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Probiotics: Healthy Gut Microbiota to Lead a Wholesome Life

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Abstract: *Microbiota in the human gut exhibit a key function in upholding healthy physical and psychological well-being in all individuals. Each person has the precise composition of microbiota colonizing their gut which possesses health benefits to the host. The beneficial microbes in humans are called probiotics which help to maintain a balanced gut microbiota. Disturbance in gut microbiota was observed in many disease conditions. Lactobacillus sp., and Bifidobacterial sp., were probiotics used to treat gastrointestinal diseases like irritable bowel syndrome, ulcerative colitis and other underlying ailments like diabetes, and obesity. Further, probiotic bacteria possess immunomodulatory functions and also the ability to ferment non-digestible fibres in food and synthesize exopolysaccharides, bacteriocins, short- chain fatty acids, and vitamins and enhance the bioavailability of nutrients in the host. The current review focus on the ability of probiotics to prevent dysbiosis and its associated diseases in human. Further, traditionally fermented foods are a rich source of probiotics to enhance nutrition and maintain gut microbiota to prolong a healthy life.*

Keywords: *Gut microbiota, probiotics, fermented foods, inflammatory bowel disease, Lactobacillus.*

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1. Introduction

Lederberg was the first to introduce the term “gut-microbiota” to the scientific group [1]. The microbiome in the human system is also called a virtual organ system as it helps in host nutrition supplementation and in maintaining homeostasis. It is important to do more research on the gut microbiome as the fact prevails that the microbial ecosystem in the gut contains genetic contents over 150 times of humans [2]. The gut environment of human is an exceedingly complicated environment where the interaction of beneficial microbial community, nutrition and cells in the host interact effectively to maintain a balanced gut microbiota and imparts healthy well-being [3]. The gut microbiota performs a crucial task in developing immunity, besides each person has a unique diversity of gut microbiome based on their dietary food intake [4]. Additionally, researchers have shown that the gut microbiota in mammals was found to be related within species rather than between species despite the geographical locations which demonstrates the co-evolution of gut microbiota along with its host [5]. The elements swaying the unique pattern of gut microbiome in each individual are depicted in Figure 1.

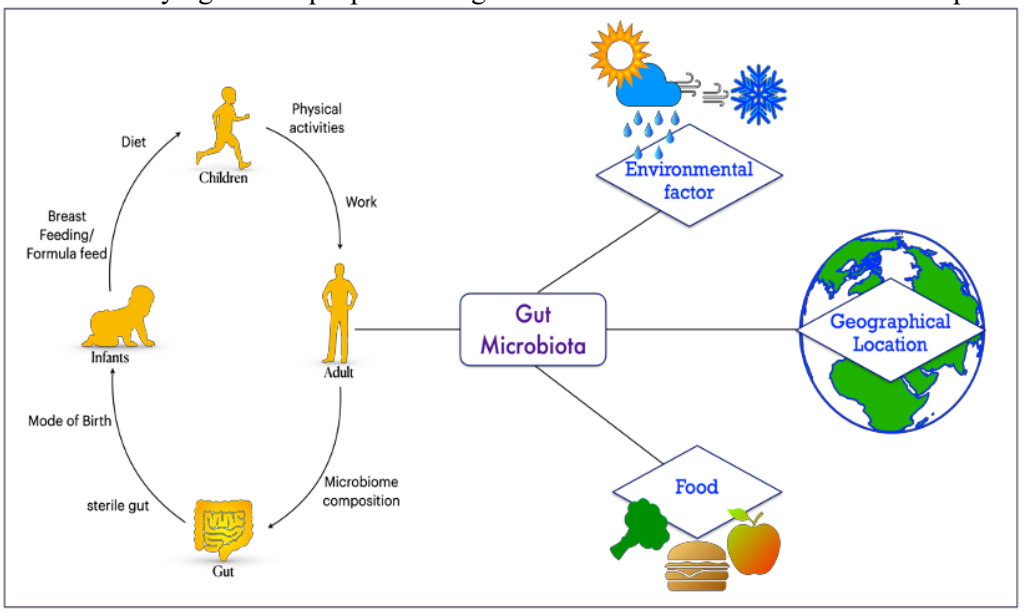

Figure 1. The factors attributing the unique composition of gut microbiota in each individual.

