Probiotics in the Treatment of Rotavirus Gastrointestinal Infections

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Contributor: Andrej Steyer , Dušanka Mičetić-Turk , Sabina Fijan

Enteric viruses, including the rotavirus, norovirus, and adenoviruses, are the most common cause of acute gastroenteritis. The rotavirus disease is especially prevalent among children, and studies over the past decade have revealed complex interactions between rotaviruses and the gut microbiota. One way to treat and prevent dysbiosis is the use of probiotics as an antiviral agent.

probiotics microbiota rotaviruses

1. Introduction

Acute gastroenteritis is one of the most frequently reported infectious diseases in the world. The most common cause of acute gastroenteritis (AGE) is various enteric viruses, including rotaviruses, noroviruses, astroviruses, adenoviruses, and other less presentable viruses [1]. Most are icosahedral nonenveloped viruses, known to present stability in the environment, resistant to many physio-chemical conditions. Their stability in the environment and on various fomites is also crucial for indirect transmission via contaminated surfaces, food, and water [2]. As the infectious dose, particularly for noroviruses, is very low [3], indirect infections are possible, and each year researchers can follow reports on food and/or waterborne infections, mostly with noroviruses.

Rotaviruses are members of the *Reoviridae* family and are characterized by their non-enveloped, segmented, double-stranded RNA genome (11 segments). Each of the 11 genes code for a single gene product. Six of the proteins are found in the virus particle (vp1, vp2, vp3, vp4, vp6 and vp7), whereas the remaining five proteins are non-structural (NDP1–NSP5). The *Rotavirus* is classified into serogroups A to E based on antigenic properties. Only groups A to C have been shown to infect humans, and the most human *Rotavirus* disease is caused by the group A *Rotavirus*. The group A *Rotavirus* is further classified into G (serotypes) and P types based on identification of antigens on the outer capsid proteins. Group A rotavirus genotypes are classified by a nucleotide-sequence-based, complete genome classification system [4][5].

Rotavirus gastroenteritis is still an important public health concern. In particular, low-income countries are fighting against the rotavirus disease, especially affecting small children [6]. Rotavirus gastroenteritis is the leading global pathogen of diarrhoea-associated mortality with the highest death rate among children under 5 years worldwide. Since 2006, efficient vaccines have been available to protect children from severe rotavirus gastroenteritis [7]. However, there are still high numbers of acute rotavirus gastroenteritis in those countries.

During the post-marketing phase of rotavirus vaccines, one of the most exceptional findings was the difference in vaccine effectiveness, being much lower in low- and middle-income countries [8][9]. One of the possible explanations was the effect of histo-blood groups, which may contribute to the virus binding on these antigens [10][11]. In parallel, a new research area of the virus–bacteria interactions opened, showing that enteric viruses may bind to bacteria surface antigens, which may influence the early phases of virus pathogenesis [12][13][14]. Consequently, it is clear now that the pathogenesis of enteric viruses is dependent not only on virus pathogenetic factors or host determinants, but also on the environment. The microbiota is therefore of high importance and can influence the effectiveness of the rotavirus or other enteric virus infections. In addition, studies on probiotics are also promising in the prevention phase, and to some extent, also in the curative phase of AGE [15][16][17].

The gastrointestinal tract is one of the most microbiologically active ecosystems with a high density of bacteria and other microbes formulating the intestinal microbiota. This microbiota has several beneficial roles for its human host, including antimicrobial activity, competitive exclusion, immunomodulation, strengthening of the epithelial barrier function, as well as influencing the immune system, central nervous system, and endocrine system [18][19][20][21]. Recent evidence-based research shows that the gut microbiota is an ally for the interaction with most human cells via the microbiota-gut-brain axis, microbiota-gut-skin axis, microbiota-gut-lung axis, microbiota-gut-liver axis, microbiota-gut-vagina axis, and many more axes. The microbiota thus aids in achieving homeostasis of skin health, respiratory health, organ health, mental health, and so forth of its host [19][20][21][22][23][24][25][26][27][28]. The intestinal microbiota coexists with microbes that reach the intestine through food intake and influences the immune cells associated with the lamina propria through the production of metabolites, crucial for the maturation of immune cells in the mucosal immune system [19][21][29]. Disruption of the homeostasis between the intestinal microbiome and the host immune system can adversely impact viral immunity [30].

