UDC 579.8+579.676+57.063.8+616.34-008.87-009.11+613.22+615.015.26]-053.2
DOI: 10.56871/CmN-W.2023.27.16.002

# PROBIOTICS. USE OF THE L. RHAMNOSUS STRAIN IN NON-INFECTIOUS DISEASES OF THE GASTROINTESTINAL TRACT

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***For citation:*** Bogdanova NM. Probiotics. Use of the *L. Rhamnosus* strain in non-infectious diseases of the gastrointestinal tract. Children's medicine of the North-West (St. Petersburg). 2023;11(1):18-31. DOI: https://doi.org/10.56871/CmN-W.2023.27.16.002

**Received: 11.09.2022** **Revised: 17.11.2022** **Accepted: 15.01.2023**

***Abstract.*** Probiotics are living, apatogenic bacteria for humans that have antagonistic activity against pathogenic and conditionally pathogenic bacteria that ensure the restoration of normal microbiota. Not every microorganism can be assigned the status of "probiotic", but only those that are considered safe and meet certain criteria. Despite the fact that most of the probiotics are represented by isolates of the indigenous microbiota, the mechanism of their action in human bionishes is not equivalent to endogenous microorganisms. Functional gastrointestinal disorders (FGID) are widespread among children of any age. Changes in the "passport" of the intestinal microbiome can affect the key mechanisms associated with the symptoms of FGIR. Very often, the causes of digestive discomfort (abdominal pain, bloating, flatulence, flatulence and diarrhea) are associated with lactose intolerance (NL). Inflammatory bowel diseases (IBD) are characterized by bidirectional mutual.

***Key words:*** *probiotic; strain-specificity; L. rhamnosus (LGG); functional gastrointestinal disorders; constipation; colic; regurgitation; abdominal pain; lactose intolerance; inflammatory bowel diseases; Crohn's disease; nonspecific enterocolitis.*

# ПРОБИОТИКИ. ИСПОЛЬЗОВАНИЕ ШТАММА *L. RHAMNOSUS* ПРИ НЕИНФЕКЦИОННЫХ ПОРАЖЕНИЯХ ГАСТРОИНТЕСТИНАЛЬНОГО ТРАКТА

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***Для цитирования:*** Богданова Н.М. Пробиотики. Использование штамма *L. Rhamnosus* при неинфекционных поражениях гастроинтестинального тракта // Children's medicine of the North-West. 2023. Т. 11. № 1. С. 18–31. DOI: https://doi.org/10.56871/CmN-W.2023.27.16.002

**Поступила: 11.09.2022** **Одобрена: 17.11.2022** **Принята к печати: 15.01.2023**

***Резюме.*** Пробиотики — это живые, апатогенные для человека бактерии, обладающие антагонистической активностью в отношении патогенных и условно-патогенных бактерий и обеспечивающие восстановление нормальной микробиоты. Не любому микроорганизму может быть присвоен статус «пробиотик», а только тем, которые считаются безопасными и соответствуют определенным критериям. Несмотря на то что большая часть пробиотиков представлена изолятами индигенной микробиоты, механизм их действия в бионишах человека не эквивалентен эндогенным микроорганизмам. Функциональные гастроинтестинальные расстройства (ФГИР) широко распространены среди детей любого возраста. Изменения в «паспорте» микробиома кишечника способны затронуть ключевые механизмы, связанные с симптомами ФГИР. Очень часто причины пищеварительного дискомфорта (абдоминальная боль, вздутие живота, метеоризм, флатуленция и диарея) связаны с непереносимостью лактозы (НЛ). Воспалительные заболевания кишечника (ВЗК) характеризуются двунаправленной взаимосвязью между дисбиозом кишечника, хроническим воспалением и прогрессированием заболевания. В настоящее время мало клинических научных исследований с высокой степенью доказательности, что прием штаммоспецифичных пробиотиков обеспечивает должный биопрофилактический и биотерапевтический эффект при неинфекционных заболеваниях пищеварительного тракта. Хотя присутствуют как экспериментальные, так и клинические работы, в которых показано, что назначение *LGG* может оказать положительный эффект при этих нарушениях.