The FDA and WHO have defined probiotics as “live microorganisms which when administered in adequate amounts confer health benefits to the host” and they were usually considered safe [1]. The popularly studied probiotics groups were Lactobacillus and Bifidobacteria [5]. Nowadays, probiotics are used in modifying gut microbiota to alleviate certain disease conditions in humans and animals. This is achieved through the development of probiotic foods by studying wide species of probiotics. Lactobacillus plantarum, Lactobacillus rhamnoses, Lactobacillus reuteri, Lactobacillus casei, Lactobacillus helviticus, Bifidobacterium, Propionibacterium, some bacillus and streptococcus species were studied in the development of functional food. The common microbiota in the human gut were Bacteroides, Firmicutes, and Actinobacteria [1]. The interaction of probiotics and gut microflora usually occurs in mucosa where the homeostasis of the gut is maintained and prevents invading pathogens. For a healthy gut, homeostasis is vital to endure an intact intestinal barrier. The damage in the

intestinal barrier leads to diseases like irritable bowel syndrome (IBS), colorectal cancer, Crohn's disease, and inflammatory bowel disease (IBD). The integrity of the intestinal barrier cells is maintained by the communication of probiotics, gut microflora and epithelial cell lining the gastrointestinal tract [5, 6] Probiotic uses mechanisms like competing for available nutrient supplements, producing substances like anti-microbial proteins (Bacteriocin), the enhanced role of the intestinal barrier, stimulated immune response [7]. Dysbiosis leads to many diseases like diabetes mellitus, non-alcoholic liver diseases, obesity, cardiovascular disorders, oxidate stress-related disease, and immune- related diseases [8].

Further, recent studies related to the gut-brain axis have proved that disturbance in the gastrointestinal microbiome is associated with the psychological condition of a person. The digestive region of the human system has a complicated network of nerves called the enteric nervous system which carries the information from the gut to the brain and vice versa [6]. The gut microbiota pattern formed in the infant stage greatly influences their health in the later stage of life. The Bacteroides and firmicutes are found higher in probiotic-consumed infants and aerobic bacteria are rich in the control group. Thus, probiotics play an important function to maintain homeostasis, improving immune response, good psychological condition and in the prevention/ treatment of diseases from infancy to the elder people [9].

2. Probiotics and Gut microbiota

The microbial colonization in a human was observed in the skin (1011 CFU), oral cavity (1011-1012 CFU), stomach (107 CFU), intestine (1011 CFU), mucosa layer (1012 CFU), colon (1014 CFU) [2]. Among these, the highest concentration of microbes was loaded in the intestine. Probiotics aid in colonization and improve the immune response. Further, probiotics possess exclusive characteristics similar to anti-diabetes, anti-obesity, anti- angiogenic and anti-inflammatory responses. The activity of probiotics was strain-specific [8]. In the intestine, probiotic bacteria colonize the intestine by competing with pathogens [10]. Probiotics can influence both innate and adaptive immunity through dendritic cells, macrophages, monocytes, lymphocytes and epithelial cells [11].

2.1. Metabolites of Gut Microbiota

The utmost role of microbiota in gut provides the indispensable capability to ferment unpalatable substratum which includes dietetic fibres and endogenic intestinal secretions. This process aids in the development of proficient microorganisms that synthesize short- chain fatty acids (SCFA) which includes acetate, propionate and butyrate [12]. Butyrate is the chief wellspring of energy for mammalian colonocytes, which induces caspase-mediated cell death of colon cancer cells and could activate gluconeogenesis in the gut, delivering a valuable impact on homeostasis and the metabolism of glucose [13]. Butyrate has a pivotal function in consuming a large quantity of oxygen through ß oxidation for the epithelial cells, which creates an environment which helps maintain oxygen equilibrium in the intestine, thus averting dysbiosis of gut microbiota [14]. In infants, dysbiosis was observed prior to the onset of necrotising colitis with an increase in Proteobacteria species and a lesser amount of Firmicutes and Bacteroides. Further, Clostridium difficle infection also contributes to gut dysbiosis. Currently, faecal microbiota transplantation is carried out throughout the world to restore probiotics in the gut [15]. Probiotics are competent in maintaining homeostasis in the gut. The effect of probiotics and dysbiosis in the gut environment is depicted in Figure 2. Moreover, the capability of probiotics to sustain the balance of microbiota in the gut largely depends on the incorporation of prebiotics in the diets [16]. Prebiotics is substances which are non-digestible by humans but enhance the growth of probiotics in the gut.

