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Review article: The Role of Probiotic Strains in Cancer Prevention

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Abstract

Probiotics are living microorganisms that confer health benefits when administered in adequate amounts. One main way that probiotics may help fight cancer is by changing bacteria in the gut. Some types of probiotics have been shown to stop the growth of harmful bacteria, make chemicals that stop cancer cells from spreading, and boost the production of short-chain fatty acids that fight inflammation and cell growth. Probiotics may also strengthen the intestinal epithelial barrier, stopping the movement of compounds that can cause cancer and stopping chronic inflammation, which is known to increase the risk of cancer. Probiotics can also change the way your immune system works. For example, some types can make natural killer cells, dendritic cells, and T cells work harder, which is very important for finding and killing cancer. Some probiotics have also been shown to lower oxidative stress and DNA damage. This makes it less likely that genetic changes that can cause cancer will occur. Although more research needs to be done on how probiotics can help prevent cancer, several clinical studies have shown encouraging results, especially when it comes to colorectal cancer. The burgeoning field of probiotics and cancer prevention holds potential for transforming our understanding of the role of the gut microbiome in cancer development and progression. Continued research is essential to optimize the use of probiotics as a complementary approach to cancer prevention and treatment.

Keywords: *Anticarcinogenic, Cancer, Probiotics*

Introduction

Cancer remains one of the leading causes of death worldwide, with the incidence of neoplastic syndrome continuing to rise despite advances in treatment. Researchers are looking for new treatments and prevention approaches to combat this disease [1]. Although genetic factors undoubtedly influence cancer risk, the immune status of the body also has a substantial impact on it. This syndrome is related to probiotics, bacteria, and commensal bacterial flora, both of which are found largely in the digestive tract. Probiotic strains, such as Bifidobacterium and Lactobacillus, are well known for their health benefits and are frequently found in fermented milk products consumed routinely [2]. This article evaluates the numerous studies that have been conducted to date on the association between the gut microbiota and cancer development. The potential use of probiotic strains in the prevention and treatment of cancer has been examined in a growing body of research [3].

Mechanisms of probiotics in cancer prevention:

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1. Modulation of the composition of the gut microbiota

To maintain homeostasis, the healthy gut microbiota must be appropriately balanced and diverse. Dysbiosis, defined as an imbalance between pathogenic and beneficial bacteria in the gut microbiota, can arise. In addition to increasing the risk of colorectal cancer and inducing a persistent inflammatory response, dysbiosis can increase the synthesis of chemicals that cause cancer [4]. In addition, associated with the start of gastrointestinal malignancies is the production of harmful and genotoxic bacterial compounds by the gut microbiota. These substances can induce mutations by interacting with intracellular signaling and binding to specific cell surface receptors. These elements may be related to the capacity of probiotics to actively exclude harmful microbes through resource competition and adherence to the gut mucosa [5]. The distal part of the colon contains few nutrients. Numerous gut microbes suffer as a result of probiotics' competition for growth-promoting substances. In a process known as biofilm development, probiotic strains compete with pathogenic bacteria for the ability to adhere to and colonize biological membranes [6]. A microbiological biofilm is created when bacteria adhere to surfaces and extracellular polymers develop, increasing adhesion and acting as a structural matrix [7]. Biofilms have a variety of proper-

ties, including structure, genetic diversity, complex interactions, together with the existence of things outside of cells, including proteins, phospholipids, polysaccharides, and nucleic acids. The adaptation to the environment results in the secretion of various substances. In a biofilm, the spaces between bacteria are filled with polysaccharide polymer molecules, which are crucial to complete adhesion. Therefore, microorganisms collaborate or polymerize to become more concentrated [8]. Polysaccharides are most abundant in the early stages of biofilm production and aid in the adhesion of the first cells to the surface. In contrast, proteins first accumulate on the cell surface before being released and making contact with the target surface. It often consists of a combination of proteins such as collagen and elastin. One of the main causes of mortality is cancer. Despite recent improvements in tumor therapy, the number of patients affected by neoplastic syndrome is still rising [9, 10] (Fig 1).

