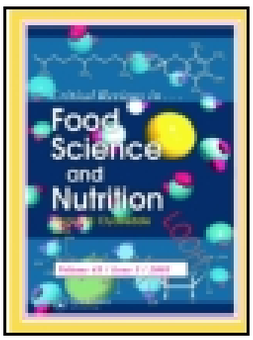

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Probiotics: The scientific evidence in the context of inflammatory bowel disease

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ABSTRACT

Inflammatory bowel disease (IBD) generally comprises Crohn's disease (CD) and ulcerative colitis (UC), and their main characteristic is the intestinal mucosa inflammation. Although its origin is not yet fully known, there is growing evidence related to genetics, intestinal microbiota composition, and the immune system factors such as precursors for the initiation and progression of intestinal conditions. The use of certain probiotic microorganisms has been touted as a possible and promising therapeutic approach in reducing the risk of inflammatory bowel disease, specifically ulcerative colitis. Several mechanisms have been proposed to explain the benefits of probiotics, indicating that some bacterial strains are able to positively modulate the intestinal microbiota and the immune system, and to produce metabolites with anti-inflammatory properties. The aim of this paper is to bring together the various results and information, based on scientific evidence, that are related to probiotics and inflammatory bowel disease, emphasizing the possible mechanisms involved in this action.

KEYWORDS

Inflammatory bowel disease; ulcerative colitis; probiotics; microbiota

Introduction

Inflammatory bowel disease (IBD) is a generic term used to describe a group of conditions—which includes Crohn's disease (CD) and ulcerative colitis (UC)—affecting the intestinal mucosa. The pathogenesis of IBD involves genetic susceptibility, associated with changes in the immune response of the intestinal mucosa in relation to the enteric microbiota, resulting in a chronic IBD (Hanauer, 2006). Often, individuals suffering from IBD have dysbiosis, an increase of potentially pathogenic bacteria and reduction of *Bifidobacterium* spp. and *Lactobacillus* spp. (Guarner et al., 2002; Neut et al., 2002).

The intestinal microbiota plays an important role on the host immune response; Thereby, the manipulation of these microorganisms can reflect positively on the development of IBD. Currently, different strains of probiotic microorganisms, particularly those belonging to lactic acid bacteria (LAB) group, have been studied as an alternative for relief of IBD symptoms, and the results are promising (Osman et al., 2006; Geier et al., 2007; Nanda-Kumar et al., 2008; Uronis et al., 2011).

The vast majority of potentially probiotic LAB belongs to the phylum *Firmicutes*, rather diverse bacteria with low G + C content in their genome and that includes the genera *Aerococcus, Enterococcus, Lactobacillus, Lactococcus, Leuconostoc, Oenococcus, Pediococcus, Streptococcus, Carnobacterium, Tetragenococcus, Vagococcus, and Weissella* (Stolaki et al., 2012). The genus *Bifidobacterium* is considered by many scientists as a member of LAB since it shares some typical characteristics of this group, such as the production of lactic acid. However, this genus belongs to the phylum Actinobacteria, a group of bacteria that has a high G+C content in their genome, and a different fermentation process of sugars if compared to LAB belonging to the phylum Firmicutes (Stolaki et al., 2012). For the sake of clarity, the genus *Bifidobacterium* in this article will be considered as a LAB member.

Most studies conducted in order to verify the effect of probiotics on IBD development have used LAB lyophilized strains belonging to *Lactobacillus* spp. and *Bifidobacterium* spp. However, the probiotic microorganisms in food can be served and consumed daily as part of the usual diet. Accordingly, such foods could also act to reduce the risk of developing the disease in susceptible individuals.

The aim of this paper is to review the results of studies using different models, to evaluate the use of probiotics in IBD control, verifying the relationship between the intestinal microbiome and development of disease, emphasizing possible associated mechanisms.

Inflammatory bowel diseases

CD and UC are the most common types of IBD characterized by intestinal chronic inflammation, and may have frequent recurrences and severe clinical forms (Jewel, 1998; Kronbluth et al., 1998; Souza et al., 2002).

