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Protection and Restitution of Gut Barrier by Probiotics: Nutritional and Clinical Implications

R. K. Rao[1] and **G. Samak**[2]

[1]Department of Physiology, University of Tennessee Health Science Center, Memphis, TN, USA

[2]DVS College of Arts and Science, Shimoga, India.

Abstract

Probiotics are beneficial bacteria present in various dietary components and many of these colonize in the human and animal intestine. In the gut probiotics help the host by assisting in maintenance of normal mucosal homeostasis. Probiotics not only help maintain normal function of the gut mucosa, but also protect mucosa from injurious factors such as toxins, allergens and pathogens. The beneficial effect of probiotics is mediated by multiple mechanisms, including cytoprotection, cell proliferation, cell migration, resistance to apoptosis, synthesis of proteins and gene expression. One of the important cytoprotective effects of probiotics in the intestinal mucosa is to strengthen the epithelial tight junctions and preservation of mucosal barrier function. Probiotics not only enhance barrier function by inducing synthesis and assembly of tight junction proteins, but also preventing disruption of tight junctions by injurious factors. Bioactive factors released by probiotics trigger activation of various cell signaling pathways that lead to strengthening of tight junctions and the barrier function. This article reviews and summarizes the current understanding of various probiotics that are involved in the protection of gut barrier function, highlights the cellular and molecular mechanisms involved in the protective effect and addresses the clinical implications of probiotic supplementation.

INTRODUCTION

Intestinal microbiome plays an important role in normal gut function. Probiotics are the beneficial microorganisms that inhabit the gastrointestinal tract. They help the host with nutritional assistance, maturation of immune system, protection of mucosal barrier function and prevention of injurious effects caused by xenobiotics and pathogens. A significant body of basic and clinical studies on probiotics has facilitated FAO/WHO to define probiotics as "live microorganisms which, when consumed in adequate amounts as part of food, confer a health benefit on the host". Maintenance of the intestinal mucosal homeostasis and promotion of gut health by probiotics offer potential therapeutic benefits in the prevention and/or treatment of many gastrointestinal diseases. At present, probiotics are used in the clinics in the treatment and prevention of inflammatory bowel diseases, diarrhea, irritable bowel syndrome, gluten intolerance, gastroenteritis and *Helicobacter pylori* infection. Gut hosts about 30 species of *Bifidobacteria*, 52 species of *Lactobacillus* and others such as *Saccharomyces*, *Streptococcus* and *Enterococcus*. Commonly used commercial probiotics include species of *Lactobacillus*, *Bifidobacterium*, *Escherichia coli*, and *Streptococcus*. Additionally, the metabolites or secretary products of probiotics are also considered to have beneficial effects in the host. *Lactococcus lactis* and *Enterococcus* species have also been used as probiotics in the treatment of different diseases [1]. The mechanism of action of

Corresponding Author: R. K. Rao, PhD, AGAF Department of Physiology University of Tennessee Health Science Center 894 Union Avenue Memphis, TN 38163 USA Tel: (901) 448-3235 Fax: (901) 448-7126 rrao2@uthsc.edu.

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probiotics is unclear at this time, however, available evidence point to activation of signaling mechanisms that affect cell division, apoptosis, barrier function and mucosal immune function in the gastrointestinal mucosa.

Most probiotic bacteria were originally isolated from healthy humans. Common organisms used in the probiotic preparations include *Lactobacillus*, *Saccharomyces* and *Bifidobacterium* species. Mixtures of these probiotics, in different combinations are applied in commercially available probiotic preparations. The type of bacteria chosen for probiotic purpose is very important. The classic criteria for a successful probiotic agent are their ability to colonize in the intestine, survival in extreme pH of gut luminal contents, ability to adhere to the intestinal epithelium, nonpathogenic and nontoxic natures, and their health benefits. Probiotics have been used to prevent diseases since mid 20th century [2-4]. In this review article, we focus our discussion on the influence probiotics have on the maintenance of normal epithelial barrier function under physiologic and pathophysiologic conditions, and the potential cellular and molecular mechanisms involved in the beneficial effects of probiotics.

