Chapter 8
Lactic Acid Bacteria and Gut Health

Haitao Li and Zhifeng Fang

8.1 Introduction

8.1.1 Gut Health

The gastrointestinal tract is a digestive organ system within any metazoan from invertebrates to vertebrates. A growing large body of scientific evidence supports the critical role of gut for human health (Flint et al. 2015). It takes in foods, digests and absorbs nutrients and energy, and finally expels the remaining waste as feces. More recently, its importance in immune system was also increasingly recognized. However, it should be pointed out that a definition of gut health is still lacking (Bischoff 2011). It is usually evaluated based on the following aspects: (1) digestion and nutrition absorption, (2) immune response, (3) gastrointestinal disorders, and (4) gut microbiome composition and functionality.

8.1.2 Gut Microbes

The gastrointestinal tract is an extremely complex dynamic ecosystem (Maccaferri et al. 2012). It is widely accepted that the trillions of gut microbiota colonize human intestinal tract. From a taxonomic viewpoint, gut microbiota mainly includes fungi, bacteria, archaea, and viruses. All gut microbiota might generate a biomass of more than 1.5 kg, and their combined genomes might be 100-fold of the human's genome (Gerard 2016). Of note, gut microbiota study has so far been focused on bacteria which might be roughly divided into three categories: beneficial bacteria, neutral bacteria, and harmful bacteria.

H. Li (✉) · Z. Fang
Jiangnan University, Wuxi, China
e-mail: liht@jiangnan.edu.cn

W. Chen (ed.), *Lactic Acid Bacteria*,
https://doi.org/10.1007/978-981-13-7832-4_8

Emerging evidence indicated a pivotal role of gut microbes in host physiology. Gut microbiota might naturally enhance food safety by suppressing food-borne illness, destroying naturally occurring toxins, and lowering allergic reactions (Hooper et al. 2002; Bäckhed et al. 2005). Gut microbiota might low the risk of certain infectious diseases by antagonizing pathogenic bacteria infection or inducing antibacterial substances. Beyond these, they also involve in biosynthesis of short-chain fatty acids (SCFAs) and certain vitamins. More recently, gut microbes have been identified as a "new organ" which might communicate with and/or complement our own organs.

It is widely accepted that the gut microbiota composition is generally stable within health adult individuals (Palmer et al. 2007). The gut microbial dysbiosis has been recently implicated in various diseases, either inside or outside the gastrointestinal tract. Various external factors such as foods, drugs, and even lifestyles were reported to profoundly affect the gut microbiome as well as host health (Faith et al. 2013; Courtney et al. 2008; Dethlefsen and Gordon 2011; Scott et al. 2013). If gut bacteria are making you ill, can swapping them makes you healthy? To answer the question above, intestinal micro-ecology has become one of the hottest research areas in biomedicine in the past 20 years (Quigley 2013).

8.1.3 Probiotic Lactic Acid Bacteria

Lactic acid bacteria are a group of gram-positive, catalase-negative, and nonsporulating, aerotolerant bacteria which might ferment carbohydrates to lactic acid (Hugenholtz and Smid 2002). They are widespread in nature ever in our gastrointestinal tracts (Vlieg et al. 2011; Stolaki et al. 2012). Although lactic acid fermentation is among the oldest forms of food preservation, accumulating evidence clearly indicates that to extend food shelf-life is only the start of which lactic acid bacteria has done to affect our life. For example, fermented foods have long had a reputation for human health benefits. Multimillion-dollar industry runs by the concept that introducing lactic acid bacteria into gut might improve our health (Patrick et al. 2014). Application of fermented foods has also been well-documented in folk medicines, but it often relies on traditional beliefs rather than sciences.

Probiotics are defined as "live microorganisms which when administered in adequate amounts confer a health benefit on the host." So far, the literature on the health benefits of probiotics has often focused on lactic acid bacteria. The original theory of probiotics is generally attributed to the Nobel Laureate Elie Metchnikoff, who hypothesized that the longevity of people in the Balkans might due to the bacteria in yogurt in 1908. Unfortunately, Metchnikoff's hypothesis remained dormant for nearly a century. Over the last two decades, interests in probiotic lactic acid bacteria have been rekindled for their potential benefits against various gastrointestinal diseases such as bacterial infection, diarrhea, irritable bowel syndrome, inflammatory bowel disease (IBD), and even tumorigenesis (Kitazawa et al. 2015). Although the molecular underpinnings remain largely elusive, probiotic lactic acid bacteria might

confer human health benefit, at least partially, by remodeling gut microbiota to be a disease-free state (Table 8.1). Taken together, it may, therefore, be possible to prevent and/or treat gastrointestinal disorders by probiotic LAB.

8.2 Irritable Bowel Syndrome

8.2.1 Epidemiology, Signs, and Symptoms

Irritable bowel syndrome (IBS), one common gastrointestinal disorder, might affect 10–15% of the general population worldwide (Didari et al. 2015). IBS not only negatively affects the patients' quality of life but also often incurs significant healthcare costs. Its primary symptoms are abdominal pain, diarrhea, constipation, and a change in bowel habits (Soares 2014).

8.2.2 Histological and Molecular Pathogenesis

It should be pointed out that IBS is currently defined by symptom criteria. So far, the etiology of IBS is still unclear as it occurs sometimes even without any obvious histopathological abnormalities (Levesque et al. 2015). The associated risk factors include genetic factors, stress, food sensitivity, small intestinal bacterial dysbiosis, and gastroenteritis infection. For example, about 33% of IBS patients have family history. More importantly, IBS patients from a same family even share a very similar signs and symptoms. Notably, stress and anxiety might trigger or aggravate symptoms of IBS. In this regard, abnormal levels of several endocrine hormones (e.g., 5-hydroxytryptamine, vasoactive intestinal peptide, somatostatin, glucagon, and prostaglandin E_2) have been observed. Although IBS is a non-communicable disease, its risk might be significantly increased once the intestinal tract infection. In addition, IBS has been associated with the genetic defects in innate immunity.

8.2.3 Gut Microbiota and Probiotic Intervention

More recently, several investigations suggest that gut microbiota might functionally mediate IBS. Although gut microbial dysbiosis has been observed in IBS, it remains to be determined whether such alternations are a cause or a consequence of IBS (Collins 2014). Of note, certain probiotics (e.g., *Bifidobacterium infantis* 35624) might greatly improve its clinical outcomes (Table 8.2). In this regard, probiotics might act through diverse mechanisms such as directly enhancing the intestinal mucosal barrier, reducing intestinal permeability, lowering bacterial translocation, modulating the gut immunity, and even affecting the intestinal nervous system and

Table 8.1 Effects of lactic acid bacteria on gut bacteria

LAB strains	Patients	Clinical tails	Dose and duration	Main results
Lactobacillus rhamnosus GG	Healthy individuals	RDBPC[c]; Finland	3 weeks; 10^{10} cfu	No significant change
	(M[a], F[b]),			
	New-born infants	Open-label; USA	6 months; 10^9 cfu	No significant change
Lactobacillus paracasei Zhang	Healthy individuals	Open-label; China	28 days; 10^{10} cfu	An increase in *Lactobacillus paracasei*
Lactobacillus reuteri DSM17938	Cystic fibrosis patients	RDBPC-CO[d]; Spain	6 months; 10^8 cfu	A decrease in *Gammaproteobacteria*
	Infants	RDBPC; Italy	21 days; 10^8 cfu	No significant change
Lactobacillus reuteri NCIMB30242	Hypercholesterolemia patients	Random; UK	4 weeks; 3×10^9~1.8×10^{10} cfu	A significant increase in the *Firmicutes*/*Bacteroidetes* ratio
Lactobacillus paracasei DG	Healthy individuals	RDBPC-CO; Italy	4 weeks; 2.4×10^{10} cfu	An increase in *Proteobacteria* and *Coprococcus*, a decrease in *Blautia*
Bifidobacterium animalis subsp. *lactis CNCM I-2494*	Healthy individuals	RDBPC; USA	4 weeks; 2.5×10^{10} cfu	No significant change
	Healthy individuals	Open-label; USA	7 weeks; 2.5×10^{10} cfu	No significant change
Bifidobacterium breve M-16V +	Pregnant women	Open-label; Japan	Pregnant women: 4 weeks	Pregnant women: a decrease in *Proteobacteria*
	Newborn infants		Infant: 6 months; 5×10^9 cfu	
Bifidobacterium longum BB536				Infant: an increase *Bacteroides*
VSL#3f	IBS patients	Open-label; HK	4 weeks; 1.8×10^{12} cfu	A significant decrease in *Bacteroides*
Lactobacillus acidophilus NCFM	Children with atopic dermatitis	RPC[e]; Denmark	8 weeks; 10^{10} cfu	An increase in *Clostridium* and *Bifidobacterium*
Bifidobacterium lactis Bi-07				