Considering the histopathological changes, there are significant differences between UC and CD. The UC is a diffuse inflammatory reaction characterized by the presence of abscesses in the crypts and infiltration of neutrophils, eosinophils, and plasma cells that attack the lining of the colon and rectum continuously (Buller et al., 2002; Podolsky,

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2002; Oliveira et al., 2010). The disease has periods of remissions and relapses that generally occur in the same area previously affected. The most common symptoms presented by individuals affected by UC are: diarrhea, rectal bleeding, tenesmus, mucus discharge, and abdominal pain (Biondo-Simões et al., 2003, Oliveira et al., 2010). On the other hand, CD is a chronic inflammation that can affect the whole intestinal segment, characterized by having the affected regions interspersed with healthy areas (Buller et al., 2002, Podolsky, 2002; Oliveira et al., 2010). It affects most frequently the terminal ileum and colon, starting typically with bouts of diarrhea, fever, recurrent abdominal pain, and weight loss. There may be local and systemic complications during the clinical evolution (Biondo-Simões et al., 2003; Oliveira et al., 2010).

IBD affects people of all ages, with a peak incidence between 15 and 30 years old, and a second peak occurring in elderly subjects (Hanauer, 2006). This disease is more common in northern Europe and in the United States (BSG, 2003) and it is considered rare in the countries of South America (D'Oliveira et al., 1984; Sonnenberg, 1986). However, researches in the last decade indicates an increased incidence of IBD in countries where socioeconomic conditions are on the rise (Ekbom et al., 1991; Steinwurz, 1998; Irvine et al., 2001; Souza et al., 2002; Appleyard et al., 2004).

The increasing IBD incidence can be partially explained by changes in the methods of diagnosis. Furthermore, a large population with access to hygienic-sanitary control has contributed to the decline of common infections in childhood. However, the delayed exposure to pathogenic agents could generate an inappropriate immunological response which may influence the susceptibility to inflammatory diseases, such as IBD.

Although the etiology is little known, individuals with a family history seem to be more susceptible to the development of IBD, and the association of genetics and environmental factors is critical for the disease manifestation. Environmental factors involved in IBD include: tobacco use, nonsteroidal anti-inflammatory drugs (NSAIDs), degree of exposure to intestinal pathogens, diet composition, and intestinal microbiota composition (Shanahan, 2002; Oliveira et al., 2010).

The studies relating diet composition and UBD development are still inconclusive. However, evidence suggests that diets rich in fatty acids and frequent intake of foods such as "fast food" increase the risk of the disease onset (Persson et al., 1992; Krishnan and Korzenik, 2002). Other studies indicate that these diseases are often associated with significant nutritional disorders, such as protein-calorie malnutrition and deficiencies of vitamins and trace elements (Oliveira et al., 2010).

Although CD and UC are chronic inflammatory diseases, the gut microbiota composition is a key factor in the development of these diseases, by directly affecting the host immune response. Studies in animal models indicate that germ-free rodents do not develop IBD. Therefore, it is believed that the disease manifestation may involve complex mucosal immune responses to antigens of enteric bacteria (Sadlack et al., 1993; Duchmann et al., 1995, 1999; Matsumoto et al., 1998, 2005).

Microbiota and inflammatory bowel diseases

Studies using molecular biology techniques show that only 7–9 bacterial phyla are present in stool samples or human intestinal mucosa. Among these phyla, *Bacteroidetes* and *Firmicutes* are found in greatest proportions, followed by *Proteobacteria, Actinobacteria, Verrucomicrobia*, and *Fusobacterium*. The most abundant bacterial genera in the human microbiota are *Bacteroides* spp., *Faecalibacterium* spp., and *Bifidobacterium* spp., with the largest individual variation occurring at lower taxonomic levels (species and strains) (Eckburg et al., 2005; Arumugam et al., 2011).

Caporaso et al. (2012) found that the human microbiota presents a phenomenon known as resilience, that is, it undergoes variations depending on the diet, intestinal transit time, medication use, and other environmental factors, but tends to return to the initial population composition. A metagenomic study conducted with adult volunteers from North America, Europe, and Japan concluded that the microbiota composition can be divided into 3 "entereotypes" identified by variation in the population of *Bacteroides* spp. (enterotype 1), *Prevotella* spp. (enterotype 2), and *Ruminococcus* spp. (enterotype 3) (Arumugam et al., 2011).

Several studies are being conducted in order to verify the relationship between entereotypes/microbiota composition and the prevalence of certain diseases (Qin et al., 2010; Arumugam et al., 2011; Bron et al., 2011).

The microbiota of patients suffering from UC presents quantitative and qualitative changes in its composition, with a significant reduction in species diversity. A study conducted by Noor et al. (2010) observed a significant difference in the microbiota composition between healthy subjects and patients with UC or irritable bowel syndrome (IBS). In both conditions, contrary to what was expected, there was a decrease of *Bacteroides* species, and this fact can be associated with a loss of the protective function of this genus of bacteria during inflammation (Ott and Schreiber, 2004; Noor et al., 2010). Although this genus is commonly associated with IBD, recent studies indicate that certain species, such as *Bacteroides vulgatus* and *Bacteroides ovatus*, have shown a protective action in UC. However, more detailed studies are needed to understand the mechanism of action that provides such benefit (Waidmann et al., 2003; Sydora et al., 2005; Conte et al., 2006; Takaishi et al., 2008; Hudcovic et al., 2009; Noor et al., 2010).

