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Bifidobacteria spp. As a Potential Probiotic for the Treatment of Various Diseases

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ABSTRACT: The objective of this review paper was to provide information on the utilization of Lactobacillus and Bifidobacterium as potential probiotic for the treatment of various diseases by harvesting information from secondary sources. *Lactobacillus* and *Bifidobacterium* are known to resist gastric acid, bile salts and pancreatic enzymes, to adhere to colonic mucosa and readily colonize the intestinal tract. Other organisms like enterococci and yeasts have also been used as probiotics. Lactobacilli are Gram-positive, non-spore-forming and non-flagellated rods or coccobacilli. They are either aerotolerant or anaerobic and strictly fermentative. Probiotics are one of the fast-growing categories within food for which scientific researchers have demonstrated therapeutic evidence. They are used in prevention of urogenital diseases, alleviation of constipation, protection against diarrhoea, reduction of hypercholesterolaemia, protection against colon cancer, and prevention of osteoporosis and food allergy. Ingestion of Lactic Acid Bacteria (LAB) has been suggested to confer a range of health benefits including immune system modulation, increased resistance to malignancy and infectious illness. It is used in terminating illness as diarrhea and abdominal discomfort. Probiotics can produce antimicrobial substances including bacteriocins that have ability to inhibit pathogenic bacteria. *Bifidobacterium* is an important composition of the probiotic mix with several health benefiting properties when administered at the appropriate dosage. Various types of probiotics have been found to exert various therapeutic properties including antiinfection, antiinflammation, anticancer, promoting host psychological and physical health, and regulating host immune system. Recent studies have suggested that probiotics have demonstrated beneficial effects to human and animal health. This review has highlighted the immense benefit of probiotics to human health.

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Probiotic is derived from the Greek word "pro bios," which means "for life." Probiotics are described as live microorganisms that are given to a host in adequate quantities to improve their health (Gismondo *et al*., 1999). Lilly and Stillwell coined the term "probiotic" in 1965 to refer to "substances secreted by one microorganism that stimulate the growth of another." While Marteau et al. described probiotics as "microbial cell preparations or components of microbial cells that have a beneficial effect on the health and well-being," Salminen et al. defined them as "food which contains live bacteria that is beneficial to health. Microbios which, when ingested, may have a positive effect in the prevention and treatment of a specific pathologic condition is how Charteris *et al*. characterized probiotics. Ultimately, probiotics can be

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regarded as therapeutic agents because they have been shown to be successful in treating a few gastrointestinal disorders (Marteau *et al*., 2001). Probiotics are live microorganisms that, when taken in sufficient amounts, change the host's natural microbiota to improve health (Ouwehand *et al*., 1999). According to Davoodabadi *et al*. (2015), probiotic bacteria must stick to intestinal epithelial cells and be resistant to bile salts and gastric acid. While there have been many definitions of the term "probiotic" over the years, the definition that best captures the essence of probiotics as they are currently understood is "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host," which was developed by the Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO, 2001) and supported by the International Scientific Association for Probiotics and Prebiotics (Reid *et al*., 2006).

Strict standards have been put forward for the selection of microorganisms as probiotics. Havenaar *et al*. (2006) suggested the following criteria for choosing probiotics: complete safety for the host, resistance to pancreatic secretions and stomach acidity, adhesion to epithelial cells, antimicrobial activity, inhibition of pathogenic bacteria's adhesion, assessment of antibiotic resistance, tolerance to food additives, and stability in the food matrix. The most widely used probiotics nowadays are strains of lactic acid bacteria, such as Lactobacillus, Bifidobacterium, and Streptococcus (S. thermophilus); these strains are known to withstand pancreatic enzymes, bile salts, and gastric acid. They also readily colonize the intestinal tract and adhere to colonic mucosa (Fioramonti *et al*., 2003). Probiotics have not been chosen based on all of these criteria.

The majority of probiotics are sold commercially as foods or medications that include live microorganisms. As a result, it's critical to take probiotic safety into account before using them (Ishibashi and Yamazaki, 2001). The majority of probiotics are sold commercially as foods or medications that include live microorganisms. As a result, it's critical to take probiotic safety into account before using them (Ishibashi and Yamazaki, 2001). Before the turn of the 20th century, the primary roles of gut flora were fully understood. Ilya Ilyich Metchnikoff, the Pasteur Institute's 1908 Nobel laureate in medicine, connected yoghurt's bacteria to longevity and good health (Metchnikoff, 2004). In 1907, he postulated that eating yoghurts containing Lactobacillus bulgaricus and Streptococcus thermophilus would help to preserve health because they would inhibit the putrefactive-type fermentations of the gut flora. Metchnikoff also suggested that the use of yogurt containing Lactobacillus species contributed to the high lifespans of Bulgarian peasants (Metchnikoff, 2004).

Foods containing Lactobacillus acidophilus, Bifidobacterium, and Lactobacillus casei have been shown to provide numerous health benefits. Although they are not intestinal inhabitants, the yoghurt starter cultures Streptococcus thermophilus and L. delbrueckii ssp. bulgaricus provide certain health benefits. Therefore, L. acidophilus, Bifidobacterium, and L. casei are added as dietary adjuncts for yoghurt to be regarded as a probiotic food. Consequently, it is standard procedure to create a product including one or more probiotic bacterial species along with starter organisms like S. thermophilus and L. delbrueckii ssp. Bulgaricus (Shah, 2007). In 2002, the FAO and WHO released criteria outlining the requirements for a product to be referred to as a probiotic (FAO/WHO, 2002). They stipulate that strains must be identified separately, properly speciated, and maintain a viable count in the specified product formulation that yields a validated clinical end-point until the end of its shelf life. According to Isolauri (2004), a crucial component in characterizing probiotics for human consumption is evaluating their safety and efficacy, as stated in the definition of probiotics. Since then, research in the field of probiotics has grown exponentially high, thereby strengthening the understanding of the role of a wide range of probiotics in enhancing or preventing chronic diseases.

