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The Role of the Gut Microbiome in Gastrointestinal Cancers

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Abstract

Cancer is a deadly malignancy of high clinical importance and remains one of the leading causes of death worldwide. Current conventional treatments for cancer include surgery, anticancer drugs, and radiation therapy. Resection surgery is the main treatment method but has a high recurrence rate. The human gut microbiome plays a crucial role in regulating various host processes, such as metabolism, inflammation, and immune and cellular responses. Moreover, it is becoming increasingly clear that the microbiome may also impact cancer development. The gut microbiota is a key component of the human microbial community, characterized by the highest number of bacteria and the greatest diversity compared to microbiomes in other parts of the body. The gastrointestinal tract (GI) extends through our natural environment, providing a suitable habitat and abundant nutrition for the microbiota. Gastrointestinal cancer encompasses a complex group of disorders and heterogeneous diseases. Both environmental and genetic risk factors can convert normal tissue into precancerous lesions, leading to the development of malignant cells. Despite advances in cancer treatment, resistance to chemotherapy and radiation therapy continues to pose a significant challenge. This is particularly relevant in light of new diagnostic and therapeutic methods for gastrointestinal tumors, which increasingly involve various strains of probiotics used as dietary supplements. As proposed treatments, probiotics may significantly benefit cancer prevention and therapy. They can enhance the metabolism of the gut microbiota during chemotherapy, potentially reducing its toxic side effects. Consequently, the potential use of probiotics as an anticancer therapy has received considerable attention in recent years. Conclusion: Current review article concentrates on the ability of probiotics to inhibit antibiotic-resistant Helicobacter pylori. However, there is a lack of studies exploring inhibitory resistance in other contexts. Despite these gaps, probiotics show considerable promise in cancer treatment and in enhancing tumor immunity.

Keywords: *gastrointestinal (GI) tract, antitumor activity, gut microbiota, microbiome, gastro-intestinal tumors*

Introduction

Cancer is the second leading cause of death worldwide. Therefore, there is a critical need for the development of drugs and treatments to improve the survival rates of those affected by cancer. During the past century, cancer incidence and mortality rates have gradually increased, particularly in developing countries, with new cases rising from 18.1 million in 2018 to 10 million (or almost one in six) in 2020 (1,2).

Anticancer drugs often have severe adverse reactions, which can include side effects such as vomiting and a decrease in white blood cell counts. Additionally, these treatments can be insufficient on their own to achieve a cure. Chemotherapy drugs and hormones target cancer cells but can also damage healthy cells. Over time, the body may develop drug resistance, which reduces or eliminates the effectiveness of treatment. Furthermore, these cytotoxic drugs pose significant risks to human health, with side effects that can be more severe than the malignancies themselves. Radiation therapy may serve as an adjunct to surgery and anticancer drugs, but it often requires an extended treatment timeline. Therefore, there is an urgent need for new treatments that have fewer side effects (1,3)

Gastrointestinal (GI) cancers, which include stomach, liver, esophageal, pancreatic, and colorectal cancers (CRC), account for more than a quarter of all cancer cases and their prevalence continues to increase. Prepandemic data for 2018 estimated 5 million new cases of GI cancer, resulting in more than 3 million associated deaths(4–6). Cancers of the gastrointestinal tract (GI) account for 26% of the global cancer burden and 35% of cancer-related deaths.

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Recent advances in immunotherapy have led to remarkable survival rates for certain types of cancers, such as melanoma and non-small cell lung cancer, but progress has been slower for GI cancers(7). Gastric cancer is also prevalent and highly dangerous. In 2018, it was the fifth most commonly diagnosed cancer and represented 8.2% of all cancer-related deaths, making it the third leading cause of cancer mortality after lung cancer (18.4%) and colorectal cancer (9.2%). The side effects of current treatments, along with their time-consuming and expensive nature, highlight the urgent need for new methods and solutions to prevent cancer(8,9).

The cases discussed highlight the importance of exploring alternative solutions for treating and preventing malignancies and various types of cancer. A promising approach involves the use of microbial products. The human digestive system hosts a diverse community of more than 100 trillion microorganisms, collectively known as the intestinal microbiota. Probiotics, a subset of these microorganisms, can provide health benefits when consumed in appropriate amounts. Lactobacillus bacteria are among the most commonly used probiotics. Research has shown that probiotics, including Lactobacilli, can inhibit the growth of many types of pathological cells. Beneficial bacteria enhance the host immune response, provide preventive effects against cancer, and help inhibit the growth of cancerous tumors (10,11).

The 'microbiome' and cancer' are among the most prominent topics in the modern age today. All human surfaces and cavities that connect to the outside environment are inhabited by a diverse ecosystem of microorganisms, including bacteria, viruses, protozoa, fungi, and archaea. This microbial population is complex, individual, and variable, with its composition influenced by the host's genetics, dietary habits, lifestyle, and microbial exposure at birth. It is estimated that the human body contains approximately ten times more bacteria than human cells, representing between 500 and 1,000 different species of microorganisms. The scientific community defines the 'microbiota' as the totality of microbial organisms present in specific environments, while 'microbiome' refers to the genetic information contained within the microbiota. The microbiome exhibits significant variability in its composition, both between different individuals and within the same individual at various anatomical sites and tissues(12–14).