Bifidobacterium longum Bar33	Healthy individuals	RDBPC; Italy	1 month; 10^9 cfu	A significant decrease in *Clostridium difficile*
Lactobacillus helveticus Bar13				
Lactobacillus rhamnosus GG	IBS patients	RDBPC; Finland	5 months; 1.2×10^9 cfu	No significant changes
LactobacillusLc705				
Propionibacterium freudenreichii subsp. *shermanii JS*				
Bifidobacterium animalis subsp. *lactis BB-12*				
Bifidobacterium animalis subsp. *lactis CNCM I-2494*	Healthy individuals	Open-label; USA	7 weeks; 2.5×10^{10} cfu	No significant changes
	IBS patients	RDBPC; UK	4 weeks; 2.5×10^{10} cfu	A decrease in *Bilophila*
Bifidobacterium animalis subsp. *lactis CNCM I-2494*	Healthy twins	Open-label; USA	7 weeks; 2.5×10^{10} cfu	An increase in polysaccharides degrading bacteria
Lactobacillus sp. *HY7801*	IBS patients	RDBPC; Korea	8 weeks; 1.2×10^{10} cfu	No significant changes
Bifidobacterium longum HY8004				
Lactobacillus brevis HY7401				

[a]*M* male, [b]*F* female, [c]*RDBPC* randomized, double-blind, placebo-controlled clinical trial, [d]*RDBPC-CO* randomized, double-blind, placebo-controlled, cross-clinical trial, [e]*RPC* randomized, placebo-controlled clinical trial (Derrien and van Hylckama Vlieg 2015)

Table 8.2 Effects of probiotic lactic acid bacteria on IBS

Strains and doses	Duration	Results	References
Lactobacillus salivarius, 1×10^{10} *cfu*	8 weeks	No differences among treatment arms	O'Mahony et al. (2005)
Bifidobacterium infantis 35624, 1×10^{10} *cfu*			
B. animalis DN173010, 1.25×10^{10} *cfu*	4 weeks	Ineffectiveness in abdominal distension and gastrointestinal transit	Agrawal et al. (2009)
Streptococcus thermophilus, 1.2×10^{9} *cfu*			
L. bulgaricus, 1.2×10^{9} *cfu*			
B. animalis DN173010, 1.25×10^{10} *cfu*	6 weeks	No significant improvement in quality of life and symptoms	Guyonnet et al. (2007)
S. thermophilus, 1.2×10^{9} *cfu*			
L. bulgaricus, 1.2×10^{9} *cfu*			
B. bifidum MIMBb75, 1×10^{9} *cfu*	4 weeks	Significant improvement after treatment	Guglielmetti et al. (2011)
L. rhamnosus GG ATCC 53103, 1×10^{7} *cfu*	20 weeks	No differences among treatment arms	Kajander et al. (2008)
L. rhamnosus Lc705 DSM7061, 1×10^{7} *cfu*			
Propionibacterium freudenreichii, 1×10^{7} *cfu*			
B. animalis subsp. *lactis*, 1×10^{7} *cfu*			
BB-12 DSM 15954, 1×10^{7} *cfu*			
L. plantarum DSM 9843, 5×10^{7} *cfu*	4 weeks	Significant improvement in pain score	Nobaek et al. (2000)
B. infantis 35624, 1×10^{6}–1×10^{10} *cfu*	4 weeks	Significant improvement	Whorwell et al. (2006)
S. thermophilus, 1×10^{8} *cfu*	4 weeks	No significant improvement in mucosal barrier function	Zeng et al. (2008)
L. bulgaricus, 1×10^{7} *cfu*			
L. acidophilus, 1×10^{7} *cfu*			
B. longum, 1×10^{7} *cfu*			
L. acidophilus CUL-60	8 weeks	Significant reduce in symptoms of IBS	Williams et al. (2009)
NCIMB 30157			
CUL-21 NCIMB 30156			
B. bifidum CUL-20			
NCIMB 30153			
B. lactis CUL-34 NCIMB 30172			
Total 2.5×10^{10} *cfu*			
L. paracasei subsp. *paracasei F19*	8 weeks	Significant improvement	Simren et al. (2010)
L. acidophilus La5			
B. animalis subsp. *lactis BB12*			
5×10^{7} *cfu, each*			

brain signals (Andrade et al. 2015; Barberi et al. 2015; Canfora et al. 2015; Chichlowski and Rudolph 2015; Kianifar et al. 2015; Martinez-Augustin et al. 2014; Mazurak et al. 2015; Meini et al. 2015; Moayyedi et al. 2010; Owaga et al. 2015; Stevenson et al. 2014).

8.3 Infectious Diarrhea

8.3.1 Epidemiology, Signs, and Symptoms

Infectious diarrhea (gastroenteritis) is a condition of having at least three loose or liquid bowel movements each day. Infectious diarrhea might represent as a leading cause of mortality among children under the age of 5, especially in those developing countries (Dinleyici et al. 2012; Weichert et al. 2012). Worse, repeated infections might lead to malnutrition, increase the risk of serious infections, and ultimately negatively affect children growth and development (Vandenplas et al. 2011). Depending on its duration, it has been classified into three main types: acute (<14 days), persistent (14–29 days), or chronic (≥30 days). The primary symptoms of infectious diarrhea include diarrhea, vomiting, and abdominal pain.

8.3.2 Histological and Molecular Pathogenesis

The primary causes of infectious diarrhea include viruses (rotavirus), bacteria (e.g., *Escherichia coli*, *Campylobacter*, *Salmonella*, *Bacillus cereus*, etc.), parasites (e.g., *Giardia*, *Cryptosporidium*, and *Cyclospora*), and fungi. Of note, antibiotic-associated diarrhea is often related with *Clostridium difficile*. Compared with adult, children are more predisposed to infectious diarrhea as they are less likely to practice good hygiene habits as well as normally under development of immunity.

8.3.3 Gut Microbiota and Probiotic Intervention

Infectious diarrhea is normally an acute and self-limiting disease. It does not require medication unless patient with dehydration or particularly severe symptoms (Gareau et al. 2010). In nature, infectious diarrhea is a condition caused by gut microbial dysbiosis (Sanders et al. 2013). Accordingly, probiotics have long been proposed for infectious diarrhea management. Although probiotics (e.g., *Saccharomyces boulardii*, *Lactobacillus rhamnosus* GG) show some promise in infectious diarrhea (Canani et al. 2007; Islek et al. 2014; Saavedra et al. 1994; Saavedra 2000; Szajewska et al. 2006; Szajewska and Kolodziej 2015), the overall results have been mixed (Table 8.3). Moreover, such approaches might not for those critically ill hospitalized patients.