Probiotic Microorganisms: Though other organisms including enterococci and yeasts have also been employed as probiotics, prominent strains of probiotics are represented by the following genera: Lactobacillus, Streptococcus, and Bifidobacterium (Shah (2007) and Chow, 2002). Some of these strains were selected using factors that were thought to be crucial to their effectiveness, including the strain's origin, its ability to adhere to intestinal cells in vitro, and its ability to survive during the gastrointestinal tract's passage (Havenaar and Ten Brink, 1992).

Safety of Probiotics: The World Health Organization (WHO) has classified probiotic bacteria as GRAS (Generally Regarded as Safe), which is a good indicator of their safety (Patel *et al*., 2014). The primary factor in the choosing of probiotics is safety for human health. Snydman (2008) stated that probiotic strains ought to be identified by their lack of virulent profile and low level of antibiotic resistance. Historically, the usage of Lactobacilli and Bidobacteria strains has been associated with an excellent safety record for these beneficial microbes (Shanahan, 2012). New probiotic bacteria must come

from strains and genera that are frequently present in the gut microbiota of healthy humans. Bacillus and Enterococcus bacteria should be used with caution since these species and strains have also been linked to infections and opportunistic pathogens (Hanchi *et al*., 2018).

The majority of probiotics are safe. Nevertheless, adverse effects have been reported sporadically, and caution of potential side effects should be taken. In 2002, a report jointly released by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) in which they proclaimed that probiotics may, at a theoretical level, be in charge of four types of collateral effects":

(i) Systemic infections;
(ii) deleterious metabolic activities;
(iii) excessive immune stimulation in susceptible individuals, and
(iv) potential gene transfer (FAO/WHO, 2002).

In reality, a number of adverse events related to the use of Lactobacillus have been documented, including infrequent occurrences of sepsis, endocarditis, and liver abscess. Furthermore, Saccharomyces boulardii use has been linked to fungemia incidents, most of which have included individuals with severe comorbidities (Snydman, 2008). Constipation, hiccups, nausea, fulgury, infection, and rash are the most frequent side effects of using probiotics. Probiotic use by acute pancreatitis patients raises the death rate rather than reducing infection complications, according to a 2008 study by Besselink and colleagues. There have also been some reports of Lactobacilli bacteremia (Salminen *et al*., 2006). Probiotic therapy throughout pregnancy and the first few months of infancy is thought to be safe and unrelated to side effects, according to Allen *et al*. (2010). Fedorak and Madsen claim that there is a weak and inadequate public knowledge of risk and risk/benefit. Although there is some uncertainty regarding the potential for probiotics to transfer antibiotic resistance, the danger appears to be minimal given the probiotic products that are currently on the market. Probiotics and their biosafety must be evaluated strain-by-strain in relation to other different types of medicinal drugs (Fedorak and Madsen, 2004). Lactic acid bacteria (LAB) strains from traditional dairy products have a long history of safe application. Since humans began consuming fermented milk as food, LAB, including various species of Lactobacillus and Enterococcus, have been consumed on a regular basis. For more than 70 years, probiotic species like Lactobacillus acidophilus have been used safely. However, as recent literature has shown, safety considerations must constantly be made, and potential negative consequences must be regularly assessed. While members of the genera Streptococcus, Enterococcus, and certain other LAB genera are regarded as opportunistic pathogens, members of the genera Lactococcus and Lactobacillus are most frequently assigned the GRAS designation. There are three approaches that can be used to assess the safety of a probiotic strain: studies on the intrinsic properties of the strain, studies on the pharmacokinetics of the strain (survival, activity in the intestine, dose–response relationships, faecal and mucosal recovery) and studies searching for interactions between the strain and the host. The Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria recognized the need for guidelines to set out a systematic approach for the evaluation of probiotics in food in order to substantiate the health claims. Consequently, a Working Group was convened by FAO/WHO to generate guidelines and recommend criteria and methodology for the evaluation of probiotics, and to identify and define what data need to be available to accurately substantiate health claims. The aims of the Working Group were to identify and outline the minimum requirements needed for probiotic status. Then, guidelines were prepared in 2002 to meet this objective. These guidelines are available in: Joint FAO/WHO Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food (FAO/WHO).

The *genus Bifidobacterium:* In 1899–1800, Tissier successfully isolated Bifidobacteria, which he named Bacillus bifidus. These rod-shaped, anaerobic, non-gas-producing microbes were found in breastfed infants' feces and had a bifidobacterial morphology. According to Sgorbati *et al*. (1995), bifidobacteria are classified as catalase-negative, non-spore-forming, non-motile, Gram-positive anaerobes. Bifidobacteria are Gram-positive, anaerobic, rod-shaped, branched, V- or Y-type, immobile, non-spore-forming, anaerobic, and catalase-negative bacteria that are members of the phylum Actinobacteria and family Bifidobacteriaceae. At the moment, there are more than 90 species in the genus Bifidobacterium. According to Ruiz *et al*. (2011), there is little variation in the growth conditions of Bifidobacteria between strains in terms of temperature, pH, and oxygen level. Many probiotic *Bifidobacteria* have shown beneficial effects on humans or animals, e.g., antiinfection, anti-depression, regulating the host immune system, and facilitating host nutrition adsorption.