GASTROINTESTINAL MUCOSAL BARRIER

Barrier function

A multifunctional, rapidly renewing, epithelial monolayer lines the luminal surface of the gastrointestinal mucosa. The epithelial monolayer forms a primary interface between luminal contents and the interstitial tissue that prevents the diffusion of potential injurious factors from the gastrointestinal lumen into the tissue and eventually into the systemic circulation [5]. This important function of the intestinal epithelium is commonly referred to as the “barrier function”. Disruption of gut mucosal integrity and barrier dysfunction results in increased permeability to allergens, toxins and pathogens, leading to immunological stress response and inflammation [6, 7]. Disruption of barrier function and increased permeability to luminal toxins, allergens and pathogens play a crucial role in the pathogenesis of a number of gastrointestinal diseases, including inflammatory bowel diseases, celiac disease and alcoholic liver disease. Intestinal permeability to macromolecules is elevated, not only in patients with Crohn's disease and ulcerative colitis, but also in their first degree relatives, who showed no symptom of the disease [8]. This indicates that disruption of mucosal barrier function is likely an initial event prior to the onset or recurrence of these inflammatory diseases. Additionally, barrier dysfunction may also contribute to progression of disease, as inflammatory cytokines such as tumor necrosis factor-α and interferon-γ [9]. Compromised intestinal mucosal integrity and breakdown of gastrointestinal mucosal barrier function, the condition generally referred to as “Leaky Gut Syndrome”, is associated with starvation [10], trauma [11], infection [12], immunosuppression [13], chemotherapy [14], parenteral feeding [15], radiation [16] and emotional stress [17]. Hence, the gastrointestinal mucosal epithelium provides a structural and immunological barrier against the broad spectrum of noxious and immunogenic substances present in gut lumen. The maintenance gut barrier function is imperative to maintain gastrointestinal mucosal homeostasis.

Tight junctions

Tight junctions, the specialized junctional complex assembled at the apical region of the lateral membranes, form the major component of epithelial barrier function. Tight junctions form circumferential belt that seals the paracellular space preventing the diffusion of macromolecules across the epithelium. Specific interactions between the transmembrane proteins, intracellular adapter proteins and the actin cytoskeleton are involved in the assembly of tight junctions [5, 18]. Occludin, claudins, junctional adhesion molecule and tricellulin are the major transmembrane proteins involved in tight junction assembly. The

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extracellular domains of these transmembrane domains form homophilic adhesion with neighboring cells. The intracellular domains of transmembrane proteins interact with adapter proteins such as ZO-1, ZO-2 and ZO-3 as well as other proteins such as symplekin, 7H6, cingulin, etc. [18, 19]. Adapter proteins interact with actin binding proteins and anchor the entire tight junction protein complex to the underlying actomyosin belt [20, 21]. Disruption of actin cytoskeleton leads to disruption of tight junctions and increase in paracellular permeability [20, 22].

Regulation of tight junction and barrier function by cell signaling

Numerous cell signaling molecules are localized at the tight junctions and physically interact with tight junction proteins such as occludin and ZO-1. Proteins kinases such as PKCζ [23], casein kinase 2 [24], PKCη [25] and tyrosine kinases such as c-Src [26] are some of the kinases that interact with occludin. Protein phosphatases such as PP2A and PP1 also interact with occludin [27]. Activities of PKCζ, PKCη and casein kinase 2 are involved in phosphorylation of occludin and likely other tight junction proteins and promote assembly of tight junctions [28]. Small G-proteins, such as Rab13 [29] interact with ZO-1 and play role in regulation of tight junction assembly and disassembly [30]. Phosphatidylinositol 3-kinase also interacts with occludin C-terminal domain and mediates hydrogen peroxide-induced tight junction disruption [31]. Other signaling elements that do not interact with tight junction proteins, but indirectly regulate tight junction integrity include MLCK [24], calcium [32], cyclic AMP [33], AMP kinase [34], Rho kinase [35], PKC isoforms [36], JNK1/2 [37], MAP kinases [38], etc.

A battery of growth factors and regulatory peptides, secreted by salivary, gastric, pancreatico-biliary and intestinal secretions, are known to preserve the gut barrier function by prevention of xenobiotic-induced barrier disruption and rapid restoration of disrupted barrier [7, 39]. A significant body of evidence indicates that probiotics regulate intestinal epithelial homeostasis by promoting cell survival and barrier function [40-42], improving intestinal microbial ecology and regulating the mucosal immune function [42]. Probiotics preserve the intestinal barrier in mouse models of colitis and reduces the intestinal permeability in human patients [43].

