

WJG 20th Anniversary Special Issues (17): Intestinal microbiota**Intestinal microbiota in health and disease: Role of bifidobacteria in gut homeostasis**

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Supported by The Spanish Ministry of Economy and Competitiveness and by FEDER European Union funds, projects No. AGL2010-14952, No. AGL2010-16525 and No. AGL2012-33278

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Received: March 19, 2014 Revised: May 8, 2014

Accepted: June 14, 2014

Published online: November 7, 2014

Abstract

The pool of microbes inhabiting our body is known as “microbiota” and their collective genomes as “microbiome”. The colon is the most densely populated organ

in the human body, although other parts, such as the skin, vaginal mucosa, or respiratory tract, also harbour specific microbiota. This microbial community regulates some important metabolic and physiological functions of the host, and drives the maturation of the immune system in early life, contributing to its homeostasis during life. Alterations of the intestinal microbiota can occur by changes in composition (dysbiosis), function, or microbiota-host interactions and they can be directly correlated with several diseases. The only disease in which a clear causal role of a dysbiotic microbiota has been demonstrated is the case of *Clostridium difficile* infections. Nonetheless, alterations in composition and function of the microbiota have been associated with several gastrointestinal diseases (inflammatory bowel disease, colorectal cancer, or irritable bowel syndrome), as well as extra-intestinal pathologies, such as those affecting the liver, or the respiratory tract (*e.g.*, allergy, bronchial asthma, and cystic fibrosis), among others. Species of *Bifidobacterium* genus are the normal inhabitants of a healthy human gut and alterations in number and composition of their populations is one of the most frequent features present in these diseases. The use of probiotics, including bifidobacteria strains, in preventive medicine to maintain a healthy intestinal function is well documented. Probiotics are also proposed as therapeutic agents for gastrointestinal disorders and other pathologies. The World Gastroenterology Organization recently published potential clinical applications for several probiotic formulations, in which species of lactobacilli are predominant. This review is focused on probiotic preparations containing *Bifidobacterium* strains, alone or in combination with other bacteria, which have been tested in human clinical studies. In spite of extensive literature on and research into this topic, the degree of scientific evidence of the effectiveness of probiotics is still insufficient in most cases. More effort need to be made to design and conduct accurate human studies demonstrating the efficacy of probiotics

in the prevention, alleviation, or treatment of different pathologies.

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Key words: Intestinal microbiota; *Bifidobacterium*; Probiotics; Dysbiosis; Inflammatory bowel disease; Irritable bowel syndrome; Colorectal cancer; Liver disease; Respiratory disease; Functional foods

Core tip: In this review we focus on how bifidobacteria can contribute to maintain a proper health status through their interactions with gut microbiota and the host. We present several gastrointestinal and extra-intestinal pathologies associated with imbalances in the microbiota composition and function, including bifidobacteria-associated dysbiosis. We review up-to-date scientific evidence sustaining the use of probiotic bifidobacteria to prevent, or treat, several disorders, and we include a list of specific *Bifidobacterium* strains that have been tested in human clinical studies.

Tojo R, Suárez A, Clemente MG, de los Reyes-Gavilán CG, Margolles A, Gueimonde M, Ruas-Madiedo P. Intestinal microbiota in health and disease: Role of bifidobacteria in gut homeostasis. *World J Gastroenterol* 2014; 20(41): 15163-15176 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i41/15163.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i41.15163>

INTRODUCTION

About 100 trillion (10^{14}) microbes inhabit the human gut, which represents 10 fold the number of eukaryotic cells in the body and contributes 1.5-2 kg of total body weight^[1]. The number and complexity of these microbial populations gradually increase from the stomach to the colon, where microorganisms reach levels of up to 10^{11} cells per gram of intestinal content^[2]. Although the colon is the more densely populated organ, microorganisms are also normal inhabitants of other parts of the body, such as the skin, vagina, throat and the upper respiratory tract^[3]. This pool of microbes is known as “microbiota” and the ensemble of their genes is named “microbiome”.

Microbiota composition

The recent advent of next generation sequencing techniques has greatly contributed to demonstrate that the human body harbours more than 1000 phylotypes at species-level, but most intestinal bacteria belong to just a few phyla. In adults, *Bacteroidetes* and *Firmicutes* usually dominate the intestinal microbiota, whereas *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia* are in considerably minor proportion (Figure 1). Methanogenic archaea (represented by *Methanobrevibacter smithii*), eukaryotes (mainly yeast) and viruses (mainly bacteriophages) are also components of this microbiota^[3,4]. A recent work identified three enterotypes in the human gut microbiome differing in species

and functional characteristics^[5]. In spite of a consistency in the global composition, the intestinal microbiota seems to be highly variable among individuals at species-level phylotypes; usually *Faecalibacterium prausnitzii* (*F. prausnitzii*), *Roseburia intestinalis*, *Bacteroides uniformis*, and species of bifidobacteria and lactobacilli are present in most people^[6]. The microbial colonization of the gut begins in infants immediately after birth. Facultative anaerobes, such as enterobacteria, enterococci and lactobacilli are the first colonizers (Figure 1). Anaerobic microorganisms, including *Bifidobacterium*, *Bacteroides* and *Clostridium* establish gradually, and contribute to a progressive decrease of the facultative anaerobes to strict anaerobes ratio in time^[7]. At about 3 years of age, the gut microbiota reaches a composition and diversity similar to adults and remains more or less stable over time in adulthood. New changes appear in the senescence, the microbiota of elderly people differing from the core microbiota and diversity levels of younger adults^[8,9].