***Ключевые слова:*** *пробиотик; штаммоспецифичность; L. rhamnosus (LGG), функциональные гастроинтестинальные расстройства; запор; колики; срыгивание; абдоминальная боль; непереносимость лактозы; воспалительные заболевания кишечника; болезнь Крона; неспецифический энтероколит.*

## HISTORY OF PROBIOTICS

The beginning of the probiotic era can be considered the mid-19th century, when French microbiologist Louis Pasteur proved that food spoilage is caused by microorganisms [1–3], and British scientist Joseph Lister isolated *Streptococcus lactis* (now known as *Lactococcus lactis*) from rancid milk [4–7].

Nobel Prize winner I.I. Mechnikov made a huge contribution to the study of probiotics. While traveling in Bulgaria, he discovered that yogurt, which is everyday food of Bulgarians, contains specific bacteria and suggested that "health and longevity can be achieved by manipulating the intestinal microbiota, meaning the replacement of harmful microbes with beneficial ones" [8–12]. He identified that lactic acid bacteria found in yogurt, create an acidic environment entering the intestine, thus preventing the development of putrefactive bacteria, which cause the degradation of food proteins to indole, scatol, and other substances that are poisonous. These substances disrupt the vital functions of the body after being absorbed into the bloodstream.

In 1954, German scientist Ferdinand Vergin used the term «probiotic» to describe "active substances essential for health" and also emphasized the adverse effects of antibiotics on the beneficial gut microbiota [13, 14]. Later, American scientists D.M. Lilly and R.H. Stillwell (1965) introduced the term "probiotic" as opposed to the term antibiotic and characterized it as a microbial factor that stimulates the proliferative growth of other microorganisms [15].

In 1974, R. Parker described probiotics as «organisms and substances that promote intestinal microbial balance» [16]. Then R. Fuller (1980) emphasized the need for the viability of probiotics and put forward the idea of their positive impact on the health of patients [17, 18]. And finally, in 2014, the International Scientific Association for Probiotics and Prebiotics (ISAPP) confirmed R. Fuller's assumption and defined probiotics as «"live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [19].

According to the WHO (2005) definition, probiotics are live, apathogenic bacteria with antagonistic activity against pathogenic and opportunistic bacteria providing restoration of normal microbiota.

Studies in recent years demonstrate the effectiveness of not only live microbes, but also certain components of microorganisms, in particular, their DNA [20].

Commensal microorganisms inhabiting the intestines of healthy people (bifidobacteria, lactobacilli), as well as bacteria actively used in the food industry (lactococci, lactic acid streptococci, propionic acid bacteria and saccharomycetes (brewer's and baker's yeast)) are selected for further production. That is why their delivery matrix is not only in pharmaceutical forms, dietary supplements, but also in various types of food products, such as dairy products, ice cream, cheese, bakery products, etc. Taking into account the above-mentioned, the European Food Safety Authority (EFSA) recommends whole genome sequence (WGS) analysis of microorganisms intended for use in the food chain [21].

Only those species (genera) of microbes that meet certain criteria can be granted the status of "probiotic".

## SELECTION CRITERIA FOR PROBIOTICS DEVELOPED FOR HUMAN USE

1. The origin of the probiotic strain must be consistent with its habitat in the host. Only isolates of human origin, namely isolates from the small and/or large intestine and breast milk are approved for the production of probiotics for human use [22].

2. Isolates should be carefully characterized and examined for their beneficial effects [19, 22].

3. According to the European Food Safety Authority (EFSA) guidelines, all microorganisms should have levels of taxonomic identification of genus, species and strain [19, 21, 23, 24].

4. Any strain should undergo a strict safety assessment [19, 22, 25–27].

5. Whole genome sequence (WGS) of candidate strains is required for further preparation of probiotics [21].

6. Selection of candidate strains requires evaluation of their mechanisms of action under simulated gastrointestinal tract conditions (*in vitro*). Probiotic candidates should have acid and bile tolerance, as well as withstand osmotic fluctuations to remain viable during their transit through the gastrointestinal tract [28].