These individual and interindividual differences are believed to contribute to many diseases and health issues, particularly in gastrointestinal (GI) cancers, making them critical to diagnosis and treatment. While cancer is recognized as a disease caused by genetic factors and environmental influences, studies suggest that microorganisms may be involved in approximately 20% of all cancers in humans. Cancers of the digestive system account for almost one-third of cancer-related deaths. At least 15% to 20% of cancers are triggered by infectious agents, while 20% to 30% are linked to tobacco use, and 30% to 35% are associated with diet, physical inactivity, and/or energy balance disorders, such as obesity. Targeted therapies have been shown to be effective for certain types of cancers, but many cancers continue to be treated with traditional chemotherapy, which can vary in efficacy and side effects. Cancer prevention remains a primary focus, and a deeper understanding of the interactions between gut microbiota, barrier function, and inflammatory responses is essential for identify new targets in cancer therapy (15–17)

The human microbiota consists of 40 trillion microorganisms, consisting of about 3,000 species, including bacteria, fungi, and viruses. This complex community exhibits variable richness among different microbes and diverse compositions among individuals, playing a crucial role in maintaining systemic homeostasis and functional stability. Most of these microorganisms, more than 97%, are found in the gastrointestinal tract, particularly in the colon, where they are called the gut microbiota. Extensive research has confirmed that the gut microbiota mediates a wide range of physiological functions, including the development of the immune system and the synthesis of certain nutrients(1). In this review, we summarize the current understanding of the relationship between the gut microbiome and cancer. We explore how the gut microbiome influences cancer development and investigate the potential to use microbial agents or their products as therapeutic options.

Microbiome and Oral Cancer

Oral cancer is a prevalent malignancy, with approximately 177,757 deaths and 377,713 new cases diagnosed globally each year. The highest incidence rates are found in South Central Asia and India. The causes of oral cancer are multifactorial, with significant contributing factors including diet habits, infections, radiation exposure, human papillomavirus (HPV), smoking, alcohol consumption, and genetics. Consequently, reducing alcohol intake and smoking is crucial to reducing the risk of oral cancer. This type of cancer falls under the category of head and neck squamous cell carcinoma (HNSCC), which is the sixth leading cause of cancer-related deaths worldwide(18,19).

Oral cancer occurs primarily in the buccal mucosa, tongue, mouth floor, and lips. Heavy alcohol consumption and tobacco use are recognized as key risk factors. Approximately 90% of cases of oral cancer are classified as oral squamous cell carcinoma (OSCC), which is not only highly prevalent but also the most aggressive and lethal form of oral cancer. Due to the lack of effective treatments, the mortality rate for oral cancer continues to increase. Even among patients who receive treatment, the recurrence of secondary oral cancer can lead to poor survival rates of only 50-60%(18–20).

Probiotics, the friendly microflora in our bodies, contribute to the production of useful metabolites with positive effects on the immune system against various diseases, such as cancer. Lactobacillus plantarum is one of the most important bacteria that live commensally in the human oral system. In the current study, the impacts of L. plantarum on the maintenance of oral system health were investigated, and the molecular mechanisms of inhibition of oral cancer KB cells mediated by L. plantarum were evaluated using real-time polymerase chain reaction (PCR) and FACS flow cytometry analyzes. The findings showed that L. plantarum is effective in the signal transduction of oral cancer cells through up-regulation and down-regulation of the PTEN and MAPK pathways, respectively. Conclusions Based on the biological effects of the candidate oral pro-

biotic candidate bacterium L. plantarum on the functional expression of the PTEN and MAPK pathways, this microorganism plays a key role in controlling the development of unwanted cancer in the oral system. Taken all, L. plantarum is proposed as a potential candidate for probiotics cancer therapy (21).

A new probiotic, Lactobacillus salivarius REN (L. salivarius REN), was isolated from centenarians in Bama, China, and demonstrated strong antigenotoxicity in initial assays. To further investigate anticancer activity, we used a 4-nitroquinoline 1-oxide (4NQO) induced oral cancer model for in vivo studies. The results revealed that oral administration of L. salivarius REN, or its secretions, effectively suppressed 4NQO-induced oral carcinogenesis in the initial and post initial stages, with inhibition observed dose-dependently. In particular, a significant reduction in the incidence of neoplasms was found (from 65% to 0%) in rats receiving a high dose of L. salivarius REN (5×1010 CFU/kg body weight per day). In vivo evidence indicated that probiotics inhibited 4NQO-induced oral cancer by protecting DNA from oxidative damage and down-regulating COX-2 expression. Treatment with L. salivarius REN significantly decreased proliferating cell nuclear antigen (PCNA) expression and induced apoptosis in a dose-dependent manner. These findings suggest that probiotics may serve as potential agents for the prevention of oral cancer. This study is the first to report on the inhibitory effect of this probiotic on oral carcinogenesis(22).

This study investigates the inhibitory mechanism of Lactobacillus Salivarius Ren in oral cancer cells (TCA-8113). We assessed the effects of L. Salivarius Ren on cell proliferation, apoptosis, and COX-2 expression. The results indicated that L. Salivarius Ren suppressed cell proliferation, increased apoptosis, and significantly reduced COX-2 mRNA levels and protein expression. These findings suggest that L. Salivarius Ren exhibits a pronounced antitumor effect, potentially, it works by inhibiting COX-2, which may lead to reduced cell proliferation and increased apoptosis (23).