Microbiota function

Gut microbiota provides nutrients and energy for the host through the fermentation of non-digestible dietary components in the large intestine. The main products of the substrate fermentation in the gut are short chain fatty acids (SCFA), which interact with the intestinal microbiota and host cells. The microbiota regulates, via different mechanisms, some important physiological functions of the host, such as those related to energy expenditure, satiety and glucose homeostasis^[10,11]. It can also act as a barrier against the establishment of foodborne pathogens. Remarkably, the intestinal microbiota is also in contact with the second largest (after the brain) neural pool of cells in the body, as well as with the largest group of immune cells in our organism^[12]. Therefore, the microbiota drives the maturation of the immune system in infancy and contributes to the maintenance of its homeostasis during life^[13,14]. Moreover, the possible influence of the microbiota in the development of the nervous system and in cognitive function currently constitutes a hot target for biomedical research^[15].

Factors affecting microbiota

Some external and internal factors of the host can influence the composition and metabolic activity of the intestinal microbiota. Diet strongly affects human health, partly through its interaction with intestinal microbiota^[16]. Distinctive features have been clearly evidenced recently across different geographic locations, which can be partly explained by differing diets^[17]. Functional immaturity of the immune system and intestinal epithelium can influence the aberrant intestinal colonization pattern occurring in preterm neonates^[18]. The type of feeding in early infancy (breast-fed *vs* formula fed) also seems to condition the microbiota establishment, as well as the maturation of the immune system. Medication, especially chronic medication, can exert a strong impact on intestinal microbiota^[19]. A misbalance of this intestinal microbi-

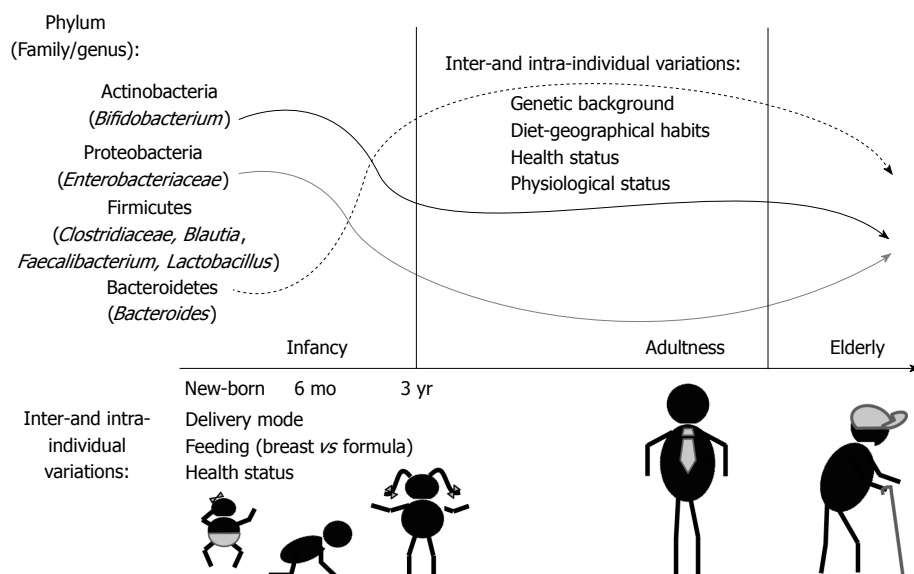


Figure 1 Evolution of some representatives of the intestinal microbiota accordingly to age.

al community can act as a source of infection, or chronic inflammation, and can be involved, as well, in gastrointestinal diseases and other extra-intestinal disorders.

MICROBIOTA AND GASTROINTESTINAL PATHOLOGY

As the gut microbiota has a well-established role in host homeostasis, several highly prevalent gastrointestinal diseases have been associated with shifts, or imbalances, in microbiota composition (dysbiosis) and function, as well as in microbiota-host interactions^[20,21]. The term dysbiosis is unhelpful if used only to describe a change in the microbiota, which is assumed to be deleterious to the host. In some instances, changed microbiota may be an appropriate response to a change in the host, or may represent an epiphenomenon without pathophysiological implications^[22]. Therefore, as the entire functional complexity of the gut microbiota is incompletely defined, with just a determination of composition by taxonomic assignment^[6], a functional analysis may provide information about metabolic and immunologic functions, as well as microbiota-host interactions^[23].