Rotaviruses infect the small intestine, an important site of colonization by the microbiota, and studies over the past decade have begun to reveal a complex set of interactions between rotaviruses and the gut microbiota, as rotavirus infection can temporarily alter the composition of the gut microbiota [13]. One way to treat and prevent dysbiosis is the use of probiotics. Probiotics are, by definition, “live microorganisms that, when administered in adequate amounts, confer a health effect on the host” [31]. Scientific evidence shows enough evidence to justify the use of probiotics for the treatment of several disorders, including gastrointestinal dysbiosis, antibiotic-associated diarrhoea, irritable bowel syndrome, and inflammatory bowel disease, as well as anxiety, depression, and wound healing [19][20][32][33][34][35]. In a review on the management of acute gastroenteritis in Jordanian children [36], it was emphasised that prevention of diarrhoea diseases should focus on the improvement of nutrition, hygiene, and sanitation. In the case of rotavirus gastroenteritis, the authors proposed the introduction of routine vaccination against the rotavirus, as well as the use of adjuvant therapies. One of these possible therapies is probiotics. Other reviews addressing gastrointestinal infections also conclude that probiotics are one of the possible adjuvant strategies for diarrhoea in children by resuming a healthy microbiota status following infection [37][38][39].

2. Rotavirus Infection and the Gut

The *Rotavirus* infects the mature enterocytes in the middle and upper parts of the villi and in the enteroendocrine cells in the small intestine, which ultimately leads to diarrhea [40]. Rotavirus infection can temporarily alter the composition of the gut microbiota, thus leading to dysbiosis [13]. According to one study, dysbios is caused by a decrease in the amount of bifidobacteria, normal *Escherichia coli,* and an increase in the amount of lactose-negative *Escherichia*. In cases of pronounced dysbiosis in young children, the clinical course of rotavirus infection is aggravated and the period of rotavirus excretion is prolonged [41]. Other studies found that patients with diarrheal stools with rotavirus had more bacterial communites at the genus level containing specific diarrheal causative bacteria than those of healthy subjects, suggesting that co-infection with the virus and bacteria could have occurred in some diarrhea cases [40]. Gut dysbiosis due to viral infection could be associated with a reduction in the populations of common and beneficial bacterial species and the resulting loss of diversity, as well as the gain of harmful bacteria. It may also be due to variations in crosstalk via direct interaction between rotaviruses and bacteria in the gut [40][42].

A symptomatic infection with rotaviruses stimulates a strong humoral IgG immune response which lasts for a lifetime. While the IgG responses are easily recorded, it is generally thought that protection from rotavirus disease is mediated by local IgA antibodies [4][43].

3. Probiotics and the Antiviral Mechanisms

Probiotic administration stimulates the immune system by inducing a network of signals mediated by various metabolites. Some probiotic strains stimulate the immune response and are therefore beneficial for patients suffering from immune deficiency, whilst other strains inhibit the immune response and are therefore beneficial for patients with conditions with immune activation. Additionally, the effects of probiotic modulation on the immune cells can be observed in lymphocytes, hematopoietic stem cells, T cells, macrophages, natural killer cells, and dendritic cells. Additionally, molecules usually associated with pathogens, such as lipopolysaccharide of gram-negative bacteria or lipoteichoic acids of gram-positive bacteria, can be produced by probiotics and interact with different toll-like receptors, and incite NF-κB-mediated antiviral gene expression [19][34][35][44][45].

It is also known that respiratory viruses can cause changes in the gut microbiome, therefore probiotics are a possible medication to treat respiratory viral infections via gut-microbiota modulation and production of immunomodulatory agents. Interactions between probiotics, macrophages, and dendritic cells are seen in the lamina propria, resulting in natural killer (NK) cell activation, which triggers interferon gamma (IFN-γ) production to defend against viruses, and efficient immune cells go to infection sites via circulatory and lymphatic systems to protect against respiratory viruses [35][44][45].

Bacteriocins produced by probiotics have also proven effective against viral infections as they exhibit antimicrobial potential against viral pathogens by prevention of viral particle aggregation and blocking the sites of host cell receptors or inhibition of viral penetration into human cells [46][47][48][49].

All above-mentioned mechanisms collectively lead to the indirect consequence of a shorter infectious period and overall reduction in the risk of viral infection [50][51][52].

