Bifidobacterium: A Promising Coadjuvant For Colorectal Carcinoma

Bifidobakteri: Kolorektal Karsinom İçin Umut Vadedici Bir Koadjuvan

Zeynep Yeğin[1], Seval Cing Yıldırım[2]

[1] *Medical Laboratory Techniques Program, Vocational School of Health Services, Sinop University, Sinop, Türkiye*
[2] *Department of Biology, Faculty of Science and Arts, İnönü University, Malatya, Türkiye*

Yazışma Adresi/Correspondence:
Zeynep YEĞİN
Medical Laboratory Techniques Program, Vocational School of Health Services, Sinop University, Sinop, Türkiye
E-posta/E-mail: zyegin1@gmail.com; zyegin@sinop.edu.tr

Geliş Tarihi/Received: 01.07.2024 Kabul Tarihi/Accepted:14.11.2024
Zeynep YEĞİN https://orcid.org/ 0000-0003-4637-0253 zyegin1@gmail.com; zyegin@sinop.edu.tr
Seval CİNG YILDIRIM https://orcid.org/ 0000-0001-7163-9512 seval.cing@inonu.edu.tr
Hippocrates Medical Journal / Hippocrates Med J, 2024, 4(3): 156-160 DOI: 10.58961/hmj.1508458

Abstract

Colorectal cancer prevalence has rapidly increased due to dietary changes to Western style. The regulation of the gut microbiota may serve as a promising approach in colorectal cancer management. The dysbiosis of the gut microbiome affects cancer development because of its roles in inflammation and genotoxicity. Cell culture studies, animal studies, and some novel clinical studies refer to the therapeutic potential of Bifidobacterium.

Keywords Bifidobacterium, Colorectal cancer, Apoptosis, Probiotics

Özet

Batı tarzı beslenme değişiklikleri nedeniyle kolorektal kanser prevalansı hızla artış göstermiştir. Bağırsak mikrobiyotasının düzenlenmesi kolorektal kanser tedavisinde ümit verici bir yaklaşım olarak hizmet edebilir. Bağırsak mikrobiyomunun disbiyozu, inflamasyon ve genotoksisitedeki rollerinden dolayı kanser gelişimini etkilemektedir. Hücre kültürü çalışmaları, hayvan çalışmaları ve bazı yeni klinik çalışmalar Bifidobakterinin terapötik potansiyeline işaret etmektedir.

Anahtar Kelimeler Bifidobakteri, Kolorektal kanser, Apoptozis, Probiyotik

Dear Editor;

Colorectal cancer (CRC) prevalence has rapidly increased due to dietary changes to Western style and consumption of low carbohydrate, high protein, low fiber, and high saturated fat (1-3). Despite the improvements in surgery and chemotherapeutic agents, prevention and treatment of CRC remains a challenge. It is the fourth leading cause of cancer death worldwide (4). The regulation of the gut microbiota may serve as a promising approach in CRC management since various studies have shown that microbiota imbalances are closely associated with CRC occurrence (5). The dysbiosis of the gut microbiome affects cancer development because of its roles in inflammation and genotoxicity (6).

