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Review article

Influence of probiotics in the eradication treatment of Helicobacter pylori

Influencia de los probióticos en el tratamiento erradicador de Helicobacter pylori

Ileana Gil Llanes [1*]https://orcid.org/0000-0002-8351-9646

Lisset Barroso Márquez [1] https://orcid.org/0000-0002-3043-1763

Marcia Samada Suárez [1] https://orcid.org/0000-0003-3795-3801

Lissette Chao González [1] https://orcid.org/0000-0003-0817-2424

Yunia Tusen Toledo [2] https://orcid.org/0000-0001-7996-239X

Kenia Yusnarkis Valenzuela Aguilera [1] https://orcid.org/0000-0002-4244-350X

[1] Medical and Surgical Research Center. Havana, Cuba.

[2] Clinical Research Center. Havana, Cuba.

*Corresponding author. Email:ileanagilllanes@gmail.com

SUMMARY

Introduction: Scientist Elie Metchnikoff proposed that consuming lactic acid bacteria in milk could reduce adverse effects and reduce harmful processes in the body. These observations laid the groundwork for the introduction into medical practice of specific microbial strains for the treatment of a wide spectrum of diseases, including the eradication of the Helicobacter pylori bacteria.

Objective: To update the usefulness of probiotics in the eradication treatment of Helicobacter pylori, as well as their relationship with the intestinal microbiota.

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Methods: Articles published in Spanish and English in the Scielo, Medline and Cochrane databases were consulted. The search terms used were Helicobacter pylori, prebiotics, probiotics and symbiotics.

Development: Currently, there is no 100 % effective treatment for the eradication of Helicobacter pylori, which is related to microbial resistance and the adverse effects produced by conventional treatments. In recent years, the usefulness of probiotics and prebiotics in combination with antibiotic therapy to achieve better cure rates has been evaluated. Studies suggest that several strains of probiotics or symbiotics are effective in reducing the occurrence and intensity of antibiotic-induced adverse effects, increasing treatment adherence and improving eradication rates.

Conclusions: Some probiotics added to antibiotics may be useful as adjuvant therapy for the eradication of Helicobacter pylori infection by increasing treatment adherence and improving eradication rates.

Keywords: probiotics; prebiotics; gut microbiota; *Helicobacter pylori*.

RESUMEN

Introducción: El científico *Elie Metchnikoff* propuso que el consumo de bacterias ácido lácticas en la leche podía disminuir los efectos adversos y reducir los procesos dañinos en el organismo. Estas observaciones sentaron las bases para la introducción en la práctica médica de cepas microbianas específicas, para el tratamiento de un amplio espectro de enfermedades, dentro de ellas la erradicación de la bacteria *Helicobacter pylori*.

Objetivo: Actualizar la utilidad de los probióticos en el tratamiento erradicador de *Helicobacter pylori*, así como su relación con la microbiota intestinal.

Métodos: Se consultaron artículos en español e inglés publicados en las bases de datos Scielo, Medline y Cochrane. Los

http://revcimeq.sld.cu/index.php/imq
revinmedquir@infomed.sld.cu

términos empleados para la búsqueda fueron *Helicobacter pylori*, prebióticos, probióticos y simbióticos.

Desarrollo: En la actualidad no existe un tratamiento 100 % eficaz en la erradicación del *Helicobacter pylori*, relacionado con la resistencia microbiana y los efectos adversos que producen los tratamientos convencionales. En los últimos años se ha evaluado la utilidad de los probióticos y los prebióticos en combinación con la antibioticoterapia para lograr mejores tasas de curación. Los estudios plantean que varias cepas de probióticos o simbióticos son eficaces para disminuir la ocurrencia e intensidad de los efectos adversos inducidos por los antibióticos, aumentar la adherencia al tratamiento y mejorar las tasas de erradicación.

Conclusiones: Algunos probióticos agregados a los antibióticos, pueden ser útiles como terapia adyuvante para la erradicación de la infección por *Helicobacter pylori* al aumentar la adherencia al tratamiento y mejorar las tasas de erradicación.