Table 8.3 Effects of probiotic lactic acid bacteria on infectious diarrhea

Strains and doses	Duration	Results	References
L. casei	5 days	Significant improvement in the duration of diarrhea in children	Yazar et al. (2016)
L. plantarum			
L. rhamnosus			
Bifidobacterium lactis			
Total $4.5 \times \mathbf{10^9}$ *cfu*			
L. reuteri DSM 17938, $1 \times \mathbf{10^8}$ *cfu*	5 days	Significantly shortens infectious diarrhea in a pediatric outpatient setting	Dinleyici et al. (2015)
L. rhamnosus R0011, $1.9 \times \mathbf{10^9}$ *cfu*	7 days	Ineffectiveness in infectious diarrhea in Indonesian children	Hegar et al. (2015)
L. acidophilus R0052, $0.1 \times \mathbf{10^9}$ *cfu*			
B. animalis subsp. *lactis*, $1 \times \mathbf{10^9}$ *cfu*	Hospitalization period	Ineffectiveness in preventing common infection in hospitalized children	Hojsak et al. (2015)
B. lactis B94, $5 \times \mathbf{10^{10}}$ *cfu*	5 days	Significant improvement in necrotizing enterocolitis	Akin et al. (2014)
L. reuteri DSM 17938, $1 \times \mathbf{10^8}$ *cfu*	5 days	Effective reduction in LOS in hospitalized children	Dinleyici and Vandenplas (2014)
L. reuteri DSM 17938, $1 \times \mathbf{10^8}$ *cfu*	3 months	Significant reduction in diarrhea in preschool children	Gutierrez-Castrellon et al. (2014)
L. acidophilus	5 days	Significant improvement in the duration of infectious diarrhea and length of hospital stay	Dinleyici et al. (2013)
L. rhamnosus			
B. bifidum			
B. longum			
Enterococcus faecium			
Total $2.5 \times \mathbf{10^9}$ *cfu*			
L. reuteri, $1 \times \mathbf{10^8}$ *cfu*	4 weeks	Significant prevention of antibiotic-associated diarrhea in hospitalized adults	Cimperman et al. 2011

8.4 Inflammatory Bowel Disease

8.4.1 Epidemiology, Signs, and Symptoms

Inflammatory bowel disease (IBD), a group of chronic inflammatory disorders of the intestinal tract, mainly includes Crohn's disease (CD) and ulcerative colitis (UC) (Kabeerdoss et al. 2015). They might affect the quality of life of 1.4 million individuals in the United States. The most common symptoms of IBD are abdominal pain, diarrhea, bloody stools, and weight loss. Compared with healthy individuals, patients suffering long-term IBD might increase the risk of colorectal cancer.

8.4.2 Histological and Molecular Pathogenesis

The etiology of IBD is incompletely understood yet. IBD is widely recognized as a complex disease which is trigged by the interaction between genetic and environmental factors (Saad et al. 2013). Compared with others, Caucasian descent especially those in developed countries are more predisposed to IBD. The dysregulation of innate immune mechanisms (e.g., TNF_{α}, IL10, and ATG16L1 signaling pathways) has been implicated in the pathogenesis of IBD (Corthe et al. 2006).

8.4.3 Gut Microbiota and Probiotic Intervention

IBD management is currently relied on nonspecific immunosuppressive agents (such as steroids) and tumor necrosis factor (TNF_{α})-targeted therapy. However, these treatments are not effective in all patients. Worse, side effects have dampened enthusiasm for their long-term use.

Emerging evidence suggested a causal role of gut microbial dysbiosis in IBD (Hardy et al. 2013). IBD patients are different from healthy individuals, either in the community membership or abundance of gut microbiota. Probiotic use in IBD management has also been successful in multiple animal studies (Ahl et al. 2016). Although highly expected by either mechanistic or animal studies (Sartor 2008; Shanahan and Collins 2010), the clinical outcomes of probiotic use in IBD have been mixed (Table 8.4). Most likely, upon rational utilization, certain probiotics (e.g., *Faecalibacterium prausnitzii*, *Bacteroides fragile*, *Bifidobacterium longum BB536*, *E. coli* Nissle 1917, and *Clostridium* species) might be helpful in IBD treatment (Kato et al. 2004; Christensen 2006; Macfarlane et al. 2006; Saad et al. 2013; Takeda 2009). One potential proposed approach is to induce rapid clinical remission by corticosteroid and/or anti-TNF_{α} therapy followed by probiotic interventions to sustain remission. Of note, fecal microbiota transplant might be another useful therapeutic strategy in IBD management. Mechanistically, probiotic might enhance clinical outcome by modulating intestinal mucosal barrier, reducing intestinal permeability, and suppressing pathogenic bacteria translocation (Sartor 2004).

8.5 Necrotizing Enterocolitis

8.5.1 Epidemiology, Signs, and Symptoms

Necrotizing enterocolitis (NEC) is the death of tissue in the intestine. Despite all modern advances in medical and surgical efforts, NEC still represents as a major cause of neonatal morbidity and death, especially in premature and low-birth-weight infants (Neu and Walker 2011; Zani and Pierro 2015). Currently, the mortality of

Table 8.4 Effects of probiotic lactic acid bacteria on IBD

Strains and doses	Duration	Results	References
Lactobacillus plantarum 299, 5×10^9 *cfu*	21 days	No significant improvement in ileal pouch function	Bengtsson et al. (2016)
Bifidobacterium infantis Cure 21, 5×10^9 *cfu*			
B. longum, 2×10^{11} *cfu*	1 month	Significant improvement in UC	Furrie (2005)
L. johnsonii LA1, 4×10^9 *cfu*	6 months	No significant improvement in CD recurrence	Marteau et al. (2006)
E. coli strain *Nissle1917*, 1×10^8 *cfu*	2 months	Significant improvement in acute distal UC	Harald et al. (2010)
VSL#3, 3.6×10^{11} *cfu*	2 months	Significant improvement in acute UC	Ng et al. (2010)
B. longum, 2×10^{11} *cfu*	6 months	Significant improvement in CD	Steed et al. (2010)
VSL#3, 3.6×10^{11} *cfu*	2 months	Significant improvement in UC	Tursi et al. (2010)
B. animalis subsp. *lactis BB-12*,	12 months	No significant improvement in UC	Wildt et al. (2011)
L. acidophilus La-5;			
Total 2.5×10^{10} *cfu*			

NEC is around 30%. Worse, even upon success treatment, the survival infants often suffer malnutrition, growth retardation, and even neurologic abnormalities. As to NEC's symptoms, they mainly include feeding intolerance, vomiting, bloating, diarrhea, and even bloody stools.

8.5.2 Histological and Molecular Pathogenesis

The exact etiology of NEC remains unclear, but growing evidence indicated that it is a multifactorial disease. The potential risk factors for NEC include premature birth, congenital heart disease, poor oxygen and blood supply, intestinal mucosal immaturity, and bacterial infection (Akin et al. 2014; Bajwa et al. 2011; Cotten et al. 2009; Cummings 2015; Mai et al. 2011; Mercado-Lubo and McCormick 2010; Nabi et al. 2006; Niemarkt et al. 2015). Compared with normal infants, the premature and/or low-birth-weight infants are more predisposed to NEC as their gut are normally under development of immunity and thus prone to inflammation as well as loss of epithelial integrity.

8.5.3 Gut Microbiota and Probiotic Intervention

The management of NEC has currently relied on bowel rest therapy, orogastric tube, intravenous fluids, and intravenous antibiotics. Accumulating evidence indicates an association between NEC and gut microbiotal alternations. In this connection, a

decreased *Firmicutes* and increased *Gammaproteobacteria* were found in the gut microbiota of infants with NEC. Most likely, such gut microbial dysbiosis might be link with the antibiotic usage. Breastfeeding and probiotic uses have been strongly recommended to lower the risk of NEC (Lin et al. 2008; Sharma and Shastri 2016; Reali et al. 2015). Indeed, certain probiotics (e.g., *Bifidobacterium*, *Lactobacillus*, and *Saccharomyces*) show promise in improving clinical outcomes for NEC (Table 8.5). The gut of the newborn baby is generally accepted as sterile, and thus the timing administration of probiotic might help them to establish rather normal gut micro-ecology. Mechanistically, probiotic might reduce the incidence and mortality of NEC by targeting pathogenic bacteria infection via their metabolic productions such as extracellular polysaccharide, lactic acid, short-chain fatty acids (SCFA), and bacteriocin (Bird et al. 2010; Fleming et al. 2015; Gorelnikova and Karpunina 2015; Hevia et al. 2015; Lim et al. 2015; Roy et al. 2006).