Beneficial Effects Exhibited by Probiotic Bifidobacteria: Antiinfection Activity: The ability to

colonize a particular area, such as the gastrointestinal system, is a requirement for becoming a probiotic strain. Additionally, the probiotic strain must be able to interact with the host and host microbiome in an efficient manner. Probiotic colonization ought to offer some defense against harmful infections to the host. Numerous studies demonstrate the antiinfection capabilities of various Bifidobacteria species. Salmonella typhimurium ATTC 13311, Escherichia coli O157:H7 ATTC 35150, and Listeria monocytogenes ATTC 19115 are just a few of the pathogens against which B. longum ATCC 15708 demonstrated antimicrobial efficacy (Igbafe *et al*., 2020). By preventing pathogens from adhering to intestinal epithelial cells, B. longum BB536 guards against gut-derived sepsis brought on by Pseudomonas aeruginosa (Matsumoto *et al*., 2008); BB536 also improves upper respiratory infections in well-nourished preschoolers, most likely by modifying the gut microbiota, or raising the amount of the genus Faecalibacterium (Lau *et al*., 2018). Early childhood dosing of B. lactis BB-12 decreases respiratory tract infections (Taipale *et al*., 2016). In addition, latent and persistent infectious strains can be eliminated with the aid of bifidobacteria. As an example, B. longum ATCC 15707 has been shown to be able to prevent Clostridium difficile infection (Yun *et al*., 2017), and B. longum 51A has been shown to be protective against lung infections caused by Klebsiella pneumoniae (Vieira *et al*., 2016). B. longum 51A was developed to lessen the parasite load of Giardia in Mongolian gerbils (Meriones unguiculatus). As a result, this strain is appropriate for use as a probiotic for both therapeutic and preventive purposes, with the goal of enhancing the health of both humans and animals (Fonseca *et al*., 2019).

Bifidobacteria not only defend against harmful bacteria but also have antiviral properties. For instance, B. longum IBG inhibits rotavirus infection in vitro and shortens the duration of diarrhea in pediatric patients (Lee *et al*., 2015); *B. adolescentis* SPM1605 inhibits human enterovirus Coxsackievirus B3, preventing the virus infection-related acute heart failure and aseptic meningitis (Kim *et al*., 2014).

Anticancer Activity: For many years, probiotics have been used to both prevent and treat cancer (Rowland *et al*., 1998; Lee *et al*., 2004; Paolillo *et al*., 2009; Ohara *et al*., 2010). In animal models of cancer, Bifidobacteria has been shown to effectively limit cancer growth. Certain human colon cancer cell lines, including HT-29 and HCT-116, are inhibited from growing by Bifidum BGN4, according to an in vitro study (Ku *et al*., 2009).

Anti-inflammation: A physiological reaction known as inflammation is typically brought on by harm to living tissues. Some oral and enteric inflammations, such as irritable bowel syndrome (Guglielmetti *et al*., 2011; Ringel-Kulka *et al*., 2011; O'Mahony *et al*., 2005), intestinal barrier functions (Krumbeck *et al*., 2018), and infant colic impairment (Kobayashi *et al*., 2019; Xiao *et al*., 2020), have been treated with bifidobacteria to both suppress and prevent these inflammations. Certain strains can also prevent cutaneous inflammations. For example, a combination of B. breve M-16V and B. longum BB536 can prevent newborns from developing eczema and atopic dermatitis (Enomoto *et al*., 2014).

Enteritis: According to an in vitro investigation, B. animalis MB5 inhibits neutrophil migration and slightly lowers pathogen adherence to shield intestinal Caco-2 cells from the inflammation-associated response (Roselli *et al*., 2006). Numerous research conducted on animals have also confirmed the anti-inflammatory properties. For instance, it was discovered that combining B. bifidum and B. longum effectively prevented harmful necrotizing enterocolitis (NEC) in an animal model (Wu *et al*., 2013); B. adolescentis IM38, on the other hand, ameliorates colitis caused by high fat diet by inhibiting the activation of NF-κB and the production of lipopolysaccharides by the gut microbiota (Lim and Kim, 2017).

Human studies have suggested that B. breve M-16V may shield newborns from developing NEC (Wong *et al*., 2019). In children with celiac disease, adding two B. breve strains (BR03 and B632) to a gluten-free diet has been found to have a beneficial effect on lowering the production of the pro-inflammatory cytokine TNF-α (Klemenak *et al*., 2015). According to Aloisio *et al*. (2012), three B. breve strains and one B. longum strain have the ability to treat neonates' gastrointestinal problems, such as infantile colic.

Lactose Intolerance: Patients who are unable to produce enough lactase in their small intestine to break down dietary lactose, which is typically found in dairy products, are said to be lactose intolerant. The gut microorganisms catabolize the undigested lactose in the colon, which causes diarrhea, gas, nausea, cramping in the stomach, and vomiting—all signs of lactose intolerance. Because B. animalis subsp. animalis IM386 promotes lactose breakdown in the small intestines, it helps people who are lactose intolerant with their diarrhea and flatulence (Roškar *et al*., 2017). In participants who were lactose intolerant, a combination of probiotics including B. animalis subsp. animalis IM386 and L. plantarum MP2026 also

reduced some gastrointestinal symptoms (Roškar *et al*., 2017).

Constipation: When treating constipation, a multi-component probiotics formula containing Bifidum, B. infantis, B. longum, L. casei, L. plantarum, and L. rhamnosus has been shown to be beneficial in reducing symptoms. Constipation is typically caused by dietary changes or an inadequate intake of fiber (Bekkali *et al*., 2007). According to Di Pierro and Pane (2021) B. longum W11 can also treat minor hepatic encephalopathy and synergize with rifaximin as an adjuvant antibiotic treatment, providing relief to individuals suffering from constipation symptoms like irritable bowel syndrome.

Promoting Psychological Health: Probiotics that are good for mental health fall into the area of psychobiotics. Psychobiotics are the functional category that includes many Bifidobacteria. Research has demonstrated that Bifidobacteria is less prevalent in the gut microbiota of stress-resilient mice than in control and susceptible animals. Furthermore, supplementing susceptible mice with Bifidobacteria markedly boosted their resilience in comparison to mice who were given a vehicle (Yang *et al*., 2017). Based on these results, it's possible that bifidobacteria provide stress resistance. According to Tian *et al*. (2021), *B. breve* CCFM1025 demonstrated that several kinds of antidepressant effect were observed in chronically stressed mice. This impact is likely attributed to the mice's ability to utilize different carbohydrates and produce neuroactive metabolites, including tryptophan, hypoxanthine, and nicotinate. According to Tian *et al*. (2020), *B. breve* CCFM1025 can also alleviate depression symptoms brought on by long-term stress. Because *B. adolescentis* 150 can create gamma-aminobutyric acid, it also shown anti-depressive characteristics when administered to mice (Yunes *et al*., 2020).

