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Review Article

Role of Probiotics in Gastrointestinal Diseases

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Abstract

The use of probiotics may induce a 'barrier' influence against common pathogens and antigens by activating macrophages, altering cytokines, increasing natural killer cell activity, and/or increasing levels of immunoglobulins. Recognition of *in vivo* and immunomodulatory roles of probiotic is now promoting opportunities for the use of these microorganisms in many fields, e.g. inflammation, infection and atopy. The survival issues of probiotics are associated with their establishment in the competitive gut ecosystem.

The generation of immune physiological regulation in the gut depends on the establishment of indigenous microflora and on the therapeutic interventions based on the consumption of cultures of beneficial live microorganisms that act as probiotics. One of possible mechanisms of probiotics is promotion of a nonimmunologic gut defence barrier, which includes the normalization of increased intestinal permeability (dysbiosis) and gut microecology.

The role and effect of probiotics in infant feeding, on the mucosal permeability and microbial flora composition and in turn on the stabilization of Th1/Th2 and IgE production has been tested.

Another possible mechanism of probiotics is improvement of the intestine's immunologic barrier, particularly through intestinal immunoglobulin and, alleviation of intestinal inflammatory reaction that promotes a gut-stabilizing effect.

Many probiotics effects are mediated through immune regulation, particularly through balance control of proinflammatory and anti-inflammatory cytokines. So, probiotics can be used as innovative tools to alleviate intestinal inflammation, normalize gut mucosal dysfunction, and down-regulate hypersensitivity reactions. There are differences that exist in the immunomodulatory effects of candidate probiotics.

Keywords: *Probiotics; Dysbiosis; Modulation; Inflammation*

Introduction

The concept of the human microbiome was first introduced to the scientific community by Joshua Lederberg who defined it as 'the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space and have been all but ignored as determinants of health and disease [1].

According to the Food and Agricultural Organization of the United Nations and the World Health Organization, probiotics are defined as 'living microorganisms, which when administered in adequate amounts confer health benefits on the host [2].

The intestinal microbiome plays an important role in the integrity and function of the gastrointestinal tract, maintenance of immune homeostasis and host energy metabolism [3].

Dysbiosis is the perturbation in the composition of microbial communities, which may result in disrupted interactions between microbes and their host. These changes may contribute to disease susceptibility, the associations between intestinal dysbiosis and chronic

low-grade inflammation has been demonstrated in several studies [4]. Interplay between obesity and associated metabolic disorders: new insights into the gut microbiota, and metabolic disorders [5].

Alterations in the composition of the intestinal microbiome have been associated with infections in the gastrointestinal tract, inflammatory bowel disease and irritable bowel syndrome [3].

Probiotics should have the following key features: should be present in the form of living cells, preferably in large quantities prior to ingestion, stable and remain active throughout the life of the product and provide health benefits to the host.

The main mode of action of probiotics

Inhibit the proliferation of pathogenic bacteria by producing organic acids and reducing pH

The *bifidobacteria*, in addition to other sanogenetic actions (the improvement of vitamin and protidic metabolism) have antibacterial action especially on pathogenic species (*E. coli, Staphylococcus aureus, Shigella, Salmonella*, etc.) through the production of short chain volatile fatty acids and substances with antibiotic action.

The *lactobacilli* produce organic acids, hydrogen peroxide and antibacterial peptides (lactocidin, acidophilin, lactacin B, etc.). Most probiotics produce lactic acid, which lowers the local pH and thus prevents the growth of sensitive bacteria in acid and renders permeable the outer membrane of Gram-negative bacteria [6,7].

Produce specific antibacterial substances such as bacteriocines [8]

Probiotics compete with non-commensal bacteria and favor their elimination through the secretion of antimicrobial factors, the increased production of antibodies and activation of macrophages. Probiotics participate in modulating nutrition by producing certain vitamins and fragmentation of undigested molecules. All these features argue in favor of a symbiotic relationship between the human organism and probiotics. This hypothesis would explain in part why administration of probiotics reduces the incidence and severity of autoimmune diseases.