Clostridium difficile infection

The only disease process in which a dysbiotic microbiota plays an undoubtedly proven role is in the case of *Clostridium difficile* infection (CDI). Treatment with antibiotics transiently alters the microbiota composition, providing the niche in which this pathogen can expand^[20]. The restoration of normal healthy microbiota, by faecal microbiota transplantation (FMT) is an effective therapy to treat CDI^[24]. FMT consists of the engraftment of microbiota from a healthy donor(s) into a recipient, which results in the restoration of the normal gut microbial community structure, with the aim of recovering metabolic and immunologic balance^[25]. FMT introduces a complete, stable,

and durable community of gut microbiota^[26], unlike probiotics, that temporarily alter the metabolic, or immunologic activity, of the native gut microbiota^[27]. The mechanism(s) that facilitates this microbiota normalization, as well as the occurrence of putative long-term side effects, still has to be determined. However, FMT represents an emerging therapy for disease states related to dysbiosis, and is a current, recommended treatment for relapsing and non-responding CDI^[28].

Inflammatory bowel diseases

There is increasing evidence of the pathogenic implication of the host microbiota in inflammatory bowel disease (IBD), as several taxonomic and functional changes, as well as imbalances in the host-microbiota cross-talk, have been described^[29]. This may be understood as a bidirectional relationship between altered immune function (mucosal barrier, innate bacterial killing, or immune regulation) and altered bacterial community (its features, functions, or metabolites)^[30]. A deregulated immune response against commensal gut bacteria, in which local tolerance mechanisms towards commensal microbes seem to be impaired, may contribute to the onset or perpetuation of IBD^[31]. Studies of faecal and gut mucosal-associated microbiota have demonstrated quantitative and qualitative changes in composition and function associated with IBD, with a shift towards an inflammatory-promoting microbiome^[32]. There is a decreased complexity in composition, with a loss of normal anaerobic bacteria^[33], a temporary composition instability during clinical remission^[34], and a dysbiosis towards selected microorganisms, with over- and under-representation of certain species^[35]. An excessive abundance of *Desulfovibrio* species has been described in ulcerative colitis (UC), which has pathogenic potential due to its ability to generate sulfides^[36]. In addition, an increase in microbial genes involved in the metabolism of cysteine (sulphur-containing amino acid)

and sulphate transport systems have been reported^[37]. UC and Crohn's disease (CD) present a low abundance of *F. prausnitzii*, which has known anti-inflammatory properties^[38], and this is associated with a higher risk of postoperative recurrence of ileal disease^[29], and with a concomitant increase in the abundance of *Escherichia coli* (*E. coli*)^[39]. Adherent-invasive *E. coli* strains are specifically associated with the CD ileal phenotype^[40]. In addition, a decrease of SCFA levels, and of genes related to SCFA metabolism, is described in CD^[41]. Clinical and basic evidence suggests that dysbiosis has a key role in the initiation and progression of chronic inflammation in the pouch reservoir^[29]. A notable increase in *Proteobacteria* (*E. coli* and other enterobacteria), with a marked decrease in *Bacteroides* and *F. prausnitzii*, has been described^[42].

Colorectal cancer

There is a strong genetic component in the development of colorectal adenomas and colorectal cancer (CRC), but there are also environmental factors linked to this disease^[43]. Considering the continuous exposure of the colonic mucosa to the microbiota and its metabolites, this microbial community has been proposed as contributing to carcinogenesis. However, the mechanisms of this association remain unknown, although there are several ways in which an altered microbiota may promote CRC^[44]. Chronic intestinal inflammation has been associated with the development of CRC and it can result from an aberrant ratio of protective (tolerogenic) to aggressive (pro-inflammatory, pro-tumorigenic) microbiota^[45]. In this regard, *Bacteroides fragilis* (*B. fragilis*) and *Streptococcus bovis* (*S. bovis*) could be linked to the development of CRC by activating immune cells to release pro-mitogenic and pro-angiogenic cytokines, mostly Interleukin-17 (IL-17)^[46]. There are also some biological activities of the intestinal microbiota that are presumed to generate metabolites involved in CRC carcinogenesis: secondary bile salt transformations, desulfuration of bile acids, production of hydrogen sulfide, production of aglycones from inactivated harmful compounds, bacterial β -glucuronidases, production of aromatic amines by azoreductases and nitroreductases, generation of acetaldehyde, and generation of reactive oxygen species^[47].

Several changes in microbiota composition are described in CRC. An increased diversity in *Clostridium leptum* (*C. leptum*) and *Clostridium coccoides* is present, while temporary instability and decreased complexity in composition are linked to colitis-associated CRC^[48,49]. The microenvironment within colorectal neoplastic lesions is significantly different from normal intestine, thus it can promote the accumulation of additional mutations and epigenetic changes. Many bacterial species were found to be enriched in colorectal tumour samples and adjacent tissue: *B. fragilis*, *Bacteroides vulgatus*, *Bifidobacterium longum*, *Clostridium butyricum*, *Mitsuokella multiacida*, *E. coli*, *Enterococcus faecalis*, and *S. bovis*^[45].

