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MINI REVIEW

THE ROLE OF PROBIOTICS IN CANCER PREVENTION: A MINI-REVIEW OF THEIR MECHANISMS AND PROTECTIVE POTENTIAL

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Abstract. *This mini-review summarizes the role of gut microbiota and probiotics in cancer prevention and treatment. The human gastrointestinal (GI) tract hosts a complex microbiota, which are crucial for maintaining health. Dysbiosis, caused by factors such as poor diet, stress, and medication, is linked to increased cancer risk due to inflammatory responses. Probiotics, beneficial bacteria, help restore microbial balance and exhibit anticancer properties by promoting apoptosis, inhibiting oncogenes, and enhancing the immune system. Specific probiotic strains like Lactobacillus and Bifidobacterium have shown potential in inhibiting cancer cell proliferation and regulating immune functions. Additionally, the gut-brain axis underscores the importance of the microbiome in both physical and mental health. Probiotics also aid in managing chemotherapy side effects and preventing complications like diarrhea and mucositis. Despite promising findings, further research is needed to fully understand the safety and efficacy of probiotics in cancer therapy, as their effects may vary based on cancer type and stage.*

Keywords: probiotics, cancer, brain-gut-axis, mechanism, prevention

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Introduction

The human gastrointestinal tract hosts a diverse and dynamic community of microorganisms, known as the gut microbiota, which plays a crucial role in maintaining health and influencing disease development. Comprising over 10^{14} bacteria, the microbiota consists primarily of *Firmicutes* and *Bacteroidetes*, which together make up about 90% of the bacterial population. This microbial ecosystem develops within the first three years of life and helps regulate energy balance and gut homeostasis. However, factors like poor diet, stress, illnesses, obesity, and medication use can disrupt this balance, leading to intestinal dysbiosis. Such imbalances may trigger inflammatory responses and contribute to the development of GI and even distant-site cancers **[1]**.

The gut microbiota plays a crucial role throughout life, while intestinal dysbiosis has been linked to the development of both GI cancers and tumors in distant organs. Cancer risk is influenced by environmental exposures such as carcinogens and UV radiation, as well as lifestyle factors, with the impact varying based on exposure duration, dose, and individual genetic background **[2]**. Tumors arise due to random driver mutations in key genes responsible for DNA replication, repair, and oxidative stress response. Over time, these mutations accumulate, allowing cancer cells to adapt and transform from normal to malignant. Due to genomic instability, epigenetic modifications (such as altered DNA methylation and miRNA imbalances), and transcriptional changes, a single tumor can evolve into a complex, heterogeneous mass composed of multiple cancer cell clones. Each clone may exhibit different molecular characteristics and varying sensitivities to anticancer therapies, making treatment more challenging **[3]**.

Probiotics are beneficial bacteria that, when consumed in sufficient amounts, promote the health of the host. Probiotics are used to manage various health conditions, including cancer, due to their ability to influence key biological processes **[4]**. They help regulate cancer development by inducing apoptosis, inhibiting mutagenic activity, downregulating oncogenes, promoting autophagy, and preventing metastasis. These effects are largely attributed to metabiotics—bioactive compounds derived from probiotics that support essential physiological and metabolic functions in the body **[2,5]**. Probiotics are mainly classified into bacterial and yeast strains. Common bacterial probiotics include *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, and *Enterococcus*, while other potential strains include *Clostridiales*, *Bacteroidales*, *Bacillus spp*., *Escherichia coli*, and *Weissella spp*. Among probiotic yeasts, *Saccharomyces cerevisiae var. boulardii* is well-recognized, along with *Candida*, *Kluyveromyces*, *Pichia*, *Debaryomyces*, *Hanseniaspora*, and *Metschnikowia* **[6]**.

According to scientific research, probiotics, particularly *Lactobacillus* strains, have been found to have anticancer effects. Specifically, *Lactobacillus* strains have been shown to have antitumor activity by inducing apoptosis, inhibiting angiogenesis, and modulating the immune system **[7]**. However, it is important to note that the evidence for the anticancer effects of probiotics is still limited, and more research is needed to establish their efficacy. Furthermore, the effects of probiotics on cancer may vary depending on the type of cancer, the stage of cancer, and the type of probiotic used. On the other hand, while probiotics, especially *Lactobacillus* strains, have shown promise in their anticancer effects, more research is needed to establish their efficacy and safety **[8]**.