7. Candidate strains for probiotic production require validation by means of preclinical trials followed by double-blind and randomized human clinical trials [29].

8. The recommended probiotic dose is between $10^8$ (one hundred million) and $10^{11}$ (one hundred billion) viable colony forming units (CFU/mL/g) per day [29].

Although most probiotics are represented by isolates of indigeneous microbiota, their mechanism of action in the human microfrola is not equivalent to endogenous microorganisms. This is most likely due to the fact that exogenous "alien" microbes are incompatible with the resident bacteria of the macroorganism [30].

## PROBIOTIC MECHANISMS FOR THE MAINTENANCE OF A HEALTH PHENOTYPE

1. Competition for nutrients that would otherwise be consumed by enteropathogenic microorganisms [31–33].

2. Synthesis of antimicrobial compounds [34]. Different species of *Bifidobacteria* and *Lactobacilli* produce different types of bacteriocins and other antimicrobial compounds that inhibit the multiplication of pathogens [35, 36].

3. Modification (fermentation) of substrates in favor of the host [35–39], i.e. formation of large amounts of organic and volatile fatty acids [40]. Probiotic-mediated bioconversion of metabolites has been reported to have antimicrobial, anticancer, anti-inflammatory and antioxidant properties.

4. Immune stimulation. Probiotics demonstrate immunomodulatory activity by suppressing inflammatory responses, activating NK (natural killer) and DC (dendritic cells), modulating TLR (Toll-like receptors) expression, secretion of specific immunoglobulin A (IgA), regulating lymphocyte proliferation and balancing the ratio of T-helper (Th1/Th2) cells [41]. Structural components of the gut microbiota are extremelly important for biological prevention and biotherapeutic approaches because they have immunostimulatory effects and can be used instead of antibiotics, as vaccine adjuvants, as well as they can improve cognitive functions [42].

5. Strengthening the intestinal mucosal barrier by [43–45]:

- probiotic bacteria competing for cell adhesion sites;
- improving transepithelial electrical resistance (TEER);
- increasing butyrate levels;
- upregulation of tight junction (TJ) proteins (ZO-1, occludin and claudin-1);
- increasing mucus secretion (by upregulating MUC1, MUC2 and MUC3 in colonic epithelial cells);
- modulation of the gut microbiota.

Many studies have demonstrated that probiotics regulate inflammatory pathways, stimulate the expression of immune-related genes, and modulate the levels of immunologic markers [46, 47].

Despite the ever-growing spectrum of probiotic-based products, microbiome-targeted therapies, and related literature, the efficacy of specific probiotic strains in many diseases is not fully understood.

## *LACTOBACILLUS RHAMNOSUS (LGG)* IN PREVENTION AND TREATMENT OF FUNCTIONAL GASTROINTESTINAL DISORDERS

Functional gastrointestinal disorders (FGID) are widespread, affecting about one third of the population. The incidence of FGID is 20–30% even in infants of the first year of life [48]. The estimated incidence and popularity of this problem varies according to diagnostic criteria and conditions.

The etiology of these disorders is not fully clarified. Factors influencing the pathogenesis of FGIDs include: impaired motor function, visceral hypersensitivity, minimal inflammatory modifications in the intestinal mucosa and immune function. Recently, FGID has been considered as a product of interaction between psychosocial factors and altered gastrointestinal physiology via the microbiota-gut-brain axis (MGBA).

The gut microcosm has been found to influence the development and function of both the enteric nervous system (ENS) and the brain, via pattern recognition receptors (PRRs) and Toll-like receptors (TLRs), products of bacterial metabolism (short-chain fatty acids (SCFAs), tryptophan metabolic products), synthesis and release of neurotransmitters (gamma-aminobutyric acid (GABA), serotonin, acetylcholine, dopamine, etc.), which penetrate the intestinal wall and cross the blood-brain barrier (BBB) not only under increased permeability but also under normal conditions [49].