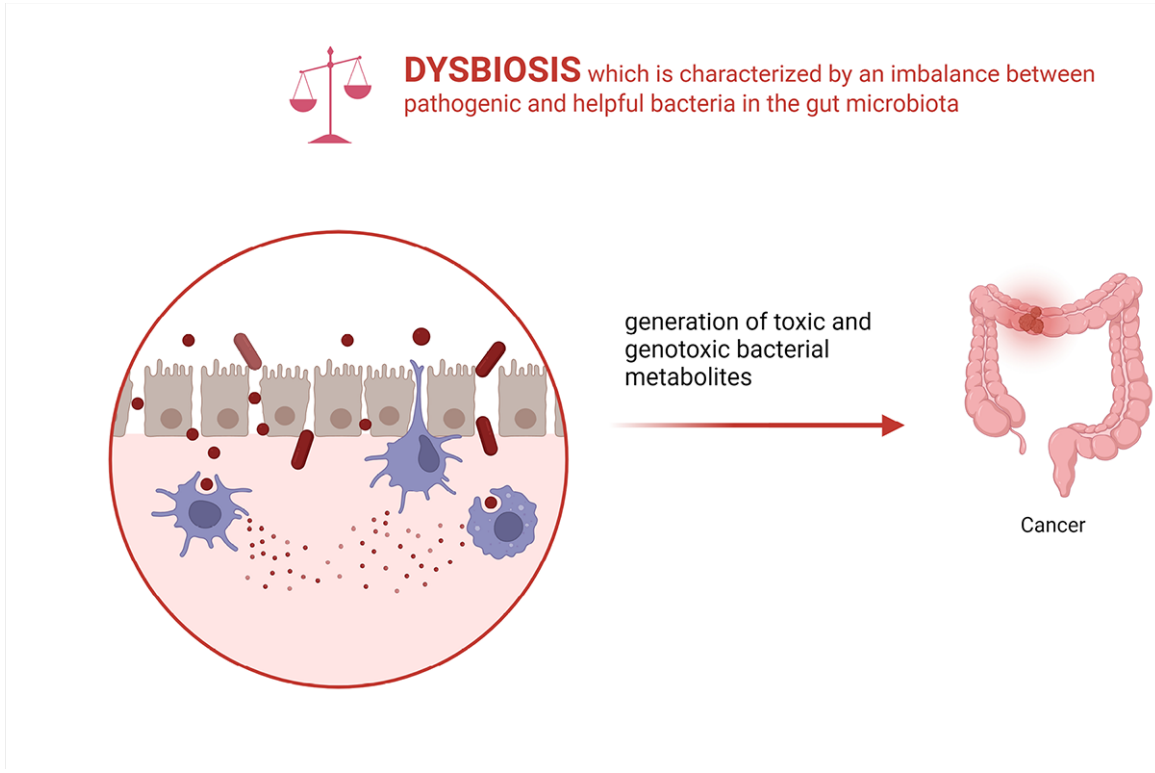

Figure-1: The composition of the gut microbiota can be altered, but a healthy microbiome must be well balanced and diversified. Dysbiosis, which is characterized by an imbalance between pathogenic and helpful bacteria in the gut microbiota. (Created with BioRender.com)

2. Compounds with Anticarcinogenic Activity

Aliphatic organic acids with one to six carbon atoms are known as short-chain fatty acids (SCFAs). Some examples of SCFAs are acetic, propionic, butyric, valeric, and caproic acids. The metabolism of light-living bacteria in the large intestine produces SCFAs as primary and secondary metabolites [11]. The intestinal lumen should contain a total of 60 to 150 mM of SCFAs in a healthy individual, and the large intestine should create 300 to 400 mM of these acids each day [12], [13]. (Acetate), propionate, and (butyrate) are produced in the colon in the following molar ratios: 60:25:15. However, these ratios might alter and fluctuate. Only around 10 mmol of their daily production, which ranges from 300 mM, are excreted. This is due to the fact that (Short-chain fatty acids (SCFAs) enter the colon at a concentration of 6 to 12 mol/cm-2/h and are focused there [14]. Colonocytes also promote the death of cancer cells. Butyric acid regulates the balance of cell division, proliferation, and death in colonocytes. The bacterial population of the gut microbiota naturally creates SCFAs. However, the quantity created might not be enough to stop the growth of colorectal cancer. The daily generation of SCFAs may increase with the use of probiotics [15]. When propionate and butyrate are present in the lumen of the large intestine, they inhibit the growth of pathogens such as Salmonella Typhimurium. Furthermore, it can block invasive genes that cause Salmonella SPI/1 pathogen islands to enter cells in the body. The fact that people with severe salmonellosis are more likely to develop colon cancer in the ascending and transverse areas makes salmonella an important consideration. [16] (Fig 2).

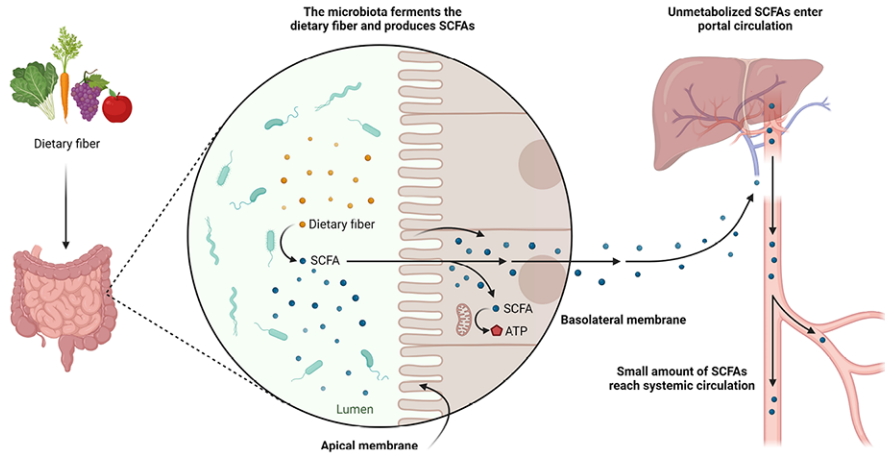

Figure 2: Short-chain fatty acids (SCFAs) function in controlling intestinal and systemic immunity (Created with BioRender.com)

3. Impact of probiotics on mutagenic and cancer-causing variables

In order to help prevent cancer, probiotics may have an impact on extra mutagenic and carcinogenic chemicals. The impact of free radicals and chemicals known to promote cancer is further reduced by their ability to change the way several enzymes involved in cellular detoxification operate. An antioxidant enzyme called glutathione S. transferase (GST) is crucial for neutralizing cancer-causing agents such as reactive oxygen species (ROS) and xenobiosis [17]. GST protects DNA from oxidative damage, which can cause mutations and thus promote cancer growth. Polymorphisms in the GST gene can influence the functionality of the enzymes generated, which can indirectly affect the degree of DNA damage and the chance of developing cancer [18]. Probiotics can increase the activity of this enzyme by using butyrate, which changes the status of histone acetylation and thus increases GST production [19]. Numerous glucuronides can be hydrolyzed by the bacterial enzyme glucuronidase, which can release carcinogens into the colon and has a broad substrate specificity, including PAH (for example, benzopyrene), a substantial risk factor for colorectal cancer [20]. Through a number of methods, including competitive exclusion of pathogenic microflora, the synthesis of antibiotic chemicals that prevent the development of other microorganisms, probiotics control the activity of bacterial enzymes in the colon, as well as the production of acids that could lower the pH [21] (Fig 3).