Probiotics, found in fermented foods like yogurt, kefir, and sauerkraut, as well as supplements, offer potential health benefits. While cancer treatments like surgery, chemotherapy, and radiation are effective, they come with significant side effects such as tissue damage, fatigue, nausea, and long-term complications. Additionally, cancer cells can develop resistance to these treatments. Researchers are working on therapies that are more selective, utilizing the immune system to reduce side effects and improve outcomes **[4].**

Mechanism of Action – Probiotics in cancer

Probiotics exert anticarcinogenic effects through several mechanisms, including balancing gut microbiota, influencing microbial metabolism, and producing anti-cancer compounds like short-chain fatty acids and conjugated linoleic acid. They also inhibit cancer cell proliferation, induce apoptosis, counteract mutagenic factors, degrade carcinogens in the gut, modulate the immune system, and strengthen the intestinal barrier **[1].**

Probiotics can impact cancer progression through several mechanisms, such as inducing apoptosis, inhibiting mutagenic activity, downregulating oncogene expression, promoting autophagy, inhibiting kinases, reactivating tumor suppressor genes, and preventing metastasis **[9].** The anticancer effects of probiotics are largely attributed to metabiotics, which include structural components, metabolites, and signaling molecules of probiotic microorganisms. These compounds can regulate host physiological functions, metabolism, and immune responses, contributing to cancer prevention and therapy **[5].**

Research suggests that probiotics can inhibit tumorigenesis and cancer progression by inducing apoptosis, though the exact mechanisms remain unclear. Apoptosis, a controlled form of cell death, prevents tumor growth through three pathways: intrinsic (mitochondrial), extrinsic (death receptor), and perforin/granzyme. Key genes involved include Tumor Necrosis Factor (TNF), caspases, B-cell lymphoma 2 (Bcl-2), and p53. Probiotics like *Lactobacillus* and

Bifidobacterium promote apoptosis by modulating Bax/Bcl-2 and caspases. Colicin from *Escherichia coli* induces apoptosis via pore formation, while nisin enhances doxorubicin's anticancer effects. Other probiotic-derived molecules, such as ferrochrome and conjugated linoleic acid, also trigger apoptosis through c-Jun N-terminal kinase (JNK) and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NFκB) pathways. Despite advances, further research is needed to fully understand probiotics' apoptotic mechanisms in cancer therapy **[5, 10].**

Oncogenes drive tumor development, while proto-oncogenes are their nonmutated precursors. Targeting oncogene downregulation is a key strategy in cancer therapy. Several probiotics, such as *L. crispatus* and *L. rhamnosus*, exhibit tumor-suppressive effects by modulating the mechanistic target of rapamycin (mTOR) related genes and the Wnt/β-catenin pathway. Studies show that L. acidophilus and *L. crispatus* downregulate cancer-testis gene expression, while probiotics combined with celecoxib can suppress KRAS, reducing colon cancer risk. Additionally, *L. lactis* and its bacteriocin nisin inhibit cyclin D1 expression, limiting cancer cell proliferation. Probiotic-derived lipoteichoic acid from *L. plantarum* also downregulates Microphthalmia-associated Transcription Factor (MITF). These findings highlight probiotics' potential in regulating oncogenes for cancer prevention and treatment **[5, 11].**

Mechanism Underlying the Gut-Brain-Axis

The brain-gut axis refers to the complex communication network between the GI tract and the central nervous system (CNS). This bidirectional signaling system involves neural, hormonal, and immune pathways that allow the gut and brain to influence each other **[12].** The vagus nerve plays a critical role in this connection, transmitting signals between the gut and the brain. In addition, the gut microbiota, which consists of trillions of microorganisms, contributes to the brain-gut communication by producing metabolites such as short-chain fatty acids (SCFAs) and neurotransmitters, including serotonin and dopamine. These metabolites influence brain function and behavior, further demonstrating the crucial role of the microbiome in this axis. Disruptions in the balance of the gut microbiota (dysbiosis) can lead to a variety of conditions, including GI disorders, mental health issues like depression and anxiety, and neurodegenerative diseases. The brain-gut axis highlights the importance of maintaining a healthy gut microbiome for overall health, both physical and mental **[13]**.