Thus, an imbalance in the intestinal microbiota leads to damage in the MGB axis and further formation of a vicious circle developing FGIDs. It is believed that administration of strain-specific probiotics *Escherichia coli DSM17252, Bifidobacterium animalis DN-173, Saccharomyces boulardii CNCM I-745, Bifidobacterium infantis 35624, Lactobacillus rhamnosus NCIMB 30174, Lactobacillus plantarum NCIMB 30173, Lactobacillus acidophilus NCIMB 30175, Enterococcus faecium NCIMB 30176* help to restore the function along the MGB axis [50, 51].

The cost-effectiveness of probiotic strain *Lactobacillus rhamnosus GG (LGG)* in FGID patients was studied at the Department of Pediatric Gastroenterology and Nutrition, Warsaw Medical University. The patients met the Rome II diagnostic criteria. The total number of participants was 104 children aged 6–16 years. For 4 weeks, one part of the children received *LGG* 3×109 CFU twice daily, while the other part received placebo [52].

Overall, 18 of 104 (17%) respondents reported successful treatment. Patients in the *LGG* group were more likely to have treatment success than those in the placebo group (25% vs. 9.6%; RB 2.6; 95% CI 1.05–6.6, NNT 7, 95% CI 4–123). Disappearance of pain attacks at the end of therapy was considered a criterion for treatment success. The authors found no significant differences between groups for any other outcome criterion [52].

In 2018, a meta-analysis evaluating the efficacy of different approaches in the treatment of patients with functional abdominal pain (FAP) was conducted [53].

A promising method for treating FAB, according to the meta-analysis, was the administration of probiotics containing *L. rhamnosus GG* and a multibiotic (VSL#3). The multibiotic includes eight strains: *Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus bulgaris, Streptococcus thermophiles* [54, 55].

Analysis of 15 studies involving 1123 children suffering from different FGID syndromes showed that the following probiotic isolates were most commonly used: *Lactobacillus rhamnosus GG* (5 trials); Lactobacillus reuteri DSM 17938 (5 trials); significantly less frequently, *Bacillus coagulans* with fructo- and oligosaccharides (FOGS) (2 trials); VSL#3 multiprobiotic (1 trial); a combination of three *Bifidobacterium strains: B. longum BB536, B infantis M-63* and *B. breve M-16 V* (1 trial) and in another case *L. plantarum LP299*. The duration of treatment ranged from 4 to 12 weeks. Most studies evaluated short-term results — in the first 3 months after the intervention. 9 studies reported a reduction in the frequency and intensity of pain episodes with the use of probiotics [56–62].

One of the first European randomized scientific trials, supervised by N. Pedersen (2014) at Herlev Hospital, University of Copenhagen, Denmark, examined the effect of a diet containing low amounts of fermentable oligosaccharides, disaccharides, monosaccharides, polyols (FODMAP). In addition to that *L. rhamnosus GG (LGG)* was administered at a dose of $1\times10^{11}$ CFU in irritable bowel syndrome (IBS). IBS was manifested by recurrent abdominal pain (IBS-A), constipation (IBS-C), or diarrhea (IBS-D). The study included 123 patients, predominantly female, 90 (73%). The mean age of the patients was 37 years, ranging from 18 to 74 years. All patients met Rome III diagnostic criteria prior to the study. They had a negative colonoscopy result, had no antibodies to transglutaminase and no lactose intolerance gene. The study continued for 6 weeks. Consequently, it was concluded that dietary adherence as well as LGG administration are effective in the treatment of patients with IBS, especially in IBS-D and IBS-A subtypes.

The efficacy of the isolate of *L. rhamnosus GG* might be explained by its ability to reduce acetylcholine-stimulated colonic contractions and to regulate the serotoninergic system, providing a prokinetic effect [63]. The way *Lactobacillus* effecting serotonin receptors and serotonin uptake mechanisms may play a key role in facilitating effective treatments of FGIDs associated with visceral hypersensitivity [64].

Thus, changes in the gut microbiome "passport" are able to affect key mechanisms associated with FGID symptoms: intestinal barrier permeability, impaired intestinal motility and visceral hypersensitivity. However, it is necessary to evaluate adherence to a FODMAP diet, satisfaction with dietitian recommendations, and improvement of symptoms in short and long term perspectives [65].