Palabras clave: probióticos; prebióticos; microbiota intestinal; *Helicobacter pylori*.

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INTRODUCTION

At the beginning of the 20th century, scientist Elie Metchnikoff postulated that lactic acid bacteria could contribute to the longevity of patients. He proposed that putrefaction processes in the intestine allowed the formation of toxins that contributed to the degeneration of the body. He also proposed that the consumption of lactic acid bacteria in milk could decrease adverse effects

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and reduce harmful processes in the body. Thus, he suggested that intestinal autointoxication and the resulting aging could be suppressed or reduced by modifying the intestinal microbiota and using helpful microbes. [1, 2]

Metchnikoff also made progress in the use of microbial strains for therapeutic purposes. He developed a preparation, which he called Lactobacillin, using lactobacilli in capsule form for ingestion. This proposal took shape at the dawn of the 20th century, in the midst of the so-called "golden age of modern microbiology." However, his theory was rejected in the face of the thesis of the German Paul Erlich, who paved the way for the antibiotic era. The immediate benefits brought by the advent of antibiotics relegated Metchnikoff's claims and they remained as bibliographical oddities. [2]

The passage of time, together with a critical appreciation of the possibilities and shortcomings of pharmacology and the desire of scientists to explore novel, traditional or alternative paths, brought about a revision of Metchnikoff's proposals. From then on, probiotics were introduced as another therapeutic tool in the treatment of a wide spectrum of diseases, including the eradication of the *Helicobacter pylori* (*H. pylori*) bacteria. [2, 3]

H. pylori is one of the etiological factors for the development of chronic gastritis, peptic ulcer, mucosa-associated lymphoid tumor (MALT) and gastric cancer. In 1994, the International Agency for the Study of Cancer classified it as a class I carcinogen, which was ratified by the World Health Organization (WHO). It is a gram-negative, microaerophilic, spiral-shaped bacterium. It is estimated that more than 50 % of the world's population is infected, with a high prevalence in underdeveloped countries (70 % in Africa and 63,4 % in Latin America). The lowest rates of infection are reported in Oceania at 24 % of the population. [4-7]

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The human stomach is infected by *H. pylori* from an early age. The bacteria have developed strategies to maintain its survival and persistence in such a hostile environment, which is possible through three fundamental mechanisms: the production of ammonia and CO2 through the action of the enzymes urease and carbonic anhydrase, the presence of flagella in the structure of the bacteria and the production of specific virulence factors. The first neutralizes gastric acid and raises the pH in the surrounding tissues, ammonia alters the tight cell junctions of the gastric epithelium and CO2 interferes with the bactericidal activity of the host, thereby creating a favorable environment for its colonization. [4]

The presence of flagella allows the bacteria to penetrate the mucus layer. Specific virulence factors include vacuolar cytotoxin A (VacA), cytotoxin-associated gene protein (CagA), sialic acid-binding adhesin A (SabA), and other specific outer membrane proteins, which cause damage to epithelial cells and are associated with the development of gastric tumors. [4, 8]

Due to the relationship described between *H. pylori* infection and chronic gastritis, peptic ulcer, gastric carcinoma and MALT lymphoma, it is necessary to establish a treatment once diagnosed. Current therapies are based on the combination of two or three antibiotics, proton pump inhibitors and bismuth in some cases, which increases eradication rates. The use of first or second line therapies one a will depend on antibiotic resistance in each region. [4, 5]

To date, there is no treatment that achieves 100% eradication of these bacteria, mostly related to microbial resistance and the adverse effects produced by conventional treatment regimens. For this reason, in recent years the usefulness of probiotics and prebiotics in combination with antibiotic therapy has been evaluated to achieve better cure rates. [1, 9, 10]

The objective of this research is to update the usefulness of probiotics in the eradication treatment of *H. pylori*, as well as its relationship with the intestinal microbiota.