A study identified Lactiplantibacillus plantarum Y33 as the most promising probiotic strain among those tested. This strain showed a high probiotic score, indicating its potential benefits for human health. Furthermore, the extracted bacteriocin from Y33, classified as a protein, showed significant cytotoxicity against KB and OSCC cancer cell lines, suggesting its potential as an anticancer agent for oral cancers. These findings propose that the Y33 strain could be used as a safe and effective probiotic supplement to enhance human health and as a therapeutic agent to treat oral cancer.(24)

Microbiome and esophageal cancer

Esophageal cancer ranks as the sixth leading cause of cancer-related deaths and is the eighth most common cancer globally (25). It is characterized by its aggressive nature, with a 5-year survival rate of less than 20% (26). This type of cancer can be classified into two main subtypes: Esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC), according to various histological types(26–28). Among these, ESCC is the predominant subtype worldwide, accounting for nearly 90% of cases, while there is a notable increase in the adenocarcinoma subtype (2,29). Given the significant role of the gut microbiome in human malignancies, understanding its relationship with esophageal cancer is becoming increasingly important. Several studies have explored the connection between the microbiome and the development of esophageal adenocarcinoma, examining whether alterations in the microbiome affect cancer progression (27,29).

Li et al. (2020) found a significant increase in H. pylori infection in esophageal tumor tissues compared to non-tumor tissues(29). The prevalence of H. pylori in tumor samples was markedly higher than in normal samples. Additionally, the study reported that the microbial environment in ESCC tissues contained more Fusobacterium and fewer Streptococci than that in non-tumor tissues(28). These differences underscore the critical role of the microbiota in cancer development and highlight specific microbial communities that may be carcinogenic. Furthermore, imbalances in the microbiome can lead to systemic metabolic changes affecting the metabolism of cysteine, methionine, fructose, galactose, and starch, as well as pathways related to DNA repair, recombination, protein translation, and chromosomal dynamics. These imbalances also up-regulate peptidase activity in the ESCC group(30).

Recently, there has been an increasing interest in the use of probiotics for gastrointestinal cancers. Probiotics can be administered as part of esophageal cancer treatment to improve nutritional status and immune function(27,29). Despite the prevalence of squamous cell carcinoma worldwide, risk factors for esophageal cancer are diverse and include tobacco and alcohol use, obesity, H. pylori infection, genetic mutations that affect the metabolism of these substances, and nutritional deficiencies. Notably, there has been a shift from squamous cell carcinoma to adenocarcinoma as the most common histological type of esophageal cancer (31,32).

Gui et al. studied the effect of the gut microbiota on lung cancer mice. They observed that commensal flora contributed to the anti-lung cancer response and that probiotic combination therapy enhanced the antigrowth and anti-apoptotic effects of cisplatin (33).

A study investigated the use of L. plantarum and its bacteriocin as a therapy for esophageal cancer. The results demonstrated that the isolate produced a high level of bacteriocin, approximately 2000 AU/ml. In addition to its antimicrobial properties, L. plantarum exhibited significant anticancer activity, with an IC50 of 51.01 CFU/ml for bacteria and 281.9 AU/ml for bacteriocin against cancer cells. Importantly, neither showed cytotoxicity towards normal REF cells. Furthermore, there was a notable increase in the induction of apoptosis and caspase-3 activity in cancer cells treated with L. plantarum and its bacteriocin compared to untreated cells. In conclusion, L. plantarum and its bacteriocin demonstrated a potent killing effect against esophageal cancer cells without affecting normal cells, indicating both safety and selectivity. The activation of apoptosis via caspase-3 induction suggests a potential clinical advantage (34)

Microbiome and Gastric cancer

Gastric cancer (GC) is the third leading cause of cancer-related deaths worldwide, after lung and colorectal cancers, resulting in 782,685 fatalities each year. Several risk factors contribute to the development of GC, including Helicobacter pylori infection, advanced age, high salt intake, low consumption of fruits and vegetables, alcohol use and smoking. In its early stages, gastric cancer often presents as asymptomatic or with nonspecific symptoms, leading to most patients being diagnosed only at an advanced stage(35,36). Gastric cancer is classified into two main types: the less common diffuse type and the more prevalent intestinal type. Diffuse type gastric adenocarcinoma typically affects younger individuals and does not progress through different histological stages(37). In contrast, intestinal type adenocarcinoma is characterized by a progression of histological changes, starting from H. pylori-associated inflammatory cell invasion to atrophic gastritis, then to intestinal metaplasia, dysplasia, and ultimately leading to adenocarcinoma(38,39)

A study investigates the effects of L. paracasei IMPC2.1, comparing it with Lactobacillus rhamnosus GG (L.GG), both viable and heat-killed, on cell proliferation and apoptosis in gastric cancer (HGC-27) and colorectal cancer (DLD-1) cell lines. Both types of cancer cells showed sensitivity to growth inhibition and apoptosis induction caused by viable or heat-killed cells from L. paracasei IMPC2.1 and L.GG. These findings suggest the potential for a food supplement based on dead probiotics, including L. paracasei IMPC2.1 cells, which could serve as an effective component of a functional food strategy aimed at inhibiting cancer growth and possibly preventing cancer(40).