Functional gastrointestinal disorders

Functional gastrointestinal disorders are defined and

categorized based upon clusters of chronic, or recurrent symptoms that can be attributed to the gastrointestinal tract in the absence of any discernible organic abnormality^[50]. An increasing body of evidence supports the physio-pathological role of microbiota in irritable bowel syndrome (IBS), although the clinical relevance of many findings still remains unclear^[51]. Clinical studies show that up to 20% of IBS is preceded by an enteric infection, which produces a profound alteration of the host microbiota^[52]. The precise mechanisms by which this alteration determines the persistency of IBS symptoms after the acute episode are not fully elucidated; a genetic susceptibility, an abnormal mucosal barrier integrity, variations in SCFA production, and an increase in mucosal entero-endocrine cells may contribute^[53,54]. A meta-analysis review showed that small intestinal bacterial overgrowth (SIBO) was present between 4% and up to 54% in IBS^[55], suggesting that microbiota alterations may play a role in a subset of patients. However, the large differences between the studies, methodological problems, such as the lack of standardization, poor sensitivity and specificity of breath tests, as well as the questioned cut-off value of cultured duodenum/jejunum aspirates ($> 10^5$ CFU/mL), make the importance of SIBO in IBS unclear^[56]. Interventional studies showing the positive effects of treatments directed at gut microbiota also support the role of microbial alterations in IBD^[57,58]. Indeed, several alterations in microbiota composition have been described, although the heterogeneity of IBS, as well as methodological variations, has resulted in contradictory reports. Nonetheless, emerging data support the existence of dysbiosis in a subset of IBS^[59]: a decreased complexity in composition^[60], temporary instability^[61], and changes in the mucosa-associated microbiota, with an increase in *Bacteroides* and *Clostridia* and a reduction in *Bifidobacterium*^[62].

There are several functional changes that may contribute to the pathophysiology of IBS. An altered fermentation process, with an increase in faecal SCFA and their producing bacteria, has been described; the highest levels being related to the severest symptoms^[63]. The alteration of intestinal barrier function, with increased gut permeability, has a major role in IBS^[64]; nevertheless, its relationship with altered microbiota remains to be fully understood. Modulation of enteric sensorimotor function, through alterations in bile acid metabolism by microbiota, has been described in several *in vitro* studies^[59]. An increase in primary bile acids in faeces, associated with the decrease in *C. leptum* (able to transform primary into secondary bile acid), was correlated with the stool consistency in diarrhoea predominant IBS^[65]. There is a growing appreciation for the hypothesis that IBS may be a condition of low-grade inflammation without strong tissue damage, but enough to alter the sensorimotor function and produce symptoms^[66]. However, there are few studies assessing a direct link between alterations in gut microbiota and low-grade inflammation or immune activation in the gut. Finally, data from animal and human studies have demonstrated the effects on the brain-gut

axis at peripheral and central levels, with an impact on the enteric nervous system, brain chemistry and behaviour^[67]; although caution must be exercised when in speculating on the implications of these findings^[68].

MICROBIOTA AND EXTRA-INTESTINAL PATHOLOGY

It has been denoted that aberrancies in intestinal microbiota may be involved in intestinal diseases. Moreover, there is increasing evidence that dysbiosis in this microbial community could be related with some extra-intestinal pathologies, such as allergies, obesity and metabolic syndrome, rheumatic disease, and degenerative processes, among others^[69-71].

Liver diseases

Modifications in intestinal microbiota have been associated with the physiopathology of non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, and total parenteral nutrition-intestinal failure liver disease, as well as in the precipitation of infectious and non-infectious complications of liver cirrhosis^[72]. Among the potential contributors of the microbiota to complications of liver cirrhosis is the presence of SIBO^[73], and a dysfunctional mucosal barrier which can contribute to bacterial (or endotoxin) translocation to the portal circulation^[74]. The pivotal role of gut microbiota in the pathogenesis of hepatic encephalopathy is supported by interventional studies showing the positive effects of treatments directed at gut microbiota in primary prophylaxis^[75]. Gut microbiota is also involved in the pathogenesis of NAFLD and its progression to non-alcoholic steatohepatitis. In obese patients, the accumulation of triglyceride-derived metabolites in the liver is due to an increased release of fatty acids from dysfunctional and insulin-resistant adipocytes. A specific microbial taxonomic and functional profile has been associated with obesity^[76] and obesity-related liver disease^[77], thus suggesting a link between microbiota and liver pathology^[78].

Respiratory diseases

The relationship between intestinal microbiota and chronic respiratory diseases is poorly understood. However, a few works have been able to establish a connection between an aberrant microbiota, allergic diseases and bronchial asthma. Several epidemiological studies have shown a clear inverse link between early exposure to microorganisms and the incidence of asthma, referring to this phenomenon as the “hygiene hypothesis”^[79]. Also, the increased use of antibiotics and changes in dietary patterns in developed countries, may lead to alterations in the composition of the intestinal microbiota and a higher risk of bronchial asthma^[80-82]. Thus, a reduction of *Bacteroidetes*, lactobacilli and bifidobacteria has been associated with an asthma phenotype^[83]. Recent research, focused on the study of airway microbiota and their potential consequences in asthmatic patients, shows that biodiver-

sity is much higher in asthmatic patients with bronchial hyper-reactivity compared with healthy subjects^[84].