According to Pinto-Sanchez *et al*. (2017), giving *B. longum* NCC3001 orally to sad patients lowers their depression levels and modifies their brain activity. Additionally, it was found that B. longum 1714TM regulates neural responses and resting neural activity to modify brain activity (Wang *et al*., 2019). Patients with Major depression Disorder experienced a significant reduction in depression symptoms when treated with a combination of *B. longum* and *L. helveticus* (Kazemi *et al*., 2019).

Decreasing Fat Accumulation: Obesity raises the risk of heart disease, diabetes, high blood pressure, and some types of cancer, among other illnesses and health issues. Certain probiotics including Bifidobacterium can help these hosts accumulate less fat. In Caenorhabditis elegans, *B. lactis* CECT 8145 can lower fat content while simultaneously modifying lipid metabolism and the antioxidant response (Martorell *et al*., 2016).

Facilitating the Host Nutrition Absorption: Studies have indicated that taking probiotics can help the body absorb minerals including vitamins and calcium ions (Ballini *et al*., 2019). By promoting the fermentation processes that arise from the microbial crosstalk between B. longum BB536 and human gut-derived microbiota, *B. longum* BB536 can increase the quantity of nutrients, including pimelate, biotin, and butyrate (Sugahara *et al*., 2015).

Promoting Bone Health: A person with osteoporosis, a common bone metabolic condition brought on by low bone mass and bone tissue degeneration, is more likely to fracture. By boosting the expression of the Sparc and Bmp-2 genes, the probiotic B. longum ATCC 15707 (Parvaneh *et al*., 2015) when used in conjunction with yacon flour (Rodrigues *et al*., 2012) can enhance bone mass density. Furthermore, by reducing systemic inflammation brought on by fractures, B. adolescentis ATCC 15703 can regulate bone repair (Roberts *et al*., 2020).

Regulating the Host Immune System: Additionally, probiotics have the ability to control the host immune system, which can help treat or prevent disease. It was discovered that *B. animalis* subsp. lactis BB-12 raised the levels of total IgA and anti-β-lactoglobulin IgA in fecal extracts, protecting mouse pups and dams from exposure to food antigens (Fukushima *et al*., 1999). By encouraging the growth of Treg, *B. breve* ATCC 15700 inhibits the skewed T helper 2 pattern responses (Zhang *et al*., 2010). By raising phagocytic activity and the anti-inflammatory cytokine IFN-α, *B. animalis* subsp. lactis HN019 can improve natural immunity in healthy older adult patients (Arunachalam *et al*., 2000). By enhancing regulatory T (Treg and Tr1) cells and lowering proliferating lymphocytes, *L. helveticus* Bar13 and *B. longum* Bar33 can work in concert to enhance the immunological status and physiologic status of older adults.

Other Beneficial Effects: Combining *B. longum* BB536 with *B. pseudocatenulatum* G4 reduces total cholesterol, LDL-cholesterol, triglyceride levels, malondialdehyde, and raises concentrations of HDL-cholesterol to alleviate cardiovascular symptoms (Al-Sheraji *et al*., 2012). The symptoms of allergen-pollen-induced rhinitis can be avoided by using a *Bifidobacteria* mixture of *B. longum* BB536, *B. infantis* M-63, and *B. breve* M-16 V (Miraglia Del

Giudice *et al*., 2017). By lowering nitric oxide release, *B. pseudocatenulatum* CECT 7765 can reverse the vascular dysfunction brought on by obesity (Mauricio *et al*., 2017). It can also stop problems originating from the stomach in experimental chronic liver disease by preserving gut homeostasis (Moratalla *et al*., 2016).

Conclusion: Probiotics can be regarded as therapeutic agents because of their demonstrated efficacy in treating a number of gastrointestinal disorders. When ingested in sufficient quantities, they offer health advantages to the host. Probiotic bacteria must stick to intestinal epithelial cells and be resistant to bile salts and gastric acid. The majority of probiotics are sold commercially as foods or medications that include live microorganisms. As a result, it is crucial to think about the probiotics' safety evaluation before using them. When given in the right amount, *bifidobacterium*, a significant component of the probiotic mix, has various health benefits. Numerous probiotic strains have been shown to exhibit a range of beneficial effects, such as anti-infection, anti-inflammatory, and anti-cancer effects, as well as enhancing the physical and mental well-being of the host and modulating the host immune system.

REFERENCES

Al-Sheraji, SH; Ismail, A; Manap, MY; Mustafa, S; Yusof, RM; Hassan, FA. (2012). Hypocholesterolaemic effect of yoghurt containing Bifidobacterium pseudocatenulatum G4 or Bifidobacterium longum BB536. *Food Chem.*, *135*(2), 356–361. https://doi.org/10.1016/j.foodchem.2012.04.120

Allen, SJ; Jordan, S; Storey, M; Thornton, CA; Gravenor, M; Garaiova, I; Plummer, SF; Wang, D; Morgan, G. (2010). Dietary Supplementation with Lactobacilli and Bifidobacteria Is Well Tolerated and Not Associated with Adverse Events during Late Pregnancy and Early Infancy. *The J Nutri*, *140*(3), 483–488. https://doi.org/10.3945/jn.109.117093

Aloisio, I; Santini, C; Biavati, B; Dinelli, G; Cencič, A; Chingwaru, W; Mogna, L; Di Gioia, D. (2012). Characterization of Bifidobacterium spp. strains for the treatment of enteric disorders in newborns. *Appl. Micro. Biotech*, *96*(6), 1561–1576. https://doi.org/10.1007/s00253-012-4138-5

Arunachalam, K; Gill, H; Chandra, R. (2000). Enhancement of natural immune function by dietary consumption of Bifidobacterium lactis (HN019). *Euro. J. Clin. Nutri*, *54*(3), 263–267. https://doi.org/10.1038/sj.ejcn.1600938