A 2015 meta-analysis of previous single studies confirmed that probiotic intervention reduces IBS symptoms [66]. Further studies revealed the efficacy of probiotic isolates such as *L. rhamnosus, L. acidophilus, S. thermophile, L. casei, L. bulgaricus, L. plantarum, L. salivarius, B. bifidum, B. longum (L. casei W56, L. acidophilus W22, L. paracasei W20, L. salivarius W24, L. plantarum W62, L. lactis W19, B. lactis W51, W52, B. bifidum W23)* in the therapy of IBS [67, 68].

A different opinion is traced in the works of C. Hill (2014) and H. Szajewska (2020). The authors mention that grouping several types of probiotics in such an analysis provides little information about the efficacy of individual strains, as they tend to have specific clinical effects [19, 69].

Lactic acid bacteria are thought to accelerate intestinal transit and improve stool consistency in constipation because they can modulate intes-

tinal motility by stimulating epithelial cells or directly affecting the enteric nervous system.

Experimental studies have shown that unidentified fermentation metabolites produced by *Lactobacillus*- and *Bifidobacterium* can ameliorate postinfectious intestinal motility disorders. However, a published systematic review concluded that the available evidence on the use of *Lactobacillus rhamnosus, Lactobacillus reuteri, Lactobacillus casei, B. lactis and Bifidobacterium longum* is insufficient to support the use of probiotics in the treatment of constipation in children [70]. According to international clinical guidelines and ESPGHAN and NASPGHAN documents, no strain has received reliable evidence of satisfactory efficacy in functional constipation [71, 72].

FGIDs in infants, especially in the first year of life, are characterized by a distinctive feature: the appearance of clinical symptoms occurs without the involvement of a psychosocial factor. The most common conditions are regurgitation, intestinal colic and functional constipation.

*Lactobacillus reuteri* DSM 17938 is the most studied and promising strain in the prevention and correction of FGID [73–76].

Literature on the cost-effectiveness of probiotic isolates in infants with regurgitation syndrome was performed with the help of MEDLINE, CINAHL and the Cochrane Central Register of Controlled Trials. As a result, six randomized controlled trials (RCTs) were identified which investigated the prevention or treatment of regurgitation in infants in the first months of life with probiotics. A meta-analysis of three RCTs showed a statistically significant reduction in regurgitation episodes in the probiotic group compared to the placebo group. However, the study sample was small and had high heterogeneity (96%). The researchers' conclusion suggests that probiotic therapy appears promising for regurgitation in infants with some evidence of benefit [77].

Colic is considered to be the equivalent of functional abdominal pain in infants. The results of a developmental study involving 89 infants aged 7–12 weeks are based on an attempt to link the composition of the gut microbiota, anxiety and duration of crying. In a double-blind RCT, the children received *LGG* for two months: the first month at a dose of $10^9$ CFU/day, the second month at a dose of $2\times10^9$ CFU/day, and were subsequently followed up for the entire first year of life. Children who were assigned to the «excessive crying» group were significantly less frequent in the *LGG* group than in the placebo group. According to the data of fecal microbiological studies, *Clostridium hydrolyticum* was detected significantly more often in children in the placebo group than in children receiving *LGG* (p=0,05).

Thus, the administration of *LGG*, as well as *L. reuteri*, may have a positive effect on such disorders as abdominal pain and intestinal discomfort in infants [78].

## *LACTOBACILLUS RHAMNOSUS* (*LGG*) *AND LACTOSE INTOLERANCE*

Symptoms of digestive discomfort (abdominal pain, abdominal bloating, meteorism, flatulence and diarrhea) are very often associated with lactose intolerance (LI) and occur as a result of bacterial fermentation of the disaccharide in the colon [79]. The causes leading to gastrointestinal disorders are attributed to the influence of both acquired and congenital factors. About 70% of the world's population has been determined to suffer from lactase deficiency due to a genetically programmed gradual decrease in lactase gene expression after weaning [80, 81].

