prevalence rates are found in Oceania (24%) and Northern America

(37%). Moreover, there has been a decline in the prevalence in Europe in the last years (34%), with Switzerland reporting the lowest prevalence recorded (19%).[11]

Various treatment regimens for H. pylori have been developed and their use vary across different geographical regions largely based on local antibiotic resistance patterns.

Treatment is usually indicated for the eradication of H. pylori in patients experiencing chronic dyspeptic symptoms for long-term improvement.[8] Recently, standard quadruple therapy (SQT) has been used as a first-line treatment, incorporating amoxicillin, clarithromycin, metronidazole or another nitroimidazole, and a proton pump inhibitor (PPI), such as omeprazole. While this therapy has shown enhanced efficacy compared to previous standard triple therapy (STT) (using clarithromycin and amoxicillin), limitations are still present due to the escalating resistance to clarithromycin-metronidazole.[12] However, in light of a substantial decline in efficacy to levels below 80–85%, STT is usually not recommended as an empirical first-line therapy for H. pylori infection, except in areas with a known clarithromycin resistance rate of <15%.[13]

The American College of Gastroenterology (ACG) has established that therapy is chosen based on antibiotics resistance and previous antibiotics exposure, separating available treatments into first line and salvage therapy.[13] Bismuth SQT (PPI, bismuth, metronidazole and tetracycline) has been recommended by the Second Asia-Pacific Consensus guidelines, the ACG and the Maastricht IV/ Florence Consensus Report as the first-line therapeutic option in regions with high clarithromycin resistance[14] although high adverse effects have been associated.[8]

The Toronto Consensus group in 2016 suggested that, due to increasing resistances and therapy failures, every H. pylori eradication regimen should be administrated for 14 days.[15]

Following current standard therapies, eradication rates are approximately 63% worldwide, showing a decline over time.[8] Concordantly, the prevalence of H. pylori antimicrobial resistance varies across geographic regions and appears to be rising each year.[16,17]

The objective of standard therapies is to reach a minimum of a 90% of H. pylori eradication rate to prevent the spread of resistant strains and the development of new resistances.[2] Kyoto Global Consensus Report recommended the same percentage as a guide to select different empirical treatments in each region.[18]

In a study of 2006 involving children from European countries, resistance rates of H. pylori treatment were 25% to metronidazole, 24% to clarithromycin and double resistance of 6.9%.[19] Currently, resistance rates are increasing, affecting eradication rates.

Antimicrobial resistance represents a major risk to public health globally and stands as a leading cause of mortality. It is estimated that, by 2050, antimicrobial resistance will result in 10 million deaths per year, becoming more lethal than cancer.[20]

In response to the increasing antibiotic resistances, several investigations are focusing on new therapeutical approaches. Complex molecular mechanisms are the main source of emerging resistances

of H. pylori strains to existing antibiotics, which are being studied and understood by advancements in sequencing technology, simplifying the testing of antibiotic susceptibility to H. pylori. [21]

Studies are giving attention to the possible reduction of H. pylori load by probiotics, the reduction of adverse effects, the improvement of gastrointestinal symptoms and the reestablishment of intestinal flora.[22,23]

Limosilactobacillus reuteri DSMZ17648 (Pylopass™) possesses strong co-aggregation activity

Different Lactobacillus strains have been investigated in several studies against H. pylori. After a detailed, multi-year screening process, Limosilactobacillus reuteri (formerly known as Lactobacillus reuteri (L. reuteri)) DSMZ17648 (LDSMZ17648) (Pylopass™) strain was collected, chosen among 8,000 different food grade strains. LDSMZ17648 was specifically selected due to its anti-H. pylori properties.[24]

LDSMZ17648 was posteriorly processed by spray-drying, constituting a postbiotic that contains 100 billion (1x10^11) of L. reuteri cells per gram. Spray-drying causes the death of L. reuteri cells, which means that LDSMZ17648 effect is independent of its probiotic activity.[25] Moreover, this processing technology allows LDSMZ17648 to survive in the acidic environment of the stomach.