PROBIOTIC EFFECTS ON GUT BARRIER FUNCTION

Although the clinical implication of probiotic was first indicated in 1954 [44], most progress in probiotic research has been done only during the past two decades. The main organ system targeted by probiotic research has been the gastrointestinal tract. Three major probiotics used in these studies are *Lactobacillus*, *Bifidobacteria* and *Saccharomyces*.

Lactobacillus species

Lactobacilli constitute a significant part of the commensal bacteria in the human gastrointestinal tract. Several species of *Lactobacillus* have been shown to be protective against pathogenic infection, and have been successfully used in clinical trials to treat diarrhea [45]. L. paracasei, L. salivarius, L. rhamnosus, L. fermentum and *L. plantarum* are major species of the *Lactobacillus* commonly found in diet and gut [46]. *Lactobacillus rhamnosus* GG (LGG) is one of the best-studied probiotic bacteria in clinical trials for treating and/or preventing several intestinal disorders, including inflammatory bowel diseases and diarrhea. In the gastrointestinal tract, LGG promotes digestion, boosts immune system, increases resistance to infection and inhibits growth of pathogenic bacteria [42]. LGG blocks oxidative stress-induced disruption of tight junctions and barrier function in Caco-2 cell monolayers [47]. It also reduces the ethanol-induced intestinal mucosal permeability and decreases oxidative stress in both small intestine and colon. Neutrophil infiltration and inflammation in colon were significantly reduced by LGG administration

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[48]. LGG inhibited enterohemorrhagic *E. coli*-induced paracellular permeability in polarized MDCK-1 and T84 cell monolayers [49].

Lactobacillus plantarum is another important probiotic reported to be effective in the treatment and prevention of colitis in mice [50]. Administration of *L. plantarum* DSM 9843(2099v) and *L. reuteri* R2LC decreases intestinal permeability in methotrexate-induced colitis [51]. Pretreatment of Caco-2 cell monolayers with *L. plantarum* significantly attenuates phorbol ester-induced redistribution of ZO-1 and occludin from the intercellular junctions and the increase in permeability [52]. *L. plantarum* ATCC 8014 was shown to inhibit the TNF-α-induced decrease in TER and IL-8 secretion in Caco-2 cells [53, 54]. Several animal studies have shown that *L. plantarum* attenuates hyper permeability associated with experimental enterocolitis and biliary obstruction [55]. *L. plantarum* CGMCC (No.1258) reversed *E. coli*-induced disruption of barrier function and alteration of peri-junctional actin filaments in Caco-2 cell monolayers [56]. *L. casei* DN-114001 protects T84 cell monolayers from *E. coli* (EPEC)-induced barrier disruption in dose-dependent manner [57]. Colonization of *L. casei* significantly mitigates the barrier disruption in trinitrobenzoyl sulfate-induced colitis in rats [58] and down regulates proinflammatory mediators in lamina propria of inflamed mucosa of Crohn's disease patients during *ex vivo* cultivation [59]. *L. casei* DN-114001 lysate blocks dextran sodium sulfate-induced intestinal inflammation by improvement of gut barrier function [60]. Treatment with *L. helveticus* and *L. rhamnosus* reduces epithelial barrier dysfunction and prevents bacterial translocation following chronic psychological stress in rats. *L. paracasei* NCC2461 restores normal gut permeability in the maternal stress model [61, 62]. Probiotic *lactobacilli* interact with various receptors of immune cells and modulate epithelial cell functions [63]. Therefore, convincing body of evidence from *in vitro* and *in vivo* experimental studies as well as clinical studies indicates that *Lactobacillus* species are helpful in preserving tight junction integrity and barrier function. These probiotics are promising to have therapeutic benefits in the treatment of gastrointestinal diseases.