The results of some studies on other chronic respiratory diseases suggest that pulmonary inflammation and intestinal inflammation are somehow related to each other, and both contribute to the progression of chronic lung disease. This relationship is more evident in some diseases such as cystic fibrosis (CF), in which the lung and intestinal habitats are interconnected through a lung-intestine axis. Evidence suggests that in CF patients the lung disease determines the vital prognosis^[85]. CF is an autosomal recessive genetic disease caused by mutations in the gene coding for the regulatory transmembrane conductance regulator (CFTR), which results in progressive lung disease, pancreatic insufficiency, and deficiencies in growth and nutrition. CFTR functions as a chloride ion channel that controls the transportation of water and ions across the apical membrane of epithelial cells. There are different genetic mutations, responsible for different degrees of severity, the DF508 mutation being associated with the most serious symptoms, and one of the most common ones. In this sense, the results of a recent study have shown that the composition of the intestinal microbiota in patients with CF is significantly different depending on the genetic variation^[86]; patients with the DF508 mutation have a marked intestinal dysbiosis, in which harmful species, such as *E. coli* and *Eubacterium bifforme*, are abundant, whereas potentially beneficial ones, such as *F. prausnitzii* and *Bifidobacterium* spp., are decreased^[86]. In general, these patients, regardless of their genetic background, display a permanent dysbiosis, motivated in part by the characteristics of the disease (thick mucus secretion and pancreatic insufficiency) and the effect related to the aggressive antibiotic therapy^[87]. Moreover, it is important to try to correlate the alterations of the airway microbiota with alterations in intestinal microbiota in CF patients. Some authors suggest a link between nutrition and the development of microbial communities in the respiratory tract^[88]. These authors note how dietary changes give rise to alterations in the microbiota of the respiratory tract, suggesting that nutritional factors and the pattern of intestinal colonization are determining microbial growth in the respiratory airways, and giving us the opportunity to evaluate the response of CF patients to probiotic and prebiotic interventions^[88].

Oral administration of prebiotics or probiotics, or a combination of both, can lead to a change in the composition of the intestinal microbiota. This can directly influence the composition of the microbial communities of the airway by the release of bacterial products or metabolites that reach the lung. These mechanisms could theoretically lead to the restoration of a microbiota that promotes a healthy status, thus having a therapeutic effect on chronic diseases^[89]. It is also important to note that probiotic treatment may modulate immune response in the lung; in particular gut microbial stimulation can enhance T regulatory response in the airway, which emphasizes the potential role of probiotics in the pulmonary

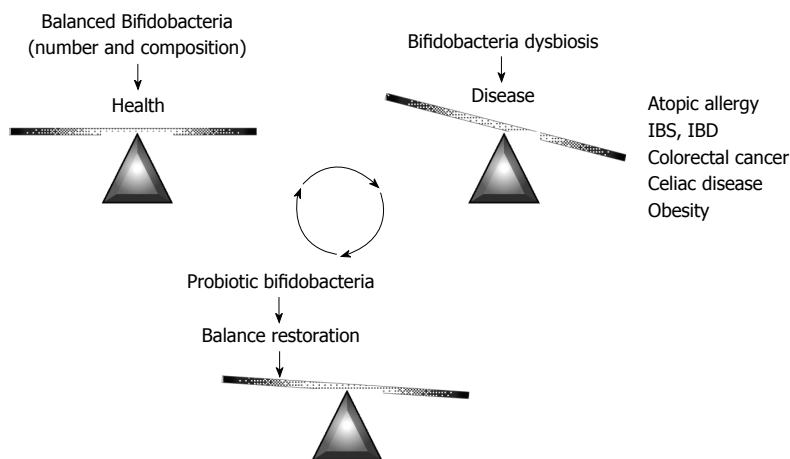


Figure 2 Bifidobacterial dysbiosis and its relationship with diseases: A target for probiotic intervention. IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome.

inflammatory response^[89]. However, the mechanisms underlying these specific effects of probiotics are far from being completely understood. Therefore, it will be of key importance to know if airway microbiota is derived from, or linked to, intestinal microbiota. This would mean that a modulation of the intestinal microbiota could have a positive effect on lung disease. Considering this, characterization, modification and the possible functional consequences of airway microbiota are emerging fields that can constitute a new way of acting on chronic lung diseases.

INTESTINAL BIFIDOBACTERIA

The genus *Bifidobacterium* belongs to the phylum *Actinobacteria* and comprises over 45 species/subspecies of high G + C (guanine and cytosine) content in their genomes; they are gram-positive, polymorphic rod-shaped bacteria and normal inhabitants of the gastro-intestinal tract of humans and animals^[90]. In the human gut the most commonly found species of *Bifidobacterium* genus include *B. adolescentis*, *B. angulatum*, *B. bifidum*, *B. breve*, *B. catenulatum*, *B. dentium*, *B. longum*, *B. pseudocatenulatum*, and *B. pseudolongum*^[91], whereas *B. animalis* subsp. *lactis* is the species most often included in functional foods and food supplements^[92]. Bifidobacteria is a dominant microbial group in healthy breastfed babies and, during an adult's life the levels remain relatively stable, tending to decrease in the senescence^[93]. During recent years this genus has been extensively studied due to both its important role within the human intestinal microbiota and the extensive use of certain *Bifidobacterium* strains in probiotic products.