Ballini, A; Gnoni, A; De Vito, D; Dipalma, G; Cantore, S; Gargiulo Isacco, C; Saini, R; Santacroce, L; Topi, S; Scarano, A; Scacco, S; Inchingolo, F. (2019). Effect of probiotics on the occurrence of nutrition absorption capacities in healthy children: a randomized double-blinded placebo-controlled pilot study. *Euro. Rev. Med. Pharm. Sci*, *23*(19), 8645–8657. https://doi.org/10.26355/eurrev_201910_19182

Bekkali, NLH; Bongers, ME; Van den Berg, MM; Liem, O; Benninga, M. A. (2007). The role of a probiotics mixture in the treatment of childhood constipation: a pilot study. *Nutri. J*, *6*(1). https://doi.org/10.1186/1475-2891-6-17

Chow, J. (2002). Probiotics and prebiotics: A brief overview. *J. Ren. Nutri*, *12*(2), 76–86. https://doi.org/10.1053/jren.2002.31759

Davoodabadi, A; Soltan Dallal, MM; Rahimi FA; Douraghi, M; Sharifi YM; Kazem; Amin HF. (2015). Antibacterial activity of Lactobacillus spp. isolated from the feces of healthy infants against enteropathogenic bacteria. *Anaerobe*, *34*(DOI: 10.1016/j.anaerobe.2015.04.014), 53–58. https://doi.org/10.1016/j.anaerobe.2015.04.014

Di Pierro, F; Pane, M. (2021). Bifidobacterium longum W11: Uniqueness and individual or combined clinical use in association with rifaximin. *Clin. Nutri. ESPEN*, *42*(DOI: 10.1016/j.clnesp.2020.12.025), 15–21. https://doi.org/10.1016/j.clnesp.2020.12.025

Enomoto, T; Sowa, M; Nishimori, K; Shimazu, S; Yoshida, A; Yamada, K; Furukawa, F; Nakagawa, T; Yanagisawa, N; Iwabuchi, N; Odamaki, T; Abe, F; Nakayama, J; Xiao, J. (2014). Effects of Bifidobacterial Supplementation to Pregnant Women and Infants in the Prevention of Allergy Development in Infants and on Fecal Microbiota. *Allerg. Interna.*, *63*(4), 575–585. https://doi.org/10.2332/allergolint.13-oa-0683

Fedorak, RN; Madsen, K. L. (2004). Probiotics and prebiotics in gastrointestinal disorders. *Curr. Opin. Gastro*, *20*(2), 146–155. https://doi.org/10.1097/00001574-200403000-00017

Finamore, A; Roselli, M; Donini, L; Brasili, DE; Rami, R; Carnevali, P; Mistura, L; Pinto, A; Giusti, A; Mengheri, E. (2019). Supplementation with Bifidobacterium longum Bar33 and Lactobacillus

helveticus Bar13 mixture improves immunity in elderly humans (over 75 years) and aged mice. *Nutri*, *63-64*(doi: 10.1016/j.nut.2019.02.005. Epub 2019 Feb 18.), 184–192. https://doi.org/10.1016/j.nut.2019.02.005

Fioramonti, J; Theodorou, V; Bueno, L. (2003). Probiotics: what are they? What are their effects on gut physiology? *Best Prac. Resear. Clin. Gastro*, *17*(5), 711–724. https://doi.org/10.1016/s1521-6918(03)00075-1

Fonseca, J; Luige BA; Álvaro CN; Silva, M; Amaral, S; Marcelo VC; Jacques RN; Neumann, E; Maria Aparecida Gomes. (2019). Probiotic effect of *Bifidobacterium longum* 5 [1A] and *Weissella paramesenteroides* WpK4 on gerbils infected with *Giardia lamblia*. *J. App. Micro*, *127*(4), 1184–1191. https://doi.org/10.1111/jam.14338

Food and Agriculture Organization/World Health Organization (FAO/WHO). (2002) Guidelines for the evaluation of probiotics in food, Report of a Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Food, London, Ontario, Canada (http://ftp.fao.org/es/esn/food/wgreport2.pdf).

Fukushima, Y; Kawata, Y; Koko M; Jun-ichi K; Tomotari M. (1999). Effect of bifidobacteria feeding on fecal flora and production of immunoglobulins in lactating mouse. *Inter. J. Food Micro*, *46*(3), 193–197. https://doi.org/10.1016/s0168-1605(98)00183-4

Gismondo, MR; Drago, L; Lombardi, A. (1999). Review of probiotics available to modify gastrointestinal flora. *Inter. J. Antimicro. Ag*, *12*(4), 287–292. https://doi.org/10.1016/s0924-8579(99)00050-3

Guglielmetti, S; Mora, D; Gschwender, M; Popp, K. (2011). Randomised clinical trial: Bifidobacterium bifidum MIMBb75 significantly alleviates irritable bowel syndrome and improves quality of life -- a double-blind, placebo-controlled study. *Alim. Pharma. Therapeu*, *33*(10), 1123–1132. https://doi.org/10.1111/j.1365-2036.2011.04633.x

Hanauer, SB. (2006). Inflammatory bowel disease: Epidemiology, pathogenesis, and therapeutic opportunities. *Inflamm. Bow. Diseas*, *12*(DOI: 10.1097/01.mib.0000195385.19268.68), S3–S9. https://doi.org/10.1097/01.mib.0000195385.19268.68

Hanchi, H; Mottawea, W; Sebei, K; Hammami, R. (2018). The Genus Enterococcus: Between Probiotic Potential and Safety Concerns—An Update. *Front. Micro*, *9*(DOI: 10.3389/fmicb.2018.01791). https://doi.org/10.3389/fmicb.2018.01791

Havenaar, R; Huis In't Veld, JHJ. (1992). Probiotics: A General View. *The Lact. Acid Bact. Vol. 1*, *DOI https://doi.org/10.1007/978-1-4615-3522-5_6*(DOI https://doi.org/10.1007/978-1-4615-3522-5_6), 151–170. https://doi.org/10.1007/978-1-4615-3522-5_6

Igbafe, J; Kilonzo-Nthenge, A; Nahashon, SN; Mafiz, AI; Nzomo, M. (2020). Probiotics and Antimicrobial Effect of Lactiplantibacillus plantarum, Saccharomyces cerevisiae, and Bifidobacterium longum against Common Foodborne Pathogens in Poultry. *Agric*, *10*(9), 368. https://doi.org/10.3390/agriculture10090368

Ilya Ilyich M. (2004). *The Prolongation of Life*. Springer Publishing Company.