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METHODS

A search was conducted in Google Scholar, Dialnet, SciELO and PubMed. Documents, articles, theses and practical guides published by different professional societies and associations both in Cuba and internationally were reviewed. This search was conducted in Spanish and English. The following descriptors were used: probiotics, prebiotics, symbiotics, *H. pylori* and intestinal microbiota. The impact of the journal and the relevance of the topic were taken into account in the selection of articles. 43 citations were used to conduct the review, 40 of them published in the last 5 years.

DEVELOPMENT

The first definition of probiotics was made in 1965 by Lily and Stillwell who defined it as “that factor of microbiological origin that stimulates the growth of other organisms”. In 1974, Parker defined it for the first time as living organisms that when ingested in adequate quantities confer a healthy benefit on the host. (11)

The original definition emerged from a meeting of experts convened by the Food and Agriculture Organization of the United Nations (FAO) and the WHO in 2001. Despite the existence of discrete semantic modifications by the International Scientific Association of Prebiotics and Probiotics, the one proposed by FAO/WHO is maintained, which makes the definitions cited below the most widely used worldwide. (1, 3)

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Probiotics: live microorganisms, which when administered in adequate amounts, confer a health benefit on the host. This definition emphasizes its three fundamental characteristics:

1. Viability of microorganisms.

2. Number or quantity of these.

3. Beneficial effects on the health of the host.

Probiotics are living organisms that can be included in food preparation, dietary supplements and medicines. The most commonly used species are: Lactobacillus and Bifidobacterium species. Multiple properties of probiotics are described, including survival in the gastrointestinal tract, adherence to the intestinal epithelium, modulation of intestinal flora, decreased intestinal permeability, immunomodulation and safety. [1, 3, 12]

In summary, the term probiotic is reserved for live microorganisms that have been shown to be beneficial to health in controlled studies in humans. To produce beneficial effects on the host, probiotics do not need to colonize the target organ, although they must arrive alive in sufficient numbers to affect its microecology and metabolism. Most probiotic strains are able to reach the colon alive (in a variable percentage); they resist exposure to stomach acid, the action of bile salts and proteolytic enzymes. [13]

There is international consensus that probiotics should be named according to the International Code of Nomenclature and the classification of prokaryotic organisms. Therefore, their identification should include the genus, species, subspecies (if applicable) and alphanumeric designation. Some examples are shown in Table 1. [1]

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Table 1. **Name of probiotics according to the International Code of Nomenclature and the classification of prokaryotic organisms**

Género	Especie	Sub especie	Designación de la cepa	Designación del depositario internacional de cepas	Apodo de la cepa	Nombre del producto
Lacticaseibacillus	*rhamnosus*	Ninguna	GG	ATCC 53103	LGG	Culturelle
Bifidobacterium	*animalis*	*lactis*	DN-173 010	CNCM I-2494	*Bifidus regularis*	Yogur Activia
Bifidobacterium	*longum*	*longum*	35624	NCIMB 41003	*Bifantis*	Align

Source: World Gastroenterology Organization Global Guidelines on Probiotics and Prebiotics. 2023.

The importance of this nomenclature lies in the fact that their health benefits are species-specific, although some mechanisms of probiotic activity are likely to be shared between different strains, species, or genera. Many probiotics may function in a similar manner with respect to their ability to promote resistance to colonization, regulate intestinal transit, or normalize altered microbiota. [1]

On the other hand, prebiotics are non-digestible dietary ingredients (usually non-starch polysaccharides and oligosaccharides poorly digested by enzymatic action), selectively fermented. Their administration modifies the intestinal environment and leads to specific changes in the composition and/or activity of the gastrointestinal flora. In addition, they stimulate the growth and activity of certain intestinal bacteria and, consequently, confer benefits to improve the health of the host. At the colon level, they produce an increase in bifidobacteria, increase calcium

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absorption and the volume of fecal matter, decrease gastrointestinal transit and blood lipid levels. [1, 14]

Prebiotics are used in foods, for example: cookies, chocolates, dairy products, among others. Among the best known are: oligofructose, inulin, galactooligosaccharide, lactulose and oligosaccharides from breast milk. [1]

Like probiotics, prebiotics must have three fundamental characteristics: [15]

1. Be non-digestible, resistant to gastric acid and proteolytic enzymes so as not to be absorbed in the proximal digestive tract.