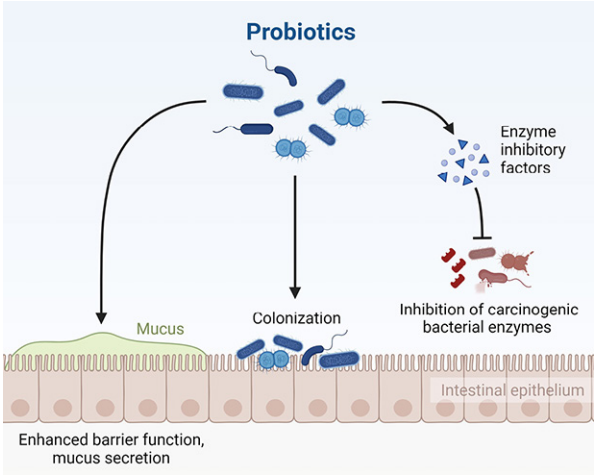

Figure – 3: Probiotics may influence other mutagenic and cancer-causing elements, such as enzymes, helping to prevent cancer. (Created with BioRender.com)

4. Induction of apoptosis in cancer cells

Cancer cell proliferation and apoptosis determine the rate at which it progresses. As cancer progresses, these cells proliferate more than they die. Since apoptosis does not harm neighboring cells or cause inflammation, and because controlling cellular proliferation and apoptosis would destroy cancer cells less aggressively, probiotics with these abilities are of considerable interest [22]. Lactic acid bacteria (LAB), for example, can activate apoptotic signaling pathways via both an internal and an external, death receptor-dependent manner. To test whether Lactobacillus acidophilus and Lactobacillus casei were effective in inhibiting the proliferation of LS513 gastric cell lines, Baldwin et al. used cellular apoptosis. According to research by Hwang et al., probiotics block NF-B and mTOR signaling, leading to death in KATO3 gastric cancer cells [23]. Cousin et al. [24]. argue that bacterial probiotics trigger a series of reactions that involve DNA damage, cell cycle arrest, apoptotic bodies, caspase activation, chromatin condensation, mitochondrial transmembrane potential inactivation, and bacterial probiotics. Because it increases cell death caused by tumor necrosis factor in human chronic myeloid leukemia cells, the probiotic Lactobacillus reuteri has been linked to blood malignancies. (Fig 4).

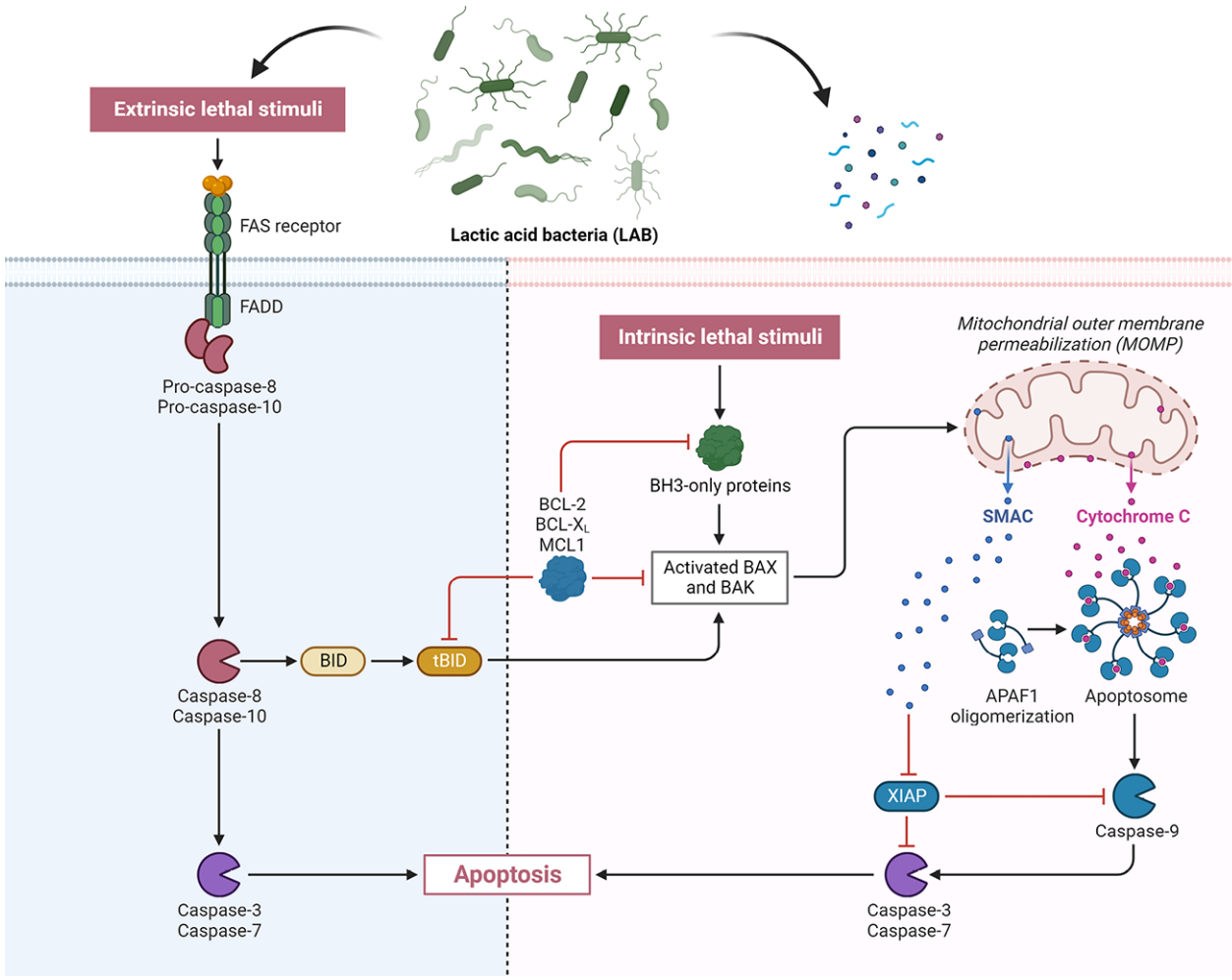

Figure 4: Mechanism of apoptotic induction of cancer cells by TNF-related apoptosis-inducing ligand (Created with BioRender.com)