Research on the gut-brain connection, known as the "gut-brain axis" (GBA), has revealed a complex communication system that maintains GI balance while also influencing emotions, motivation, and cognitive functions. This system integrates gut functions with emotional and cognitive brain centers, affecting processes like immune activation, intestinal permeability, reflexes, and entero-

endocrine signaling. The GBA operates through neuro-immuno-endocrine mediators. This two-way communication network involves the CNS, autonomic nervous system, enteric nervous system, and the hypothalamic-pituitary-adrenal (HPA) axis. The autonomic system sends signals from the gut to the CNS and vice versa. The HPA axis, part of the limbic system, manages stress responses. Stress and inflammation activate the HPA axis, triggering the release of cortisol, a stress hormone that affects many organs, including the brain. Neural and hormonal signals enable the brain to influence intestinal cells, such as immune cells, epithelial cells, and neurons. These cells are also influenced by the gut microbiota, which plays a key role in brain-gut communication, giving rise to the emerging concept of a microbiome-GBA **[14, 15].**

The Use of Probiotics in Cancer

Significant progress in cancer therapy over the past century has reduced side effects and improved patient compliance. Probiotics are used to enhance treatment safety and mitigate GI side effects like diarrhea and mucositis, which are common in cancer therapies **[1].** They are cost-effective and generally considered safe, with proven benefits in managing antibiotic- and *Clostridium difficile*-associated diarrhea, as well as respiratory infections. Administering probiotics helps restore gut microbiota balance, often disrupted by cancer treatments. However, risks for immunocompromised patients include opportunistic infections and antibiotic resistance **[16].** Despite these concerns, clinical trials show probiotics help rebalance intestinal microbiota and alleviate therapy-induced GI damage. *Lactobacillus*-based probiotics, in particular, have been recommended to prevent diarrhea and ease mucositis in patients undergoing chemotherapy or radiation for pelvic cancers **[17].**

L. johnsonii helps protect gut health by adhering to the colonic mucosa, reducing harmful pathogens, and modulating local immunity. Similarly, *L. acidophilus* and *Bifidobacterium longum* have been shown to prevent radiation-induced diarrhea in cancer patients. A probiotic mix containing 10 bacterial strains, including *Lactobacilli* and *Bifidobacteria*, has been found effective in reducing diarrhea and GI dysfunction in colorectal cancer (CRC) patients undergoing irinotecan-based chemotherapy. Additionally, a synbiotic mix of prebiotics and probiotics has been shown to lower the risk of post-operative irritable bowel syndrome (IBS) in CRC patients after surgery. *Saccharomyces boulardii* further contributes to gut health by reducing inflammation through the downregulation of pro-inflammatory cytokines. Moreover, the perioperative administration of synbiotics has been found to significantly decrease post-surgical infection rates in CRC patients **[3].**

Probiotics and Specific Cancers

GI cancers, including those of the esophagus, liver, pancreas, stomach, intestines, colon, and rectum, represent a significant global health burden, accounting for 25% of all cancers and 9% of cancer-related deaths. Colorectal, gastric, and esophageal cancers are among the most prevalent, with their development influenced by genetic, epigenetic, immune, environmental, dietary, and lifestyle factors, all of which interact with the gut microbiota [18]. Probiotic therapy has gained increasing attention for preventing and managing GI disorders such as IBS, inflammatory bowel diseases (IBD), infections, and antibiotic-associated diarrhea. Additionally, epidemiological studies suggest probiotics may offer protection against cancer. Research indicates that probiotics exhibit anti-proliferative and pro-apoptotic effects, particularly in colon and gastric cancers, by modulating gut microbiota, enhancing immune responses, and influencing cellular pathways involved in tumor development. These findings highlight the potential of probiotics as a complementary approach in GI cancer prevention and treatment **[19].**