Lepage et al. (2011) observed that patients with UC have a different gene expression in the intestinal mucosa, low bacterial diversity, and higher amounts of aerobic bacteria compared to their healthy twins. The mucosa genetic profile appears to interact with the intestinal microbiota, but this interaction was not seen in patients with UC, indicating that some bacterial functions such as production of butyrate, may affect mucosa gene expression. In addition, the healthy siblings of the study showed a larger population of *Faecalibacterium prausnitzii* compared to patients with UC, and this microorganism has received attention for its anti-inflammatory properties (Sokol et al., 2009).

Several studies relate intestinal microbiota, immune response, and genetics as the three main factors for the development of IBD. However, the manner through which these

factors interact has not been fully elucidated, representing a great challenge to researchers (Lepage et al., 2011).

Patients with CD also frequently show dysbiosis (Tamboli et al., 2004). A clinical study done by Manichanh et al. (2006) suggests that patients with CD have a reduced bacterial diversity of the phylum *Firmicutes* compared to healthy patients. This observation was made for the period of remission and can be the result of a primary modification of microbiota, that is, before the typical changes caused by the inflammation process.

Some studies were conducted in order to investigate the differences in the microbiota of healthy subjects and patients with CD. The results show that while healthy individuals have a higher population of *Faecalibacterium prausnitzii*, in individuals with CD the species *Escherichia coli* was over representative (Willing et al., 2009; Mondot et al., 2011).

Pathogenesis of inflammatory bowel disease

The mechanism involved in the development of IBD is complex and not yet fully known. However, studies indicate that CD and UC may be the result of an abnormal immune response in relation to the intestinal microbiota in genetically predisposed individuals (Kaser et al., 2010).

The change in tolerance of intestinal microbiota results in the activation of macrophages and T cells with cytokine production, increased adhesion molecules and chemokines, followed by recruitment of neutrophils, eosinophils, and monocytes. These effector cells pass through the mucosa, and crypt abscesses are formed with interruption of the normal function of the epithelial barrier. This process increases the access of bacteria to the mucosa, increasing or perpetuating the inflammatory process. In addition, changes in the regulation of the production of pro-inflammatory and anti-inflammatory cytokines also operate to a function failure of the epithelial barrier (Dionne et al., 1999; Shanahan, 2000; Van Heel et al., 2001, 2002). In CD there is an increase in the response mediated by T-helper 1 cells (TH1) with an increase in IFN-γ, TNF-α, and IL-2, whereas during UC there is excessive activation of T-helper 2 (TH2) cells and increased production of IL-4, IL-5, IL-13, and IL-1β, among others. The mucosal inflammation is also influenced by the reduction of anti-inflammatory cytokines, such as IL-10 and TGF-β, which results in loss of tolerance to common antigens, contributing to the perpetuation of the inflammatory process (Shanahan, 2000; Bouma and Strober, 2003; Hanauer, 2006).

Treatment of inflammatory bowel diseases

IBD is considered one of the major problems of modern populations, as it directly influences the quality of life, resulting in changes in the social, psychological, and professional spheres. Studies also show a high incidence of adverse problems during pregnancy in women with IBD. It was observed that women with CD or UC had a greater chance of premature birth and having children with low birth weight (Cornish et al., 2007; Mahadevan et al., 2007; Schnitzler et al., 2011). Another factor that aggravates the situation of patients with IBD in some countries is the lack of studies and restricted dissemination on these diseases, contributing to a delay in diagnosis and increased morbidity (Oliveira et al., 2010). In this sense, the choice of an appropriate treatment is essential to improve the quality of life of patients with IBD.

Conventional treatment with the use of drugs has been increasingly researched and aims to decrease the symptoms and inflammation. Antiperistaltics, sedatives, and antidiarrheal are recommended to let the inflamed bowel rest and recover (Smeltzer and Bare, 2002). The aminosalicylates are considered a good option for IBD patients, especially the 5-aminosalicylic acid (5-ASA) (Green et al., 1998; Pearson, 2004). Corticosteroids, particularly prednisone, hydrocortisone, and budenisonide, have brought good results in the IBD treatment by inhibiting inflammation rapidly, and consequently reducing its symptoms. However, prolonged use of this type of drug may cause other diseases such as hypertension, diabetes, and osteoporosis, thus compromising treatment success (Biondo-Simões et al., 2003, Pearson, 2004; Oliveira et al., 2010). Twenty percent of IBD patients undergoing the therapies mentioned above do not respond positively, forcing the use of immunosuppressive therapy, with the administration of azathioprine, methotrexate, and cyclosporine (Pearson, 2004).