Probiotics have been shown to induce and lead to changes in physicochemical conditions that further lead to degradation of carcinogens. Nowak et al. studied the Lactobacillus casei probiotic DN114001 and determined the probiotic's ability to metabolize heterocyclic aromatic amines (HCA). These compounds have a high potential mutagenic contribution to the development of colon and gastric cancers, and this probiotic effectively degraded this carcinogen(41).

Maleki-Kaklar et al. demonstrated that probiotics, particularly L. plantarum, may influence H. pylori-associated gastric carcinogenesis by regulating PTEN / AKT signaling pathways. Laboratory studies involving probiotics such as L. plantarum and L. rhamnosus have shown an increased expression of the MUC2 and MUC3 genes, which indicates their potential to restore gastric mucosal permeability and inhibit the adhesion of pathogenic bacteria(42).

Chen et al. discovered that treatment with Lactobacillus strains significantly reduced the attachment and invasion of H. pylori to gastric epithelial cells, as well as the production of IL-8(43).

Recent research has revealed a specific correlation between daily human life and intestinal flora. A healthy intestinal flora can promote the treatment of tumor patients. Investigating the effect of Lactobacillus cockerel on intestinal tumors. Some studies have revealed that probiotics can also decrease tumor formation and metastasis by regulating the microbiota, improving intestinal barrier function, and anti-inflammatory activity, in addition to the direct benefits of moderate intake of probiotics in improving host gut microbiota. Studies on many human cancer cells/cell lines have revealed that probiotics have an antiproliferative or pro-apoptotic activity effect, with colon cancer cells and gastric cancer cells being studied. The latest studies have shown that the cytoplasmic fractions of Lactobacillus acidophilus and Bifidobacterium longum indicate significant antitumor activity in certain cancer cell lines(44).

Microbiome and its relationship with intestinal and colon cancer.

Intestinal cancer, also known as small intestine cancer or small intestine cancer, typically originates in the lining of the small intestine. It can spread from the digestive system to other areas of the body. Most cases occur in the duodenum, which is the upper part of the small intestine(45,46). Colorectal cancer, including colon cancer, is the third most commonly diagnosed cancer in both men and women, with approximately 75% of patients having sporadic forms of the disease. CRC is the second leading cause of cancer-related death, with approximately 1.8 million new cases worldwide. More than 90% of CRC cases occur sporadically, highlighting the importance of risk factors in addition to well-established cancer-related genes. Furthermore, the global increase in CRC rates may be associated with environmental risk factors, such as unhealthy eating patterns, overweight, obesity, type 2 diabetes, sedentarism, smoking, and alcohol consumption (47.28). Probiotics are a group of microorganisms, particularly lactic acid bacteria, which provide beneficial effects to the host animal when ingested. They improve the balance of intestinal microbes and are increasingly recognized for their ability to influence gastrointestinal diseases and disorders, including colorectal cancer.

Sugimura et al. found that its culture supernatant significantly promoted apoptosis in rectal cancer-like organs. Furthermore, Lactobacillus cockerel promoted the enrichment of indole-3-lactic acid (ILA), inhibiting intestinal tumorigenesis in vivo (49).

Blackwood et al. (2017) investigated necrotizing small intestinal colitis (NEC) using in vivo and in vitro models of Lactobacillus rhamnosus and Lactobacillus plantarum probiotics. These probiotics were pretreated and cultured using human intestinal Caco-2 cells for in vitro experiments. The tight junctions (TJ) were disrupted to mimic NEC, transepithelial resistance (TER), and fluorescein isothiocyanate dextran fluxes were determined. The structure of TJTJ was evaluated using ZO-1 immunofluorescence, which indicated that Lactobacillus strengthened intestinal barrier function and preserved TJ integrity(50).

Lactobacillus gallinarum modulates the intestinal microbiota and produces anticancer metabolites to protect against colorectal tumorigenesis. L. gallinarum significantly reduced intestinal tumor number and size compared to E. coli MG1655 and phosphate buffered saline in male and female murine intestinal tumorigenesis models. Fecal microbiology profiling revealed an enrichment of probiotics and depletion of pathogenic bacteria in mice treated with L. gallinarum. Culture of CRC cells with L. gallinarum culture supernatant (5%, 10%, and 20%) concentration-

dependently suppressed cell proliferation and colony formation. L. gallinarum culture-supernatant significantly promoted apoptosis in CRC cells and patient-derived CRC organoids, but not in normal colon epithelial cells. Only the L. gallinarum culture supernatant with fraction size <3 kDa suppressed proliferation in CRC cells. Using LC-MS/ MS, enrichments of indole-3- lactic acid (ILA) were identified in both L. gallinarum culture supernatant and the gut of L. gallinarum treated mice. ILA showed anti-CRC growth in vitro and inhibited intestinal tumorigenesis in vivo(49).

Research involving azomethane-induced mouse models of colorectal cancer (CRC) treated with a probiotic mixture of seven strains, including Lactobacillus, Bifidobacterium, and Streptococcus, demonstrated that colon cancer was inhibited through modulation of MUCOS CD4+ T polarization and overall gene expression(51) .