As has been highlighted in the previous sections, intestinal microbiota dysbiosis has been described in different diseases. Given the attention traditionally paid to the genus *Bifidobacterium*, aberrancies in specific bifidobacterial microbiota, such as decreased numbers, or atypical species composition, have been identified in some of them (Figure 2); these include atopic disease^[94,95], IBS^[96,97], IBD^[98-101], CRC^[102], or celiac disease^[103,104]. Additionally,

bifidobacteria dysbiosis has been reported to precede obesity^[105]. It is important to stress that no definitive proof is available on the relationship between reduced bifidobacterial levels, or altered species composition, and disease. However, an aberrant bifidobacterial number or composition is perhaps the most frequently observed intestinal microbiota alteration, being present in many different diseases. This fact suggests an important role for the bifidobacteria population in the intestinal homeostasis. Therefore, on one hand, the bifidobacteria fingerprint could be used as a potential biomarker to understand the intestinal status pointing to a putative dysbiosis. On the other hand, increasing bifidobacterial levels in the gastrointestinal tract could be considered a target to prevent and/or alleviate microbiota-associated diseases. In this regard, several health-promoting effects have been attributed to some specific strains of this genus. The use of functional foods towards the oral delivery of beneficial bifidobacteria (probiotics), alone, or in combination with substrates (prebiotics) that promote the growth of beneficial microbes in the gut, are the basis of dietetic intervention strategies to amend or attenuate intestinal dysbiosis.

Probiotics were defined in 2001 by a group of experts, joined by the World Health Organization and the Food Agriculture Organization of the United Nations, as “live microorganisms, which when administered in adequate amounts confer a health benefit on the host”^[106]. However, interest in the use of living bacteria as therapeutic agents started at the beginning of the 1900s with the observations of the Nobel Prize winner Ellie Metchnikoff, and the pediatrician Henry Tissier, both working at the Pasteur Institute. Indeed, Tissier detected that bacteria with “bifid” shape, which were abundant in the faeces of healthy children, were absent in those suffering from diarrhoea; thus he proposed the use of (bifido)-bacteria to restore a healthy microbiota^[107]. Afterwards, the use of pro-life (probiotic) microorganisms did not receive much attention in the scientific community in the West. However, around 1930 Dr. Minoru Shirota,

Table 1 Reviews obtained from the search into “probiotics”

Probiotics	Author's conclusions	Ref.
Treating acute infectious diarrhea	Beneficial effects	[109]
Prevention of pediatric antibiotic associated diarrhea	Evidence of a protective effect	[110]
Treating persistent diarrhea in children	Limited evidence	[111]
Treatment of <i>Clostridium difficile</i> (<i>C. difficile</i>)-associated colitis in adults	Insufficient evidence	[112]
Prevention of <i>C. difficile</i> -associated diarrhea in adults and children	Moderate quality evidence	[113]
Prevention of necrotizing enterocolitis in preterm infants	Prevents severe necrotizing enterocolitis	[114]
Induction of remission in ulcerative colitis	Limited evidence	[115]
Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis	Probiotic VSL#3 was more effective than placebo	[116]
Maintenance of remission in ulcerative colitis	Insufficient evidence	[117]
Maintenance of remission in Crohn's disease	No evidence	[118]
Induction of remission in Crohn's disease	Insufficient evidence	[119]
Prevention of post-operative recurrence of Crohn's disease	Insufficient randomized trials	[120]
Non-alcoholic fatty liver disease and/or steatohepatitis	Lack of randomized clinical trials	[121]
Patients with hepatic encephalopathy	Need of efficacy demonstration	[122]
Treatment of bacterial vaginosis	No sufficient evidence	[123]
Preventing preterm labour	Insufficient data	[124]
For prevention of allergic disease and food hypersensitivity (in infants)	Insufficient evidence	[125]
Treating eczema	No effective treatment	[126]
Preventing acute upper respiratory tract infections	Limited evidence	[127]

Reviews obtained from the search into “probiotics” in the Cochrane Library (<http://onlinelibrary.wiley.com/cochranelibrary/search>) of the Cochrane Database of Systematic Reviews journal.

working at the Medicine School of Kyoto, cultured a bacterium strain (*Lactobacillus casei* strain Shirota) that became the first probiotic commercialized in 1935 by the Japanese company Yakult^[108]. The market for foods containing probiotics, including bifidobacteria, is growing at a high rate in recent years. Research on this topic is also receiving a lot of attention, since the use of probiotics in preventive medicine to keep a healthy intestinal function is well documented, and probiotics are also proposed as therapeutic agents for gastrointestinal disorders and other pathologies^[27].