New therapy options for IBD are being researched, including the noteworthy use of monoclonal anti-TNF-α administration and probiotic microorganisms that can modulate the intestinal microbiota and interfere with the host immune response (Osman et al., 2006; Howarth, 2008; Juillerat et al., 2008).

Probiotics and inflammatory bowel diseases

Probiotics are live microorganisms which, when administered in adequate amounts, confer a health benefit on the host (FAO/WHO, 2002). In recent years, there has been a significant advance in understanding the mechanisms of action of different probiotic strains and how they relate to IBD (Fedorak and Madsen, 2004).

It is known that IBD occurs in individuals with a genetic predisposition and it represents an abnormal inflammatory response in relation to pathogenic bacteria present in the intestinal lumen. Furthermore, these bacteria present in the lumen not only appear to be part of the initiation but also in the perpetuation of the inflammatory process. In several studies with animal models, it has been observed that intestinal inflammation is initiated and perpetuated in the presence of different enteric bacteria, while the use of germ-free animals decreased the risk or dramatically attenuated development of the disease. Furthermore, additional studies suggest that bacteria present in the intestinal lumen are able to penetrate the mucosa and intensify inflammation of the intestinal epithelium (Swidsinski et al., 2002; Darfeuille-Michaud et al., 2004; Sartor, 2006; Clavel and Haller, 2007; Haller et al., 2010).

In this context, the function of probiotic bacteria includes positive change in the gut microbiota composition, by modulating the immune response and by production of substances involved in regeneration of the intestinal mucosa (Fedorak and Madsen, 2004; Haller et al., 2010).

The required amount of probiotic microorganisms to achieve beneficial health effects may vary depending on the strain and product. In general, products containing probiotic

microorganisms must show a minimal number of viable bacteria with proven efficacy (as found by testing in humans), estimated between 10^6 and 10^8CFU/g of product or 10^8–10^{10} CFU/day (considering the daily intake of 100g of probiotic product) (Champagne et al., 2011). However, there are few dose-response studies to determine the "minimum effective dose" required to reduce the IBD risk. These studies could explain some discrepancies found in the results obtained in several *in vivo* studies (Chen et al., 2013).

In this line, Chen et al. (2013) evaluated the administration of different doses (10^4, 10^5, 10^6, 10^7, or 10^8 CFU/10 g body weight) of *L. acidophilus* in mice with colitis induced by dextran sulfate sodium (DSS). The authors concluded that the dose of 10^5 CFU/ 10 g body weight provides satisfactory therapeutic effect in experimental colitis, and the relief of symptoms was correlated with a modulation of the microbiota composition of the distal colon.

Understanding the mechanisms of action of probiotic bacteria, especially in IBD, will allow the development of criteria for the selection of probiotic strain suitable for each type of disease, the determination of optimal doses, time of administration, and also enable synergistic combinations between different bacterial species (Fedorak and Madsen, 2004).

Different mechanisms have been proposed to explain the probiotics beneficial effect in patients with IBD, which include: reduction of pathogens by competition and production of antimicrobial substances (lactic and acetic acids, hydrogen peroxide and bacteriocins); immunomodulation or stimulation of the immune system associated with the epithelial cells, with production of anti-inflammatory interleukins, such as IL-10; maintenance and improvement of the intestinal barrier function; and production of short chain fatty acids (SCFA) and polyamines (Fedorak and Madsen, 2004; O'Hara and Shanahan, 2007; Howarth, 2008).

The functioning of the immune system, both systemic and on the intestinal mucosa, can be modulated by some bacterial strains (Fedorak and Madsen, 2004). Several studies indicate that different species of *Lactobacillus* spp. and *Bifidobacterium* spp. naturally possess anti-inflammatory properties and are capable of increasing lymphocyte proliferation, improving innate and adaptive immune response, and stimulating the production of anti-inflammatory cytokine IL-10 (Rolfe, 2000). According to Medina et al. (2007), the strain of *Bifidobacterium longum* ATCC 15707 induces the production of IL-10 and may be used to control IBD. Rachmilewitz et al. (2004) found that a mixture of probiotic microorganisms (VSL#3: *L. paracasei, L. plantarum, L. acidophilus, L. delbrueckii* subsp. *bulgaricus, B. longum, B. breve*, and *B. infantis*) were effective in reducing the risk of induced colitis in animals. Other studies demonstrated the efficacy of the same mixture of probiotics in reducing inflammation and in the remission of UC in adults and children (Bibiloni et al., 2005; Miele et al., 2009). In another study, administration of *Bifidobacterium infantis* strains (DSM 15158 and DSM 15159), associated or not with prebiotics (inulin and oligofructose), resulted in improvement in the context of acute colitis induced by DSS, with reduced IL-1β production and increased SCFA production (Osman et al., 2006).