LDSMZ17648 presents specific structures that specifically recognize and bind to surface on H. pylori. Its unique mechanism of action is based on the formation of co-aggregates between LDSMZ17648 cells and H. pylori cells that are eliminated from the organism through the gastrointestinal tract, even under harsh stomach conditions. These co-aggregates not only prevent the adhesion of free H. pylori cells to the stomach epithelium, but also eliminate the bacteria that have already colonized it.

LDSMZ17648 allows to control H. pylori without harming the human microbiome, since it does not co-aggregate with common members of the intestinal flora[26]. The selectivity of LDSMZ17648 against H. pylori and its regular consumption as anti H. pylori infection agent could play a key role in the limitations of current common antibiotic treatments.

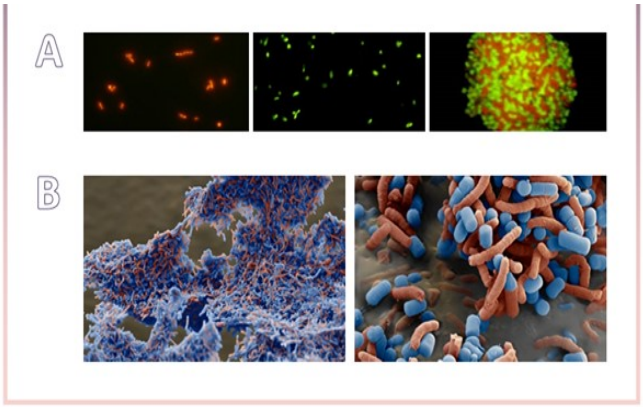

Figure 4. Co-aggregation of *L. reuteri* DSM17648 with *H. pylori*. In the *in vitro* co-aggregation test, *L. reuteri* DSM17648 bound strongly to *H. pylori*. *L. reuteri* DSM17648 (middle, green fluorescent protein (GFP)- tagged) and *Helicobacter pylori* (left, red fluorescent protein (RFP)- tagged) formed co-aggregates (right) in artificial stomach juice. Scanning electron microscopy images of co-aggregates formed by *L. reuteri* DSM17648 (blue) and *Helicobacter pylori* (red) (left - 1800x magnification, right - 11000x magnification).

Figure 2. Co-aggregation of LDSMZ17648 with H. pylori in vitro (Figure will be modified)

Clinical studies of LDSMZ17648 on Helicobacter Pylori infection

In vitro and in vivo studies have demonstrated that LDSMZ17648 can specifically bind to the surface of H. pylori and verified the efficacy and safety, as shown in the following table.

Year	Duration	Intervention	Population	Outcome	Reference
2013	14 days + 24 weeks follow-up	Single-blinded Placebo-controlled LDSMZ17648 vs placebo	*H. pylori* positive adults n=22	Spray-dried LDSMZ17648 reduced significantly *H. pylori* load, showing similar efficacy than other preparation processes	2013, Mehling et al[25]
2014	14 days + 4-6 weeks follow-up	Single-blinded Randomized Placebo-controlled LDSMZ17648 vs placebo	*H. pylori* positive asymptomatic adults n=27	Majority of subjects showed a decrease in *H. pylori* colonization	2014, Holz et al[27]
2015	4 weeks	Monotherapy of LDSMZ17648	*H. pylori* positive adults n=23	LDSMZ17648 reduced bacterial load in a percentage of patients and there was a decrease in the degree of inflammation	2015, Bordin et al[28]
2015	4 weeks	LDSMZ17648 monotherapy vs STT (control group) vs LDSMZ17648+STT	*H. pylori* positive children with chronic associated gastroduodenal diseases n=49	Monotherapy with LDSMZ17648 had an eradication rate of 50% and combination, 60%, whereas control group, 68.75%. LDSMZ17648 reduced adverse reactions and inflammation	2015, Parolova et al[29]
2016	4 weeks + 2 months follow-up	LDSMZ17648 concomitant to non-bismuth STT vs non-bismuth STT vs bismuth STT	*H. pylori* positive adult patients with associated duodenal ulcer n=60	Supplementation with LDSMZ17648 had an eradication rate comparable with bismuth antibiotic therapy. Moreover, it showed a positive influence in clinical symptoms and a good tolerability and safety profile	2016, Uspienskiy et al[30]
2017	4 weeks	Monotherapy of LDSMZ17648 200 mg once a day vs LDSMZ17648 200 mg twice a day	*H. pylori* positive adult patients n=60	LDSMZ17648 showed a reduction of *H. pylori* load in the stomach and statistically significant decrease of the degree of inflammation of the gastric mucosa, with no side effects	2017, Bordin et al[31]
2018	8 weeks	Single-blinded Placebo-controlled LDSMZ17648 vs placebo	*H. pylori* positive adult patients n=24	There was a reduction rate of around 65% and no side effects were reported. Moreover, there was a significant improvement in gastrointestinal symptoms	2018, Buckley et al[32]