On the other hand, the disruption of intestinal microbial communities, known as dysbiosis, can lead to various inflammatory, immune, and infectious diseases and can be associated with the development of malignancies such as lymphoma, breast cancer, and colorectal cancer, as well as complications related to chemotherapy. Dysbiosis can increase susceptibility to infections by opportunistic pathogens that secrete toxins, which can contribute to genomic instability, tumor initiation, and progression in susceptible cells. For example, pathogenic E. coli carrying pks toxicity genes has been linked to local tissue inflammation and colon carcinogenesis (52).

Cachexia, a wasting syndrome, is associated with significant changes in the composition and diversity of the intestinal microbiota in mouse models of leukemia and colon cancer. Although animal studies indicate that the intestinal microbiota plays a role in the pathogenesis of cancer cachexia, data in humans are limited. Research has shown substantial differences in the composition of the gut microbiota between colorectal cancer patients and healthy individuals. These differences are characterized by increased species richness and an increase in potentially carcinogenic species such as Fusobacterium, Bacteroides, Porphyromonas, and Escherichia, along with a decrease in potentially protective species. For instance, F. nucleatum can adhere to and invade colonic epithelial cells, promoting carcinogenesis via FadA, which binds to E-cadherin, activates β-catenin signaling, and modulates inflammatory and oncogenic responses(53,54) Furthermore, Enterococcus faecalis has been found to be significantly more prevalent in colorectal cancer patients than in healthy controls(55).

A study by Khodavardi et al. in 2021 examined the relative frequency of enterotoxigenic B. fragilis and E. faecalis in colorectal tissue samples from both colorectal cancer patients and healthy individuals, revealing a significant increase in these bacteria among cancer patients. Notably, the frequency of these bacteria was higher in advanced cancer stages (III/IV) compared to early stages (I/II) (56).

A study by Compare and Nardone found that probiotics, including VSL#3, *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *Lactobacillus gasseri*, improved colon cancer outcomes by reducing tumor burden and size. Additionally, the consumption of inulin alongside *B. longum* and *Bifidobacterium lactis* resulted in a reduction of chemically induced colorectal cancer and enhanced apoptotic responses (57).

In 2020, Kenfack Momo and colleagues investigated a new derivative of pyran with antioxidant and anticancer properties isolated from the probiotic strain *Lactobacillus plantarum* H24. The compounds were screened for their antioxidant and cytotoxic activities against colon cancer cells (Caco-2), leading to the conclusion that they could serve as useful anticancer agents. Consequently, *L. plantarum* H24 may help prevent oxidative stress and its related damages, thereby improving human health(58).

In 2022, Sheng and colleagues explored a new exopolysaccharide derived from the probiotic strain *Lactobacillus pantheris* TCP102, highlighting its immune-boosting and anticancer properties. They showed that these exopolysaccharides significantly induced the production of nitric oxide (NO), TNF-α, and IL-6 in Ana-1 cells and peritoneal macrophages, indicating their immune-boosting and anticancer activities. Furthermore, exopolysaccharides significantly suppressed the proliferation of HCT-116, BCG-803 and, in particular, A-2780 cells. These findings suggest that the three new exopolysaccharides isolated from *L. pantheris* TCP102 could be considered for potential applications in functional foods and as natural anti-tumor agents (59).

Zhang et al. showed that L. salivarius Ren effectively countered the adverse changes in the colon microbiota caused by dimethylhydrazine (DMH) injection and suppressed DMH-induced colon cancer in mice(60).

In a mouse model of colon cancer, γ-amastigotes were shown to induce resistance to gemcitabine, which could be countered with Ciprofloxacin. These findings imply that bacteria in human pancreatic ductal adenocarcinoma may modulate the antitumor activity of Gemcitabine (61).

Lactic acid bacteria (LAB), such as Lactobacillus fermentum, have been shown to enhance the levels of fecal short-chain fatty acids (SCFAs). SCFAs are recognized for their beneficial roles in colon health and their ability to produce anticarcinogenic compounds, indicating potential for the prevention of colorectal cancer (CRC). This study aims to characterize the metabolic and anticancer properties of L. fermentum NCIMB 5221 compared to two other species of Lactobacillus. They generated a free fatty acid (FFA) profile and investigated the antiproliferative and apoptotic effects of bacterial cell-free extracts. We also assessed the impact of these extracts on the growth of CRC cells versus nonneoplastic colon cells. The production of various SCFAs by probiotic bacteria and the efficacy of their composition were analyzed(62).

The results indicated that the FFA profile of L. fermentum was distinctive (~368 MAE, 16 h, $p < 0.01$) compared to L. acidophilus ATCC 314 and L. rhamnosus ATCC 53103. In particular, extracts of L. fermentum significantly inhibited cancer cell growth by approximately 40% and induced apoptosis in SW-480 CRC cells by approximately 30% (24 h, $p < 0.05$) compared to untreated cells. While L. fermentum did not inhibit the growth of CRL-1831 non-neoplastic colon cells, it exhibited a significant antiproliferative effect against Caco-2 cancer cells (~60%, 72 h, $p < 0.001$)

relative to untreated cells, which correlated with the higher levels of SCFAs produced (~377 mg/L).). Similar concentrations of SCFA formulations, corresponding to those produced by L. fermentum, demonstrated the same inhibitory effect on Caco-2 cells without affecting CRL-1381 cells. Overall, L. fermentum NCIMB 5221 showed a greater potency in suppressing CRC cells and promoting the growth of normal epithelial colon cells through SCFA production. Therefore, it may be considered a biotherapeutic agent to support colon health and prevent CRC(62).