The SCFA (acetate, propionate, and butyrate) are formed in the colon by anaerobic bacterial fermentation of undigested carbohydrates which are not absorbed in the small intestine (Assumpção et al., 1999). Studies correlating SCFA with UC are still controversial. However, it is known that SCFA—especially butyrate—play an important role in the normal physiology of the colon. They constitute a major source of energy for the enterocyte, stimulate epithelial cell proliferation, visceral blood flow and increase sodium and water absorption (Roediger, 1980; Scheppach et al., 1992; Hove and Mortesen, 1995; Campos et al., 1999; Segain et al., 2000).

Other substances produced by some strains of probiotic bacteria which are associated with reduced IBD risk are the polyamines putrescine, spermidine, spermine, and cadaverine. The polyamines are widely distributed in the body and are involved in the synthesis and stabilization of protein, DNA and RNA, adjustment of enzymatic activity and cell proliferation and differentiation (Matsumoto et al., 2001).

Studies indicate that polyamines are of utmost importance for the intestinal mucosa regeneration. Kaouass et al. (1996) found that the intestinal mucosa of rats was totally regenerated 48 hours after oral administration of spermidine. Other studies have also found that administration of spermine in young rats promoted early maturation of cells of the intestinal mucosa (Dorhout et al., 1997; Dufour et al., 1988).

A study in elderly subjects showed an increase in fecal polyamines after the daily intake of a probiotic yogurt containing *Bifidobacterium lactis* LKM512. Whereas the original feed polyamines are rapidly absorbed in the small intestine, the increase in fecal concentrations of these substances is probably due to the metabolism of the probiotic microorganism (*B. lactis* LKM512) in the large intestine (Bardocz et al., 1993; Matsumoto *et al.*, 2001). The authors also noted that the intake of probiotic yogurt significantly reduced levels of mutagenicity ($p < 0.05$) and that these results were negatively correlated with the concentration of fecal polyamines (Matsumoto et al., 2001).

Matsumoto et al. (2011) used the same organism, *B. lactis* LKM512, to study longevity in mice. The results showed an increased longevity in the group treated with the probiotic, possibly due to chronic suppression of inflammation in the colon, suggesting that the intake of some specific probiotic can substantially improve intestinal health and increase the animals' life span.

A product based on soy, fermented with *Enterococcus faecium* CRL 183 and *Lactobacillus helveticus* 416, has been intensively investigated. Among the positive effects of their regular intake these are noteworthy: modulation of intestinal microbiota, with an increase in the population of *Bifidobacterium* spp. and *Lactobacillus* spp. and reduction of enterobacteria (Cavallini et al., 2011), modulation of immune system (Vendramini, 2002), and reduction in the development of colon cancer (Sivieri et al., 2008). A recent study evaluated the effect of this fermented product, supplemented with *Bifidobacterium longum* ATCC 15707, in the development of colitis induced by DSS in rats considered specific pathogen free (SPF). The animals received daily, by gavage, 2 mL of the product (10^8 CFU), and administration was started seven days before the induction of colitis and continued for 16 days after the induction period (seven days), totaling 30 days of treatment (Cavallini et al., 2013; Celiberto et al., 2013). The addition of *B. longum* ATCC 15707 is justified by its

immunoregulatory properties, associated with the known ability of the genus *Bifidobacterium* spp. to increase production of SCFA (Medina et al., 2007).

The results showed that the fermented soy beverage (*E. faecium* CRL 183 and *B. longum* ATCC 15707) positively affected the rats' microbiota by increasing the population of *Lactobacillus* spp. and *Bifidobacterium* spp., which are important in the maintenance and integrity of the epithelial cells in the colon. Furthermore, the group of animals that consumed the probiotic drink also showed reduction in the colitis symptoms compared to the control group, showing lower disease activity (DAI). The intestines of animals that received the fermented beverage had only an infiltrate of inflammatory cells, without ulceration areas or alterations in the crypts and epithelium in the colon, suggesting that probiotics may have lessened the severity of inflammation (Cavallini et al., 2013; Celiberto et al., 2013).