5. Degradation of Carcinogenic Compounds Present in the Intestinal Lumen

The cell walls of some probiotic bacteria may come into contact with cancer-causing chemicals. The cationic exchange that takes place in some probiotics' cell membranes in bacteria and carcinogens is thought to be connected to this. Probiotic bacteria have cell membranes rich in negatively charged phospholipids and other molecules. These negative charges can attract and bind positively charged ions in the environment (e.g., calcium, magnesium). When probiotics are ingested, they can exchange cations from their cell membranes with those of the intestinal environment. This exchange can enhance the stability and integrity of the bacterial cell membrane. Therefore, feces would eliminate bacteria and cancer-causing substances [25]. Some strains of Bifidobacterium longum, Lactobacillus acidophilus, and Streptococcus salivarius have been shown to bind to and release mutagens such as TrpP2 indole acetate, 5-phenyl-2-amino-l-methylimidazo [4,5-f] pyridine and 5-h pyrido 3-amino-1-methyl [4,3-b] [26], [27]. Lactobacillus bacteria removed dimethyl-nitrosamine the most vigorously, according to in vitro investigations by Rowland and Grasso on the reactions of bacteria from the genera Lactobacillus, Bifidobacterium and Streptococcus [28]. The amine was converted to dimethylamine, which was then transformed into various volatile metabolites. However, Morotomi and Mutai found that Lactobacillus casei effectively detoxified cancer-causing heterocyclic amines, a process that required live bacteria, suggesting that detoxification is likely mediated by bacterial metabolism or enzymatic activity [29]. Because heat-inactivated bacteria lacked this capacity, live bacteria were used in their research. This might suggest that active bacteria create metabolic products or accelerate activities that result in amine detoxification (Fig 5).

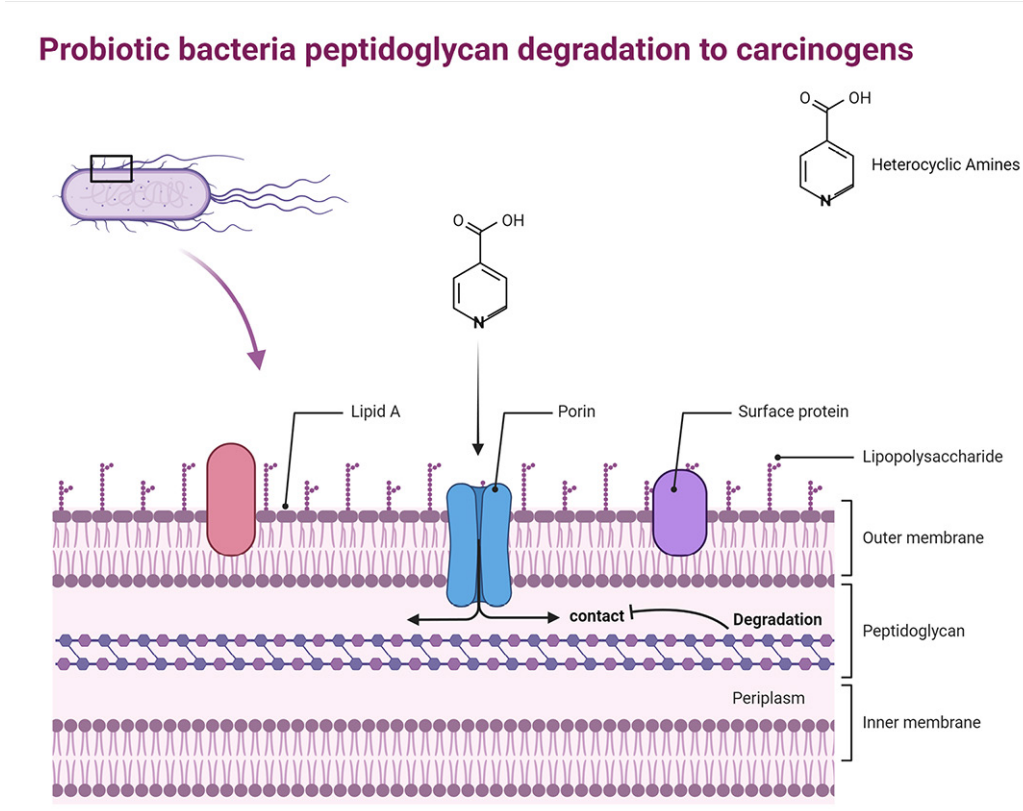

Figure 5: cell walls of probiotic bacteria contacted by carcinogenic substances. (Created with BioRender.com)

6. Immunomodulation

Cancer can weaken the immune system by spreading to the bone marrow. The bone marrow produces blood cells that are essential to fight infection [30]. Some cells of the immune system can recognize cancer cells as abnormal and kill them. The immune system is predominantly activated by bacteria from the intestinal microbiota, which is required for the lymphoid tissues of the immune system to grow [31]. The immunomodulatory effects of the gut microbiota, which includes probiotic microorganisms, are based on three seemingly independent processes: Promoting and maintaining immunological tolerance to environmental antigens (for example, those contained in food and air) [32]. A controlled immune response is induced in response to bacterial and viral diseases. Protecting against allergy and autoimmune reactions. Enhanced immunoglobin synthesis, increased macrophage and lymphocyte activity, and increased interferon production are other markers of probiotic immunological activation [33]. Because of an increase in lysosomal digestive enzymes and free oxygen radicals*, the constituents of the lactic acid bacteria cell wall activate macrophages, which can rapidly destroy germs. Probiotic bacteria may induce immunocompetent intestinal cells to release cytokines [34]. Some probiotics can affect the immune system in a way that kills cancer cells in their early stages by stimulating phagocytes and keeping the immune system on high alert [35]. The adaptive immune response is based on antigen-specific T and B cells, in contrast to the reaction of the innate immune system to pathogen-associated molecular patterns (PAMPs), which are present in many diseases. Immune system proteins, called PAMP-binding recognition pattern receptors (PPRs), initiate the first line of defense against viruses [36]. The Toll-like receptors (TLRs) are the most studied PPRs. All sorts of cells, from immune system cells like B cells and macrophages to nonimmune cells like dendritic cells (DCs) and epithelial cells (fibroblasts and endothelial cells), have transmembrane proteins known as Toll-like receptors (TLRs). Probiotics help reduce inflammatory responses in the intestines by lowering TLR expression, inhibiting NF-B signaling in enterocytes, and perhaps releasing substances that block TNF- from reaching blood mononuclear cells [37]. NK cell function is also influenced by probiotic bacteria. The probiotic Lactobacillus casei subsp. casei can stimulate NK cell function more effectively when dextran is present. The ability of intestinal epithelial cells to secrete IL-15, a cytokine necessary for the function of NK cells, may be related to this feature [38]. The studies show that Lactobacillus casei Shirota increased NK cell activity, which was associated with the generation of IL-12, a cytokine linked to NK cell activity [39]. (Fig 6).