In addition to gastrointestinal problems, individuals with LI have an increased risk of developing extraintestinal diseases, including cancer [82]. The clinical features can be modified by several predictors, including the dose of the disaccharide consumed, residual expression of the lactase enzyme, concurrent intake of other food components, the time of carbohydrate transit through the intestine, and the composition of the intestinal microbiome [79]. For this reason, it is pathogenetically validated that probiotic bacteria will help to alleviate the clinical symptoms of LI with the help of heterogeneous delivery matrices (dosage form, dietary supplements, fermented and non-fermented dairy products) [83].

The efficacy of probiotics in the treatment of LI was evaluated using MEDLINE (via PUBMED) and SCOPUS databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and included 15 randomized double-blind studies.

The risk of systematic error was determined for each selected study according to the Cochrane Collaboration methodology.

The presented studies examined eight probiotic strains with the greatest number of proven benefits, namely heat tolerance during production, high proteolytic and peptidolytic properties as they pass through the host digestive tract, re-

lease of smaller molecules of bioactive peptides during bacterial fermentation and other processes that stimulate the enzyme lactase to help humans digest the milk sugar, lactose.

Lactic acid bacteria (LAB) are among probiotic isolates possessing these properties: *Lactobacillus delbrueckii sub sp. bulgaricus, Streptococcus thermophilus, L. casea, L. rhamnosus (GG)* and some species of bifidobacteria [84]. The results of studies demonstrate heterogeneity in efficacy, however there is a generally positive correlation between probiotics and LI with respect to specific strains and concentrations [85, 86].

The research conducted at Clinica Medica «A. Murri», Department of *Biomedical Sciences* and Human Oncology, University of Bari Medical School, Italy (2019), proved the hypothesis that therapy with *Bifidobacterium longum BB536* and *Lactobacillus rhamnosus HN001* in combination with vitamin B6 alleviates LI symptoms through positive modulation of gut microbial composition and metabolism.

Twenty-three patients with persistent symptoms of LI were included in a crossover randomized double-blind study. The patients followed a lactose-free diet. Clinical manifestations, microbiome and metabolome were evaluated at bathe beginning of the study and after 30 days. Probiotic and vitamin $B_6$ administration significantly reduced abdominal bloating (p=0.028) and constipation (p=0.045) compared to placebo. The fecal microbiome differed between the groups. Administration of a probiotic with vitamin B6 promoted the enrichment of several genera of microbes involved in lactose digestion, including Bifidobacerium. In addition, the relative content of acetic acid, 2-methylpropanoic acid, nonenal (a chemical compound subsumed into unsaturated fatty aldehydes that naturally occurs in the form of cis- and trans-isomers) and indolizin-3-methyl increased, while phenol decreased.

Thus, the results emphasized the importance of considering the composition of probiotics prescribed to alleviate symptoms and normalize gut dysbiosis in patients with HL and persistent functional gastrointestinal disorders [87].

### *LACTOBACILLUS RHAMNOSUS (LGG) AND PREVENTION OF INFLAMMATORY BOWEL DISEASES (CROHN'S DISEASE, NECROTISING ENTEROCOLITIS)*

Inflammatory bowel diseases (IBD) are caused by a wide range of disorders characterized by intestinal dysbiosis, chronic inflammation, mucosal ulceration and ultimate loss of intestinal function [88, 89].

Recent achievements demonstrate a bidirectional relationship between gut dysbiosis and disease progression [89].

The molecular mechanisms by which probiotics induce an anti-inflammatory response have been studied. One of these studies identified a protective mechanism of breast milk and probiotics in necrotising enterocolitis (NEC) [90].

NEC is a serious gastrointestinal disease in preterm infants caused by invasion of pathogenic bacteria, followed by inflammation in the colon, which accelerates perforation and permeability of the intestine, leading to generalization of infection and death.

Prevention of the pathology is challenging, however, it has been observed that feeding a preterm infant with decanted native breast milk together with probiotics provides the best protection [91, 92]. The mechanism of protection is provided by indole-3-lactic acid (ILA), which is a tryptophan metabolite of breast milk. ILA has been identified as an anti-inflammatory molecule that induces an anti-inflammatory response through interaction with the aryl hydrocarbon transcription factor receptor (AHR) and suppresses IL-1β-induced transcription of IL-8, i.e., attenuates the synthesis of the pro-inflammatory cytokine IL-8 [90].