Bifidobacteria

Bifidobacterium infantis probiotic bacteria were effective in reducing colonic permeability and attenuating inflammation in mouse model of colitis. Pretreatment of T84 cell monolayers with *B. infantis* conditioned medium significantly attenuates TNF-α and IFN-γ–induced drop in transepithelial electrical resistance and redistribution of occludin and claudin-1 from the intercellular junctions [64]. Supplementation of exogenous *Bifidobacteria* improves the gut barrier function and attenuated bacterial/endotoxin translocation after thermal injury in rats [65]. *B. bifidum* improves the intestinal integrity in rat model of necrotizing enterocolitis [66]. Pretreatment of mice with *Bifidobacterium* species significantly reduces the illness after challenge with rotavirus. Similarly, *B. lactis* found to be effective against EHEC-induced mucosal dysfunction [67, 68]. Probiotic mixture VSL#3 (L. casei, L. plantarum, L. acidophilus, L. delbrueckii, B. longum, B. infantis, *B. brevo and Streptococcus salivarius*) protects the intestinal epithelial barrier against acute colitis by preventing redistribution of tight junction proteins, occludin, ZO-1 and claudins; it also affected the expression of occludin and ZO-1 [69, 70]. Therefore, *Bifidobacterium* species are another group of probiotics that help preserve tight junction integrity in the gastrointestinal mucosa. These probiotics are likely to provide therapeutic benefits in the treatment of gastrointestinal diseases.

Saccharomyces

S. boulardii and certain strains of *S. cerevisae* were found to have probiotic effects [71]. *S. boulardii*, a nonpathogenic yeast, ameliorates antibiotic-associated diarrhea, *C. difficile* colitis and rotavirus associated gastroenteritis [72]. *S. boulardii* also ameliorates C.

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rodentium-induced inflammation by helping to maintain tight junction integrity [73]. Certain strains of *S. cerevisae* also seem to have beneficial effect on the gastrointestinal tract. Lifree, made of fruits fermented using a mixture of probiotics, including *S. Cerevisae*, promotes tight junction formation [74]. *S. cerevisae* UFMG 905 preserves gut barrier and immune system during the intestinal obstruction injury [75]. Therefore, some of *Saccharomyces* species and strains may have clinical applications in the treatment of gastrointestinal diseases.

Escherichia coli

Some other microorganisms with probiotic potential include *Escherichia coli Nissle* 1917. This is a widely used probiotic that enhances the expression of ZO-2 and its junctional localization in T84 cell monolayers and protects barrier function from EPEC-induced disruption in this epithelium [76]. The effect of *Escherichia coli Nissle* 1917 on tight junction was associated with elevated expression and redistribution of PKCζ. *Escherichia coli Nissle* 1917 provides significant protection against intestinal barrier dysfunction in mice and the intestinal epithelial cells isolated from these mice exhibited a more pronounced expression of ZO-1 [77]. Barrier function of T84 cell monolayers was found to be enhanced by *Escherichia coli Nissle* 1917 [78], while it increases the resistance to microbial pathogens [79].

CELLULAR AND MOLECULAR MECHANISMS OF PROBIOTIC-MEDIATED BARRIER REGULATION

Several mechanisms appear to be associated with the mucosal protective role of probiotics. Probiotics protect the gastrointestinal mucosa from a variety of insults including infection by pathogenic bacteria. Several strains of *Lactobacillus* and *Bifidobacterium* are able to compete with pathogens for binding to intestinal epithelial cells and displace pathogens from host cells. Probiotics interfere with adhesion of gastrointestinal pathogens by steric hindrance and competitive exclusion. Probiotics also stabilize cellular cytoskeleton and gut barrier integrity to prevent epithelial invasion [80]. Some *Bifidobacteria* and *Lactobacilli* prevent adhesion of pathogenic bacteria by secreting lectin-like bacteriocins [81].

The barrier protective effect of probiotics involves release of metabolic or other molecules, which in turn regulates the tight junction integrity. One group of metabolic products released by probiotics is short chain fatty acids, including butyrate. Short chain fatty acids enhance the intestinal epithelial barrier by regulating the expression and assembly of tight junction proteins [82]. Metabolites secreted by LGG, *B. bifidum, B. breve*, *Streptococcus thermophilus*, and *Ruminicoccus gnavus* are shown to contribute to intestinal homeostasis and barrier function. Treatment of Caco-2 cells with cell-free supernatant of *B. lactis*-420 enhances epithelial tight junction integrity [64, 83]. Oral administration of bioactive factors from *B. infantis* reduced colonic permeability and attenuates inflammation in mouse model of colitis [84]. This protective effect was mediated by alteration in the expression of tight junction proteins by a MAP kinase-dependent mechanism.