A search in the Cochrane Library (<http://onlinelibrary.wiley.com/cochranelibrary/search>) for research into “probiotics” in human health shows several systematic reviews about the use of these microorganisms for prevention, or treatment, of several diseases (Table 1)^[109-127]. The overall picture of these studies indicates that the degree of scientific evidence of the effectiveness of probiotics on several pathologies, mainly gut-associated diseases, is insufficient, or the data were not enough to arrive at a conclusion. In most reviews, the selection of human intervention trials with probiotics was a miscellaneous of studies, without defined criteria: probiotic strains were not completely defined (at strain level, dose, vehicle of delivery, duration of the intervention, *etc.*); the placebo group was not accurate; often probiotics were used in combination with other therapies (*e.g.*, antibiotics); the human target population was not clearly delimited (age, physio-pathological state of the disease, *etc.*); among others. This lack of definition could mask any beneficial findings obtained with probiotics, and it could hinder a real progress in obtaining effective products. Therefore, more attention should be paid to design, conduct and accurate reporting human studies on probiotics.

Bifidobacteria as probiotic in gastrointestinal pathology

In spite of the above mentioned limitations, the World Gastroenterology Organization (WGO) has recently published potential clinical applications for several probiotic formulations, in which species of *Lactobacillus* play a predominant role^[128]. In the current review, we have compiled a series of human intervention studies, showing beneficial effects in gastrointestinal health, which have been made with bifidobacterial strains (Table 2)^[129-154]. It is worth noting that only a few *Bifidobacterium* strains, such as the case of *B. animalis* subsp. *lactis* HN019 and *B. infantis* 35624, have been studied alone, and not in combination with other strains, which limits the conclusions obtained regarding the specific effects of bifidobacteria strains. The studies carried out with the strain 35624 show that it was effective in reducing the pro-inflammatory state of patients with IBD^[142,143], as well as with UC^[144]; besides, the immune modulation effect of *B. infantis* 35624 was extended to systemic level since it was effective in reducing inflammatory biomarkers in patients with non-gastrointestinal inflammatory processes, such as chronic fatigue syndrome and psoriasis^[144]. Most bifidobacteria strains were tested in combination with other probiotics (lactobacilli and propionibacteria) and/or food-starter bacteria (*Streptococcus thermophilus*, *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Lactococcus lactis*) (Table 2); thus, the reported beneficial effects cannot be exclusively assigned to a specific bifidobacterial strain. Indeed, the two strains of *B. breve* included in the table were tested together with some of these bacteria^[139,141], or even with prebiotics such as galacto-oligosaccharides^[140]. In the case of *B. animalis* subsp. *lactis* strains, they were often used as bio-ingredients of yogurt-like fermented milks; thus the additional beneficial effect of this food itself cannot be obviated. Nevertheless, most human studies car-

Table 2 Some *Bifidobacterium* strains tested in human intervention studies showing positive effects on gastrointestinal functions

Bifido species	Bifido strain	Other species	Reported effect	Ref.
<i>B. animalis</i> subs. <i>lactis</i>	Bb12	+ <i>S. thermophilus</i>	Antibiotic associated diarrhoea–children	[129]
		No	Prevent infection in child care centres	[130]
		+ <i>L. rhamnosus</i> (GG and Lc705), <i>P. freudenreichii</i> ssp. <i>shermani</i> JS	Alleviate symptoms of IBS	[131]
	DN-173010	+ <i>S. thermophilus</i> , <i>L. delbureckii</i> subsp. <i>bulgaricus</i> , <i>L. lactis</i> (= fermented milk)	Improve symptoms of IBS	[132,133]
			Improve GI well-being in women with minor digestive symptoms	[134,135]
<i>B. bifidum</i>	HN019	No	Affect brain activity (emotion and sensation) in healthy women	[136]
	NCDO 1453	+ <i>L. acidophilus</i> NCDO 1748	Improve functional GI symptoms in adults	[137]
<i>B. breve</i>	Bb99	+ <i>L. rhamnosus</i> (GG and Lc705), <i>P. freudenreichii</i> ssp. <i>shermani</i> JS	Prevent NEC in very low birth weight preterm infants	[138]
	Yakult	+ prebiotic GOS + <i>L. casei</i> Shirota	Alleviate symptoms of IBS	[139]
<i>B. infantis</i>	35624	No	Improve clinical conditions of patients with UC	[140]
		No	Improve symptoms and decrease H ₂ production in lactose-intolerant patients	[141]
		No	Alleviate symptoms of IBS	[142]
Infloran® (<i>B. infantis</i>)	Unknown	+ <i>L. acidophilus</i>	Relieve symptoms of IBS in woman	[143]
			Reduce systemic pro-inflammatory biomarkers in GI and no-GI conditions	[144]
ABC Dophilus (<i>B. infantis</i> , <i>B. bifidum</i>)	Unknown	+ <i>S. thermophilus</i>	Prevent NEC in very low birth weight preterm infants	[145]
VSL#3® (<i>B. breve</i> , <i>B. infantis</i> , <i>B. longum</i>)	Unknown	+ <i>S. thermophilus</i> , <i>L. acidophilus</i> , <i>L. plantarum</i> , <i>L. paracasei</i> , <i>L. delbrueckii</i> subsp. <i>bulgaricus</i>	Prevent NEC in very low birth weight neonates	[146]
			Remission of UC in children	[147]
			Ameliorate symptoms in children with IBS	[148]
			Reduce symptoms in mild to moderate UC patients	[149,150]
			Maintain remission in recurrent or refractory pouchitis	[151,152]
			Reduce the pouchitis activity index in IPAA patients	[153]
			Reduce the incidence of AAD in risk hospital inpatients	[154]