8.6 Colorectal Cancer

8.6.1 Epidemiology, Signs, and Symptoms

Colorectal cancer (CRC) is a malignant tumor that occurred in the colon or rectum. It represents the third most common noncutaneous malignancy and affords the third leading cause of cancer-related death (Brenner et al. 2014a, b). Despite the recent improvements in preventive strategies, screening techniques, and development of surgery and chemotherapy, the median survival period for metastatic colorectal cancer patients is only 24 months. The common symptoms of CRC might include bloody stools, a change in bowel habits, body weight loss, and fatigue (e.g., extreme tiredness or lack of energy).

8.6.2 Histological and Molecular Pathogenesis

During colorectal carcinogenesis, the transition from normal mucosa to adenoma and final carcinoma is a protracted event as well as a multifactorial process (Baert-Desurmont et al. 2016). The potential risk factors of CRC include family history, obesity, lack of physical activity, high-fat diet, low dietary fiber intake, high red meat intake, and smoking and alcohol use (Botteri et al. 2008; Crockett et al. 2011; Declercq et al. 2015; Gallagher and LeRoith 2011; Germansky and Leffler 2011; Fedirko et al. 2011; Han et al. 2015; Hannan et al. 2009; Odegaard et al. 2011; Pajares and Perea 2015; Raufman et al. 2015; Wani et al. 2014). Molecular analyses of colorectal carcinomas have led to a genetic model of colon carcinogenesis which stemmed from the accumulation of a number of genetic alterations (e.g., APC, p53, and K-Ras) and oncogenic protein overexpression (e.g., COX-2 and EGFR).

Table 8.5 Effects of probiotic lactic acid bacteria on NEC

Strains and doses	Duration	Results	References
B. breve BBG-001, 6.7×10^7~6.7×10^9 cfu	37 months	No effect on premature infant NEC	Costeloe et al. (2016)
B. infantis	6 weeks	Effectively reduced the risk of NEC in very-low-birth-weight neonates	Bin-Nun et al. (2006)
S. thermophilus			
B. bifidus			
Total 1 $\times$ 10^9 *cfu*			
L. casei	30 days	Significantly reduced the morbidity of NEC in very-low-birth-weight preterm infants	Braga et al. (2011)
B. breve			
Total 3.5×10^7~3.5×10^9 *cfu*			
B. breve BBG-001, 1×10^9 *cfu*	36 weeks	Invalid for NEC in very preterm infants	Costeloe et al. (2015)
LGG, 6×10^9 *cfu*	7 days	Ineffectiveness in NEC prevention	Dani et al. (2002)
Saccharomyces boulardii, 5×10^9 *cfu*	During hospitalization	Ineffectiveness in reducing the morbidity of NEC, but significant improvement in feeding tolerance and sepsis	Demirel et al. (2013)
B. lactis, 5×10^9 *cfu*	8 weeks	Effectiveness in NEC prevention	Dilli et al. (2015)
L. acidophilus, 1×10^9 *cfu/g*	During hospitalization	Effectiveness in NEC prevention in preterm newborns weighing less than 1500 g	Fernándezcarrocera (2013)
L. rhamnosus, 4.4×10^8 *cfu*			
L. casei, 1×10^9 *cfu*			
L. plantarum, 1.76×10^8 *cfu*			
B. infantis, 2.76×10^7 *cfu*			
S. thermophilus, 6.6×10^5 *cfu/*			

8.6.3 Gut Microbiota and Probiotic Intervention

It is well-known that both high-fat diet and low dietary fiber intake might increase the risk of CRC. Considering the fact that both of them greatly affect the composition of the intestinal microbiota, gut microbial dysbiosis has long been suspected to functionally mediate CRC development (Louis et al. 2014; Sears and Pardoll 2011). Compared with healthy ones, CRC patients have a lower gut bacterial diversity but more *Fusobacterium nucleatum* and *Escherichia coli* (Castellarin et al. 2012). Further studies confirmed that they might potentiate intestinal tumorigenesis by modulating the tumor-immune microenvironment. Certain probiotics show some promise in CRC management (Table 8.6), but it still leaves much to be desired (Ishikawa et al. 2005; Ma et al. 2010; Pearson et al. 2009; Pala et al. 2011; Rafter

Table 8.6 Effects of probiotic lactobacillus on CRC

Strains and doses	Duration	Results	References
L. casei BL23, 1×10^9 *cfu*	10 weeks	Effectiveness in chemoprevention of DMH-induced CRC in C57BL/6 mice	Lenoir (2016)
VSL#3, 1.3×10^6 *cfu*	8 weeks	Effectiveness in chemoprevention of western-style diet-induced CRC in Balb/C mice	Chung et al. (2017)
L. rhamnosus R0011	12 weeks	Improvement in the quality of life in CRC survivors	Lee et al. (2014)
L. acidophilus R0052			
Total 2×10^9 *cfu*			
L. plantarum CGMCC 1258	Pre-operation 6 days	Significantly improve the integrity of gut mucosal barrier and lower infectious complications	Liu et al. (2011)
L. acidophilus LA-11	Post-operation 10 days		
B. longum BL-88			
Total 2.6×10^{14} *cfu*			
B. longum BB 536, 1×10^7 *cfu*	Pre-operation 3 days	La1, but not BB 536, reduces the concentration of pathogens and modulates local immunity	Gianotti et al. (2010)
L. johnsonii La1, 1×10^9 *cfu*	Post-operation 3 days		
Lactobacillus rhamnosus GG, 1×10^7 *cfu*	Pre-radiation, 3 days	Effectively reduced radiation-induced epithelial injury and improve crypt survival in mice	Ciorba et al. (2012)
Bifidobacterium	7 and 14 days	Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy	Sivan et al. (2015)
B. lactis, 1×10^{11} cfu	30 weeks	The synbiotic combination of RS and *B. lactis* significantly protects against AOM-induced CRC	Leu et al. (2010)
B. lactis, 1×10^{11} cfu	4 weeks	Induced unique changes in fecal microflora, but did not significantly alter serum or epithelial variables	Worthley et al. (2009)
L. acidophilus LA-5, 1.75×10^9 *cfu*	Pre-operation 15 days	Significantly reduced risk of postoperative complications	Kotzampassi et al. (2015)
L. plantarum, 0.5×10^9 *cfu*	Post-operation 15 days		
B. lactis BB-12, 1.75×10^9 *cfu*			

2002; Rafter et al. 2007; Rowland et al. 1998; Rowland 2009). It is worth noting that probiotics might reduce side effects of radiation therapy (Ciorba et al. 2012) while potently enhancing cancer immunotherapy (Chitapanarux et al. 2010; Moreno de LeBlanc and Perdigón 2010; Vétizou et al. 2015).

8.7 Probiotic Lactic Acid Bacteria: To the Future and Beyond

8.7.1 Challenges to Probiotic Intervention

Accumulating data suggested the implication of gut microbial dysbiosis in multiple gastrointestinal diseases. If gut bacteria are making you ill, can swapping them make you healthy? Accordingly, gut microbiota is proposed as one promising molecular target for gastrointestinal disorder management. People reasoned that probiotic intervention might remodel a disease-prone microbiota pattern into a disease-free state. Indeed, probiotics have shown some promise in several gastrointestinal disorders such as irritable bowel syndrome, infectious diarrhea, inflammatory bowel disease, and even colorectal cancer, but the following bench-to-bedside translation remains to be a big issue (Klein et al. 2010; Floch et al. 2011).

A success in clinical trial mainly depends on two factors: an effective and safe drug and a selectively responsive subpopulation. In precision medicine, one trend is rational drug design, which is largely based on a definite molecular target. The first and most important question is how gut microbiota affect host physiology. Although altered gut microbiota have been associated with various gastrointestinal diseases, their causality remains to be further defined (Bäckhed et al. 2012). A better understanding of the etiology of gastrointestinal disorders as well as their cause-and-effect relationship among gut microbiota, microbe-derived gut metabolites, and host is thought to be an essential step forward.