Ishibashi, N; Yamazaki, S. (2001). Probiotics and safety. *The Ameri. J. Clin. Nutri*, *73*(2), 465s470s. https://doi.org/10.1093/ajcn/73.2.465s

Isolauri, E; Arvola, T; SUtas, Y; Moilanen, E; Salminen, S. (2000). Probiotics in the management of atopic eczema. *Clin. Experimen. Aller*, *30*(11), 1605–1610. https://doi.org/10.1046/j.1365-2222.2000.00943.x

Kazemi, A; Noorbala, AA; Azam, K; Eskandari, MH; Djafarian, K. (2019). Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: A randomized clinical trial. *Clin. Nutri*, *38*(2), 522–528. https://doi.org/10.1016/j.clnu.2018.04.010

Kim, MJ; Lee, DK; Park, JE; Park, IH; Seo, JG; Ha, N. J. (2014). Antiviral activity of Bifidobacterium adolescentis SPM1605 against Coxsackievirus B3. *Biotech*, *Biotech. Equip*, *28*(4), 681–688. https://doi.org/10.1080/13102818.2014.945237

Klemenak, M; Dolinšek, J; Langerholc, T; Di Gioia, D; Mičetić-Turk, D. (2015). Administration of Bifidobacterium breve Decreases the Production of TNF-α in Children with Celiac Disease. *Digest. Diseas. Sci*, *60*(11), 3386–3392. https://doi.org/10.1007/s10620-015-3769-7

Kobayashi, Y; Kinoshita, T; Matsumoto, A; Yoshino, K; Saito, I; Xiao, JZ. (2018). Bifidobacterium Breve A1 Supplementation Improved Cognitive Decline In Older Adults With Mild Cognitive Impairment: An Open-Label, Single-Arm Study. *The J. Prevent. Alzheimer's Dis, DOI: 10.14283/jpad.2018.32*(DOI: 10.14283/jpad.2018.32), 1–6. https://doi.org/10.14283/jpad.2018.32

Krumbeck, JA; Rasmussen, HE; Hutkins, RW; Clarke, J; Shawron, K; Keshavarzian, A; Walter, J. (2018). Probiotic Bifidobacterium strains and galactooligosaccharides improve intestinal barrier function in obese adults but show no synergism when used together as synbiotics. *Microbiome*, *6*(1). https://doi.org/10.1186/s40168-018-0494-4

Ku, S; Hyun JY; Geun EJ. (2009). Enhancement of Anti-tumorigenic Polysaccharide Production, Adhesion, and Branch Formation of Bifidobacterium bifidum BGN4 by Phytic Acid. *Food Sci. Biotech*, *18*(3), 749–754.

Lau, ASY; Yanagisawa, N; Hor, YY; Lew, LC; Ong, JS; Chuah, LO; Lee, YY; Choi, SB; Rashid, F; Wahid, N; Sugahara, H; Xiao, JZ; Liong, MT. (2018). *Bifidobacterium longum* BB536 alleviated upper respiratory illnesses and modulated gut microbiota profiles in Malaysian pre-school children. *Benefi. Micro*, *9*(1), 61–70. https://doi.org/10.3920/bm2017.0063

Lee, DK; Park, JE; Kim, MJ; Seo, JG; Lee, JH; Ha, NJ. (2015). Probiotic bacteria, B. longum and L. acidophilus inhibit infection by rotavirus in vitro and decrease the duration of diarrhea in pediatric patients. *Clin. Resear. Hepa. Gastro*, *39*(2), 237–244. https://doi.org/10.1016/j.clinre.2014.09.006

Lee, JW; Shin, JG; Kim, EH; Kang, HE; Yim, IB; Kim, JY; Joo, HG; Woo, HJ. (2004). Immunomodulatory and antitumor effects in vivo by the cytoplasmic fraction of Lactobacillus casei and Bifidobacterium longum. *J. Veter. Sci*, *5*(1), 41. https://doi.org/10.4142/jvs.2004.5.1.41

Marteau, PR; Vrese, MD; Cellier, CJ; Schrezenmeir, J. (2001). Protection from gastrointestinal diseases with the use of probiotics. *The Americ. J. Clin. Nutri*, *73*(2), 430s436s. https://doi.org/10.1093/ajcn/73.2.430s

Martorell, P; Llopis, S; González, N; Chenoll, E; López-Carreras, N; Aleixandre, A; Chen, Y; Karoly, ED; Ramón; Genovés, S. (2016). Probiotic StrainBifidobacterium animalissubsp.lactisCECT 8145 Reduces Fat Content and Modulates Lipid Metabolism and Antioxidant Response inCaenorhabditis elegans. *J. Agric. Food Chem*, *64*(17), 3462–3472. https://doi.org/10.1021/acs.jafc.5b05934

Matsumoto, T; Ishikawa, H; Tateda, K; Yaeshima, T; Ishibashi, N; Yamaguchi, K. (2008). Oral administration of Bifidobacterium longum prevents gut-derived Pseudomonas aeruginosa sepsis in mice. *J. Appl. Micro*, *104*(3), 672–680. https://doi.org/10.1111/j.1365-2672.2007.03593.x

Mauricio, MD; Serna, E; Fernández-Murga, ML; Portero, J; Aldasoro, M; Valles, SL; Sanz, Y; Vila, J. M. (2017). Bifidobacterium pseudocatenulatum CECT 7765 supplementation restores altered vascular function in an experimental model of obese mice. *Inter. J. Med. Sci*, *14*(5), 444–451. https://doi.org/10.7150/ijms.18354