To evaluate the cytotoxic, antiproliferative and apoptotic effects of the lactobacillus rhamnosus probiotic supernatant on the HT-29 cell line. Molecular identification of probiotic L. rhamnosus was carried out using specific primers of the 16S rRNA gene and sequencing. HT-29 cells were treated with different concentrations of bacterial supernatants at 24, 48, and 72 hours. The MTT assay, Annexin V-FITC, real-time PCR, cell cycle analysis, and DAPI staining tests were performed to evaluate the induction of apoptosis. The level of cyclin D1 protein was measured by immunocytochemistry method. L. rhamnosus supernatant inhibited the growth of HT-29 cancer cells in a dose and time dependent manner. The results of flow cytometry confirmed apoptotic cell death. The probiotic bacterial supernatant caused upregulation of pro-apoptotic genes, including caspase-3, caspase-9, and Bax. In addition, they resulted in down-regulation of Bcl2 and a decrease in the expression levels of the cyclin D1, cyclin E, and ERBB2 genes. Cancer cells were arrested in the G0/G1 phase of the cell cycle. The immunocytochemical results showed a significant down-regulation of the cyclin D1 protein during 48-hour treatment with bacterial supernatant compared to untreated cells. Conclusion: The supernatant of probiotic L. rhamnosus has a great potential to inhibit the proliferation of HT-29 cells and the induction of apoptosis. L. rhamnosus could be used as a biological anticancer factor in the prevention and treatment of colon cancer (63).

Fermentation of dietary fiber by the microflora improves the levels of effective metabolites, which are potentially protective against colon cancer. The specific addition of probiotics may enhance the efficiency of wheat aleurone fermentation, a source of dietary fiber. We investigated the effects of aleurone, fermented with fecal slurries with the addition of probiotics LGG and Bb12 (aleurone(+)), on cell growth, apoptosis, and differentiation, as well as the expression of genes related to growth and apoptosis using two different human colon cell lines (HT29: adenocarcinoma cells; LT97: adenoma cells).). The efficiency of aleurone fermentation was only slightly enhanced by adding LGG / Bb12, resulting in an increased concentration of butyrate. In LT97 cells, the growth inhibition of aleurone(+) was stronger than in HT29 cells. In HT29 cells, arrest of the cell cycle in G(0)/G(1) and alkaline phosphatase activity, a marker of differentiation, were enhanced by aleurone (+). Treatment with all fermentation supernatants resulted in a significant increase in apoptosis and an up-regulation of genes involved in cell growth and apoptosis (p21 and WNT2B). In conclusion, fs aleurone(+) modulated markers of cancer prevention, namely inhibition of cell growth and promotion of apoptosis, as well as differentiation(64).

B. adolescentis SPM0212 inhibited the proliferation of three human colon cancer cell lines: HT-29, SW 480, and Caco-2. SPM0212 also dose-dependently inhibited TNF-á production and changes in cellular morphology. B. adolescentis SPM0212 inhibited harmful fecal enzymes, including â-glucuronidase, â-glucosidase, tryptophanase, and urease. Therefore, B. adolescentis SPM0212 exerts an anticancer effect and inhibits harmful fecal enzymes(65).

Bacillus polyfermenticus (B.P.), a probiotic bacterium, has been clinically utilized for various gastrointestinal disorders in East Asia. This study investigates the effect of B.P. on tumor growth and its potential mechanisms of action. The conditioned medium of B.P. cultures (B.P. CM) inhibited the growth of human colon cancer cells, including HT-29, DLD-1, and Caco-2 cells. Furthermore, BP CM suppressed the colony formation of HT-29 cells cultured on soft agar and reduced carcinogen-induced colony formation in normal colonocytes. In a mouse xenograft model of human colon cancer, mice injected with B.P. CM exhibited reduced tumor size compared to those injected with E. coli conditioned medium. Exposure of HT-29 cells to B.P. CM for 24 hours, 48 hours and 2 weeks resulted in decreased protein expression and ErbB2 and ErbB3 mRNA levels. Furthermore, cyclin D1 expression, which is necessary for ErbB-dependent cell transformation, was also reduced by BM CM. The transcription factor E2F-1, which regulates cyclin D1 expression, was also reduced after exposure to B.P. CM (66).

These results indicate that B.P. inhibits tumor growth, and its anticancer activity may, at least in part, be mediated through the suppression of ErbB2 and ErbB3. Collectively, these findings suggest that probiotics such as B.P. could be used clinically as a prophylactic treatment to prevent the development of colon cancer (66).

Scientific studies have shown that live Lactobacillus casei (L. casei) ATCC393 and its components have strong antiproliferative, growth-inhibitory and pro-apoptotic effects. In vitro studies using CT26 and HT29 human colon carcinoma celllines, as well as in vivo research conducted in 6- to 8-week-old female BALB/c mice, highlight the potential significance of this probiotic in food intervention programs. The use of these cell lines and oral administration of live L. casei ATCC 393 and its components to mice demonstrated a notable antiproliferative effect. This effect is associated with up-regulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and down-regulation of survivin(67).