The second question is how to design a clinical study on probiotics. Is it based on epidemiological data and/or evidence-based medicine (Sanders and Levy 2011)? Probiotic products are currently marketed as foods or dietary supplements, which are normally not regulated as disease management. Then, how do we conduct studies to test the potential health benefit of probiotic in healthy ones? If performed among a disease population, such kind of study should follow the standards of drugs. Efficacy of probiotic intervention might be dependent on the probiotic strains and/or dosage used. How the optimizing probiotic LAB strain, dose and even product formulation are weight and judged? As outcomes must be clear and measurable in a clinical study, what are the validated biomarkers used for targeted diseases? In addition, has the optimal target population been clearly defined? To this end, nutrition standards, dietary guidelines, and even genetic background of targeted populations must be considered.

Another issue is the safety of probiotics. Although probiotics are generally considered safe as they derived from traditional fermented foods or health gut, they might cause adverse health consequences in certain cases (Guarner et al. 2011). If gut bacteria are making you ill, can swapping them make you healthy? Please keep in mind, probably, the reverse is also true. For example, some probiotics might cause excessive immunity response, affect the metabolism of some drug, and even carry and spread antibiotic resistance genes. Although probiotic might sometimes

rectify gut microbial dysbiosis, its administration in wrong way might further profound microbial dysbiosis and thereby causes serious side effects, especially on certain subgroup of populations. The suitability and safety of probiotic should be studied by randomized, double-blind, placebo-controlled trials.

Taken together, before a large-scale clinical trial can be discussed, all those basic information about the targeted populations as well as microbe used is required.

8.7.2 The Future of Probiotic Intervention

Recent studies clearly indicated that the gut microbiota play a critical role in host physiology. However, an understanding of how they affect the host health is only beginning to be elucidated. For example, beyond probiotic supplement, there are many factors (e.g., as age, genetics, drug, diet, and even stress) influencing the composition of human microbiome. As a saying goes, you are what you eat. Diet strongly affects human health, at least partially, by modulating gut microbiome. And long-term dietary interventions may allow modulation of an individual's enterotype to improve health. To this end, the relationships among diet-microbe-host should be more thoroughly studied and elucidated in the future.

Tomorrow's probiotics might probably move beyond the microorganisms commonly used as probiotics today. For example, despite the presence of fungal and viral members, studies in gut microbe so far have focused on the bacteria, and the probiotics available to consumers also solely belong to lactic acid bacteria. Actually, lactic acid bacteria itself is also a term which has no strict taxonomic significance. Not surprisingly, such paradigm might be changed. Upon recent progression and understanding of the gut microbiota, some specific strains (e.g., *Akkermansia muciniphila*, *Bacteroides fragilis*, and *Faecalibacterium prausnitzii*) might be the next-generation probiotics. Probiotic interventions outside the gastrointestinal tract (e.g., diabetes, obesity, the metabolic syndrome, liver diseases, etc.) are also increasingly recognized (Hojsak et al. 2010). Moreover, probiotics are normally nonpathogenic and noninvasive and non-colonizing bacterium, and thus recombinant probiotics may represent an interesting direction in the future, especially to deliver oral vaccine, improve natural immune responses, and restore antigen-specific tolerance (Takiishi et al. 2012). Advancements in this direction might largely lie in our better understanding of their genetic-metabolic networks.

In summary, probiotics might have a huge potential in clinical application. Although the overall efficacy of current probiotic intervention is still far to meet the standard of medical care required for evidence-based medicine and some data might be inconsistent or somewhat ever contradictory with each other, targeting gut microbial dysbiosis by probiotics opens a new avenue to gastrointestinal diseases management. Exciting times are definitely coming up for food microbiologist and gastroenterologists. Working together, we might create the next epoch in this area.

References

Agrawal A, Houghton LA, Morris J et al (2009) Clinical trial: the effects of a fermented milk product containing Bifidobacterium lactis DN-173 010 on abdominal distension and gastrointestinal transit in irritable bowel syndrome with constipation. Aliment Pharmacol Ther 29(1):104–114

Ahl D, Liu H, Schreiber O et al (2016) *Lactobacillus reuteri* increases mucus thickness and ameliorates DSS-induced colitis in mice. Acta Physiol 217(4):300–310

Akin MA, Yikilmaz A, Gunes T et al (2014) Quantitative assessment of hepatic blood flow in the diagnosis and management of necrotizing enterocolitis. J Matern Fetal Neonatal Med 28(18):2160–2165

Andrade MER, Araujo RS, de Barros PAV et al (2015) The role of immunomodulators on intestinal barrier homeostasis in experimental models. Clin Nutr 34(6):1080–1087

Bäckhed F, Ley RE, Sonnenburg JL et al (2005) Host-bacterial mutualism in the human intestine. Science 307(5717):1915–1920

Bäckhed F, Fraser CM, Ringel Y et al (2012) Defining a healthy human gut microbiome: current concepts, future directions, and clinical applications. Cell Host Microbe 12(5):611–622

Baert-Desurmont S, Charbonnier F, Houivet E et al (2016) Clinical relevance of 8q23, 15q13 and 18q21 SNP genotyping to evaluate colorectal cancer risk. Eur J Hum Genet 24(1):99–105

Bajwa NM, Berner M, Worley S et al (2011) Population based age stratified morbidities of premature infants in switzerland. Swiss Med Wkly 141:w13212

Barberi C, Campana S, de Pasquale C et al (2015) T cell polarizing properties of probiotic bacteria. Immunol Lett 168(2):337–342

Bengtsson J, Adlerberth I, Östblom A et al (2016) Effect of probiotics (*Lactobacillus plantarum* 299 plus bifidobacterium cure21) in patients with poor ileal pouch function: a randomised controlled trial. Scand J Gastroenterol 51(9):1–6

Bin-Nun A, Bromiker R, Wilschanski M et al (2006) Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. J Pediatr 147(2):192–196

Bird AR, Conlon MA, Christophersen CT et al (2010) Resistant starch, large bowel fermentation and a broader perspective of prebiotics and probiotics. Benefic Microbes 1(4):423–431

Bischoff SC (2011) Gut health: a new objective in medicine? BMC Med 9:24

Botteri E, Iodice S, Bagnardi V et al (2008) Smoking and colorectal cancer: a meta-analysis. JAMA 300(23):2765–2778

Braga TD, Da SG, de Lira PI et al (2011) Efficacy of bifidobacterium breve and *Lactobacillus casei* oral supplementation on necrotizing enterocolitis in very-low-birth-weight preterm infants: a double-blind, randomized, controlled trial. Am J Clin Nutr 93(1):81–86

Brenner H, Kloor M, Pox CP (2014a) Colorectal cancer. Lancet 383(9927):1490–1502

Brenner H, Stock C, Hoffmeister M (2014b) Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. BMJ 348(apr09 1):g2467

Canani RB, Cirillo P, Terrin G et al (2007) Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. BMJ 335(7615):1–6

Canfora EE, Jocken JW, Blaak EE (2015) Short-chain fatty acids in control of body weight and insulin sensitivity. Nat Rev Endocrinol 11(10):577–591

Castellarin M, Warren RL, Freeman JD et al (2012) Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Res 22(2):299–306

Chichlowski M, Rudolph C (2015) Visceral pain and gastrointestinal microbiome. J Neurogastroenterol Motil 21(2):172–181

Chitapanarux I, Chitapanarux T, Traisathit P et al (2010) Research randomized controlled trial of live *Lactobacillus acidophilus* plus bifidobacterium bifidum in prophylaxis of diarrhea during radiotherapy in cervical cancer patients. Radiat Oncol 5:31