The effects of probiotics on the intestinal epithelium

Studies *in vitro* and *in vivo* have shown that certain species and bacterial strains produce extracellular glycosidase which degrades the glycoproteins or intestinal mucins and that others are able to stimulate the secretion of mucus, although specific data on probiotics are relatively sporadic [9-11]. Some probiotics produce metabolites that directly affect the epithelial permeability and enhance the permeability barrier *in vitro*. The evidence from studies on both animals and people shows that probiotics can restore damaged epithelial permeability and also support the existence of such a mechanism [12]. Probiotics produce H_2O_2 and prevent the adhesion of pathogenic bacteria to the intestine's wall. They also produce metabolites that are able to neutralize bacterial toxins "*in situ*" or to inhibit their production. Due to the mitigation of the intra-digestive catabolism, there appears a reorientation of gut microbiota in order to reduce the absorption of toxic substances such as NH_3, amines, indoles and the decrease of the bio-transformations of bile salts and fatty acids into the toxic products

The Effects of Probiotics on the Immune System

Probiotics affect non-specific immunity. It includes two systems: a system that works by antibodies secreted by B lymphocytes (humoral immunity) and another operating system that functions through direct T lymphocytes (cell mediated immunity). The two systems communicate with each other through chemicals called interleukins. The increase of the specific immune response translates into an activation of T and B lymphocytes which causes an increase in the level of interleukins and circulating antibodies (immunoglobulin M and immunoglobulin G). The probiotics also have an effect on the production of antibodies (mainly immunoglobulin A) in the intestinal lumen.

In contact with antigens present in the digestive content, the immunoglobulin A is very important in the digestive tract, representing a first defense against infection.

They are produced by the plasma cells of its own lamina, transported through the epithelium and secreted into the intestinal lumen as secretor IgA in combination with a secretory compound.

Immunoglobulin A can inhibit the adhesion of pathogenic bacteria in the mucosal surface of the digestive tract by [13]:

- The agglutination of bacteria
- The adhesive proteins present on the surface of bacteria;
- The interference of the adhesive complex substances/cell receptors.

The probiotics of *Lactobacillus* strains inhibit the secretion of the tumor necrosis factor TNFα, a pro-inflammatory cytokine produced by murine macrophages. Schultz has shown that these may be recognized through TLR2 by antigen-presenting cells in Peyer plates and can stimulate the production of cytokines such as TNFα and IL8. Several Lactobacillus strains can inhibit the proliferation of CD4+ lymphocytes without affecting the production of TNFα, IL4, IL5 and IL10, both in healthy individuals and in patients with inflammatory intestinal disease [14].

There is experimental evidence supporting the influence of ingested probiotic strains on the composition and metabolic activity of gut microbiota in healthy individuals. The survival of probiotics ingested in different segments of the digestive tract varies from one strain to another. Some strains are rapidly inactivated in the stomach, while specific strains of lactic acid bacteria can pass through the entire gastrointestinal tract in large quantities.

Use of Probiotics in Prevention and Treatment of Clinical Diseases

Treatment of acute gastroenteritis

In 2014, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) provided recommendations for the use of probiotics for the treatment of acute gastroenteritis in previously healthy infants and children based on a systematic review. The use of the following probiotics may be considered in the management of children with acute gastroenteritis in addition to rehydration therapy: *Lactobacillus rhamnosus* GG (LGG) (low quality of evidence; strong recommendation) and *S. boulardii* (low quality of evidence; strong recommendation). Less compelling evidence is available for *Lactobacillus reuteri* DSM 17938 (very low quality of evidence; weak recommendation) [15,16].

In summary, in line with current European guidelines, the use of probiotics with documented efficacy may be considered in the management of acute gastroenteritis.

Prevention of nosocomial diarrhea

A 2011 meta-analysis included three RCTs that compared LGG administration with placebo in 1092 children during their hospital stay was associated with significantly lower rates of diarrhoea (two RCTs, n = 823, RR 0.37, 95% CI 0.23 to 0.59) and symptomatic rotavirus gastroenteritis (three RCTs, n = 1043, RR 0.49, 95% CI 0.28 to 0.86) [17]. A placebo-controlled, double-blind RCT performed in 106 children aged 1 - 48 months concluded that *L. reuteri* DSM 17938 did not significantly affect the risk of developing nosocomial diarrhoea (RR 1.06, 95% CI 0.7 to 1.5) or rotavirus infection (RR 1.04, 95% CI 0.6 to 1.6) [18].

Another double-blind, placebo controlled RCT demonstrated that administration of *Bifidobacterium animalis* subsp. lactis BB-12 was not effective in preventing nosocomial infections occurring > 48h after admission in hospitalized children older than 1 year [19].