The Lactobacilli cocktail (L. cocktail) exhibits antitumor effects on HT-29 cells by modulating the Notch and Wnt/β-catenin pathways. Consequently, using lactobacilli probiotic as nutritional supplements may help prevent colon cancer. When Lactobacillus species are used in cocktails, they demonstrate growth-inhibitory potential by downregulating cell proliferation induced by the Notch or Wnt pathways. This inhibition of the Wnt and Notch pathways leads to apoptosis and reduced proliferation in vitro. Therefore, live Lactobacillus species can be considered a cost-effective and safe option for treating colorectal cancer (CRC)(68).

Kumar et al. studied the effects of Lactobacillus plantarum

(L. plantarum) AS1, which was isolated from fermented food, on colon tumors induced by the potent carcinogen 1,2-dimethylhydrazine in male albino Wistar rats. This probiotic strain, L. plantarum AS1, modulates the development of colon carcinogenesis induced by 1,2-dimethylhydrazine through an antioxidant-dependent mechanism. Humans can be exposed to 1,2-dimethylhydrazine and other hydrazines through environmental sources. L. plantarum AS1 may inhibit colon cancer through several mechanisms: producing antimutagenic compounds, binding to and degrading potential carcinogens, enhancing the host's immune response, and influencing the physiology of the host (69).

In contrast, several studies indicate that the intake of probiotics (or prebiotics) significantly reduces the incidence of colon cancer in animal models through immunomodulatory effects(70). These studies have shown elevated levels of natural killer cells (NK) or increased cytotoxicity in rats and mice treated with probiotics. Furthermore, probiotics may enhance the immune function by boosting the phagocytic activity of macrophages (70).

Microbiome and liver cancer

Hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). Together, these types account for 75–85% of all liver cancer cases. The disease is characterized by a poor prognosis, leading to closely aligned incidence and mortality patterns. In fact, liver cancer ranks third in both incidence and mortality among gastrointestinal cancers. Additionally, it is the sixth to seventh most commonly diagnosed cancer worldwide and the fourth leading cause of cancer-related deaths worldwide (71).

Recent studies have highlighted differences in the composition of the gut microbiota between cancer patients and healthy individuals. Certain bacteria, such as E. coli producing colibactin, Bacteroides fragilis, Fusobacterium nucleatum, and Providencia, have been implicated in colorectal carcinogenesis, while there is a significant decrease in bacteria producing butyrates such as Roseburia and Faecalibacterium. The intestinal and oral microbiota of patients with pancreatic cancer (PC) also differ from those of healthy individuals, with the bacteria present in the PC tissues associated with the patient's prognosis (72).

In a study conducted by Li et al., a new probiotic mixture named Prohep, which contains L. rhamnosus GG, E. coli Nissle 1917, and heat-inactivated VSL#3, significantly reduced the growth of hepatocellular carcinoma (HCC) in mice. Prohep achieved its antitumor effects by inducing the secretion of the anti-inflammatory cytokine IL-10, suppressing Th17 cell differentiation in the intestinal tract, modulating the intestinal microbiota, depleting Th17 cells, and attenuating angiogenesis in liver tumors, ultimately leading to reduced tumor growth. In an in vitro study by Elshaer, early administration of L. plantarum in Wistar rats with thioacetamide-induced liver cirrhosis resulted in decreased expression of Toll-like receptor 4 (TLR4), CXCL9, and PREX-2, along with improved liver function. The reduction in TLR4 expression indicated a decrease in inflammation. Furthermore, a study by Kumar et al. investigated the chemopreventive effects of milk fermented with probiotics and chlorophyllin on HCC induced by aflatoxin B1 (AFB1) in rats. The use of probiotics resulted in lower levels of c-myc, bcl-2, cyclin D1, and ras-p21, as well as a reduced incidence of HCC, demonstrating the protective capacity of probiotics(73).

Kumar et al. conducted a study to investigate the chemopreventive effects of fermented milk with probiotics and chlorophyllin on aflatoxin-induced hepatocellular carcinoma (HCC) in rats. The findings indicated that the use of probiotics resulted in decreased levels of c-myc, bcl-2, cyclin D1, and ras-p21, along with a reduced incidence of HCC. This study highlighted the protective role of probiotics against AFB1-induced liver cancer. Beyond their direct modulation of the intestinal microbiota, probiotics exert anticancer effects by enhancing immunity, reducing bacterial translocation, improving intestinal barrier function, and demonstrating anti-inflammatory and antipathogenic activities. Additionally, they play a role in decreasing tumor formation and metastasis (74).

In addition to gut microbiota, bacteria present in the tumor environment can influence the response to cancer therapy. They may alter the chemical structure of chemotherapeutic agents, affecting their activity and local concentration (75,76) . Geller et al. (2017) analyzed tissue samples from both normal human pancreas and pancreatic cancer, discovering bacterial DNA in 86 out of 114 (76%) pancreatic tumor samples, compared to only 3 out of 20 (15%) samples from normal human pancreas. The species most frequently identified in pancreatic tumor samples was γ-amastigotes. This phylum is abundant in the duodenum, suggesting that the bacteria in pancreatic tumors may originate in the duodenum through retrograde migration. Furthermore, immune cells in the tumor microenvironment may be suppressed, allowing for bacterial residency (77).