On the other hand, previous bacterial infections in children may increase the risk of rotavirus infections by disrupting the balance of the intestinal microbiota, leading to dysbiosis and increasing the ratio of pathogenic bacteria [53][54]. Co-infection with bacterial diarrhoea-related bacterial pathogens, such as *Escherichia, Shigella, Klebsiella,* and *Campylobacter* spp., can cause a more severe course of the rotavirus disease [40]. Although it is well-established that probiotics display antibacterial activities against common pathogenic bacteria, including competitive exclusion, bacteriocin production, enhancing intestinal barrier function, and stimulation of host antimicrobial defences [43], these bacterial infections can antagonise the antivirus effects of probiotics while they are fighting off bacterial pathogens. Therefore, more research into the complex mechanisms of actions of probiotics and pathogens is warranted.

4. Clinical Trials with Established Antiviral Effect of Probiotics against Rotaviruses

Researchers used the search strategy: “probiotics” AND rotavirus in various databases (PubMed, Web of Science, Scopus) and included clinical trials, which found a statistically significant antiviral effect of probiotics in the treatment of rotavirus gastroenteritis. Clinical trials without the full text available and in languages other than English were excluded. Clinical trials where rotaviruses were not determined or detected were also excluded. A total of 19 clinical studies with a statistically significant antiviral effect of probiotics against rotaviruses were found. These studies were conducted in Argentina, Bangladesh, Bolivia, Brazil, Croatia, Denmark, Egypt, Greece, India, Israel, Italy, the Republic of Korea, the Netherlands, Poland, Portugal, Slovenia, Taiwan, Turkey, and the United Kingdom.

Researchers included two additional clinical trials [55][56] compared to the 2020 review [57] and several more compared to the 2015 review [58] which selected clinical trials published until the year 2013. Strain-specific antiviral activity of probiotic strains, as well as the concentration of probiotic supplements and duration of supplementation, seem to be the most important factors that influence the efficiency of probiotics on rotavirus disease in children [52].

Rotaviruses can cause significant diarrhoeal disease in infants and young ones of various mammalian and avian species [15]. According to European Society for Paediatric Gastroenterology, Hepatology and Nutrition/ESPGHAN/ESMAD, the standard recommended treatment for acute diarrhoea in children, whether due to the rotavirus, norovirus, bacterial or other infection, includes oral rehydration solutions (ORS) and continuance of feeding. Adjuvant therapy with micronutrients, probiotics, or anti-diarrhoea agents are also rendered useful. The recommended probiotics are *Lacticaseibacillus rhamnosus* GG (ATCC 53103), also known as LGG, and the yeast *Saccharomyces cerevisiae* var. *boulardii* [59][60][61][62].

The underlying mechanism against rotavirus infections is immune enhancement, as certain strains of lactobacilli promote immunological responses. This includes increasing concentrations of anti-rotavirus-specific IgA [52][63],

reducing intestinal microbiota imbalance, enhancing the colonization of probiotics [64][65], and reducing the incidence of diarrhoea [66]. One important activity of probiotics is also increasing the clearance of stool rotavirus by reducing faecal rotavirus shedding, and thus aiding the epidemiological importance in the transmission of rotaviruses [67][68].

Some studies divided the intervention groups of children into more than one group to ascertain the effect of different combinations of probiotics or different concentrations on rotavirus diarrhoea. Five of these studies investigated the single-strain probiotic *Lactobacillus rhamnosus* GG [69][70][71][72][73]. *Saccharomyces boulardii* was investigated in six studies [55][74][75][76][77][78]. One aforementioned study [55] also investigated the effectiveness of *Lactiplantibacillus plantarum* LRCC5310 on rotavirus infection. Two other aforementioned studies [77][78] also investigated multi-strain probiotics. All the remaining studies investigated various multi-strain probiotics [52][56][79][80][81][82][83][84].

Two abstracts of additional studies in the English language were found [85][86] that noted a beneficial effect of the probiotics in the abstract, but a full text with all relevant data was not available despite contacting the authors. Two studies [65][87] in the Chinese language also found a beneficial effect of probiotics for the prevention of diarrhoea in children, some of which tested positive for the rotavirus in stool samples; however, they were not included as only the abstract was in English. According to the abstracts, both studies found that probiotic supplementation with lactobacilli and/or bifidobacteria (species not specified in abstract) significantly decreased the incidence and duration of diarrhoea. Another study in the French language [88] also found an antiviral effect of *Saccharomyces cerevisiae* var. *boulardii* supplementation in children with acute diarrhoea (15 with rotavirus infection) and found a significant decrease in the duration of diarrhoea.