AAD: Antibiotic associated diarrhoea; GI: Gastrointestinal; IBS: Irritable bowel syndrome; IPAA: Ileal pouch anal anastomosis; NEC: Necrotizing enterocolitis; UC: Ulcerative colitis; *S. thermophilus*: *Streptococcus thermophilus*; *L. rhamnosus*: *Lactobacillus rhamnosus*; *L. delbureckii*: *Lactobacillus delbrueckii*; *L. lactis*: *Lactococcus lactis*; *L. acidophilus*: *Lactobacillus acidophilus*; *L. casei*: *Lactobacillus casei*; *L. plantarum*: *Lactobacillus plantarum*; *L. paracasei*: *Lactobacillus paracasei*; *P. freudenreichii*: *Propionibacterium freudenreichii*; *B. animalis*: *Bifidobacterium animalis*; *B. bifidum*: *Bifidobacterium bifidum*; *B. breve*: *Bifidobacterium breve*; *B. infantis*: *Bifidobacterium infantis*; *B. longum*: *Bifidobacterium longum*.

ried out with this species, mainly with the strains Bb12, DN-173010 and HN019, showed that they are effective in reducing IBS symptoms helping to improve the well-being of the individuals^[131,132,134-137]. Different bifidobacteria species (*B. animalis* subsp. *lactis*, *B. bifidum*, or *B. infantis*), mostly combined with *St. thermophilus* and/or *Lb. acidophilus*, have been shown to be effective in the prevention and treatment of antibiotic associated diarrhea^[129,130], as well as in the prevention of necrotizing enterocolitis in children^[138,145,146]. Finally, the inflammatory conditions of different IBD types (Crohn's disease, UC and pouchitis) were reduced, to variable extents, after the use of bifidobacteria-containing probiotic products. Particularly the product VSL#3, which includes three bifidobacteria in combination with five lactic acid bacteria, seems to be efficient in the reduction of symptoms, or maintaining remission of IBD in children and adults^[147-154].

Bifidobacteria as probiotic in respiratory pathology

During the last few years, it has been shown that a few

probiotic strains have a potential role in reducing the symptoms of asthma and other allergic respiratory troubles. For instance, a hydrolyzed formula with *B. breve* and a galacto/fructo-oligosaccharide mixture (prebiotics) was able to prevent asthma-like symptoms in infants with atopic dermatitis^[155]. However, one of the more promising applications of probiotic bacteria in respiratory diseases is the use of some *Lactobacillus* and *Bifidobacterium* strains in the treatment of allergic rhinitis. In a double-blind, randomized, cross-over study, involving 31 adults with allergic rhinitis to grass pollen, Perrin and colleagues demonstrated that short-term consumption of *Lactobacillus paracasei* NCC2461 reduced subjective nasal pruritus, whilst not affecting nasal congestion^[156]. Regarding *Bifidobacterium* strains, oral administration of *B. animalis* subsp. *lactis* NCC2818 mitigates immune parameters and allergic symptoms in adult subjects suffering from allergic rhinitis during seasonal exposure^[157]. Also, the strain *B. longum* BB536 has shown promising applications in relieving symptoms of cedar pollinosis^[158,159]. Furthermore,

a combination of probiotics, including one strain of *L. acidophilus* and two strains of *B. animalis* subsp. *lactis*, was shown to be associated with changes in faecal microbiota composition and was able to prevent the pollen-induced infiltration of eosinophils into the nasal mucosa in birch pollen allergy, and indicated a trend for reduced nasal symptoms^[160].

CONCLUSION

The human gut is colonised by a myriad of microorganisms commonly referred to as intestinal microbiota. This complex and dynamic bacterial community plays an important role in human health. Alterations, or dysbioses, in microbiota composition and function have been related to different intestinal and extra-intestinal diseases. Among human gut microbiota members the genus *Bifidobacterium* has attracted lot of scientific interest. Alterations in intestinal bifidobacteria levels, or species composition, are often present in cases of intestinal microbiota dysbiosis. Indeed, deviations in intestinal bifidobacteria have been observed in different diseases, including allergies, IBD, IBS or CRC. Therefore, modulating the intestinal bifidobacteria population has often been considered a target for dietary interventions, providing the rationale for the use of microorganisms of the genus *Bifidobacterium* as probiotics. Different strains have been assessed as probiotics for different diseases, with different results obtained depending on both the strain and the disease tested. Nevertheless, some *Bifidobacterium* strains have shown very promising results, improving IBD, IBS, diarrhoea, and allergy symptoms.

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P- Reviewer: Ortiz LT, Zhang J S- Editor: Gou SX
L- Editor: A E- Editor: Wang CH





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