2019	8 weeks	Randomized Therapy with LDSMZ17648, de-glycyrrhizinated liquo-rice and calcium car-bonate vs STT	*H. pylori* positive adult patients n=70	*H. pylori* eradication reached 54% of patients in LDSMZ17648 group versus 77% in antibiotic group. LDSMZ17648 treatment showed very good tolerabil-ity and compliance	2019, Mihai et al[30]
2019	12 weeks	Randomized LDSMZ17648 + pan-toprazole vs STT	*H. pylori* positive adult patients with symptoms of functional dyspepsia n=46	LDSMZ17648 demonstrat-ed to be an optimal alterna-tive for patients with chron-ic dyspepsia for the eradica-tion of *H. pylori* infection. Its efficacy is similar to the triple therapy (65% eradica-tion in LDSMZ17648 group vs 73% in STT group)	2019, Pop Muresan et al[33]
2020	8 weeks	Double-blinded Randomized Placebo-controlled Monotherapy of LDSMZ17648 200 mg twice a day vs LDSMZ17648 + STT vs placebo + STT	*H. pylori* positive chil-dren with associated chronic gas-tritis n=103	LDSMZ17648 monothera-py presents advantages over STT, reducing symptoms and gastric mucosa inflam-mation. Long-term mono-therapy has a similar effica-cy to STT and the combina-tion of both of them had a higher efficacy. Symptoms, inflammation and atrophy were decreased	2020, Kornienko et al[34]
2021	14 days	Double-blinded Randomized LDSMZ17648 + STT vs STT	*H. pylori* 13C urea breath test-positive adults n=90	Symptoms and severity of the disease were significant-ly reduced in patients re-ceiving STT+ LDSMZ17648. Adding LDSMZ17648 to STT in-creased the rate of eradica-tion	2021, Parth et al[35]
2021	8 weeks	Randomized Double-blinded Placebo-controlled LDSMZ17648 pre-treatment to LDSMZ17648 + STT vs placebo pretreat-ment to placebo + STT	*H. pylori* positive adult patients n=200	No significant differences were found in eradication rates of both groups. GI symptoms, such as diarrhea or abdominal distention were significantly lower with LDSMZ17648 supple-mentation	2021, Yang et al[36]
2022	14 days + 8 weeks follow-up	Double-blind Randomized Placebo-controlled LDSMZ17648 con-comitant to SQT vs Saccharomyces bou-lardii concomitant to SQT vs placebo + SQT	*H. pylori* positive adult patients n=156	LDSMZ17648 supplemen-tation along with SQT im-proved the eradication rate, but it was not statistically significant	2022, Naghibzadeh et al[37]
2023	8 weeks	Randomized Double-blinded Placebo-controlled LDSMZ17648 adjunct treatment to STT vs placebo + STT	*H. pylori* positive adult patients n=90	There was a significant in-crease in *H. pylori* eradica-tion rate and attenuation of symptoms and adverse treatment effects when LDSMZ17648 was given as an adjunct treatment	2023, Ismail et al[38]

Table 1. Clinical trials of LDSMZ17648 classified chronologically

Clinical application of LDSMZ17648 in H. pylori

Decrease of the bacterial load in the stomach

As proven by the clinical evidence shown in Table 1, LDSMZ17648 can reduce H. pylori load in the stomach in both adults and children. This can be explained by the ability of LDSMZ17648 to form co-aggregates, allowing the elimination of a considerable number of H.pylori cells from the organism.