Table 1 presents some studies with animal models showing the probiotics effect on IBD.

Various strains of *B. longum* have been tested *in vitro* by Medina et al. (2007), in order to assess their effects on immunomodulatory activity and their application in clinical practice. The results indicated pro-inflammatory or anti-inflammatory effects for each particular strain, suggesting that different strains of *B. longum* may find various applications in specific health conditions. Some of the tested strains of *B. Longum* (ATCC15707, NCC2705, BIF53, NCIMB8809, and BB536) were able to positively modulate the immune system by increasing the production of IL-10, thus suggesting a protective role in the body's defenses.

Although several studies withstand the hypothesis that probiotics present a positive effect on IBD, other studies show conflicting results (Table 2). Wildt et al. (2011) found, from a double-blind randomized placebo-controlled study, that patients who consumed capsules containing *Lactobacillus acidophilus* LA-5 and *Bifidobacterirum animalis* BB-12 for 52 weeks had fewer relapses and longer periods of remission. However, these differences were not statistically significant compared to the placebo group. According to the authors, the observed results could be shown to be more significant with the use of different probiotic strains or other daily doses.

In this line, based on a meta-analysis, Shen et al. (2009) have suggested that administration of *Lactobacillus johnsonii* LA1 and *Lactobacillus rhamnosus* LGG in maintenance therapy of CD was not effective in reducing the incidence of relapses. In addition, compared with the placebo group, the administration of LGG as maintenance therapy may increase the relapse rate in CD. According to the authors, no evidence suggested a significant benefit of LA1 and LGG for maintenance therapy in adults and in children with CD.

Fujimori et al. (2009) performed a randomized placebo-controlled study to assess the effectiveness of *B. longum* (10^9 CFU/day) and psyllium (8 g/day) administered to volunteers individually (*B. longum* or psyllium) or associated (*B. longum* + psyllium) in the treatment of UC. The authors found that only the

Table 1. Publications showing results with the use of probiotics to IBD in animal models.

Condition	Product	Probiotic strain and dose	Results	References
TNBS-induced colitis	Probiotic culture	*Lactobacillus acidophilus* NCFM and *Lactobacillus plantarum* Lp-115 (10^{10}UFC: 1x daily for 5 days before induction).	– There was no significant difference compared to the untreated group	Daniel et al. (2006)
TNBS-induced colitis	Probiotic culture conveyed by skim milk	*Lactobacillus fermentum* 5716 (10^8CFU: 1x daily for 3 weeks starting 2 weeks prior to induction).	– Modulation of the intestinal microbiota – Recovery of inflamed tissue – ↓ enzyme TNF-α, NO and MPO	Peran et al. (2006)
DSS-induced colitis	Probiotic culture conveyed by skim milk	*Lactobacillus fermentum* BR11 (10^8CFU: 2x day for 2 weeks, starting 1 week prior to induction).	– ↓ DAI and ↑ weight gain – Prevention of colon shortening and crypt hyperplasia	Geier et al. (2007)
Oxazolone-induced colitis	Probiotic culture	*Lactobacillus acidophilus* (10^7 CFU; 1x daily for 14 days).	– ↓ DAI – ↓ CRP, TNF-α and IL-6	Abdin and Saeid (2008)
DSS-induced colitis	Probiotic culture conveyed by saline	*Lactobacillus plantarum* K68 (10^9 CFU; 1x day for 1 week, starting 1 week prior to induction).	– ↓ DAI – histopathological Scores – ↓ proinflammatory cytokines (TNF-α, IL-1β, IL-6) – ↓ the expression levels of RNAm de TNF-α, COX-2, FOXp3, SOCS3 and TLR4	Liu et al. (2011)
TNBS-induced colitis	Probiotic culture conveyed by water	VSL#3 (10^9CFU: 1x daily for 18 weeks, starting 1 week prior to induction)	– ↓ severity of chronic colitis	Uronis et al. (2011)
TNBS-induced colitis	Probiotic culture conveyed by skim milk	*Lactobacillus fermentum* CFR 2195 (10^8CFU: 1x daily for 3 weeks starting 2 weeks prior to induction).	– ↑ anti-inflammatory activity – ↓ DAI and MPO – ↓ histological damage in tissue	Girishkumar et al. (2012)
DSS-induced colitis	Probiotic culture	*Bifidobacterium breve* NCC2950 (10^{10}UFC: 1x daily for 3 weeks starting two weeks before induction).	– ↓ severity of chronic colitis – ↑ intestinal barrier function	Natividad et al. (2012)
DSS-induced colitis	Probiotic culture conveyed by saline	*Lactobacillus crispatus* M206119 (10^9UFC: 1x daily for 2 weeks starting 2 days before induction).	– ↑ Disease severity – ↑ shortening of the colon – ↑ diarrhea and blood in stool – ↑ histological damage	Zhou et al. (2012)
TNBS-induced colitis	Probiotic culture	*Bifidobacterium longum* BB536 (10^6UFC: 1x daily for 1 week, starting 1 week prior to induction).	– ↑ anti-inflammatory activity – ↑ weight gain and ↓colon shortening - ↓ON and MPO	Ócon et al. (2013)