2. Be fermented by the intestinal microbiota and promote the growth of beneficial bacteria.

3. Be able to produce beneficial effects on health.

Synbiotics are products that contain probiotics and prebiotics, thereby modulating the intestinal microbiota. The fundamental objective of synbiotics is that when probiotics reach the intestine, they do so accompanied by prebiotic substances, which contributes to promoting the growth and colonization of the former. [16]

The concept of synbiotics includes two types: complementary synbiotics and synergistic synbiotics. The former are a mixture of probiotics and prebiotics used at a previously defined dose to produce a health benefit. The latter are a mixture of a selected live microbe to be used together with a substrate, without the need to meet the criteria of a probiotic or prebiotic, but both must provide a documented health benefit. [1]

The functions of prebiotics, probiotics and symbiotics are closely related to the microbes that colonize humans, which is why knowledge of the intestinal microbiota is essential.

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Gut microbiota

The term microbiota refers to the set of microorganisms that coexist with the host in a state of symbiosis. It is a complex and dynamic ecosystem recognized as an organ with active metabolism. The intestinal microbiota plays an important role in maintaining the homeostasis of the digestive system and intervening in the regulation of the response of the mucosal immune system, in the elimination of pathogens, in energy metabolism with the production of nutrients and in detoxification. [17-19]

Lifestyle, long-term use of antibiotics and proton pump inhibitors, as well as *H. pylori* infection are factors that influence it. At the gastric level, the microbiota describes five main phyla: Firmicutes, Proteobacteria, Actinobacteria, Fusobacteria and Bacteroidetes. [19]

In patients infected with *H. pylori*, this bacterium is the dominant microorganism and induces dysbiosis of the gastric microbiota, although the same phyla are maintained with different percentages compared to uninfected individuals. The presence of *H. pylori* leads to a greater abundance of Proteobacteria and a lower presence of Actinobacteria, Bacteroides and Firmicutes. Some studies suggest that the gastric microbiota can be restored after the eradication of *H. pylori*, although there are controversies on this matter. [20-22]

The mechanism by which *H. pylori* causes alterations in the gastric microbiota is not clear. This bacterium induces an inflammatory cascade, which causes a reduction in gastric secretion from parietal cells and an increase in intragastric pH, which is why colonization by other microorganisms in the stomach is sometimes observed. On the other hand, there is evidence suggesting that alterations in the gastric microbiota predispose to the development of stomach cancer, which is related to modifications in the homeostatic functions of intestinal commensals, with the emergence of dysbiosis, inflammation and susceptibility to pathogens. [21, 23]

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In recent years, the relationship between dysbiosis and *H. pylori* infection has been studied, due to the negative effect that this microorganism produces on the gastric microbiota. The infection triggers different gastroenterological and non-gastroenterological diseases. Since its discovery, there have been multiple efforts to identify the most effective therapeutic regimen for its eradication. However, antibiotic resistance, lack of adherence to treatment, high bacterial density, as well as the internalization of the bacteria in the gastric mucosa, are challenges that conspire against a 100 % effective treatment. [24]

Multiple combinations of one or more drugs have been used with very uneven results. However, only three groups of drugs are effective when used in combination, at established doses and frequencies for 7, 10 or 14 days according to the different regimens: proton pump inhibitors, bismuth compounds and antibiotics. [4, 25]

At present, only treatment guidelines that meet a series of criteria are accepted: [26]

1. Eradication rates above 90 %.

2. Side effects less than 5 %.

3. Easy to complete by the patient.

4. Low rates of antibiotic resistance.

5. Short duration (between 10 or 14 days).

6. Low cost.

On the other hand, in addition to the effect that the presence of the bacteria has on the microbiota, the use of antibiotics further alters the gastrointestinal microecology. It is necessary to search for treatment alternatives that induce a positive impact on their efficacy and reduce the negative