Conclusion

The gut microbiota shows great promise for therapeutic applications in cancer treatment. The role of probiotics as beneficial bacterial substrates in the colon is becoming increasingly recognized for their positive effects on host health. While only a limited number of probiotics currently demonstrate anti-cancer properties, further research is needed to explore the potential of other strains. As adjunctive treatments, probiotics may provide significant benefits in cancer prevention and treatment. They can improve gut microbiota metabolism during chemotherapy, potentially reducing its toxic side effects. Currently, probiotic cancer treatment often involves combination therapies, such as radiation therapy and heat-killed Lactobacillus therapy, with additional therapies awaiting exploration. Current review focuses primarily on the ability of probiotics to inhibit antibiotic resistant Helicobacter pylori (Campylobacter pylori) C. pylori. However, there is a lack of studies on inhibitory resistance in other contexts. Despite these gaps, probiotics still have considerable potential for cancer treatment and tumor immunity (Figure-1).

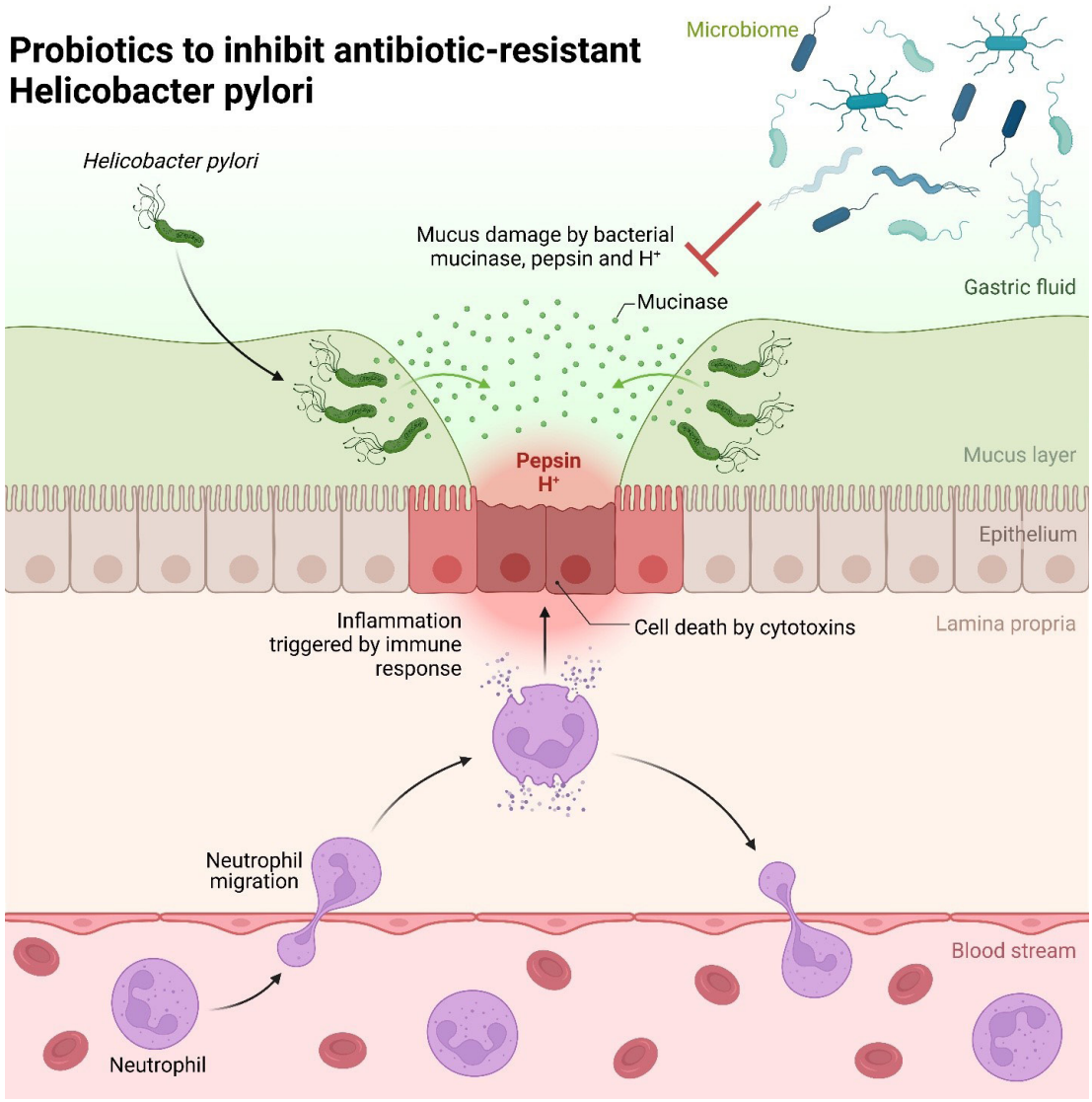

Figure-1, Probiotics, as beneficial gut bacteria, can inhibit antibiotic-resistant Helicobacter pylori and improve gut health during cancer treatment. They enhance metabolism during chemotherapy, reducing toxic side effects, and hold potential in combination therapies for cancer prevention and treatment. Despite limited current anti-cancer strains, research into probiotics for tumor immunity is promising.

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