The effect of different multi-strain probiotics on rotavirus diarrhoea was significant after supplementation with *Bifidobacterium longum* BORI and *Lactobacillus acidophilus* AD031 [56], *Bifidobacterium longum* IBG, *Bifidobacterium lactis* BL, *Lactobacillus acidophilus* LA, *Lacticaseibacillus rhamnosus* LRH, *Lactiplantibacillus plantarum*, and *Pediococcus pentosaceus* [52], *Enterococcus faecalis* T-110, *Clostridium butyricum* TO-A and *Bacillus mesentericus* TO-A [79], unspecified strains of *Lactobacillus acidophilus*, *Lacticaseibacillus rhamnosus,* and *Saccharomyces boulardii* [77][80], VSL#3, containing four lactobacilli strains, three bifidobacteria strains, and one strain of *Streptococcus thermophilus* [81], BIFILAC, containing strains of *Enterococcus faecalis*, *Clostridium butyricum*, *Bacillus mesentericus* and *Bacillus coagulans* [82], Lakcid L, containing *Lacticaseibacillus rhamnosus* 573L/1, 573L/2, 573L/3 [83], *Lactobacillus casei and Lactobacillus acidophilus strains* CERELA [78] and *Lacticaseibacillus rhamnosus* 19070-2 and *L. reuteri* DSM 12,246 [84]. However, several studies did not report the strains used, which decreased the quality and reproducibility of the studies.

The probiotic strain *Lacticaseibacillus rhamnosus* GG, previously known as *Lactobacillus rhamnosus* GG (LGG), is a gram-positive lactobacillus, known to promote immunological responses and influence the intestinal microbiota by producing both a biofilm that can mechanically protect the mucosa, and different soluble factors beneficial to the gut by enhancing intestinal crypt survival, diminishing apoptosis of the intestinal epithelium, and preserving cytoskeletal integrity [89]. The ESPGHAN recommends LGG as an adjuvant therapy for gastrointestinal infections in

children [59][62]. It was used in a large multi-centre European trial [72] with patients from Poland, Egypt, Croatia, Italy, Slovenia, the Netherlands, Greece, Israel, the United Kingdom, and Portugal. Administering the oral rehydration solution containing LGG to children with acute diarrhoea was found safe and resulted in a shorter duration of diarrhoea, less chance of a protracted course, and faster discharge from the hospital. There is also a large cohort of other studies using the same strain LGG that also confirms this effect [69][70][71][73]. A study by Szajewska et al. [90] that investigated the prevention of nosocomial diarrhoea found that supplementation with *Lacticaseibacillus rhamnosus* GG resulted in a reduced risk of nosocomial diarrhoea in children. A systematic review also confirms the reduction in the duration of rotavirus-induced diarrhoea, where a higher dose was efficient [91]. Another important factor to consider is the possible effect of rotavirus immunisation on the effectiveness of LGG, as noted in the meta-analysis [92], where the authors concluded that rotavirus immunisation affected the efficacy of LGG for the treatment of children with acute diarrhoea, which could be one of the underlying reasons for the mixed results. However, other reviews conclude that probiotics as adjuvants in vaccination should be considered in future studies, especially in the elderly and in children, where vaccine effectiveness and duration of immunisation really matter [38] [93].

The probiotic yeast *Saccharomyces cerevisiae* var. *boulardii* is the only yeast used in clinical practice and is recommended for the prevention of antibiotic-associated diarrhoea and acute gastroenteritis in children as an adjunct [61][94] The mechanisms of action include inhibition of growth and invasion of pathogens by interfering with pathogen attachment, production of small peptides that inhibit endotoxins, as well as stimulation of short-chain fatty acids, especially butyrate, that restore intestinal functions and immunoregulation. However, the effect of *Saccharomyces cerevisiae* var. *boulardii* against common viruses responsible for diarrhoea, such as the rotavirus, adenovirus or norovirus, is still very limited, and further research is advocated [94]. *Saccharomyces cerevisiae* var. *boulardii* was efficient in the treatment of rotavirus gastroenteritis in children in six clinical studies [55][74][75][76][77][78].