Clinical trials have demonstrated that a combination of *Lactobacillus* spp. and *Bifidobacterium spp. (L. rhamnosus ATCC 53103* and *B. longum subsp. infantis; or L. casei* and *B. breve; or L. rhamnosus, L. acidophilus, L. casei, B. longum subsp. infantis, B. bifidum* and *B. longum subsp. longum; or L. acidophilus* and *B. longum subsp. infantis; or L acidophilus* and *B. bifidum; or L. rhamnosus ATCC 53103* and *B. longum Reuter ATCC BAAA. longum Reuter ATCC BAA-999; or L. acidophilus, B. bifidum, B. animalis subsp. lactis,* and *B. longum subsp. longum); or B. animalis subsp. lactis (including DSM 15954) or L. reuteri (DSM 17938 or ATCC 55730); or L. rhamnosus (ATCC 53103 or ATC A07FA or LCR 35)* prevents NEC (medium to high level of evidence) in preterm infants (gestational age less than 37 weeks) and infants with low weight. A systematic review of RCTs also showed a reduced risk of death in groups of preterm infants treated with probiotics [93].

The effectiveness of probiotics in maintaining remission of Crohn's disease (CD) was searched in the electronic databases MEDLINE (from the creation to July 6, 2020), Embase (from the creation

to July 6, 2020), the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Register of Specialized Trials IBD Review Group, the World Health Organization (WHO) International Clinical Trials Registry Platform, and ClinicalTrials.gov.

There were found only two RCTs which comparing probiotics with placebo or any other non-biotic intervention for inducing remission in Crohn's disease (CD).

One study, conducted in Germany, involved 11 adults with mild to moderate CD who were treated with a week-long course of corticosteroids and antibiotics (ciprofloxacin 500 mg twice daily and metronidazole 250 mg three times daily) followed by randomized group assignment: *Lactobacillus rhamnosus* strain GG or placebo.

In another study conducted in the United Kingdom (UK), 35 adult participants with active CD (CDAI score between 150 and 450) were randomized to receive a synbiotic treatment consisting of lyophilized Bifidobacterium longum and a commercial product or placebo.

Cumulatively, both studies presented (n=46) showed no difference between probiotic and placebo use in inducing remission of BC after 6 months (OR 1.06; 95% CI 0.65–1.71), as well as no difference in the development of adverse events (OR 2.55; 95% CI 0.11–58.60).

Thus, the available evidence is very uncertain regarding the efficacy or safety of probiotics compared to placebo for inducing remission of Crohn's disease. Although, there are works supporting the high anti-inflammatory potential of probiotics and their efficacy in restoring the microbial landscape, with preservation of intestinal barrier integrity and reduction of intestinal inflammation. Further strain-specific RCTs are needed to understand the efficacy of probiotics in Crohn's disease [94].

## CONCLUSIONS

The history of probiotic development spans over 170 years. The ultimate breakthrough in this field started from the middle of the twentieth century. At present, the production of probiotics continues to grow steadily as the demand for them is high both as prescription and over-the-counter drugs. However, the constantly expanding base of probiotic products is often mislabeled by industry and misunderstood by consumers. Inconsistencies must be avoided in the probiotic industry, including proper product labeling, safety and efficacy. In addition, probiotic strains must be able to withstand manufacturing processes and environmental factors to remain viable and retain the ability to colonize the gastrointestinal tract.

It is worth remembering that probiotic microorganisms are both strain and disease specific, meaning that each probiotic strain contains its own unique set of functional genes. Therefore, a particular product cannot be comprehensive for every condition when it comes to the functionality of probiotics.

The selection of an appropriate probiotic must be based on probiotic and host specific factors for successful treatment. Probiotic-specific factors include: origin of a strain, strain-specific genetic markers of a probiotic, type of formulation, viability of a strain, and amount of dose prescribed. Host-specific factors include: type of disease or indication, composition of a gut microflora, diet, age, anthropometric measurements and host lifestyle. Only after taking all these aspects into account it is possible to expect positive effects of probiotics.

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