Probiotics and *Bifidobacterium*

According to the FAO/WHO definition, probiotics are live microorganisms that provide health benefits to the host when administered in adequate amounts (7). They can modify the host's microbiota and thus exert beneficial health effects (5). Most commercially available probiotics belong to the genera *Lactobacillus* and *Bifidobacterium* spp. and they are reported to play a role in regulating apoptosis and proliferation (2, 4, 8). Besides with the modulation of the intestinal microbiota, beneficial effects of probiotics also include the production of anti-tumorigenic or anti-mutagenic compounds and improvement of the host's immune response (3). Probiotics were associated with decreased levels of pro-inflammatory cytokines and better clinical outcomes in patients with colorectal cancer (9). Bifidobacteria are widely distributed in the gut of social animals whose offspring are dependent on parental care (10). Human-Residential Bifidobacteria (HRB) may affect host health via their metabolic and physiological activities. For example, adult-type HRB facilitate the metabolism of complex carbohydrates which can not be digested by human intestinal enzymes or by other gut bacteria. On the other hand, infant-type HRB play significant functional roles in physiological activities such as the production of folate and indole-3-lactic acid and the degradation of food-derived opioid peptides (11). Coherently with these metabolic activities, heat-inactivated *Bifidobacterium bifidum* MIMBb75 (SYN-HI-001) was shown to substantially alleviate irritable bowel syndrome and its symptoms (12). A further study evaluated the effects of probiotics (*Bifidobacterium lactis* UBBLa-70) or symbiotics (*Bifidobacterium lactis* UBBLa-70 and fructooligosaccharide) on body weight and serum metabolite profile in women with obesity. Both probiotics and symbiotics promoted changes in metabolites implying a decrease in inflammation (13). Though it is not the scope of this paper, *Bifidobacterium* supplementation also seems to have a role in the management of several psychiatric pathophysiologies, possibly due to the inflammation link and this is an innovative topic of recent years. For instance, probiotic supplementation (*Lactobacillus rhamnosus* strain GG and *Bifidobacterium animalis* subsp. *lactis* strain Bb12) for 24 weeks was found to be associated with a lower rate of rehospitalization in patients with mania (14). *Bifidobacterium* spp. are Gram-positive, non-motile, non-spore, Y- or V-shaped, anaerobic bacteria and the dominant member of the early-life gut microbiome (2, 6). Lactic and acetic acids, the main metabolism products of *Bifidobacterium* spp. increase the acidity in the intestine and thus inhibit the growth and attachment of harmful microorganisms to epithelial cells (2). The specific gut microbiota including *Fusobacterium nucleatum*, *Bacteroides fragilis*, and *Escherichia coli* is associated with adenoma and carcinoma development due to DNA damage and impaired immune and gut barrier functions (6). Of these members, *Fusobacterium nucleatum* received widespread attention since it is one of the highly enriched bacteria in both stools and CRC tissues of the patients. *F. nucleatum* is accepted as a mutualist, infectious agent and oncogenic microorganism. It invades the mucosa with adhesion and virulence factors, interacts with the host immune system and thus promotes the occurrence of CRC (15-17). *F. nucleatum* orchestrates a molecular network of the Toll-like receptor, microRNAs, and autophagy to manage colorectal cancer chemoresistance (18). Immune checkpoint blockade therapy with anti-PD-1 monoclonal antibody (mAb) is a treatment for CRC although some patients remain unresponsive to PD-1 blockade. It was found that the patients with metastatic CRC who failed to respond to immunotherapy had a greater abundance of *Fusobacterium nucleatum* and increased succinic acid. Interestingly, treatment with the antibiotic metronidazole reduced intestinal *F. nucleatum* abundance and serum succinic acid levels and resensitized tumors to immunotherapy in vivo (19).These data prove the significance of *F. nucleatum* control both to prevent CRC and better manage therapy regimens. It seems that *Bifidobacterium also* has a promising potential to inhibit this oncobacterium. A recent study evaluated the potential effect of a novel probiotic formula (*B. adolescentis*, *B. longum*, and *B. bifidum*) to reduce CRC-associated bacteria and thus modulate CRC risk. The three individual bifidobacteria significantly

inhibited the growth of *F. nucleatum* (24~65% inhibition) while the greatest inhibitory effect (70% inhibition) was obtained with the combination of the three (20).

Therapeutic potential of *Bifidobacterium* for colorectal carcinom

Cell culture studies

Various studies have proven the therapeutic potential of *Bifidobacterium* for CRC. The butanol extract of *Bifidobacterium adolescentis* SPM0212 dose-dependently (at 200 µg/mL) inhibited the growth of Caco-2, HT-29, and SW480 cells by 70%, 30%, and 40%, respectively (21). Moreover, similar findings were reported in another study and it was also shown that *Bifidobacterium adolescentis* SPM0212 was able to inhibit harmful fecal enzymes (1). It was demonstrated that cell-free supernatants (CFS) of *B. bifidum* inhibited colon cancer cells (SW742) (2). Cell-free supernatants of five species of Bifidobacteria (*B. adolescentis*, *B. animalis subsp. lactis*, *B. animalis subsp. animalis*, *B. bifidum*, and *B. angulatum*) reduced the survival rates of colon cancer cell lines (Caco-2 and HT-29). The highest percentage of apoptosis was achieved by *B. bifidum*, followed by two subspecies of *B. animalis* and *lactis* in the Caco-2 cells (4).