Christensen JSR (2006) Aerococcus urinae. Apple Trees Productions, New York

Chung EJ, Do EJ, Kim SY et al (2017) Combination of metformin and VSL#3 additively suppresses western-style diet induced colon cancer in mice. Eur J Pharmacol 794:1–7
Cimperman L, Bayless G, Best K et al (2011) A randomized, double-blind, placebo-controlled pilot study of *Lactobacillus reuteri* ATCC 55730 for the prevention of antibiotic-associated diarrhea in hospitalized adults. J Clin Gastroenterol 45(9):785–789
Ciorba MA, Riehl TE, Rao MS et al (2012). Lactobacillus probiotic protects intestinal epithelium from radiation injury in a TLR-2/cyclo-oxygenase-2-dependent manner. Gut 61(6):829–38.
Collins SM (2014) A role for the gut microbiota in ibs. Nat Rev Gastroenterol Hepatol 11(8):497–505
Corthesy B, Gaskins HR, Mercenier A (2006) Cross-talk between probiotic host immune system. J Nutr 137:781S–790S
Costeloe K, Hardy P, Juszczak E et al (2015) *Bifidobacterium breve* BBG-001 in very preterm infants: a randomised controlled phase 3 trial. Lancet 387(10019):649–660
Costeloe K, Bowler U, Brocklehurst P et al (2016) A randomised controlled trial of the probiotic *Bifidobacterium breve* BBG-001 in preterm babies to prevent sepsis, necrotising enterocolitis and death: The probiotics in preterm infants (pips) trial. Health Technol Assess 20(66):1–194
Cotten CM, Taylor S, Stoll B et al (2009) Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. Pediatrics 123(1):58–66
Courtney J, Liebelt D, Nett MP et al (2008) The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. PLoS Biol 6(11):e280
Crockett SD, Long MD, Dellon ES et al (2011) Inverse relationship between moderate alcohol intake and rectal cancer: analysis of the north carolina colon cancer study. Dis Colon Rectum 54(7):887–894
Cummings CJSSP (2015) Gut bacteria and necrotizing enterocolitis cause or effect. Trends Microbiol 23(6):332–333
Dani C, Biadaioli R, Bertini G et al (2002) Probiotics feeding in prevention of urinary tract infection, bacterial sepsis and necrotizing enterocolitis in preterm infants. Biol Neonate 82(2):103–108
Declercq V, Mcmurray DN, Chapkin RS (2015) Obesity promotes colonic stem cell expansion during cancer initiation. Cancer Lett 369(2):336–343
Demirel G, Erdeve O, Celik IH et al (2013) *Saccharomyces boulardii* for prevention of necrotizing enterocolitis in preterm infants: a randomized, controlled study. Acta Paediatr 102(12):e560–e565
Derrien M, van Hylckama Vlieg JET (2015) Fate, activity, and impact of ingested bacteria within the human gut microbiota. Trends Microbiol 23(6):354–366
Dethlefsen L, Gordon JI (2011) Colloquium paper: incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. Proc Natl Acad Sci U S A 108(Suppl 1):4554–4561
Didari T, Mozaffari S, Nikfar S et al (2015) Effectiveness of probiotics in irritable bowel syndrome: updated systematic review with meta-analysis. World J Gastroenterol 21(10):3072–3084
Dilli D, Aydin B, Fettah ND et al (2015) The propre-save study: effects of probiotics and prebiotics alone or combined on necrotizing enterocolitis in very low birth weight infants. J Pediatr 166(3):545–551
Dinleyici EC, Vandenplas Y (2014) *Lactobacillus reuteri* DSM 17938 effectively reduces the duration of acute diarrhoea in hospitalised children. Acta Paediatr 103(7):e300
Dinleyici EC, Eren M, Ozen M et al (2012) Effectiveness and safety of *Saccharomyces boulardii* for acute infectious diarrhea. Expert Opin Biol Ther 12(4):395–410
Dinleyici EC, Cagri E, Dalgic N et al (2013) The effect of a multispecies synbiotic mixture on the duration of diarrhea and length of hospital stay in children with acute diarrhea in turkey: Single blinded randomized study. Eur J Pediatr 172(4):459–464
Dinleyici EC, Dalgic N, Guven S et al (2015) *Lactobacillus reuteri* DSM 17938 shortens acute infectious diarrhea in a pediatric outpatient setting. J Pediatr 91(4):392–396

Faith JJ, Guruge JL, Mark C et al (2013) The long-term stability of the human gut microbiota. Science 341(6141):1237439

Fedirko V, Tramacere I, Bagnardi V et al (2011) Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Ann Oncol 22(9):1958–1972

Fernándezcarrocera LA (2013) Double-blind, randomised clinical assay to evaluate the efficacy of probiotics in preterm newborns weighing less than 1500 g in the prevention of necrotising enterocolitis. Arch Dis Child Fetal Neonatal Ed 98(1):F5–F9

Fleming P, Hall NJ, Eaton S (2015) Probiotics and necrotizing enterocolitis. Pediatr Surg Int 31:1111–1118

Flint HJ, Duncan SH, Scott KP et al (2015) Links between diet, gut microbiota composition and gut metabolism. Proc Nutr Soc 74(1):13–22

Floch MH, Walker WA, Madsen K et al (2011) Recommendations for probiotic use-2011 update. J Clin Gastroenterol 45(Suppl):S168–S171

Furrie E (2005) Synbiotic therapy (*Bifidobacterium longum*/synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: a randomised controlled pilot trial. Gut 54(2):242–249

Gallagher EJ, LeRoith D (2011) Minireview: Igf, insulin, and cancer. Endocrinology 152(7):2546–2551

Gareau MG, Sherman PM, Walker WA (2010) Probiotics and the gut microbiota in intestinal health and disease. Nat Rev Gastroenterol Hepatol 7(9):503–514

Gerard P (2016) Gut microbiota and obesity. Cell Mol Life Sci 73(1):147–162

Germansky KA, Leffler DA (2011) Best practice & research clinical gastroenterology. Best Pract Res Clin Gastroenterol 25:387–395

Gianotti L, Morelli L, Galbiati F et al (2010) A randomized double-blind trial on perioperative administration of probiotics in colorectal cancer patients. World J Gastroenterol 16(2):167–175

Gorelnikova EA, Karpunina LV (2015) Effect of lactobacilli exopolysaccharides on phagocyte and cytokine activity *in vitro* and in animal organism during infectious process modeling. Zhurnal Mikrobiologii Epidemiologii Immunobiologii 2015(5):44–50

Guarner F, Sanders ME, Gibson G et al (2011) Probiotic and prebiotic claims in europe: Seeking a clear roadmap. Br J Nutr 106(11):1765–1767

Guglielmetti S, Mora D, Gschwender M et al (2011) Randomised clinical trial: *Bifidobacterium bifidum* MIMBB75 significantly alleviates irritable bowel syndrome and improves quality of life —a double-blind, placebo-controlled study. Aliment Pharmacol Ther 33(10):1123–1132

Gutierrez-Castrellon P, Lopez-Velazquez G, Diaz-Garcia L et al (2014) Diarrhea in preschool children and lactobacillus reuteri: a randomized controlled trial. Pediatrics 133(4):904–909

Guyonnet D, Chassany O, Ducrotte P et al (2007) Effect of a fermented milk containing bifidobacterium animalis dn-173010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized, double-blind, controlled trial. Aliment Pharmacol Ther 26(3):475–486

Han C, Shin A, Lee J et al (2015) Dietary calcium intake and the risk of colorectal cancer: a case control study. BMC Cancer 15(1):1–11

Hannan LM, Jacobs EJ, Thun MJ (2009) The association between cigarette smoking and risk of colorectal cancer in a large prospective cohort from the united states. Cancer Epidemiol Biomark Prev 18(12):3362–3367

Harald M, Thomas K, Manfred G et al (2010) Clinical trial: Probiotic treatment of acute distal ulcerative colitis with rectally administered *Escherichia coli* Nissle 1917(EcN). BMC Complement Altern Med 10(1):1–8

Hardy H, Harris J, Lyon E et al (2013) Probiotics, prebiotics and immunomodulation of gut mucosal defences homeostasis and immunopathology. Nutrients 5:1869–1912

Hegar B, Waspada IM, Gunardi H et al (2015) A double blind randomized trial showing probiotics to be ineffective in acute diarrhea in indonesian children. Indian J Pediatrics 82(5):410–414

Hevia A, Delgado S, Sanchez B et al (2015) Molecular players involved in the interaction between beneficial bacteria and the immune system. Front Microbiol 6:1285