In a small clinical study conducted in the Republic of Korea by Shin and co-authors [55], 50 hospitalized children with rotavirus enteritis were divided into three groups. The first group received a novel strain *Lactiplantibacillus plantarum* LRCC5310; however, neither the concentration of the probiotic nor the dosage was specified. Group II was the control group that did not receive any probiotics, and group III received a probiotic containing the *Saccharomyces cerevisiae* species according to the treatment policy of the hospital. Group III was retrospectively analysed through medical records. The novel strain LRCC5310 improved clinical symptoms and was comparable to, or more effective than the probiotic containing a *Saccharomyces cerevisiae* species. Several rotavirus genotypes were detected in stools, including: G9P8, G1P8, G1P18, G3P8, G2P4, G4P6, and G9P4. The rotavirus titre was significantly reduced in patients that received the novel strain LRCC5310 compared to those who did not take any probiotic formulations (Group II). Intake of LRCC5310 was found to be effective in the suppression of viral symptoms, as well as in prognosis and treatment, via virus titre reduction. The authors did not discuss the mechanisms involved, but the most likely mechanisms of the antiviral effect of the probiotic was due to modulation of the intestinal microbiota and the improvement of immune function, as several *Lactiplantibacillus plantarum* strains have exhibited enhancement of immune activity during infectious and inflammatory conditions, as well as improving lower gastrointestinal symptoms and modulation of intestinal microbiota after dysbiosis due to infections

[95][96][97][98][99][100][101][102]. Although some probiotic traits are strain-specific, other core traits are in fact species-specific [31].

The study by Lee and co-authors [52] investigated the antiviral influence of a multi-strain probiotic against viral gastroenteritis in paediatric patients. Nine of the twenty-nine patients had a rotavirus infection. A six-species supplement containing *Bifidobacterium longum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus*, *Lacticaseibacillus rhamnosus*, *Lactiplantibacillus plantarum*, and *Pediococcus pentosaceus* (strains not specified) proved effective in statistically significantly reducing the duration of diarrhoea in the probiotic group. Similarly, another multi-species probiotic, containing *Lactobacillus acidophilus*, *Lacticaseibacillus rhamnosus*, *Bifidobacterium longum,* and *Saccharomyces boulardii* (strains not specified) was also efficient [77][80]. Supplementation with bifidobacteria, including the probiotic *Bifidobacterium bifidum* Bb12, has been shown to protect against rotavirus infection, as children receiving this probiotic had a statistically significant lower concentration of the rotavirus-specific IgA antibody compared to the control group [103]. The well-known probiotic VSL#3 was also used in a study by Dubey et al. [81], conducted in India, and found a statistically significant lower duration and frequency of rotavirus diarrhoea in the probiotic group compared to the control group. Interestingly, the authors report that the statistically significant differences were still observed on day 4, but by day 8 the control group also spontaneously improved, and the results became comparable with the probiotic group. The antiviral effect of the multi-strain probiotic Bifilac was also found [82]. However, the author does not specify the composition of the supplement in the clinical trial.

Huang et al. [79] found that supplementation with a three-strain probiotic containing *Enterococcus faecalis* T-110, *Clostridium butyricum* TO-A, and *Bacillus mesentericus* TO-A resulted in a significant decrease in the duration of severe diarrhoea in the probiotic group compared to the placebo in children with infectious gastroenteritis. In the patients with rotavirus, a statistically significant decrease in gastroenteritis (Vesikari score) and diarrhoea frequency was also observed in the probiotic group. The three strains acted symbiotically to facilitate the proliferation of the others. The dosage was different compared to other clinical trials as the probiotic was given three times daily, whereas other clinical studies supplemented their patients once or twice a day.

Some of the clinical studies were not double-blind, but either single-blind [76][80] or open-labelled [69][79], which enhances the possibility of bias due to knowledge of the patient's treatment group [104].

Besides probiotics, prebiotics [105], synbiotics [106], postbiotics [107], or even fermented foods [108] could have positive effects for rotavirus diarrhoea due to enhancement of the natural intestinal microbiota, as a combination of probiotics and prebiotics (synbiotics) could have a synergistic effect; in some cases, heat-killed probiotics or postbiotics could even be safer than viable microorganisms. Some human and animal studies have addressed these effects [66][109][110][111], opening the possibility for more well-designed clinical studies.

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