Miraglia Del Giudice, M; Indolfi, C; Capasso, M; Maiello, N; Decimo, F; Ciprandi, G. (2017). Bifidobacterium mixture (B longum BB536, B infantis M-63, B breve M-16V) treatment in children with seasonal allergic rhinitis and intermittent asthma. *Itali. J. Pedia*, *43*(1). https://doi.org/10.1186/s13052-017-0340-5

Moratalla, A; Gómez-Hurtado, I; Moya-Pérez, Á; Zapater, P; Peiró, G; González-Navajas, JM; Gómez Del Pulgar, EM; Such, J; Sanz, Y; Francés, R. (2016). Bifidobacterium pseudocatenulatum CECT7765 promotes a TLR2-dependent anti-inflammatory response in intestinal lymphocytes from mice with cirrhosis. *Euro. J. Nutri*, *55*(1), 197–206. https://doi.org/10.1007/s00394-015-0837-x

O'Mahony, L; McCarthy, J; Kelly, P; Hurley, G; Luo, F; Chen, K; O'Sullivan, GC; Kiely, B; Collins, JK; Shanahan, F; Quigley, EMM. (2005). Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*, *128*(3), 541–551. https://doi.org/10.1053/j.gastro.2004.11.050

Ohara, T; Yoshino, K; Kitajima, M. (2011). Possibility of preventing colorectal carcinogenesis with probiotics. *PubMed*, *57*(104), 1411–1415.

Ouwehand, AC; Lagström, H; Suomalainen, T; Salminen, S. (2002). Effect of Probiotics on Constipation, Fecal Azoreductase Activity and

Fecal Mucin Content in the Elderly. *Ann. Nutri. Meta*, *46*(3-4), 159–162. https://doi.org/10.1159/000063075

Paolillo, R; Romano CC; Sorrentino, S; Mazzola, N; Rizzo, A. (2009). Immunomodulatory effects of Lactobacillus plantarum on human colon cancer cells. *Interna. Immuno*, *9*(11), 1265–1271. https://doi.org/10.1016/j.intimp.2009.07.008

Parvaneh, K; Ebrahimi, M; Sabran, MR; Karimi, G; Hwei, ANM; Abdul-Majeed, S; Ahmad, Z; Ibrahim, Z; Jamaluddin, R. (2015). Probiotics (Bifidobacterium longum) Increase Bone Mass Density and Upregulate Sparc and Bmp-2 Genes in Rats with Bone Loss Resulting from Ovariectomy. *BioMed Resear. Interna*, *2015*(DOI: 10.1155/2015/897639). https://doi.org/10.1155/2015/897639

Patel, A; Shah, N; Prajapati, J. B. (2014). Clinical application of probiotics in the treatment of Helicobacter pylori infection—A brief review. *J. Micro, Immuno. Infect*, *47*(5), 429–437. https://doi.org/10.1016/j.jmii.2013.03.010

Pinto-Sanchez, MI; Hall, GB; Ghajar, K; Nardelli, A; Bolino, C; Lau, JT; Martin, FP; Cominetti, O; Welsh, C; Rieder, A; Traynor, J; Gregory, C; De Palma, G; Pigrau, M; Ford, AC; Macri, J; Berger, B; Bergonzelli, G; Surette, MG; Collins, SM. (2017). Probiotic Bifidobacterium longum NCC3001 Reduces Depression Scores and Alters Brain Activity: A Pilot Study in Patients With Irritable Bowel Syndrome. *Gastroenterology*, *153*(2), 448-459.e8. https://doi.org/10.1053/j.gastro.2017.05.003

Reid, G; Jass, J; Sebulsky, MT; McCormick, JK. (2003). Potential Uses of Probiotics in Clinical Practice. *Clin. Micro. Rev*, *16*(4), 658–672. https://doi.org/10.1128/cmr.16.4.658-672.2003

Ringel-Kulka, T; Palsson, OS; Maier, D; Carroll, I; Galanko, JA; Leyer, G; Ringel, Y. (2011). Probiotic bacteria Lactobacillus acidophilus NCFM and Bifidobacterium lactis Bi-07 versus placebo for the symptoms of bloating in patients with functional bowel disorders: a double-blind study. *J. Clin. Gastro*, *45*(6), 518–525. https://doi.org/10.1097/MCG.0b013e31820ca4d6

Roberts, JL; Liu, G; Darby, TM; Fernandes, LM; Diaz-Hernandez, ME; Jones, RM; Hicham Drissi. (2020). Bifidobacterium adolescentis supplementation attenuates fracture-induced systemic sequelae. *Biomed. Pharmacothera*, *132*(doi:10.1016/j.biopha.2020.110831), 110831–110831. https://doi.org/10.1016/j.biopha.2020.110831

Rodrigues, FC; Castro, ASB; Rodrigues, VC; Fernandes, SA; Fontes, EAF; de Oliveira, TT; Martino, HSD; de Luces Fortes Ferreira, CL. (2012). Yacon flour and Bifidobacterium longum modulate bone health in rats. *J. Medicin. Food*, *15*(7), 664–670. https://doi.org/10.1089/jmf.2011.0296

Roselli, M; Finamore, A; Britti, MS; Mengheri, E. (2006). Probiotic bacteria Bifidobacterium animalis MB5 and Lactobacillus rhamnosus GG protect intestinal Caco-2 cells from the inflammation-associated response induced by enterotoxigenic Escherichia coli K88. *Brit. J. Nutri*, *95*(6), 1177–1184. https://doi.org/10.1079/bjn20051681

Roškar, I; Švigelj, K; Štempelj, M; Volfand, J; Štabuc, B; Malovrh, Š; Rogelj, I. (2017). Effects of a probiotic product containing Bifidobacterium animalis subsp. animalis IM386 and Lactobacillus plantarum MP2026 in lactose intolerant individuals: Randomized, placebo-controlled clinical trial. *J. Function. Foods*, *35*(DOI: 10.1016/j.jff.2017.05.020), 1–8. https://doi.org/10.1016/j.jff.2017.05.020