NO = nitric oxide; MPO = myeloperoxidase enzyme; DAI = disease activity index, CRP = C-reactive protein.

Table 2. Publications showing results with the use of probiotics to IBD in human models.

Condition	Product	Probiotic strain and dose	Results	References
Ulcerative colitis	Lyophilized probiotic culture	VSL#3 (10^{11}UFC; 1x daily for 12 months)	– Upregulation of microbiota – Decreased risk of disease recurrence	Venturi et al. (1999)
Ulcerative colitis	Probiotic culture	BIFICO (combination of *Bifidobacterium spp.*, *Lactobacillus spp.*, and *Enterococcus spp.*) (1.26 g; 1x daily for 8 weeks)	– Positive modulation of the microbiota – ↓TNF-α, IL-1β and ↑ IL-10	Cui et al. (2004)
Ulcerative colitis	Fermented milk with probiotics	*Bifidobacterium breve* Yakult, *Bifidobacterium bifidum* Yakult, *Lactobacillus acidophilus* (10^{9}CFU; 1x daily for 12 weeks)	– Decreased risk of disease recurrence	Kato et al. (2004)
Ulcerative colitis	Lyophilized probiotic culture	VSL#3 (10^{9}CFU; 2x daily for 12 weeks)	– ↓ DAI – ↓ the frequency of evacuation and rectal bleeding	Makharia et al. (2008)
Ulcerative colitis	Lyophilized probiotic culture	VSL#3 (10^{10}CFU; 1x daily for 12 months)	– Decreased risk of disease recurrence	Miele et al. (2009)
Ulcerative colitis	Lyophilized probiotic culture	VSL#3 (3.6×10^{12}CFU; 2x daily for 12 weeks).	– ↓ DAI at week 6 – Clinical remission at week 12	Sood et al. (2009)
Ulcerative colitis	Lyophilized probiotic culture	VSL#3 (10^{10}CFU; 2x daily for 8 weeks)	– Clinical improvement in patients treated with VSL # 3 – ↑ IL-10 and ↓ IL-12p40 and TLR-2	Ng et al. (2010)
Ulcerative colitis	Capsules containing lyophilized probiotic culture	*L. acidophilus* La-5 and *B. animalis* Bb-12 (2.5×10^{12}CFU; 3x daily for 52 weeks)	– Not effective	Wildt et al. (2011)

DAI = disease activity index.

group that consumed the probiotic + psyllium showed a significant improvement of the IBD questionnaires scores, suggesting that a combination is more effective than *B. longum* or psyllium alone in the remission maintenance in patients with UC.

In a crossover study conducted by Ahmed et al. (2013) there was no evident change in the composition of the intestinal microbiota of patients with UC and CD who had consumed capsules containing probiotics (*L. acidophilus* LA-5, *Lactobacillus delbrueckii* subsp. *bulgaricus* LBY-27, *B. animalis* subsp. *lactis* BB-12, and *Streptococcus thermophilus* STY-31; 4×10^{9} CFU/capsule) plus oligofructose (15 g/day) for 1 month. The authors also stressed that this study had some limitations due to the limited number of volunteers, the short period of probiotics administration, and the lack of a wash-out period in the experimental protocol.

Despite the limitations involving clinical studies there seems to be a consensus among specialists in this area that some probiotic strains may be effective in treating IBD, although the beneficial effects exhibit different degrees and may be limited to dose and duration of probiotics administration to the patients.

In parallel, studies using healthy volunteers have shown results less clear with regard to the beneficial probiotics effects, and this fact can also be attributed to different schemes of administration and dosage of the microorganism, and the difference between strains of the same bacterial species. It is also important to note that clinical trials with healthy subjects have not properly validated any reliable biomarkers for quantifying a "health status," thus representing a major challenge in the evaluation of the probiotics effects in healthy humans. Another factor to be considered is that the response to consumption of probiotics depends on the initial state of the consumer's health, and this may affect the immunomodulatory impact of interventions caused by the organism, because it seems that the effect of probiotics in individuals is also influenced by genetic characteristics (Bron et al., 2011).