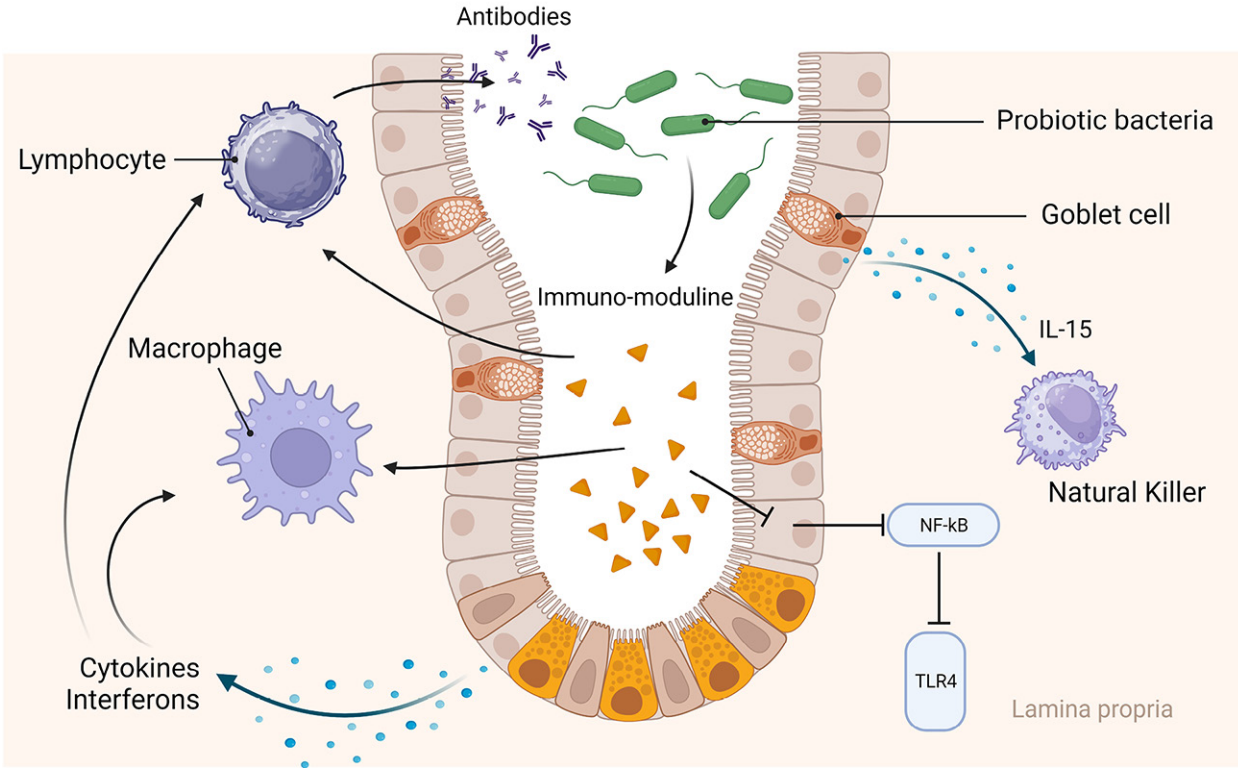

Figure 6: The immunomodulatory effects of probiotics (Created with BioRender.com)

7. Improvement of the intestinal barrier

The composition and function of gut bacteria might affect the way the barrier functions. Probiotics can alter intracolonic pH, mucin formation, cellular junction proteins, and other components of the intestinal barrier to decrease intestinal permeability [40]. The action of bacterial enzymes that create carcinogenic chemicals is inhibited by a lower intracolonic pH (acidity), which in turn reduces the growth of pathogenic and putrefactive bacteria [41], [42]. When differentiating between internal and external pH control, in particular, in order to thrive under acidic conditions, probiotics can control their internal pH. Fast lactic acid production gives them this effect by making their internal pH higher than the ambient pH [43]. We found that inhibition occurred exclusively when the pH of the incubation medium was acidic, not neutral. Due to their ability to control intracellular pH, probiotics can carry out metabolic processes even in environments with low pH. The rapid synthesis of lactic acid by cells makes this feasible by raising the cytoplasmic pH to a level higher than the environment that sustains life, which is alkaline [44]. In addition, molecules resistant to biological membranes are protons and lactic acid molecules. Therefore, the cytoplasm is separated from its living environment by a pH gradient (pH) [45]. Goblet cells use gel-forming glycoproteins as lubricants and a barrier between the body and the outside environment; they build the mucin protective layer. At least nine mucin (MUC) genes have been identified in humans; these include MUC1, MUC2, MUC3, MUC4, and MUC5AC. The small and large intestines use MUC2 as their main mucin to form a gel, and this mucus gel is primarily composed of structure (Fig 7). Throughout the carcinogenic process, mucin and glycosylation production is reduced [46], [47].