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effects on the intestinal microbiota, thereby achieving high eradication rates with minimal side effects. One of the options that have been evaluated is the use of probiotics. [26, 27]

Probiotics and *H. pylori*

Probiotics have demonstrated their ability to block the action of bacterial pathogens. Their functions are multiple and varied: [24, 25]

- They reduce intestinal pH by producing lactic acid and short-chain fatty acids (SCFA). These acids have antibacterial activity against *H. pylori* by inducing cytoplasmic acidification and the accumulation of toxic anions.
- They synthesize vitamins such as vitamin B and K.
- They synthesize antibacterial molecules such as bacteriocins, produced mainly by Lactobacillus and Lactococcus, with the ability to inhibit the formation of the bacterial wall and form pores in it.
- They stimulate the immune response by increasing macrophage activity and modulating the secretion of immunoglobulins or cytokines. On the other hand, they indirectly influence the immune response by reinforcing the intestinal epithelial barrier and altering mucus secretion.

However, consensus on *H. pylori* eradication therapy does not recommend the use of probiotics in treatment. There is insufficient evidence to support the efficacy of a probiotic alone, without concomitant antibiotic therapy. [28-30]

However, several studies suggest that various strains of probiotics or symbiotics have been shown to be effective in reducing the occurrence and intensity of antibiotic-induced adverse effects. Recent studies suggest that supplementing anti-*H. pylori* antibiotic regimens with certain probiotics could be useful in patients in whom eradication treatment fails. [25-27, 30, 31]

A study by Cifuentes et al. [32] reported a decrease in genes related to resistance to tetracyclines and beta-lactams, with the supplemental use of Saccharomyces boulardii (S. boulardii) strains, during the eradication of *H. pylori*. Zhang M et al. [33] indicate in a meta-analysis that supplementation with probiotics for more than 10 days improves the eradication rate compared to short-term use. Hamzavi et al. [34] concluded that the use of probiotics together with quadruple therapy increases the eradication rates of the bacteria.

There are great expectations regarding the beneficial effects produced by fermented milks with probiotic microorganisms, since it has been proven that they not only have a high nutritional value, but also provide a boosting effect on the immune system, detoxifying and anticancer activity. In addition, they offer a preventive action against cardiovascular diseases, a broad spectrum of inhibition on enteropathogenic invaders, among others. [35-38]

The production of these milks shows a rapid development worldwide, the most commonly used genera of microorganisms are: Bifidobacterium and Lactobacillus, among these the use of lactic acid bacteria of intestinal origin such as L. acidophilus stands out. Several species of Lactobacillus (commonly present in yogurt and other commercial products) have an effect against *H. pylori*. [39, 40]

Studies have been conducted with other strains of lactobacilli, such as Lactobacillus reuteri (L. reuteri), which have demonstrated a preponderant role in the treatment of infection and in reducing inflammation, due to its ability to interfere with the mobility of the bacteria and its adhesion to the gastric mucosa. Several clinical trials conducted in different countries demonstrate the safety and efficacy of L. reuteri in eradication treatment with higher eradication rates and fewer side effects than antibiotics. [41, 42]

*Naghibzadeh N*et al. [43] conducted a double-blind, randomized, placebo-controlled clinical trial on 156 patients infected with *H. pylori*. The objective was to investigate the effects of treatment with S. boulardii and L. reuteri on eradication and the adverse effects of treatment. For this purpose, three groups were formed, one with quadruple therapy (proton pump inhibitor, bismuth subcitrate, clarithromycin and amoxicillin), the other with the same quadruple therapy supplemented with S. boulardii and a third group supplemented with L. reuteri. The highest eradication rate (over 90 %) with fewer adverse effects was for patients who received treatment supplemented with probiotics. The control group eradicated 85 %.

CONCLUSIONS

There is evidence to suggest that certain probiotics added to antibiotics may be useful as adjuvant therapy for the eradication of *H. pylori* infection by increasing treatment adherence and improving eradication rates.

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Conflicts of interest

The authors report no conflicts of interest.