Taken together, the scientific evidence on the probiotics effects are more compelling in the case of UC, whereas for CD the results are still scarce. Additionally, the number of clinical studies evaluating the effect of probiotics on IBD is still limited, which justifies the need to conduct further studies in this area (Lyra et al., 2012).

Probiotics in the context of human individuality

Advances in molecular biology techniques and their application in different approaches and experiments have led to a rapid proliferation of genomics, nutrigenomics, proteomics, transcriptomics, metabolomics, and so on. Researchers and health professionals are increasingly using these new technologies in order to analyze the molecular basis of certain specific dietary components that also exert their effects (Rimbach et al., 2008).

Nutrigenomics studies the influence of nutrition on the human being individually. In other words, this science seeks to understand how nutrients modulate the genome functioning and how the characteristics of the genome influence the response to food, nutrient requirements, and risk for diet-related chronic diseases, thereby understanding the mechanisms underlying these genetic predispositions. In this context, health promotion will be possible through the establishment of personalized nutritional recommendations (Muller and Kersten, 2003; Debusk et al., 2005).

Genetics plays a fundamental role in determining an individual's risk of developing a certain disease. Population differences in single nucleotide polymorphisms (SNPs) can have a major effect on the disease risk, and inter-individual genetic variation may be a determinant of differences in the nutritional requirements (Grody, 2003; Muller and Kersten, 2003).

Several studies have shown beneficial probiotics effects in certain diseases, such as UC, diarrhea caused by antibiotics, and hypercholesterolemia (Cavallini et al., 2009a, 2009b, 2011; Alfaleh et al., 2010; Deshpande et al., 2010; Holubar et al., 2010; Kale-Pradham et al., 2010; Natividad et al., 2012; Ocon et al., 2013). However, some studies did not observe consistent positive results in other situations such as treatment of eczema (Boyle et al., 2009), IBS (Moayyedi et al., 2010) and IBD (Zhou et al., 2012), indicating that the probiotic effects are strain-specific and provide more significant beneficial effects in immunocompromised

individuals or with pre-existing health problems and, in some cases, may even exacerbate disease processes (Rioux and Fedorak, 2006; Geier et al., 2007; Bron et al., 2011).

One proposed mechanism by which probiotics act is through bacterial molecules produced that modulate the host immune system. The innate and adaptive immune systems are closely integrated with other functions of the intestine, because more than 80% of intestinal epithelial cells are involved in nutrient absorption and metabolic functions. The epithelial layer has a bimodal function, maximizing the absorption of nutrients, while preventing the passage of undesirable components such as certain bacteria (O'Hara et al., 2006; Bron et al., 2011).

Some studies indicate that not all people show similar physiological effects with probiotic interventions, since these responses depend strongly on molecular interactions in the body of each individual. This can be one of the reasons why some volunteers do not respond to intervention with probiotic microorganisms, indicating that the application will be more effective in a personalized approach where individuals are divided into groups of phenotypes already predefined (De Ross and Katan, 2000; Muller and Kersten, 2003; Szajewska et al., 2006; Bron et al., 2011).

The molecular individuality in the intestinal mucosal tissue has not been fully elucidated, but it is increasingly apparent that the responses depend on a variety of potentially interrelated factors, such as the host genotype, lifestyle, and eating habits, as well as the composition of the endogenous microbiota (Qin et al., 2010; Arumugan et al., 2011; Bron et al., 2011).

Conclusion

Scientific evidence indicates that an unbalanced intestinal microbiota can contribute to the development of many diseases, and among them IBD. Probiotics may support the intestinal homeostasis, since they may affect the intestinal microbiota, the intestinal barrier, and the innate and adaptive immune response of the host. Several *in vivo* studies have highlighted the beneficial effects arising from the use of probiotics in IBD treatment, in particular UC. It is noteworthy that the effects and the mechanisms involved are considered strain-specific. The selection of probiotic strains should be directed to the desirable effects presented by the microorganisms of interest, proven by tests *in vitro* and *in vivo*, alone and when incorporated into food or even a pharmaceutical formulation, with a personalized approach. It is very important that further research be conducted in order to better understand the interactions between gut microbiota and host. This would contribute to an understanding of the therapeutic potential of probiotics in diseases related to the imbalance of the intestinal microbiota. In this regard, clinical randomized placebo-controlled studies, using, for example, a large number of participants must be performed in order to clarify the effectiveness of the probiotic therapy against IBD.

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