Hojsak I, Abdovic S, Szajewska H et al (2010) *Lactobacillus* GG in the prevention of nosocomial gastrointestinal and respiratory tract infections. Pediatrics 125:e1171–e1177

Hojsak I, Tokić PV, Močić PA et al (2015) *Bifidobacterium animalis* subsp. *lactis* fails to prevent common infections in hospitalized children: a randomized, double-blind, placebo-controlled study. Am J Clin Nutr 101(3):680–684

Hooper LV, Midtvedt T, Gordon JI (2002) How host-microbial interactions shape the nutrient environment of the mammalian intestine. Annu Rev Nutr 22(1):283–307

Hugenholtz J, Smid EJ (2002) Nutraceutical production with food-grade microorganisms. Curr Opin Biotechnol 13:497–507

Ishikawa H, Akedo I, Otani T et al (2005) Randomized trial of dietary fiber and *Lactobacillus casei* administration for prevention of colorectal tumors. Int J Cancer 116(5):762–767

Islek A, Sayar E, Yilmaz A et al (2014) The role of *Bifidobacterium lactis* b94 plus inulin in the treatment of acute infectious diarrhea in children. Turk J GastroenterolOff J Turk Soc Gastroenterol 25(6):628–633

Kabeerdoss P, Jayakanthan J, Pugazhendhi S et al (2015) Alterations of mucosal microbiota in the colon of patients with inflammatory bowel disease revealed by real time polymerase chain reaction amplification of 16S ribosomal ribonucleic acid. Indian J Med Res 142:23–32

Kajander K, Myllyluoma E, Rajili M et al (2008) Clinical trial: multispecies probiotic supplementation alleviates the symptoms of irritable bowel syndrome and stabilizes intestinal microbiota. Aliment Pharmacol Ther 27(1):48–57

Kato K, Mizuno S, Umesaki Y et al (2004) Randomized placebo-controlled trial assessing the effect of bifidobacteria-fermented milk on active ulcerative colitis. Aliment Pharmacol Ther 20:1133–1141

Kianifar H, Jafari SA, Kiani M et al (2015) Probiotic for irritable bowel syndrome in pediatric patients: a randomized controlled clinical trial. Electron Physician 7(5):1255–1260

Kitazawa H, Alvarez S, Suvorov A et al (2015) Recent advances and future perspective in microbiota and probiotics. Biomed Res Int 2015:1–2

Klein M, Sanders ME, Duong T et al (2010) Probiotics: from bench to market. Ann N Y Acad Sci 1212(Suppl 1):E1–E14

Kotzampassi K, Stavrou G, Damoraki G et al (2015) A four-probiotics regimen reduces postoperative complications after colorectal surgery: a randomized, double-blind, placebo-controlled study. World J Surg 39(11):2776–2783

Lee JY, Chu SH, Jeon JY et al (2014) Effects of 12 weeks of probiotic supplementation on quality of life in colorectal cancer survivors: a double-blind, randomized, placebo-controlled trial. Dig Liver Dis 46(12):1126–1132

Lenoir M (2016) *Lactobacillus casei* BL23 regulates Treg and Th17 t-cell populations and reduces DMH-associated colorectal cancer. J Gastroenterol 51(9):1–12

Leu RKL (2010) Synbiotic intervention of bifidobacterium lactis and resistant starch protects against colorectal cancer development in rats. Carcinogenesis 31(2):246–251

Levesque BG, Sandborn WJ, Ruel J et al (2015) Converging goals of treatment of inflammatory bowel disease from clinical trials and practice. Gastroenterology 148(1):37–51

Lim JC, Golden JM, Ford HR (2015) Pathogenesis of neonatal necrotizing enterocolitis. Pediatr Surg Int 31(6):509–518

Lin HC, Hsu CH, Chen HL et al (2008) Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. Pediatrics 122(4):693–700

Liu Z, Qin H, Yang Z et al (2011) Randomised clinical trial: the effects of perioperative probiotic treatment on barrier function and post-operative infectious complications in colorectal cancer surgery—a double-blind study. Aliment Pharmacol Ther 33(1):50–63

Louis P, Hold GL, Flint HJ (2014) The gut microbiota, bacterial metabolites and colorectal cancer. Nat Rev Microbiol 12(10):661–672

Ma EL, Choi YJ, Choi J et al (2010) The anticancer effect of probiotic *Bacillus polyfermenticus* on human colon cancer cells is mediated through ErbB2 and ErbB3 inhibition. Int J Cancer 127(4):780–790

Maccaferri S, Klinder A, Cacciatore S et al (2012) *In vitro* fermentation of potential prebiotic flours from natural sources: Impact on the human colonic microbiota and metabolome. Mol Nutr Food Res 56(8):1342–1352

Macfarlane S, Macfarlane GT, Cummings JH (2006) Review article prebiotics in the gastrointestinal tract. Aliment Pharmacol Ther 24:701–714

Mai V, Young CM, Ukhanova M et al (2011) Fecal microbiota in premature infants prior to necrotizing enterocolitis. PLoS One 6(6):e20647

Marteau P, Lémann M, Seksik P et al (2006) Ineffectiveness of *Lactobacillus johnsonii* La1 for prophylaxis of postoperative recurrence in crohn's disease: a randomised, double blind, placebo controlled GETAID trial. Gut 55(6):842–847

Martinez-Augustin O, Rivero-Gutierrez B, Mascaraque C et al (2014) Food derived bioactive peptides and intestinal barrier function. Int J Mol Sci 15(12):22857–22873

Mazurak N, Broelz E, Storr M et al (2015) Probiotic therapy of the irritable bowel syndrome: why is the evidence still poor and what can be done about it? J Neurogastroenterol Motil 21(4):471–485

Meini S, Laureano R, Fani L et al (2015) Breakthrough *Lactobacillus rhamnosus* GG bacteremia associated with probiotic use in an adult patient with severe active ulcerative colitis: case report and review of the literature. Infection 43(6):777–781

Mercado-Lubo R, McCormick BA (2010) A unique subset of peyer's patches express lysozyme. Gastroenterology 138(1):36–39

Moayyedi P, Ford AC, Talley NJ et al (2010) The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review. Gut 59(3):325–332

Moreno de LeBlanc A, Perdigón G (2010) The application of probiotic fermented milks in cancer and intestinal inflammation. Proc Nutr Soc 69(3):421–428

Nabi G, Hummaida TI, Saidy KM (2006) Necrotizing enterocolitis in a very low birth weight (VLBW). JK-Practitioner 13:100–102

Neu J, Walker WA (2011) Medical progress: necrotizing enterocolitis. N Engl J Med 364(3):255–264

Ng SC, Plamondon S, Kamm MA et al (2010) Immunosuppressive effects via human intestinal dendritic cells of probiotic bacteria and steroids in the treatment of acute ulcerative colitis. Inflamm Bowel Dis 16(8):1286–1298

Niemarkt HJ, de Meij TGJ, van de Velde ME et al (2015) Necrotizing enterocolitis: a clinical review on diagnostic biomarkers and the role of the intestinal microbiota. Inflamm Bowel Dis 21(2):436–444

Nobaek S, Johansson ML, Molin G et al (2000) Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. Am J Gastroenterol 95(5):1231–1238

O'Mahony L, Mccarthy J, Kelly P et al (2005) Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. Gastroenterology 128(3):541–551

Odegaard AO, Koh WP, Yu MC et al (2011) Body mass index and risk of colorectal cancer in chinese singaporeans. Cancer 117(16):3841–3849

Owaga E, Hsieh RH, Mugendi B et al (2015) Th17 cells as potential probiotic therapeutic targets in inflammatory bowel diseases. Int J Mol Sci 16(9):20841–20858

Pajares JA, Perea J (2015) Multiple primary colorectal cancer: individual or familial predisposition? World J Gastrointest Oncol 7(12):434–444

Pala V, Sieri S, Berrino F et al (2011) Yogurt consumption and risk of colorectal cancer in the italian european prospective investigation into cancer and nutrition cohort. Int J Cancer 129(11):2712–2719