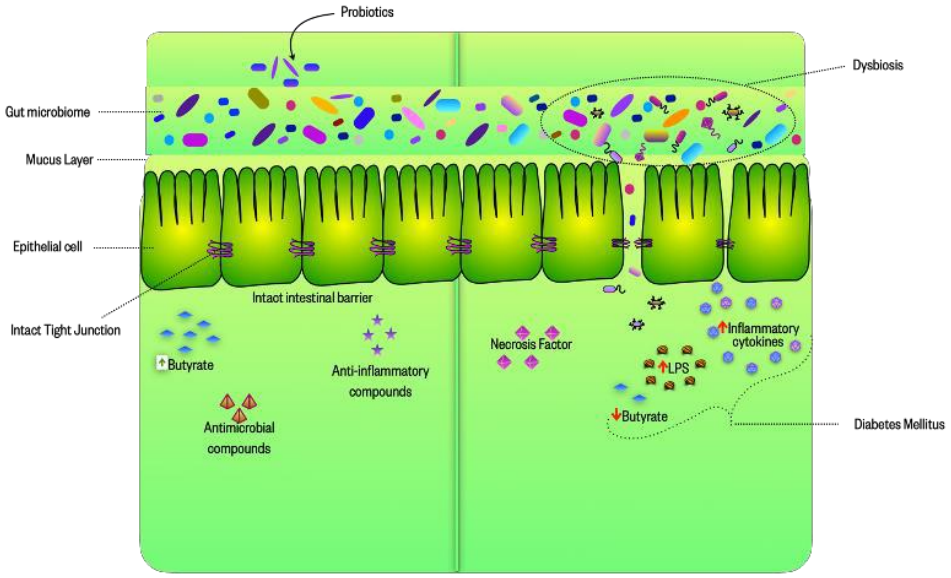

Figure 2. The healthy gut environment with the administration of probiotics and the effect of dysbiosis and its associated diseases.It has been reported that L. plantarum 90sk and Bifidobacterium adolescentis 150 possess antagonistic activity, and antioxidant properties and can produce GABA a secondary metabolite of probiotics which serves as psychobiotics [17]. The profuse SCFA produced is acetate which is an indispensable metabolite for the progression of more microbes which contact the marginal layers of the gut where it is utilized in metabolizing cholesterol and may emulate in regulating vital hunger. Arbitrarily, manipulated trials have revealed a greater yield of SCFA synchronizes through less food intake prompted weight gain [18] along with decreased resistance to insulin [19]. Next, the produced propionate enters the liver where it governs gluconeogenesis and enhances inflammatory signalling through interplay with the endogenous receptors [13]. In mice, butyrate and propionate seem to regulate the endogenous hormones which decrease the consumption of foods. The enzymes from gut microbiota aid in bile acid metabolism and aid in host essential pathways [20]. Some notable products of the intestinal microbiota were found to be implicated directly in

the health of humans. Two such products include trimethylamine and indole-propionic acid. The intake of meat and dairy, the dietary sources aid in the production of trimethylamine which depends mainly upon the intestinal microbes and considerably lowers the risk of occurrence of diabetes mellitus [21]. Probiotics have shown good outcomes in previous research and the list of diseases treated with probiotics is given in Table 1.

3. Diseases associated with alterations in gut microbiota

3.1. Diabetes

Diabetes is a disease condition with a multifactorial origin and one of the factors were linked to the alteration of gut microbes. Change in intestinal microbiota leads to increased permeability of the intestine and ensures decreased tight junction protein expression. In the due course, it facilitates bacterial lipopolysaccharide translocation resulting in resistance to insulin and

metabolic endotoxemia. The increased reactive oxygen species will decrease the mucus layer and lesser the quantity of Bifidobacterium Recent research has evidenced that probiotic supplementation has improved gut health and is an effective adjuvant therapy for insulin resistance [47]. In the case of type 2 diabetes mellitus the number of opportunistic bacteria like Clostridium clostridioforme, Clostridium hathewayi, Clostridium symbiosum, Bacteroides caccae, Clostridium ramosum, E.coli and Eggerthella sp. was found to be a higher and lesser quantity of butyrate synthesizing bacteria's like Eubacterium rectale, Faecalibacterium prausnitzii, Roseburia intestinalis and Roseburia inulinivorans. Enhanced sensitivity to insulin was observed in an increased quantity of butyrate and Roseburia sp. The desired energy source of colon epithelial cells was butyrate. In diabetic patients, Firmicutes and Bacteroides were observed to be less compared to beta proteobacteria. The greater number of beta proteobacteria is associated with a higher glucose level in plasma [48]. The intestinal permeability was reduced by the administration of probiotics like L. acidophilus, L. rhamnosus, and L. fermentutm can alter the expression of adhesion molecules. It has been evidenced that L. johnsonii has accelerated the Paneth cell growth in rats. The Paneth cells are components of the intestinal barrier responsible for producing antimicrobial substances and preventing intestinal permeability. Thus, the inclusion of probiotics in diabetes-prone rat models has prevented the incidence of the formation of

diabetes [47]. Further, engineered probiotics were developed to alleviate the use of insulin injections by diabetic patients. In studies conducted with rats, the incorporation of engineered Lactobacillus lactis NZ9000, Bifidobacterium longum, Lactobacillus gasseri ATCC 33323, Lactobacillus paracassei have delayed the onset of diabetes mellitus and enhanced the insulin secretion from β cells in pancreas [26]. (Chua et al., 2017). Further, it has been reported that probiotics prevent the risk of diabetes like cardiovascular diseases [49].