Although investigation on probiotics has been exploding during the past two decades, very little is known about the bioactive factors that are produced by various probiotics. Even though the experimental evidence of beneficial effects of probiotics have been very quickly applied in commercialization of multiple products in the market, the intracellular mechanisms involved in the beneficial effects of probiotics are poorly understood. Only hand-full of studies have attempted to identify the bioactive factors produced by probiotics that are responsible for the beneficial effects of probiotics. Histamine was identified as one of the bioactive molecule. Histamine is released by *Lactobacillus* species [85], and the histamine released by *L reuteri* suppresses TNFα release by modulating PKA and ERK

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activities [86]. Exopolysaccharides in *Lactobacillus* species are involved in the beneficial effect in the host by modulating its immune system [87]. *L. helveticus* produces bioactive peptides that have anti-hypertensive effects [88]. *B. amyloliquifaciens* are known to produce antibacterial peptides, collectively named as bacteriocin [89]. LGG secrete large proteins, identified as P40 and P75 that protect the intestinal mucosa by modulating apoptosis and cell proliferation [40]. Another group of common bioactive molecules released by *Lactobacillus* species are polyphosphates [90]. Evidence indicates that polyphosphates released by probiotics preserve the epithelial integrity in mouse intestine and in Caco-2 cell monolayers *in vitro*.

A growing body of evidence indicates that metabolites and bioactive molecules released by different probiotics enhance tight junction integrity and prevent its disruption induced by injurious factors. Polyphosphates produced by *lactobacilli* and other probiotic bacteria enhance the intestinal epithelial barrier function, suppress oxidative stress-induced barrier disruption and maintain intestinal homeostasis by an integrin-p38 MAP kinase-dependent mechanism [52]. The soluble proteins of LGG, p40 and p75, are effective in protecting the epithelial tight junctions from oxidative stress by activating intracellular signaling mechanisms involving PKC and MAP kinase signaling pathways. The barrier protective effects of p40 and p75 involve inhibition of hydrogen peroxide-induced redistribution of tight junction and adherence junction proteins. This effect on tight junction was mediated by the activation of PKCε, PKCβ1 and ERK1/2 [91]. Expression of these soluble proteins of *Lactobacilli* is strain specific, produced in *L. casei*, but not in *L. acidophilus* [92]. LGG prevents cytokine-induced apoptosis in the intestinal epithelial cells through activation of Akt and prevention of p38-MAPK activation [41]. More importantly, constituents recovered from LGG culture broth supernatant stimulate Akt action to prevent cytokine-induced apoptosis in intestinal epithelial cells [41]. LGG inhibited TNF-α-induced IL-8 production in Caco-2 cells via interference with NFκB activation [90]. Incubation of Caco-2 cells with *L. plantarum* reverses TNF-α-induced increase in paracellular permeability and IL-8 secretion, suggesting that probiotic signaling starts prior to cytokine challenge [53]. Mechanism of regulation of human epithelial tight junction proteins by *L. plantarum* was shown to be dependent on Toll-like receptor (TLR 2) [52, 64]. There are only few studies addressing the identification of the protective factors expressed in probiotics. This is possibly due to the natural source probiotics and safety of using the intact probiotics in therapeutics. However, identification and characterization of the protective factors may provide additional benefits to apply them in the treatment of many gastrointestinal diseases.

Protection of the gut barrier from disruption by induction of changes in expression and distribution of tight junction proteins and mucus may be the key mechanism of probiotic function. Administration of *B. infantis* Y1 metabolites increases ZO-1 and occludin expression in T84 Cells. The effect of *B. infantis* condition medium on the gut barrier protection was mediated by activation of ERK1/2. *L. plantarum* MB452 treatment increased transcription of occludin and cingulin genes in Caco-2 cells, indicating a probiotic-induced gene expression in improving tight junction integrity [64, 93].