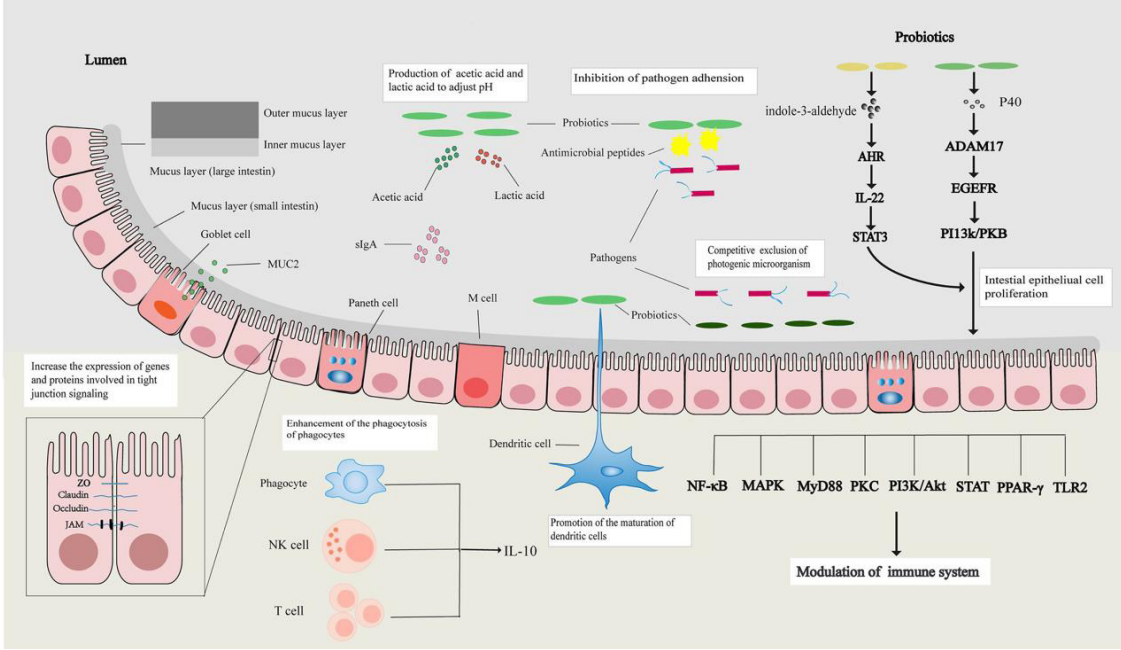

Figure-7: Probiotics regulate the intestinal barrier (47)

Safety Assessment of Probiotics

As a kind of external active bacterium, it is crucial to determine whether probiotics have any harmful side effects. Infections throughout the body, adverse effects in the gastrointestinal tract or skin, antibiotic resistance genes, undesirable effects of probiotic metabolites, and ineffective activation of the immune system are all examples of such problems. Those who are most vulnerable include infants, the elderly, those in hospitals, and those with compromised immune systems due to heredity or disease [48]. The probability of bacteremia in those using probiotics is around 1 in 5.6 million, according to studies that use inaccurate statistical reporting. There is less than one in one million chances of adverse effects when using yeast-based probiotics; for further information, visit here [49], [50]. Most of the patients had severe preexisting diseases, according to another major epidemiological study, and infections caused by Bifidobacteria and Lactobacillus accounted for 0.05% to 0.4% of cases of infective endocarditis and bacteremia [51]. The risk of infection and some characteristics were associated with the kind and number of probiotics taken. Studies showed that compared to the Bifidobacterium, Lactobacillus was the most infectious bacterium [52].

Conclusions

Certification standards for the safety and effectiveness of probiotics are weak. Although certain strains of probiotics have shown promise in improving health, most of them have not yet received scientific confirmation of their health-promoting effects. Relevant advertising for probiotic products almost never mentions the possible risks. Multiple studies exploring the potential protective effects of probiotic therapy against side effects associated with anticancer treatments found that patients' immune systems were better protected when given a combination of probiotic strains. Patients with severely impaired immunological function, especially those with neutropenia, should be approached with caution. The rush for large-scale clinical trials is necessary due to the fact that malignancies have a complex pathophysiology, which means that different people will have different treatment options and different strains will have different effects. Finding the best strains for cancer prevention and treatment requires comprehensive research into the associations between various strains and clinical effects. Finding out how to use probiotics and their products to control patients' flora is the next challenge after identifying a helpful flora for cancer prevention and therapy. However, more research is required to validate the relevance of gut flora as a cancer biomarker, as it seems to react to changes in the pathophysiological environment, according to emerging research.

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Authors' contributions

All authors participated in the design of the review strategy, the analytical strategy for this study, the quality assessment, the interpretation of the data, and the final approval of the research was provided by all authors.

Conflict of Interest: The authors declare no competing interests.

References:

1. Rawla P, Barsouk A. Epidemiology of gastric cancer: global trends, risk factors and prevention. Gastroenterology Review/ Przegląd Gastroenterologiczny. 2019 Nov;14(1):26-38. doi: 10.5114/pg.2018.80001
2. Lin L, Zhang J. Role of intestinal microbiota and metabolites on gut homeostasis and human diseases. BMC immunology. 2017 Dec;18:1-25, doi: org/10.1186/s12865-016-0187-3
3. Sanders ME, Guarner F, Guerrant R, Holt PR, Quigley EM, Sartor RB, Sherman PM, Mayer EA. An update on the use and investigation of probiotics in health and disease. Gut. 2013 May 1;62(5):787-96, doi: 10.1136/gutjnl-2012-302504
4. Jurjus A, Eid A, Al Kattar S, Zeenny MN, Gerges-Geagea A, Haydar H, Hilal A, Oueidat D, Matar M, Tawilah J, Hussein IH. Inflammatory bowel disease, colorectal cancer and type 2 diabetes mellitus: The links. BBA clinical. 2016 Jun 1;5:16-24. doi: 10.1016/j.bbacli.2015.11.002
5. Pickard JM, Zeng MY, Caruso R, Núñez G. Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. Immunological reviews. 2017 Sep;279(1):70-89, doi: 10.1111/imr.12567
6. Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients. 2017 Sep 15;9(9):1021, doi: 10.3390/nu9091021
7. Brindhadevi K, LewisOscar F, Mylonakis E, Shanmugam S, Verma TN, Pugazhendhi A. Biofilm and Quorum sensing mediated pathogenicity in Pseudomonas aeruginosa. Process Biochemistry. 2020 Sep 1;96:49-57, doi: 10.3389/fmicb.2021.676458
8. Wingender J, Neu TR, Flemming HC. What are bacterial extracellular polymeric substances?. Springer Berlin Heidelberg; 1999, doi: 10.1007/978-3-642-60147-7_1
9. Eapen MS, Hansbro PM, Larsson-Callerfelt AK, Jolly MK, Myers S, Sharma P, Jones B, Rahman MA, Markos J, Chia C, Larby J. Chronic obstructive pulmonary disease and lung cancer: underlying pathophysiology and new therapeutic modalities. Drugs. 2018 Nov;78:1717-40, doi: 10.1007/s40265-018-1001-8
10. Fane M, Weeraratna AT. How the ageing microenvironment influences tumour progression. Nature Reviews Cancer. 2020 Feb;20(2):89-106, doi: 10.1038/s41568-019-0222-9
11. Śliżewska K, Markowiak-Kopeć P, Śliżewska W. The role of probiotics in cancer prevention. Cancers. 2020 Dec 23;13(1):20, doi: 10.3390/cancers13010020
12. Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiological reviews. 2001 Jul 1;81(3):1031-64, doi: 10.1152/physrev.2001.81.3.1031
13. Pomare EW, Branch WJ, Cummings JH. Carbohydrate fermentation in the human colon and its relation to acetate concentrations in venous blood. The Journal of clinical investigation. 1985 May 1;75(5):1448-54, doi: 10.1172/JCI111847
14. Hove H, Holtug K, Jeppesen PB, Per Mortensen B. Butyrate absorption and lactate secretion in ulcerative colitis. Diseases of the colon & rectum. 1995 May;38:519-25, DOI: 10.1007/BF02148853
15. Wang G, Yu Y, Wang YZ, Wang JJ, Guan R, Sun Y, Shi F, Gao J, Fu XL. Role of SCFAs in gut microbiome and glycolysis for colorectal cancer therapy. Journal of cellular physiology. 2019 Oct;234(10):17023-49, DOI: 10.1002/jcp.28436
16. Tran TH, Everaert N, Bindelle J. Review on the effects of potential prebiotics on controlling intestinal enteropathogens Salmonella and Escherichia coli in pig production. Journal of animal physiology and animal nutrition. 2018 Feb;102(1):17-32, DOI: 10.1111/jpn.12666
17. Śliżewska K, Markowiak-Kopeć P, Śliżewska W. The role of probiotics in cancer prevention. Cancers. 2020 Dec 23;13(1):20. doi: 10.3390/cancers13010020
18. Klusek J, Głuszek S, Klusek J. GST genes polymorphisms and the risk of colorectal cancer development. Contemporary Oncology/Współczesna Onkologia. 2014 May 20;18(4):219-21. doi: 10.5114/wo.2014.41388
19. Berni Canani R, Di Costanzo M, Leone L. The epigenetic effects of butyrate: potential therapeutic implications for clinical practice. Clinical epigenetics. 2012 Dec;4:1-7. doi: 10.1186/1868-7083-4-4
20. Kim DH, Jin YH. Intestinal bacterial β-glucuronidase activity of patients with colon cancer. Archives of pharmacal research. 2001 Dec;24:564-7. DOI: 10.1007/BF02975166
21. Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Mechanisms of action of probiotics. Advances in nutrition. 2019 Jan 1;10:S49-66. doi: 10.1093/advances/nmy063
22. Wang RA, Li QL, Li ZS, Zheng PJ, Zhang HZ, Huang XF, Chi SM, Yang AG, Cui R. Apoptosis drives cancer cells proliferate and metastasize. Journal of cellular and molecular medicine. 2013 Jan;17(1):205-11. doi: 10.1111/j.1582-4934.2012.01663.x
23. Zhong L, Zhang X, Covasa M. Emerging roles of lactic acid bacteria in protection against colorectal cancer. World journal of gastroenterology: WJG. 2014 Jun 6;20(24):7878. doi: 10.3748/wjg.v20.i24.7878
24. Cousin FJ, Jouan-Lanhouet S, Dimanche-Boitrel MT, Corcos L, Jan G. Milk fermented by Propionibacterium freudenreichii induces apoptosis of HGT-1 human gastric cancer cells. PloS one. 2012 Mar 19;7(3):e31892. DOI: 10.1371/journal.pone.0031892
25. Bahuguna A, Dubey SK. Overview of the Mechanistic Potential of Probiotics and Prebiotics in Cancer Chemoprevention. Molecular Nutrition & Food Research. 2023 Oct;67(19):2300221. DOI: 10.1002/mnfr.202300221
26. Hsieh ML, Chou CC. Mutagenicity and antimutagenic effect of soymilk fermented with lactic acid bacteria and bifidobacteria. International journal of food microbiology. 2006 Aug 15;111(1):43-7. DOI: 10.1016/j.ijfoodmicro.2006.04.034
27. Zacarchenco PB, Massaguer-Roig S. Properties of Streptococcus thermophilus fermented milk containing variable concentrations of Bifidobacterium longum and Lactobacillus acidophilus. Brazilian Journal of Microbiology. 2006;37:338-44. doi.org/10.1590/S1517-83822006000300025
28. Nowak A, Kuberski S, Libudzisz Z. Probiotic lactic acid bacteria detoxify N-nitrosodimethylamine. Food Additives & Contaminants: Part A. 2014 Oct 3;31(10):1678-87. DOI: 10.1080/19440049.2014.943304
29. Bahuguna A, Dubey SK. Overview of the Mechanistic Potential of Probiotics and Prebiotics in Cancer Chemoprevention. Molecular Nutrition & Food Research. 2023 Oct;67(19):2300221. DOI: 10.1002/mnfr.202300221
30. Ahmed AU, Rolle CE, Tyler MA, Han Y, Sengupta S, Wainwright DA, Balyasnikova IV, Ulasov IV, Lesniak MS. Bone marrow mesenchymal stem cells loaded with an oncolytic adenovirus suppress the anti-adenoviral immune response in the cotton rat