Animal studies

In CRC rat model, *Bifidobacterium infantis* was shown to attenuate chemotherapy-induced intestinal mucositis by decreasing Th1 and Th17 response and increasing $CD4^+$ $CD25^+$ $Foxp3^+$ Tregs response (22). Treatment with microencapsulated *Bifidobacterium bifidum* and *Lactobacillus gasseri* individually or in combination with the flavonoid quercetin inhibited CRC development in a CRC mouse model (3). In MC38 colon carcinoma-bearing mice, either of two *Bifidobacterium breve* strains (JCM92 and Bb03) reduced tumor growth. One strain (JCM92) also boosted the efficiency of therapeutics via oxaliplatin and programmed cell death protein-1 (PD-1) blockade (6). In CRC mice model, probiotic powder combined of *Bifidobacterium* and *Lactobacillus* exerted anti-CRC effects. This powder increased the abundance of *Bifidobacterium animalis*, reduced the abundance of *Clostridium cocleatum*, inhibited Treg cell activity, and upregulated pro-apoptotic protein BAX in tumor tissues (5). Sometimes, the use of synbiotics, a combination of probiotics and prebiotics, maybe a better strategy for the prevention of colorectal cancer. It was demonstrated in the study by Lin et al. (8) who administered the combination of germinated brown rice (GBR) and *L. acidophilus* and/or *B. animalis* subsp. *lactis* in rats. This combination resulted in the inhibition of preneoplastic lesions and regulated antioxidative enzyme and apoptosis-related proteins in the colon. Probiotics (*Bifidobacterium longum*) and lycopene supplementation in CRC mice model resulted in significant chemopreventive effect via the modulation of insulin/insulin-like growth factor (IGF) system (23).

Clinical studies

Intratumour *Bifidobacterium* spp. were detected in 30% of CRC patients but not in the vast majority of the remainder and this was associated with the size of the signet ring cells, indicating a distinct tumour characteristic (24). In a clinical trial conducted with CRC patients, the effects of six viable microorganisms of *Lactobacillus* and *Bifidobacteria* strains for six months were investigated for clinical outcomes and inflammatory cytokines. A significant decline in the level of pro-inflammatory cytokines (TNF-α, IL-6, IL-10, IL-12, IL-17A, IL-17C and IL-22) was reported in CRC patients receiving probiotics compared to pre-treatment level. This study also implied that probiotics administered 4 weeks after surgery for CRC were safe since they did not result in diarrhea and also influenced pro-inflammatory cytokine level as a health benefit (25). An other clinical study reported that a probiotic containing eight bacterial cultures including *Bifidobacterium* species significantly decreased postoperative complications while all complications were more frequent in untreated CRC patients (26).

Conclusion

Bifidobacterium seems to have potential to serve as a chemopreventive agent for colorectal cancer. The limitations of the summarized studies include that most of the cell culture studies lack of molecular mechanism investigations which need to be improved. Afterwards, both animal and especially clinical studies must be accelerated deeply with a focus on molecular mechanisms. In sum, the role of *Bifidobacterium* species in the molecular mechanisms, microflora balance, and biochemical parameters must be searched more comprehensively. The summarized studies indicate that *Bifidobacterium* seems as a promising coadjuvant therapeutic agent for tailor-made approaches in the prevention and management of colorectal cancer.

Conflict of interest: The authors report no conflict of interest.

REFERENCES

1.Kim Y, Lee D, Kim D, Cho J, Yang J, Chung M, et al. Inhibition of proliferation in colon cancer cell lines and harmful enzyme activity of colon bacteria by Bifidobacterium adolescentis SPM0212. Arch Pharm Res. 2008;31(4):468–473

2. Bahmani S, Azarpira N, Moazamian E. Anti-colon cancer activity of Bifidobacterium metabolites on colon cancer cell line SW742. Turk J Gastroenterol. 2019;30(9):835–842.

3. Benito I, Encío IJ, Milagro FI, Alfaro M, Martínez-Peñuela A, Barajas M, et al. Microencapsulated Bifidobacterium bifidum and Lactobacillus gasseri in Combination with Quercetin Inhibit Colorectal Cancer Development in ApcMin/+ Mice. Int J Mol Sci. 2021;22(9):4906.

4. Faghfoori Z, Faghfoori MH, Saber A, Izadi A, Yari Khosroushahi A. Anticancer effects of bifidobacteria on colon cancer cell lines. Cancer Cell Int. 2021;21(1):258.

5. Yang X, Cao Q, Ma B, Xia Y, Liu M, Tian J, et al. Probiotic powder ameliorates colorectal cancer by regulating Bifidobacterium animalis, Clostridium cocleatum, and immune cell composition. PloS One. 2023;18(3): e0277155.

6. Yoon Y, Kim G, Jeon BN, Fang S, Park H. Bifidobacterium Strain-Specific Enhances the Efficacy of Cancer Therapeutics in Tumor-Bearing Mice. Cancers (Basel). 2021;13(5):957.

7. FAO/WHO. Probiotics in food. Health and nutritional properties and guidelines for evaluation. FAO Food and Nutrition Paper. 2006;85.

8. Lin PY, Li SC, Lin HP, Shih CK. Germinated brown rice combined with Lactobacillus acidophilus and Bifidobacterium animalis subsp. lactis inhibits colorectal carcinogenesis in rats. Food Sci Nutr. 2018;7(1):216–224.