PROBIOTIC RICH FOOD

Probiotics are consumed in fermented dairy and nondairy foods since the time immemorial. However, the investigations on their beneficial effects have been addressed only during the past decade. Probiotic and prebiotic consumption has gained momentum, and varieties of foods and drinks both natural and those fortified with probiotic strains of proven health benefits are available in market today. For successful delivery in foods, probiotics must survive during food processing and long shelf life. FAO/WHO (food and agriculture organization of World Health Organization) recommends minimum viable count of

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probiotic strain at the end of shelf life of probiotic foods should be more than 10^6 CFU/gram or cm^3. Hence probiotic food product should be regularly consumed in sufficient quantities to deliver required amount of bacteria to the gut and their viability during gastric transit is important. The probiotic contents of some of the commonly used probiotic-rich foods are listed in table 1. Many of them are dairy products fortified with probiotic agents. Allergy to dairy products, fat content and lactose intolerance are the reasons for the development of nondairy probiotic foods.

CLINICAL IMPLICATIONS

During the past two decades several clinical trials have been conducted to determine the role in improving the gastrointestinal health as well as in the treatment of gastrointestinal diseases. Most studies indicated that probiotics might serve as a potential supplement in the treatment of diseases such as diarrhea, Crohn's disease, ulcerative colitis and irritable bowel syndrome (IBS). Oral administration of LGG significantly reduced the incidence of diarrhea during antibiotic treatments [94]. LGG attenuated gastrointestinal side effects during the treatment for *Helicobacter pylori* [95, 96]. LGG administration also protects tight junction integrity and gastric mucosal barrier function from indomethacin-induced hyper permeability [97], and *L. casei* given in a probiotic beverage improves gastrointestinal symptoms in patients with chronic constipation [98]. VSL#3, a mixture of probiotics, [99] and E. Coli strain Nissle 1917 [100] were found to be effective in reducing the symptoms of ulcerative colitis. A randomized double-blind placebo-controlled pilot study showed that LGG improves gut barrier function and clinical status in children with moderately active Crohn's disease [101]. Oral administration of LGG enhanced IL-10 generation and caused anti-inflammatory effects in atopic children [102]. Oral supplementation with *B. brevi* and *L. casei* reduced the occurrence of NEC in premature infants [103]; this was likely due to the improvement in gastrointestinal motility. Administration of a probiotic multivitamin preparation was also found to significantly reduce the stress or exhaustion symptoms in healthy subjects [104]. Another major gastrointestinal disease targeted to test probiotic application is irritable bowel syndrome (IBS). Administration of VSL#3 significantly improved gastrointestinal transit and bowel function in IBS patients [105]. This observation was supported by other studies showing significant relief in IBS symptoms by oral supplementation with either another probiotic mixture [106] or *Bacillus coagulans* GBI-30, 6086 strain [107]. Therefore, probiotics are likely to have beneficial effects in the treatment of gastrointestinal diseases such as Crohn's disease, ulcerative colitis, diarrhea, necrotizing enterocolitis and irritable bowel syndrome. Probiotics may also be beneficial in relieving discomfort due to constipation as well as in ameliorating stress and/or exhaustion symptoms.

Although experimental studies on the gastrointestinal mucosal protective role of probiotics have been mostly successful, the clinical studies have not always been positive. The beneficial effects of probiotics in treatment of inflammatory bowel diseases has been modest, strain-specific and limited to certain symptoms of the disease [108] and therefore, the clinical efficacy of application of probiotics in the treatment of IBD needs further verification [109]. LGG did not improve symptoms in a subgroup of IBS patients in a randomized double-blind placebo-controlled study [110], and failed to improve symptoms in children with IBS [111]. Oral administration of *L. johnsonil, LA1* or *Nissle* species failed to prevent early endoscopic recurrence in Crohn's disease patients and therefore, there is no convincing evidence of reduced recurrence of Crohn's disease by probiotics [112]. Therefore, there is a significant level of uncertainty in the use of probiotics for the treatment of different gastrointestinal diseases. It appears that it is imperative to distinguish different strains of probiotics and their combinations in formulation of probiotic therapy and to understand the cellular and molecular mechanisms that underlie beneficial role of different probiotics prior to use therapeutic application of probiotics in gastrointestinal diseases.