3.2. Obesity

The microbiota in the gut enacts a vital function in developing and progressing obesity. A characteristic decrease in the diversity of gut microbiota shows dysbiosis which leads to weight gain and obesity [50]. A study shows an increased weight gain when a germ-free mouse receives the faecal microbes from an obese human than the mouse which receives microorganisms from a vigorous human with ideal weight. A massive investigation of UK look-alikes shows that Christensenella sp. was occasionally observed in obese people then once subjected to germ-free mouse models, it prevents weight gain [51]. This microbe and others such as Akkermansia are associated with lesser accumulation of fat in the gut [52]. Regardless of the fact, nearly all confirmatory data from mice studies show that long-lasting gaining of weight for more than 10 years in humans is connected with less gut microbial diversity and in association with low dietary intake of fibre would further aggravate the conditions [53]. Dysbiosis of gut microbiota presumably promotes weight gain and difficulties in metabolism which includes dysregulation of the immune response, alteration in regulating energy, and trouble in regulating gut hormone and pro-inflammatory responses [54].

3.3. Gastrointestinal diseases

Bowel diseases occur due to the imbalance between the gut microbiome and intestinal immune response. Synthesis of pro-inflammatory and anti-inflammatory cytokines through Th-1 and Th-2 cells are responsible for maintaining homeostasis. Usually, the inflammatory response was observed to be higher during gastrointestinal diseases like ulcerative colitis and chron diseases It has been evidenced that probiotics produce anti-inflammatory cytokines which would prevent these gastrointestinal disorders.Irritable bowel syndrome, along with Crohn's disease and Ulcerative colitis was the most complex immune disorder which manifests a genetic basis. The studies done by the Genome- Wide Association (GWASs) show that the development of

the above-mentioned diseases correlates with the host's genes, but not all the genetic abnormalities develop the disease [55]. A study performed with genetically modified mice with varied strains of Lactobacillus and Bifidobacteria has shown that some of the attributes of IBD are alleviated by probiotics which ameliorate the gut function, reduce the inflammation, and avert disease advancement to Ulcerative Colitis [56]. Lactobacillus reuteri was found to modulate gut immune response [6].

In humans, the efficacy of probiotics was found to be less positive and the current meta- analysis has shown that probiotics haven't rendered good remedial effect for the remission of Crohn's Disease [57]. It was stated that including probiotics along with standard treatment for ulcerative colitis does not offer complete remission but possibly provides a decreased disease activity [58]. However, multiple probiotic strains were commercialized as VSL#3 was recommended for the treatment of ulcerative colitis and it has shown healing progress in patients for the remission of ulcerative colitis and pouchitis [34]. Further arbitrary trials with varied strains of bacteria are used to investigate the effects of probiotics on IBDs. L. rhamnosus has been proven in ex-vivo studies in the therapy of necrotizing colitis in infants [11]. Clostridium difficle bacterium was observed to be dominant in patients with colitis along with disturbed intestinal microflora whereas, Lactobacillus plantarum was the predominant microflora in healthy individuals [35]. Usual antibiotic therapy for Helicobacter pylori was aided with a single strain and multiple strains of lactobacillus have improved the eradication of H. pylori also the consequences associated with antibiotics were highly reduced in the probiotic supplementation group than the control group without probiotics [37].

Probiotics were proven to be effective against acute diarrhoea in children. A predominant study was carried out in Lactobacillus rhamnosus GG and Lactobacillus reuteri which reduces the interval of diarrhoea by one day Preterm infants with low birth weight were prone to necrotizing enterocolitis and administration of probiotic consortia has enhanced the immune response and helped to prevent death in infants [29]. Probiotics were categorized as vaccines by the U.S. Drug and Administration as it prevent necrotizing colitis. The candidate probiotics for necrotizing colitis studied were Lactobacillus rhamnosus GG and Lactobacillus reuteri given in 109 CFU for neonates.

4. Future Perspectives

- Engineered probiotics would become an effective biotherapeutic method as an alternative to current therapeutic strategies as it could become a tailor-made treatment for specific ailments in patients.
- To discover the mechanisms of probiotic strains involved in healing human diseases.
- The probiotics predominantly studied were Lactobacillus and Bifidobacteria, newly discovered probiotics with potential activities that need to be brought into clinical trials so that they can be used as adjuvant therapy in curing diseases.
- The evolution of new probiotics in the market needs to be monitored and further research is required for their application in biomedical fields.