Prevention of allergy

The European Academy of Allergy and Clinical Immunology (EAACI) in 2014, stated that there is no evidence to support the use of probiotics (also prebiotics) for food allergy prevention [20].

The World Allergy Organization (WAO) published guidelines in 2015 [21]. These guidelines are based on the findings from the systematic review [22], which concluded that there are significant benefits of probiotic supplements in reducing the risk of eczema when used by women during the last trimester of pregnancy (RR 0.71, 95% CI 0.60 to 0.84), when used by breastfeeding mothers (RR 0.57, 95% CI 0.47 to 0.69) or when given to infants (RR 0.80, 95% CI 0.68 to 0.94).

Prevention of necrotising enterocolitis

The enteral administration of probiotics reduces the risks of NEC and mortality in preterm infants as demonstrated in a number of meta-analyses. In a Cochrane review that included 24 RCTs, preterm neonates in the probiotics group had reduced risks of NEC stage ≥ 2 (20 RCTs, n = 5529, RR 0.43, 95% CI 0.33 to 0.56) and all-cause mortality (17 RCTs, n = 5112, RR 0.65, 95% CI 0.52 to 0.81), compared with the control, and also reduced the time until full enteral feeding [23,24].

Six RCTs (n = 1778) that focused on *L. reuteri* DSM 17938 showed that the administration of *L. reuteri* DSM 17938 significantly reduced the time to full feeds (two RCTs, n = 1071, mean difference (MD) -1.34 days, 95% CI -1.81 to -0.86), duration of hospitalisation (three RCTs, n = 837, MD -10.77 days, 95% CI -13.67 to -7.86) and risk of late-onset sepsis (four RCTs, n = 2347, RR 0.66, 95% CI 0.52 to 0.83).

Infantile colic

The administration of *L. reuteri* DSM 17938 is likely to reduce crying times in breastfed infants with infantile colic. A meta-analysis of three RCTs that compared the administration of *L. reuteri* DSM with placebo showed that it reduced crying time on day 21 by approximately 43 min (MD -43 min/day, 95% CI -68 to -19). This effect was mainly seen in breastfed infants [25].

Another RCT that included 589 breastfed and formula-fed infants revealed that compared with placebo the administration of L. reuteri DSM 17938 daily from day 3 to 90 days resulted in a significant reduction of crying time by approximately 51 min/day at 1 month and 33 min/day at 3 months [26].

***Helicobacter pylori* infection**

Four meta-analyses of RCT's have been conducted to determine the efficacy of probiotics in *H. pylori* eradication therapy in children showed that the supplementation of probiotic strains (e.g., *Saccharomyces boulardii, Lactobacillus* or *Bifidobacterium* strains) with triple therapy (amoxicillin, clarithromycin, omeprazole), effectively increased the eradication rate of *H. pylori*, in comparison with a monotherapy of two antibiotics plus a proton pump inhibitor [27,28].

Furthermore, the addition of probiotics reduced side effects from the antibiotic therapies mainly diarrhea.

Treatment of inflammatory bowel diseases

A RCT that included 29 children with newly diagnosed chronic ulcerative colitis were randomly assigned to receive either VSL#3 or a placebo for 1 year had promising results [29].

All patients received standard corticosteroid induction therapy combined with mesalamine maintenance therapy. Remission occurred in 13 patients (92.8%) in the VSL#3 group and 4 patients (36.4%) in the placebo group (P .001). Relapse occurred in 3 of 13 (23%) patients in the VSL#3 group versus 11 of 15 (73.3%) in the placebo group within the 1-year study period (RR: 0.32 [95% CI: 0.25 - 0.773]; P .014). Despite that these results are promising, more studies are needed in larger numbers of children with mild-to-moderate chronic ulcerative colitis.

One RCT in which LGG was used in pediatric patients with Crohn disease resulted in no significant benefit [30] Because of the lack of efficacy, treatment of Crohn disease with probiotics cannot be recommended for children.

Conclusion

Probiotics are a helpful tool in specific infectious, inflammatory and functional disorders. They have demonstrated efficacy in preventing and treating various medical conditions, particularly those involving the gastrointestinal tract in children. In addition, available literature shows a statistically significant benefit in decreasing intensity, duration and number of consultations for acute gastroenteritis caused by various infectious agents, mostly viral and parasitic-related illnesses, when specific probiotics are combined with oral rehydrating solution.

Due to strain specificity, only clinically tested probiotics can be recommended to treat pediatric patients.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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