Rowland, I. (1998). Effect of Bifidobacterium longum and inulin on gut bacterial metabolism and carcinogen-induced aberrant crypt foci in rats. *Carcinogenesis*, *19*(2), 281–285. https://doi.org/10.1093/carcin/19.2.281

Ruiz, L; Ruas-Madiedo, P; Gueimonde, M; de los Reyes-Gavilán, CG; Margolles, A; Sánchez, B. (2011). How do bifidobacteria counteract environmental challenges? Mechanisms involved and physiological consequences. *Gen. Nutri.*, *6*(3), 307–318. https://doi.org/10.1007/s12263-010-0207-5

Salminen, MK; Rautelin, H; Tynkkynen, S; Poussa, T; Saxelin, M; Valtonen, V; Jarvinen, A. (2006). Lactobacillus Bacteremia, Species Identification, and Antimicrobial Susceptibility of 85 Blood Isolates. *Clin. Infect. Diseas*, *42*(5), e35–e44. https://doi.org/10.1086/500214

Sgorbati B; Biavati B; Palenzona D. (1995). The Genus Bifidobacterium. In: The Lactic Acid Bacteria, Vol. 2, B.J.B. Wood, W.H. Holzapfel

(Eds.), Chapman and Hall, London, UK pp. 279–306.

Shah, NP. (2007). Functional cultures and health benefits. *Interna. Dair. J*, *17*(11), 1262–1277. https://doi.org/10.1016/j.idairyj.2007.01.014

Shanahan, F. (2012). A Commentary on the Safety of Probiotics. *Gastro. Clin. Nort. Ameri*, *41*(4), 869–876. https://doi.org/10.1016/j.gtc.2012.08.006

Snydman, DR. (2008). The Safety of Probiotics. *Clin. Infect. Diseas*, *46*(s2), S104–S111. https://doi.org/10.1086/523331

Sugahara, H; Odamaki, T; Fukuda, S; Kato, T; Xiao, J; Abe, F; Kikuchi, J; Ohno, H. (2015). Probiotic Bifidobacterium longum alters gut luminal metabolism through modification of the gut microbial community. *Scientif. Report. 5*(DOI: 10.1038/srep13548). https://doi.org/10.1038/srep13548

Taipale, TJ; Pienihäkkinen, K; Isolauri, E; Jokela, JT; Söderling, E. M. (2015). Bifidobacterium animalis subsp. lactis BB-12 in reducing the risk of infections in early childhood. *Pediatric Research*, *79*(1), 65–69. https://doi.org/10.1038/pr.2015.174

Tian, P; Bastiaanssen, TFS; Song, L; Jiang, B; Zhang, X; Zhao, J; Zhang, H; Chen, W; Cryan, JF; Wang, G. (2021). Unraveling the Microbial Mechanisms Underlying the Psychobiotic Potential of a Bifidobacterium breve Strain. *Molecular Nutrit. Food. Res. 65*(8), e2000704. https://doi.org/10.1002/mnfr.202000704

Tian, P; O'Riordan, KJ; Lee, Y; Wang, G; Zhao, J; Zhang, H; Cryan, JF; Chen, W. (2020). Towards a psychobiotic therapy for depression: Bifidobacterium breve CCFM1025 reverses chronic stress-induced depressive symptoms and gut microbial abnormalities in mice. *Neurobio. Stress*, *12*(DOI: 10.1016/j.ynstr.2020.100216), 100216. https://doi.org/10.1016/j.ynstr.2020.100216

Wang, H; Braun, C; Murphy, EF; Enck, P. (2019). Bifidobacterium longum 1714™ Strain Modulates Brain Activity of Healthy Volunteers during Social Stress. *Am. J. Gastroentero*, *114*(7), 1152–1162. https://doi.org/10.14309/ajg.0000000000000203

Wu, SF; Chiu, HY; Chen, AC; Lin, HY; Lin, HC; Caplan, M. (2013). Efficacy of Different Probiotic Combinations on Death and Necrotizing Enterocolitis in a Premature Rat Model. *Journal of Pediatric Gastroentero. Nutri*, *57*(1), 23–28. https://doi.org/10.1097/mpg.0b013e3182929210

Xiao, J; Katsumata, N; Bernier, F; Ohno, K; Yamauchi, Y; Odamaki, T; Yoshikawa, K; Ito, K; Kaneko, T. (2020). Probiotic Bifidobacterium breve in Improving Cognitive Functions of Older Adults with Suspected Mild Cognitive Impairment: A Randomized, Double-Blind, Placebo-Controlled Trial. *J. Alzheimer's Diseas*, *77*(1), 1–9. https://doi.org/10.3233/jad-200488

Yang, C; Fujita, Y; Ren, Q; Ma, M; Dong, C; Hashimoto, K. (2017). Bifidobacterium in the gut microbiota confer resilience to chronic social defeat stress in mice. *Sci. Reports*, *7*(1). https://doi.org/10.1038/srep45942

Yun, B; Song, M; Park, DJ; Oh, S. (2017). Beneficial Effect of Bifidobacterium longum ATCC 15707 on Survival Rate of Clostridium difficile Infection in Mice. *Korea. J. Food Sci. Anim. Resourc*, *37*(3), 368–375. https://doi.org/10.5851/kosfa.2017.37.3.368

Yunes, RA; Poluektova, EU; Vasileva, EV; Odorskaya, MV; Marsova, MV; Kovalev, GI; Danilenko, VN. (2019). A Multi-strain Potential Probiotic Formulation of GABA-Producing Lactobacillus plantarum 90sk and Bifidobacterium adolescentis 150 with Antidepressant Effects. *Prob. Antimicro Prot*, *12*(3), 973–979. https://doi.org/10.1007/s12602-019-09601-1

Zhang, LL; Chen, X; Zheng, PY; Luo, Y; Lu, GF; Liu, ZQ; Huang, H; Yang, PC. (2010). Oral *Bifidobacterium* modulates intestinal immune inflammation in mice with food allergy. *J. Gastroenterolo. Hepato*, *25*(5), 928–934. https://doi.org/10.1111/j.1440-1746.2009.06193.x