5. Conclusion

The probiotics rich in natural foods and in the intestine as normal microflora of the gut performs a key function in upholding healthy life in an individual. The probiotics and gut microflora regulate the intestinal immune cells and help to alleviate diseases. Further, probiotics metabolism in the intestine produces butyrate, anti-inflammatory cytokines, and anti-microbial compounds. The in vivo studies have also proven that probiotic has prevented diabetes mellitus, obesity, necrotizing colitis

and intestinal bowel syndrome. Thus, probiotics aid in maintaining gut homeostasis and help to lead a healthy long life. The functional foods in the market are growing nowadays due to increased awareness among people on the healthy choice of foods. However, the therapeutic effect of probiotics is strain- specific and so advanced research was required to detect the precise therapeutic effect of each stain against different diseases. New research on the mechanism of probiotics on gut- brain axis would prove the outcome of probiotics on the psychological state of an individual is emerging. Thus, gut microbiota and probiotics are essential to maintain the overall wellness of a person.

6. Conflict of Interest

"The authors declare no conflict of interest."

7. References

1. Azad AK, Sarker M, Li T, Yin J. Probiotic species in the modulation of gut microbiota: An Overview. Biomed Res Int. 2018; 2018:9478630. doi: 10.1155/2018/9478630.
2. Gareau MG, Sherman PM, Walker WA. Probiotics and the gut microbiota in intestinal health and diseases. Nat. Rev. Gastroenterol. Hepatol. 2010; 503-514. doi: 10.1038/nrgastro.2010.117.
3. Butel M-J. Probiotics, gut microbiota and health. Med. Mal. Infect. 2014; 44 (1):1-8. http://doi.org/10.1016/j.medmal.2013.10.002.
4. Martín-Peláez S, Cano-Ibáñez N, Pinto-Callardo M, Amezcua-Prieto C. The impact of probiotics, prebiotics, and synbiotics during pregnancy or lactation on the intestinal nicrobiota of children born by cesarean section: A systematic Review. Nutrients. 2022; 14(2):341. http://doi.org/10.3990/nu14020341.
5. O'Flaherty S, Klaenhamme TR. The role and potential of probiotic bacteria in the gut, and the communication between gut microflora and gut/host. Int. Dairy. J. 2010; 20(4): 262-268. http://doi.org/10.1016/j.idairyj.2009.11.011.
6. Hemarajata P, Versalovic J. Effect of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. Therap. Adv. Gastroenterol. 2013; 6(1): 39-51. doi:10.1177/1756283X12459294.
7. O'Toole WP, & Cooney JC. Probiotic bacteria influence the composition and function of the intestinal microbiota. Perspect Infect Dis. 2008; 2008:175285. doi: 10.1155/2008/175285.
8. Mishra S, Acharya S. A brief overview on probiotics: The health friendly microbes. Biomed. Pharmacol. J. 2021; 14(4). 1869-1880.
9. Savino F, Fornasero S, Ceratto S, De Marco A, Mandras N, Roana J, Tullio V, Amisano G. Probiotics and gut health in infants: A preliminary case-control observational study about early treatment with Lactobacillus reuteri DSM 17938. Clinical Chimica Acta. 2015; 451: 82-87. doi: 10.1016/J.CCA.2015.02.027.
10. Amara AA, Shibl A. Role of Probiotics in health improvement, infection control and disease treatment and management. Saudi Pharm J. 2015; 23(2):107-14. doi: 10.1016/j.jsps.2013.07.001.
11. Cristofori F, Dargenio VN, Dargenio C, Miniello VL, Baronw M, Francavilla R. Anti- inflammatory and Immunomodulatory effects of probiotics in gut inflammation: A door to the body. Front. Immunol. 2021; 26, 12:578386. doi: 10.3389/fimmu.2021.578386.
12. Wong JM, de Souza R, Kendell CW, Emam A, Jenkins DJ. Colonic health: fermentation and short chain fatty acids. J. Clin. Gastroenterol. 2006; 40:235-43. doi: 10.1097/00004836-200603000-0001.
13. De Vadder F, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchampt A, Bäckhed F, Mithieux G. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell. 2014; 16, 156(1-2):84-96. doi: 10.1016/j.cell.2013.12.016.
14. Byndloss MX, Olsan EE, Rivera-Chávez F, et al. Microbiota-activated PPAR-gamma signaling inhibits dysbiotic Enterobacteriaceae expansion. Science. 2017; 11, 357(6351):570-575. doi:10.1126/science.aam9949.
15. Tsai Y-L, Lin T-L, Chang C-J, Wu T-R, Lai W-F, Lu C-C, & Lai H-C. Probiotics, prebiotics and amelioration of diseases. J. Biomed. Sci. 2019; 26(3). doi:10.1186/s12929-018-0493-6.
16. Ma C, Wasti S, Huang S, Zhang Z, Mishra R, Jiang S, You Z, Wu Y, Chang H, Wang Y, Huo D, Li C, Sun Z, Sun Z, Zhang J. The gut microbiome stability is altered by probiotic ingestion and improved by the continuous supplementation of galactooligosaccharide. Gut Microbes, 2020; 1–13. doi:10.1080/19490976.2020.1785252.