Lung cancer is characterized by the growth, infiltration, and spread of malignant cells. Beneficial bacteria found in the gut flora, when consumed in sufficient amounts, can have positive effects on the host and act as probiotics [20]. These probiotics help restore the intestinal barrier, reduce GI infections, and maintain gut balance. One such probiotic, *C. butyricum*, has been shown to regulate gut homeostasis, reduce inflammation, and alleviate diarrhea in conditions like IBD. As a result, *C. butyricum* is used to treat GI issues, including IBD and antibiotic-associated diarrhea. Probiotics offer multiple potential health benefits, such as inhibiting tumor progression, boosting immune responses, binding and degrading mutagens, reducing chemotherapy side effects, combating food-borne pathogens, and aiding in recovery from surgeries. However, some microorganisms may negatively impact cancer prognosis by producing toxins and metabolites that promote oncogenic effects **[4].**

Several studies have examined the effects of probiotics on breast cancer (BC). In one study, mice fed milk fermented with *L. helveticus* R389 showed increased Interleukin-10 (IL-10) and decreased Interleukin-6 (IL-6) levels, leading to inhibited tumor growth. Other studies found that L. acidophilus can increase the production of immune-regulating Interleukin-12 (IL-12) and slow tumor growth. Additionally, *L. reuteri* and *L. plantarum LS/07* demonstrated potential in inhibiting early stages of BC through immune modulation. Research on *E. faecalis* and *Staphylococcus hominis* showed that their heat-killed cells reduced cell proliferation and induced apoptosis in BC cells. Kefir water also exhibited anti-tumor effects by promoting apoptosis, modulating the immune system, and inhibiting metastasis and angiogenesis **[21]**.

Conclusions

The human GI tract hosts a diverse community of microorganisms, collectively known as the gut microbiota, which plays a significant role in maintaining health and influencing disease development. This microbial ecosystem consists of trillions of bacteria, predominantly from the *Firmicutes* and *B. phyla*, which make up about 90% of the bacterial population. The gut microbiota plays a key role in regulating energy balance, gut homeostasis, and overall immunity. Its composition and balance are crucial for the body's health, and any disruptions to this equilibrium—due to factors like poor diet, stress, illnesses, medication use, or obesity—can lead to intestinal dysbiosis, a state of microbial imbalance. Dysbiosis has been associated with inflammatory responses and has the potential to contribute to the development of various cancers, including GI and even distant-site cancers.

Furthermore, the gut microbiota's influence extends beyond GI health, affecting systemic processes, including cancer development. Tumors result from genetic mutations that accumulate over time, often triggered by environmental factors such as carcinogens or radiation. These mutations may lead to tumorigenesis, where cancer cells adapt and proliferate. However, probiotics have shown potential in modifying the gut microbiota and positively influencing cancer progression. Probiotics can regulate key biological processes such as apoptosis (programmed cell death), inhibition of cancer cell proliferation, and modulation of the immune system. By producing metabiotics, bioactive compounds derived from probiotics, they can influence host metabolism and immune responses, which in turn, supports cancer prevention and therapy.

While the evidence for probiotics' direct anticancer effects is still emerging, certain strains, particularly *Lactobacillus* and *Bifidobacterium*, have shown promise in cancer prevention and treatment. Probiotics may help suppress the growth of tumors by modulating oncogene expression, inducing apoptosis in cancer cells, and reducing inflammation. Additionally, they may play a role in strengthening the intestinal barrier and reducing the toxicity of cancer therapies. For instance, probiotics have been used to alleviate GI side effects like diarrhea and mucositis that commonly arise during chemotherapy and radiation treatments. Clinical studies also suggest that probiotics may be used to restore gut microbiota balance, thus helping to prevent the negative side effects of cancer treatments.

Overall, probiotics offer a promising complementary approach in cancer therapy, particularly in managing the side effects of conventional treatments and potentially improving patient outcomes. However, further research is needed to fully understand the specific mechanisms through which probiotics exert their anticancer effects and to determine their efficacy and safety in diverse cancer types and stages. Probiotics, especially when used in conjunction with standard

cancer therapies, could contribute significantly to improving cancer prevention, treatment, and the quality of life of cancer patients

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