model. Molecular Therapy. 2010 Oct 1;18(10):1846-56. DOI: 10.1038/mt.2010.131
31. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell. 2014 Mar 27;157(1):121-41. doi: 10.1016/j.cell.2014.03.011
32. Hemarajata P, Versalovic J. Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. Therapeutic advances in gastroenterology. 2013 Jan;6(1):39-51. DOI: 10.1177/1756283X12459294
33. Youssef M, Ahmed HY, Zongo A, Korin A, Zhan F, Hady E, Umair M, Shahid Riaz Rajoka M, Xiong Y, Li B. Probiotic supplements: their strategies in the therapeutic and prophylactic of human life-threatening diseases. International Journal of Molecular Sciences. 2021 Oct 19;22(20):11290. DOI: 10.3390/ijms222011290
34. Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients. 2017 Sep 15;9(9):1021. doi: 10.3390/nu9091021
35. Mazziotta C, Tognon M, Martini F, Torreggiani E, Rotondo JC. Probiotics mechanism of action on immune cells and beneficial effects on human health. Cells. 2023 Jan 2;12(1):184. DOI: 10.3390/cells12010184
36. Mogensen TH. Pathogen recognition and inflammatory signaling in innate immune defenses. Clinical microbiology reviews. 2009 Apr;22(2):240-73. DOI: 10.1128/CMR.00046-08
37. Mogensen TH. Pathogen recognition and inflammatory signaling in innate immune defenses. Clinical microbiology reviews. 2009 Apr;22(2):240-73. DOI: 10.1128/CMR.00046-08
38. Zhao J, Liao Y, Wei C, Ma Y, Wang F, Chen Y, Zhao B, Ji H, Wang D, Tang D. Potential ability of probiotics in the prevention and treatment of colorectal cancer. Clinical Medicine Insights: Oncology. 2023 Aug;17:11795549231188225. doi: 10.1177/11795549231188225
39. Takeda K, Suzuki T, Shimada SI, Shida K, Nanno M, Okumura K. Interleukin-12 is involved in the enhancement of human natural killer cell activity by Lactobacillus casei Shirota. Clinical & Experimental Immunology. 2006 Oct;146(1):109-15. DOI: 10.1111/j.1365-2249.2006.03165.x
40. Camilleri M. Human intestinal barrier: effects of stressors, diet, prebiotics, and probiotics. Clinical and translational gastroenterology. 2021 Jan 1;12(1):e00308. DOI: 10.14309/ctg.0000000000000308
41. Rafter, J., 2003. Probiotics and colon cancer. Best Practice & Research Clinical Gastroenterology, 17(5), pp.849-859. doi.org/10.1016/S1521-6918(03)00056-8
42. Edyta G, Natalia S, Marlena S, Natalia W, Joanna L, Arent Z, Magdalena S. The in vitro effects of probiotic bacteria on genital pathogens of female dogs. BMC Veterinary Research. 2023 Jul 8;19(1):82. DOI: 10.1186/s12917-023-03635-y
43. Fayol-Messaoudi D, Berger CN, Coconnier-Polter MH, Lievin-Le Moal V, Servin AL. pH-, Lactic acid-, and non-lactic acid-dependent activities of probiotic Lactobacilli against Salmonella enterica Serovar Typhimurium. Applied and environmental microbiology. 2005 Oct;71(10):6008-13. doi: 10.1128/AEM.71.10.6008-6013.2005
44. Corcoran BM, Stanton C, Fitzgerald GF, Ross R. Survival of probiotic lactobacilli in acidic environments is enhanced in the presence of metabolizable sugars. Applied and environmental microbiology. 2005 Jun;71(6):3060-7. DOI: 10.1128/AEM.71.6.3060-3067.2005
45. Guan N, Liu L. Microbial response to acid stress: mechanisms and applications. Applied microbiology and biotechnology. 2020 Jan;104(1):51-65. DOI: 10.1007/s00253-019-10226-1
46. Pelaseyed T, Bergström JH, Gustafsson JK, Ermund A, Birchenough GM, Schütte A, van der Post S, Svensson F, Rodríguez-Piñeiro AM, Nyström EE, Wising C. The mucus and mucins of the goblet cells and enterocytes provide the first defense line of the gastrointestinal tract and interact with the immune system. Immunological reviews. 2014 Jul;260(1):8-20. DOI: 10.1111/imr.12182
47. Gou HZ, Zhang YL, Ren LF, Li ZJ, Zhang L. How do intestinal probiotics restore the intestinal barrier?. Frontiers in microbiology. 2022 Jul 14;13:929346. doi: 10.3389/fmicb.2022.929346.
48. Zheng M, Zhang R, Tian X, Zhou X, Pan X, Wong A. Assessing the risk of probiotic dietary supplements in the context of antibiotic resistance. Frontiers in microbiology. 2017 May 19;8:908. DOI: 10.3389/fmicb.2017.00908
49. Rannikko J, Holmberg V, Karppelin M, Arvola P, Huttunen R, Mattila E, Kerttula N, Puhto T, Tamm Ü, Koivula I, Vuento R. Fungemia and other fungal infections associated with use of Saccharomyces boulardii probiotic supplements. Emerging infectious diseases. 2021 Aug;27(8):2090. DOI: 10.3201/eid2708.210018
50. Miller, L. E., et al. (2021). "Probiotic Use in Patients with Hematological Malignancies: A Review of Risks and Benefits." Current Hematologic Malignancy Reports. doi: 10.3390/ijms22031026
51. Borriello SP, Hammes WP, Holzapfel W, Marteau P, Schrezenmeir J, Vaara M, Valtonen V. Safety of probiotics that contain lactobacilli or bifidobacteria. Clinical infectious diseases. 2003 Mar 15;36(6):775-80. DOI: 10.1086/368080
52. Borriello SP, Hammes WP, Holzapfel W, Marteau P, Schrezenmeir J, Vaara M, Valtonen V. Safety of probiotics that contain lactobacilli or bifidobacteria. Clinical infectious diseases. 2003 Mar 15;36(6):775-80. DOI: 10.1086/368080.