17. Yunes RA, Poluektova EU, Vasileva EV, Odorskaya MV, Marsova MV, Kovalev GI, & Danilenko VN. A Multi-strain Potential Probiotic Formulation of GABA-Producing Lactobacillus plantarum 90sk and Bifidobacterium adolescentis 150 with Antidepressant Effects. Probiotics & Antimicro. Prot. 2020; 12: 973–979. https://doi.org/10.1007/s12602-019-09601-1.
18. Lin HV, Frassetto A, Kowalik EJ Jr, Nawrocki AR, Lu MM, Kosinski JR, Hubert JA, Szeto D, Yao X, Forrest G, Marsh DJ. Butyrate and propionate protect against diet-induced obesity and regulate gut hormones via free fatty acid receptor 3-independent mechanisms. PLoS One 2012; 7:e35240. doi: 10.1371/journal pone.0035240.
19. Zhao L, Zhang F, Ding X, Wu G, Lam YY, Wang X, Fu H, Xue X, Lu C, Ma J, Yu L, Xu C, Ren Z, Xu Y, Xu S, Shen H, Zhu X, Shi Y, Shen Q, Dong W, Liu R, Ling Y, Zeng Y, Wang X, Zhang Q, Wang J, Wang L, Wu Y, Zeng B, Wei H, Zhang M, Peng Y, Zhang C. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science. 2018; 359(6380):1151-1156. doi:10.1126/science.aao5774.
20. Long SL, Gahan CGM, Joyce SA. Interactions between gut bacteria and bile in health and disease. Mol. Aspects Med 2017; 56:54-65. doi: 10.1016/j.mam.2017.06.002.
21.de Mello VD, Paananen J, Lindström J, Lankinen MA, Shi L, Kuusisto J, Pihlajamäki J, Auriola S, Lehtonen M, Rolandsson O, Bergdahl IA, Nordin E, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Landberg R, Eriksson JG, Tuomilehto J, Hanhineva K, Uusitupa M. Indolepropionic acid and novel lipid metabolites are associated with a lower risk of type 2 diabetes in the Finnish Diabetes Prevention Study. Sci Rep. 2017; 7:46337. doi: 10.1038/srep46337.
22. Zhai L, Wu J, Lam YY, Kwan HY, Bian Z-X, Wong HLX. Gut-Microbial Metabolites, Probiotics and Their Roles in Type 2 Diabetes. Int. J. Mol. Sci. 2021; 22(23):12846. https://doi.org/10.3390/ijms222312846.
23. Mullish BH, Marchesi JR, McDonald JAK, Pass DA, Masetti G, Michael DR, Plummer S, Jack AA, Davies TS, Hughes TR & Wang D. Probiotics reduce self-reported symptoms of upper respiratory tract infection in overweight and obese adults: should we be considering probiotics during viral pandemics? Gut Microbes 2021; 13:1. DOI: 10.1080/19490976.2021.1900997.
24. Crovesy L, El-Bacha T, & Rosado EL. Modulation of the gut microbiota by probiotics and symbiotics is associated with changes in serum metabolite profile related to a decrease in inflammation and overall benefits to metabolic health: a double-blind randomized controlled clinical trial in women with obesity. Food Funct. 2021; 12(5): 2161–2170. doi:10.1039/d0fo02748k.
25.Odun-Ayo F, Reddy L. Gastrointestinal Microbiota Dysbiosis Associated with SARS-CoV-2
Infection in Colorectal Cancer: The Implication of Probiotics. Gastroenterol. Insights 2022; 13: 35-59. https://doi.org/10.3390/gastroent13010006.
26. Chua KJ, Kwok WC, Aggarwal N, Sun T, & Chang MW. Designer probiotics for the prevention and treatment of human diseases. Curr. Opin. Chem. Biol. 2017; 40, 8–16. doi:10.1016/j.cbpa.2017.04.011.
27. Chen J, Chen X and Ho CL. Recent Development of Probiotic Bifidobacteria for Treating Human Diseases. Front. Bioeng. Biotechnol. 2021;9:770248. doi: 10.3389/fbioe.2021.770248.
28. Hilton E, Kolakowski P, Singer C, & Smith M. Efficacy of Lactobacillus GG as a Diarrheal Preventive in Travelers. J. Travel Med. 1997; 4(1), 41–43. doi:10.1111/j.1708-8305.1997.tb00772.x.
29. Liu Y, Tran DQ, Rhoads JM. Probiotics in Disease Prevention and Treatment. J Clin Pharmacol.2018; 58(10), S164-S179. doi: 10.1002/jcph.1121.
30. Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Immune-Mediated Mechanisms of Action of Probiotics and Synbiotics in Treating Pediatric Intestinal Diseases. Nutrients. 2018; 10(1):42.
https://doi.org/10.3390/nu10010042.
31. Li Q, Cheng F, Xu Q, Su Y, Cai X, Zeng F, & Zhang Y. The role of probiotics in coronavirus disease-19 infection in Wuhan: A retrospective study of 311 severe patients. Int. Immunopharmacol.2021; 95, 107531. doi:10.1016/j.intimp.2021.107531.
32. Baindara P, Chakraborty R, Holliday ZM, Mandal SM, Schrum AG. Oral probiotics in coronavirus disease 2019: connecting the gut–lung axis to viral pathogenesis, inflammation, secondary infection and clinical trials. New Microbes New Infect. 2021; 40:100837.
https://doi.org/10.1016/j.nmni.2021.100837.
33. Penner R, Fedorak R, & Madsen K. Probiotics and nutraceuticals: non-medicinal treatments of gastrointestinal diseases. Curr. Opin. Pharmacol. 2005; 5(6), 596–603. doi:10.1016/j.coph.2005.06.009.
34. Silva NOE, de Brito BB, da Silva FAF, Santos MLC, de Melo FF. Probiotics in inflammatory bowel disease: Does it work? World J Meta-Anal 2020; 8(2): 54-66. DOI: 10.13105/wjma.v8.i2.54.
35. Wullt M, Hagslätt MJ, & Odenholt I. Lactobacillus plantarum 299v for the Treatment of Recurrent Clostridium difficile-associated Diarrhoea: A Double-blind, Placebo-controlled Trial. Scand. J. Infect. Dis. 2003; 35(6-7), 365–367. doi:10.1080/00365540310010985.
36. Barra M, Danino T, Garrido D. Engineered probiotics for detection and treatment of inflammatory intestinal diseases. Front. Bioeng. Biotechnol. 2020; 8:265.https://doi.org/10.3389/fbioe.2020.00265.