Palmer C, Bik EM, Digiulio DB et al (2007) Development of the human infant intestinal microbiota. PLoS Biol 5(7):e177

Pearson JR, Gill CI, Rowland IR (2009) Diet, fecal water, and colon cancer-development of a biomarker. Nutr Rev 67(9):509–526
Patrick MD, Thomas J, Kim IS et al (2014) The art of strain improvement of industrial lactic acid bacteria without the use of recombinant DNA technology. Microb Cell Fact 13 Suppl 1(1):1–13
Quigley EM (2013) Gut bacteria in health and disease. Gastroenterol Hepatol 9(9):560–569
Rafter J (2002) Lactic acid bacteria and cancer: mechanistic perspective. Br J Nutr 88(S1):S89–S94
Rafter J, Bennett M, Caderni G et al (2007) Dietary synbiotics reduce cancer risk factors in polypectomized and colon cancer patients. Am J Clin Nutr 85(2):488–496
Raufman JP, Dawson PA, Rao A et al (2015) Slc10a2-null mice uncover colon cancer-promoting actions of endogenous fecal bile acids. Carcinogenesis 36(10):1193–1200
Reali A, Greco F, Marongiu G et al (2015) Individualized fortification of breast milk in 41 extremely low birth weight (ELBW) preterm infants. Clin Chim Acta 451:107–110
Rowland IR (2009) The role of the gastrointestinal microbiota in colorectal cancer. Curr Pharm Des 15(13):1524–1527
Rowland I, Rumney C, Coutts J et al (1998) Effect of bifidobacterium longum and inulin on gut bacterial metabolism and carcinogen-induced aberrant crypt foci in rats. Carcinogenesis 19(2):281–285
Roy CC, Kien CL, Bouthillier L et al (2006) Short-chain fatty acids: ready for prime time? Nutr Clin Pract 21(4):351–366
Saad N, Delattre C, Urdaci M et al (2013) An overview of the last advances in probiotic and prebiotic field. LWT-Food Sci Technol 50(1):1–16
Saavedra J (2000) Probiotics and infectious diarrhea. Am J Gastroenterol 95(Supp. l):S16–S18
Saavedra JM, Bauman NA, Oung I et al (1994) Feeding of bifidobacterium bifidum and streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus. Lancet 344(8929):1046–1049
Sanders ME, Levy DD (2011) The science and regulations of probiotic food and supplement product labeling. Ann N Y Acad Sci 1219(s1):E1–E23
Sanders ME, Guarner F, Guerrant R et al (2013) An update on the use and investigation of probiotics in health and disease. Gut 62(5):787–796
Sartor RB (2004) Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: antibiotics, probiotics, and prebiotics. Gastroenterology 126:1620–1633
Sartor RB (2008) Microbial influences in inflammatory bowel diseases. Gastroenterology 134(2):577–594
Scott KP, Gratz SW, Sheridan PO et al (2013) The influence of diet on the gut microbiota. Pharmacol Res 69(1):52–60
Sears CL, Pardoll DM (2011) Perspective: alpha-bugs, their microbial partners, and the link to colon cancer. J Infect Dis 203(3):306–311
Shanahan F, Collins SM (2010) Pharmabiotic manipulation of the microbiota in gastrointestinal disorders, from rationale to reality. Gastroenterol Clin N Am 39(3):721–726
Sharma D, Shastri S (2016) Lactoferrin and neonatology-role in neonatal sepsis and necrotizing enterocolitis: present, past and future. J Matern Fetal Neonatal Med 29(5):763–770
Simrén M, Öhman L, Olsson J et al (2010) Clinical trial: the effects of a fermented milk containing three probiotic bacteria in patients with irritable bowel syndrome-a randomized, double-blind, controlled study. Aliment Pharmacol Ther 31(2):218–227
Sivan A, Corrales L, Hubert N et al (2015) Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 350(6264):1084–89
Soares RL (2014) Irritable bowel syndrome: a clinical review. World J Gastroenterol 20(34):12144–12160
Steed H, Macfarlane GT, Blackett KL et al (2010) Clinical trial: the microbiological and immunological effects of symbiotic consumption-a randomized double-blind placebo-controlled study in active crohn's disease. Aliment Pharmacol Ther 32(7):872–883
Stevenson C, Blaauw R, Fredericks E et al (2014) Randomized clinical trial: effect of *Lactobacillus plantarum* 299v on symptoms of irritable bowel syndrome. Nutrition 30(10):1151–1157

Stolaki M, de Vos W M, Kleerebezem M, et al (2012) Lactic acid bacteria in the gut. In: Lactic acid bacteria: microbiology and functional aspects, pp 385–401

Szajewska H, Kolodziej M (2015) Systematic review with meta-analysis: *Lactobacillus rhamnosus* GG in the prevention of antibiotic-associated diarrhoea in children and adults. Aliment Pharmacol Ther 42(10):1149–1157

Szajewska H, Ruszczynski M, Radzikowski A (2006) Probiotics in the prevention of antibiotic-associated diarrhea in children: A meta-analysis of randomized controlled trials. J Pediatr 149:367–372

Takeda KOK (2009) Effects of a fermented milk drink containing *Lactobacillus casei* strain Shirota on the human NK-cell activity. J Nutr 137:791S–793S

Takiishi T, Korf H, van Belle TL et al (2012) Reversal of autoimmune diabetes by restoration of antigen-specific tolerance using genetically modified *Lactococcus lactis* in mice. J Clin Invest 122(5):1717–1725

Tursi A, Brandimarte G, Papa A et al (2010) Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. Am J Gastroenterol 105(10):2218–2227

Vandenplas Y, Veereman-Wauters G, Greef ED et al (2011) Probiotics and prebiotics in prevention and treatment of diseases in infants and children. J Pediatr 87(4):292–300

Vétizou M, Pitt JM, Daillère R et al (2015) Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 350(6264):1079–84

Vlieg JEVH, Veiga P, Zhang C et al (2011) Impact of microbial transformation of food on health-from fermented foods to fermentation in the gastro-intestinal tract. Curr Opin Biotechnol 22(2):211–219

Wani MA, Jan FA, Khan NA et al (2014) Cancer trends in kashmir: common types, site incidence and demographic profiles: National cancer registry 2000–2012. Indian J Cancer 51(2):133–137

Weichert S, Schroten H, Adam R (2012) The role of prebiotics and probiotics in prevention and treatment of childhood infectious diseases. Pediatr Infect Dis J 31(8):859–862

Whorwell PJ, Altringer L, Morel J et al (2006) Efficacy of an encapsulated probiotic bifidobacterium infantis 35624 in women with irritable bowel syndrome. Am J Gastroenterol 101(7):1581–1590

Wildt S, Nordgaard I, Hansen U et al (2011) A randomised double-blind placebo-controlled trial with *Lactobacillus acidophilus* la-5 and *Bifidobacterium animalis* subsp. *lactis* bb-12 for maintenance of remission in ulcerative colitis. J Crohns Colitis 5(2):115–121

Williams EA, Stimpson J, Wang D et al (2009) Clinical trial: a multistrain probiotic preparation significantly reduces symptoms of irritable bowel syndrome in a double-blind placebo-controlled study. Aliment Pharmacol Ther 29(1):97–103

Worthley DL, Leu RKL, Whitehall VL et al (2009) A human, double-blind, placebo-controlled, crossover trial of prebiotic, probiotic, and synbiotic supplementation: effects on luminal, inflammatory, epigenetic, and epithelial biomarkers of colorectal cancer. Am J Clin Nutr 90(3):578–586

Yazar AS, Güven Ş, Dinleyici EÇ (2016) Effects of zinc or synbiotic on the duration of diarrhea in children with acute infectious diarrhea. Turk J Gastroenterol Off J Turk Soc Gastroenterol 27(6):537–540

Zani A, Pierro A (2015) Necrotizing enterocolitis controversies and challenges. F1000 Research 4:1–10

Zeng J, Li YQ, Zuo XL et al (2008) Clinical trial: effect of active lactic acid bacteria on mucosal barrier function in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther 28(8):994–1002