Monotherapy with LDSMZ17648 significantly reduces H. pylori colonization in most patients, comparable to STT. Kornienko et al. demonstrated that long-term monotherapy had similar efficacy to STT. Monotherapy showed eradication rates around 50-65%, while antibiotic therapies exhibited eradication rates between 60-80% depending on the patients, regions, etc, showing a decline attributed to the increasing antimicrobial resistances.

Moreover, the combination of standard antibiotic therapies with LDSMZ17648 considerably increased eradication rates. While Uspienskiy et al. showed that LDSMZ17648 supplementation had a similar eradication rate to bismuth STT, other studies additionally demonstrated that the combination had a higher efficacy. On the contrary, Naghibzadeh et al. demonstrated that LDSMZ17648 supplementation along with STT did not show statistically significant improvements in eradication rates.

Improvement of the gastrointestinal symptoms

LDSMZ17648 showed an improvement in gastrointestinal symptoms in subjects that are H. pylori positive without any side effects reported. Particularly, some studies have demonstrated that supplementation with LDSMZ17648 alongside antibiotic therapies had a significant positive effect on the clinical manifestations and severity of H. pylori infection, showing a safe and optimal tolerability, which resulted in supplementation adherence.

Symptoms such as diarrhea, abdominal pain, abdominal distention, and indigestion showed improvement with LDSMZ17648 supplementation, ameliorating standard antibiotic therapies.

Monotherapy with LDSMZ17648 also decreased the symptoms of H. pylori infection, further supporting the potential to replace existing antibiotic therapies with alternative treatments, such as this strain of L. reuteri.

Reduction of the side effects related to antibiotic therapy

Adverse events commonly occur during antibiotic therapy against H. pylori. Combinations of amoxicillin, metronidazole and a bismuth compound increase the risk of secondary effects, such as nausea, diarrhea, inflammation, abdominal pain, etc, leading to severe discomfort in patients, especially those with ulcer disease.[39] Consequently, this can lead to treatment interruption, negatively impacting eradication rates.

LDSMZ17648 supplementation reduced adverse reactions of STT and SQT, showing fewer side effects than the placebo.

Therefore, LDSMZ17648 supplementation may improve treatment compliance and eradication rates by reducing the risk of side effects caused by standard therapies and ameliorating gastrointestinal symptoms.

Reduction of the gastric mucosa inflammation and atrophy

LDSMZ17648, when used as monotherapy, significantly decreases the degree of inflammation of the gastric mucosa in adult patients. Moreover, LDSMZ17648 monotherapy in H. pylori-positive children with associated chronic gastritis also reduced gastric mucosa inflammation, and the co-administration to STT bismuth therapy decreased the inflammation and atrophy of the mucosa.

Conclusion

Clinical studies on more than 1000 participants revealed that Limosilactobacillus reuteri DSMZ17648 (Pylopass™) supplementation represents a positive contribution to H. pylori eradication and on the attenuation of the gastrointestinal symptoms. The administration of Pylopass™ used whether as a supplement alongside antibiotic therapy, as an adjunct therapy or as monotherapy improved gastrointestinal well-being.

Pylopass™ supplementation reduces H. pylori load, due to its novel selective mechanism of action. The use of Pylopass™ could have a direct impact on reducing the use of antibiotics and subsequently reducing the spread of antibiotic resistances.

Furthermore, Pylopass™ intake has shown significant benefits in alleviating gastrointestinal symptoms, mucosal inflammation and atrophy, thereby ameliorating the severity of H. pylori infection. Pylopass™ can also contribute positively to the reduction of common side effects associated with antibiotic treatment, which negatively impact treatment compliance.

Additionally, since the co-aggregation activity of Pylopass™ with H. pylori surface structures remains unaffected by temperature conditions, its transportation and conservation are relatively simple. This suggests a potential application as a treatment in developing countries, where antibiotic resistance rates are among the highest worldwide.

In summary, findings from 15 clinical interventions involving more than 1000 participants revealed that Pylopass™ constitutes a promising option, either as a monotherapy, adjunct therapy, adjuvant to STT and SQT therapies, or even as a prophylactic measure for H. pylori infections, gastric and extra gastric diseases.

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