37. Compare D, Sgamato C, Nardone OM, Rocco A, Coccoli P, Laurenza C, & Nardone G. Probiotics in gastrointestinal diseases: All that glitters is not gold. Dig. Dis. 2022; 40: 123-132. doi:10.1159/000516023.

38. Yan F, Polk DB. Probiotics: progress toward novel therapies for intestinal diseases. Curr Opin Gastroenterol. 2010; 26(2):95-101. doi: 10.1097/MOG.0b013e328335239a.
39. Zhang T, Ji X, Lu G, & Zhang F. The potential of Akkermansia muciniphila in inflammatory bowel disease. Appl. Microbiol. Biotechnol. 2021; 105(14-15): 5785–5794. doi:10.1007/s00253-021-11453-1.
40. Trivić I, Niseteo T, Jadrešin O, Hojsak I. Use of probiotics in the treatment of functional abdominal pain in children—systematic review and meta-analysis. Eur J Pediatr 2021; 180 (2): 339–351. https://doi.org/10.1007/s00431-020-03809-y.
41. Nguyen T, Brody H, Radaic A, Kapila Y. Probiotics for periodontal health—Current molecular findings. Periodontol 2000. 2021; 87: 254– 267. https://doi.org/10.1111/prd.12382.
42. Oniszczuk A, Oniszczuk T, Gancarz M, Szymańska J. Role of Gut Microbiota, Probiotics and Prebiotics in the Cardiovascular Diseases. Molecules. 2021; 26(4):1172. https://doi.org/10.3390/molecules26041172.
43. Abdi M, Lohrasbi V, Asadi A, Esghaei M, Jazi FM, Rohani M, & Talebi M. Interesting probiotic traits of mother's milk Lactobacillus isolates; from bacteriocin to inflammatory bowel disease improvement. Microb. Pathog. 2021; 158: 104998. doi:10.1016/j.micpath.2021.104998 .
44.Wauters L, Slaets H, De Paepe K, Ceulemans M, Wetzels S, Geboers K, Torth J, Thys W, Dybajlo R, Walgraeve D, Biessen E, Verbeke K, Tack J, de Wiele TV, Hellings N, Vanuytse T. Efficacy and safety of spore-forming probiotics in the treatment of functional dyspepsia: a pilot randomised, double-blind, placebo-controlled trial. Lancet Gastroenterol. Hepatol. 2021; 6(10): 784–792. doi:10.1016/s2468-1253(21)00226-0.
45.Kaźmierczyk-Winciorek M, Nędzi-Góra M, & Słotwińska S. The immunomodulating role of probiotics in the prevention and treatment of oral diseases. Cent. Eur. J. Immunol. 2021; 46(1): 99-104. https://doi.org/10.5114/ceji.2021.104412
46. Lin CW, Chen YT, Ho HH, Hsieh PS, Kuo YW, Lin JH, Liu CR, Huang YF, Chen CW, Hsu CH, Lin WY, Yang SF. Lozenges with probiotic strains enhance oral immune response and health. Oral Dis. 2022; 28 (6): 1723– 1732. https://doi.org/10.1111/odi.13854.
47. Gomes AC, Bueno AA, de Souza RGM, Mota JF. Gut microbiota, probiotics and diabetes. Nutr.J. 2014; 13: 60. https://doi.org/10.1186/1474-2891-13-60.