9. Mohammed C, Fuego JP, Garcia KV, Jamil H, Rajesh RY, Escobar AS, et al. A Mini Literature Review of Probiotics: Transforming Gastrointestinal Health Through EvidenceBased Insights. Cureus. 2024;16(3):e57055.

10. Turroni F, van Sinderen D, Ventura M. Genomics and ecological overview of the genus Bifidobacterium. Int J Food Microbiol. 2011;149(1):37-44.

11. Wong CB, Odamaki T, Xiao JZ. Insights into the reason of Human-Residential Bifidobacteria (HRB) being the natural inhabitants of the human gut and their potential healthpromoting benefits. FEMS Microbiol Rev. 2020;44(3):369- 385.

12. Andresen V, Gschossmann J, Layer P. Heat-inactivated Bifidobacterium bifidum MIMBb75 (SYN-HI-001) in the treatment of irritable bowel syndrome: a multicentre, randomised, double-blind, placebo-controlled clinical trial. Lancet Gastroenterol Hepatol. 2020;5(7):658-666.

13. 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.

14. Dickerson F, Adamos M, Katsafanas E, Khushalani S, Origoni A, Savage C, et al. Adjunctive probiotic microorganisms to prevent rehospitalization in patients with acute mania: A randomized controlled trial. Bipolar Disord. 2018;20(7):614-621.

15. Brennan CA, Garrett WS. Fusobacterium nucleatum - symbiont, opportunist and oncobacterium. Nat Rev Microbiol. 2019;17(3):156-166.

16. Luo K, Zhang Y, Xv C, Ji J, Lou G, Guo X, et al. Fusobacterium nucleatum, the communication with colorectal cancer. Biomed Pharmacother. 2019;116:108988.

17. Yang Z, Ji G. Fusobacterium nucleatum-positive colorectal cancer. Oncol Lett. 2019;18(2):975-982.

18. Yu T, Guo F, Yu Y, Sun T, Ma D, Han J, et al. Fusobacterium nucleatum Promotes Chemoresistance to Colorectal Cancer by Modulating Autophagy. Cell. 2017;170(3):548-563.e16.

19. Jiang SS, Xie YL, Xiao XY, Kang ZR, Lin XL, Zhang L, et al. Fusobacterium nucleatum-derived succinic acid induces tumor resistance to immunotherapy in colorectal cancer. Cell Host Microbe. 2023;31(5):781-797.e9.

20. Liang JQ, Zeng Y, Lau EYT, Sun Y, Huang Y, Zhou T, et al. A Probiotic Formula for Modulation of Colorectal Cancer Risk via Reducing CRC-Associated Bacteria. Cells. 2023;12(9):1244.

21. Lee DK, Jang S, Kim MJ, Kim JH, Chung MJ, Kim KJ, et al. Anti-proliferative effects of Bifidobacterium adolescentis SPM0212 extract on human colon cancer cell lines. BMC Cancer. 2008;8:310.

22. Mi H, Dong Y, Zhang B, Wang H, Peter CCK, Gao P, et al. Bifidobacterium Infantis Ameliorates ChemotherapyInduced Intestinal Mucositis Via Regulating T Cell Immunity in Colorectal Cancer Rats. Cell Physiol Biochem. 2017;42(6):2330–2341.

23. Valadez-Bustos N, Escamilla-Silva EM, García-Vázquez FJ, Gallegos-Corona MA, Amaya-Llano SL, Ramos-Gómez M. Oral Administration of Microencapsulated B. Longum BAA999 and Lycopene Modulates IGF-1/IGF-1R/IGFBP3 Protein Expressions in a Colorectal Murine Model. Int J Mol Sci. 2019;20(17):4275.

24. Kosumi K, Hamada T, Koh H, Borowsky J, Bullman S, Twombly TS, et al. The Amount of Bifidobacterium Genus in Colorectal Carcinoma Tissue in Relation to Tumor Characteristics and Clinical Outcome. Am J Pathol. 2018;188(12):2839–2852.

25. Zaharuddin L, Mokhtar NM, Muhammad Nawawi KN, Raja Ali RA. A randomized double-blind placebo-controlled trial of probiotics in post-surgical colorectal cancer. BMC Gastroenterol. 2019;19(1):131.

26. Bajramagic S, Hodzic E, Mulabdic A, Holjan S, Smajlovic SV, Rovcanin A. Usage of Probiotics and its Clinical Significance at Surgically Treated Patients Sufferig from Colorectal Carcinoma. Med Arch. 2019;73(5):316–320.