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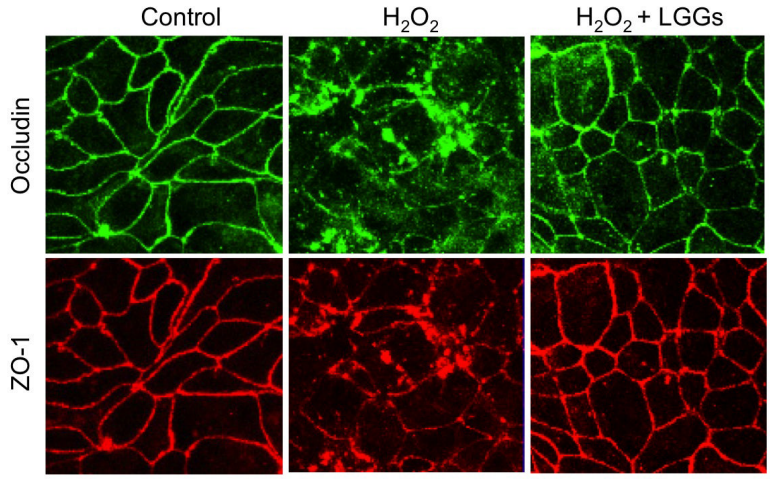

Figure 1.
Caco-2 cell monolayers, pretreated with or without *Lactobacillus rhamnosus GG* supernatant (LGGs), were exposed to hydrogen peroxide for 3 hours. Fixed cell monolayers were stained for occludin and ZO-1 by immunofluorescence method and confocal microscopy.

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Table 1

Probiotic-rich diets

Diets	Probiotic contents	Reference
Yogurt -Fermented milk product	*L. delbrueckii* subspecies *bulgaricus* (2.4×10^7 cfu/g) *S. thermophilus* (2×10^8 cfu/g)	[113]
Kombucha -Tea	*Acetobacter xylinum, A. xylinoides, A. aceti, A. pasteurianus, Bacterium xylinum, Bacterium gluconicum, Acetobacter Ketogenum* Yeasts – *Schizosaccharomyces pombe, Saccharomyces cerevisiae, Saccharomycodes ludwigii, Kloeckera apiculata, Zygosaccharomyces bailii, Brettanomyces bruxellensis, B. lambicus, B. custersii, Candida* and *Pichia* species. *Gluconacetobacter kombuchae, Zygosaccharomyces kombuchaensis*	[114]
Kefir -Fermented milk beverage	80% of total *Lactobacillus: L. kefiri.* 20% or total *Lactobacilli: L. paracasei subsp. Paracasei, L. plantarum, L. acidophilus, L. delbrueckii subsp. Bulgaricus and L. kefiranofaciens* Other probiotic bacteria: *Lactococcus lactis* subsp. *cremonis, Lactococcus lactis* subsp. *lactis.Acetobactor* and *Leuconostoc* species Yeast species: *Saccharomyces cerevisiae, S. unisporous, Candida kefyr, Kluyveromyces maxiamus, subspec. maxiamus*	[115]
Sauerkraut	20 isolates of *Lactobacillus*, predominently *L. plantarum. L. curvatus,L. Sakei ,L paraplantarum,L coryniformis, L.brevis, Lactococcus lactis subsp lactis, Leuconostoc mesenteroides, Leuconostoc fallax, Leuconostoc citreum,Leuconostoc argentinum, Pediococcus pentosaceus.* Yeasts *<100/ml*	[116]
Kimchi Korean fermented vegetable food	*Leuconostoc mesenteroides*, *Leuconostoc dextranicum, Leuconostoc citreum, Lactobacillus brevis, Lactobacillus fermentum, Lactobacillus plantarum, Pediococcus pentosaceus, and Streptococcus faeculis* Total microorganisms count reaches maximum $1\times10^{8\text{-}9}$ cells/ml.	[117]
Probiotic Cheddar Cheese	10^{10} cfu/g of the probiotic strain *Lactobacillus paracasei* NFBC 338	[118]
Probiotic milk candies	Probiotic bacteria *bifidobacteria, lactococci* and *Lactobacillus acidophillus* (10^7 cfu/100 g)	[119]
Yakult	*Lactobacillus casei shirota* 10^8 cfu/ml *Lactobacillus acidophilus, Bifidobacterium* spp., and *Lactobacillus casei.*	[120]
Probiotic Suassages	Fermented sausages contain *Lactobacillus casei, L. paracasei* and *Lactobacillus rhamnosus* strains and also *Staphylococcus xylosus.*	[121]
Prodentis probiotic chewing gum-BioGaia	*Lactobacillus reuteri*, Prodentis (ATCC 55730 and ATCC PTA 5289, 1×10^8 cfu of each strain	[122]