48. Tonucci BL, Santos KOD, Ferreira CLLF, Ribeiro SMR, Oliveira LL, Martino HSD. Clinical Application of Probiotics in Diabetes Mellitus: Therapeutics and New Perspectives. Crit. Rev. Food Sci. Nutr. 2015; 57(11): 2296-2309. DOI:10.1080/10408398.2014.934438
49.Hendijani F, & Akbari V. Probiotic supplementation for management of cardiovascular risk factors in adults with type II diabetes: A systematic review and meta-analysis. Clin. Nutr. 2018;37(2), 532–541. doi:10.1016/j.clnu.2017.02.015.
50. Scher JU, Ubeda C, Artacho A, Attur M, Isaac S, Reddy SM, Marmon S, Neimann A, Brusca S, Patel T, Manasson J, Pamer EG, Littman DR, Abramson SB. Decreased bacterial diversity characterizes the altered gut microbiota in patients with psoriatic arthritis, resembling dysbiosis in inflammatory bowel disease. Arthiritis Rheumatol. 2015; 67(1): 128-39. doi: 10.1002/art.38892.
51. Goodrich JK, Waters JL, Poole AC, Sutter JL, Koren O, Blekhman R, Beaumont M, Van Treuren W, Knight R, Bell JT, Spector TD, Clark AG, Ley RE. Human genetics shape the gut microbiome. Cell. 2014; 6, 159(4):789-99. doi: 10.1016/j.cell.2014.09.053
52. Beaumont M, Goodrich JK, Jackson MA, Yet I, Davenport ER, Vieira-Silva S, Debelius J, Pallister T, Mangino M, Raes J, Knight R, Clark AG, Ley RE, Spector TD, Bell JT. Heritable components of the human fecal microbiome are associated with visceral fat. Genome Biol. 2016; 26, 17(1):189. doi: 10.1186/s13059-016-1052-7.
53. Menni C, Jackson MA, Pallister T, Steves CJ, Spector TD, Valdes AM. Gut microbiome diversity and high-fibre intake are related to lower long-term weight gain. Int. J. Obes (Lond.) 2017; 41: 1099-105. doi: 10.1038/ijo.2017.66.
54. Gabele E, Dostert K, Hofmann C, et al. DSS induced colitis increases portal LPS levels and enhances hepatic inflammation and fibrogenesis in experimental NASH. J.Hepatol. 2011; 55:1391-9. doi: 10.1016/j.jhep.2011.02.035.
55. Leone V, Chang EB, Devkota S. Diet, microbes, and host genetics: the prefect storm in inflammatory bowel diseases. J. Gastroenterol.. 2013; 48(3):315-321.
56. O' Mahony L, Feeney M, O'halloran S, Murphy L, Kiely B, Fitzgibbon J, Lee G, O'Sullivan G, Shanahan F, Collins JK. Probiotic impact on microbialflora, inflammation and tumour development in IL-10 knockout mice. Aliment. Pharmacol. Ther. 2001; 15 (8): 1219-1225.
57. Rahimi R, Nikfar S, Rahimi F, Elahi B, Derakhshani S, Vafaie M, Abdollahi M.A meta-analysis on the efficacy of probiotics for maintenance of remission and prevention of clinical and endoscopic relapse in Crohn's disease. Dig Dis Sci. 2008; 53(9): 2524- 2531. . doi: 10.1007/s10620-007-0171-0.
58. Mallon P, McKay D, Kirk S, Gardiner K. Probiotics for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD005573. doi:10.1002/14651858.CD005573.pub2.