ISSN (Online) 2456 -1304

International Journal of Science, Engineering and Management (IJSEM)

Volume 12 Issue 08 August 2025

Probiotic Intervention in Colorectal Cancer: The Protective Role of Bifidobacterium Against Gut Dysbiosis

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Abstract— ***Colorectal cancer is among the leading causes of cancer deaths worldwide. Recent research indicates that gut dysbiosis, or the gut microbiota dysbiosis-an imbalance in the composition of intestinal microorganisms-plays a crucial role in the initiation and progression of Colorectal cancer due to the increase in opportunistic bacteria and other factors. Dysbiosis leads to chronic inflammation, disrupts the mucosal barrier, interferes with host immune responses and produces genotoxic metabolites. These genotoxic metabolites include secondary bile acids and hydrogen sulfide. Bacteria such as Fusobacterium nucleatum, B. fragilis and E. coli with pks island have been linked to DNA damage and pro-tumorigenic signaling pathways. Thus, there is an urgent need for a non-invasive, microbiota-targeted strategies to prevent or slow down the colon cancer progression. Probiotic bacteria such as Bifidobacterium have shown great potential in restoring microbial balance, reducing the inflammation, producing anti-cancer metabolites and inhibiting oncogenic pathways such as NF-kB and Wnt.***

Index Terms— ***Colorectal Cancer, Gut Microbiota, Gut Dysbiosis, Genotoxic Metabolites, Bifidobacteria, Probiotics, Inflammation***

I. INTRODUCTION

Colorectal cancer, often diagnosed in older individuals, is now seeing a hike in younger adults, colorectal cancer is the third most common cancer contributing 10% of all cancer cases globally. It is the second leading cause of cancer death making it a huge concern for adapting a healthy lifestyle. Increasing research suggests that gut microbiota's contribution Is significant in colorectal tumorigenesis. Dysbiosis is marked by the growth of harmful bacteria and the reduction of beneficial ones. These harmful bacteria produce genotoxic metabolites, trigger inflammation and cause barrier damage and breakdown. Among all the beneficial probiotic microbes, Bifidobacterium has gained immense attention for its exceptional potential to reverse dysbiosis and suppress the tumor growth.

II. GUT MICROBIOTA DYSBIOSIS IN CRC

A. Pro-inflammatory mediators in gut dysbiosis

Gut dysbiosis leads to increased pro-inflammatory condition due to overproduction of cytokines such as the TNF- α and IL-6. These mediators cause damage to the mucosal barrier and enhance angiogenesis, favoring tumor cell survival and growth. This initiates tumor progression and DNA damage.

B. Genotoxicity

A weakened intestinal barrier is caused due to gut dysbiosis. This compromises the epithelial cell lining leading to various complications. One such would be the ability of microbial-associated molecular patterns and other microbial components to cross the upper epithelial layer and come in contact with lamina propria and sometimes the submucosal layer triggering an immune response. This immune response causes chronic inflammation and leads to the release of reactive oxygen species (ROS). Additionally, the imbalance of microbes which causes the production of genotoxins that induce mutations directly. The various strains encoding colibactin lead to instability of dsDNA and cause epithelial stress. The production of B. fragilis toxin that activates the β-catenin signaling causes proliferation.

C. Pro-Carcinogenic microbes

- Fusobacterium nucleatum- a bacterium commonly found in the mouth but when in gut is associated with dysbiosis and leads to conditions like colorectal cancer and inflammatory bowel disease.
- B. fragilis- plays a huge role in gut homeostasis. Due to genotoxicity and mutated strains, they could cause diarrhea and dysbiosis.
- E. coli- a common bacterium in the gut that is usually beneficial. Under certain conditions like inflammation these tend to become pathogenic and release genotoxins their overgrowth disrupts the balance of gut ecosystem.

III. THERAPEUTIC POTENTIAL OF BIFIDOBACTERIUM

A. Microbial Rebalancing and Probiotic Bacterium

A probiotic bacterium called the Bifidobacterium inhibits the pathogenic invasion through biotic exclusion. It produces antimicrobial compounds which play a huge role in maintaining microbial homeostasis in the gut. While controlling the pathogenic microbes they also increase the number of commensal bacteria. These commensal bacteria are generally involved in the synthesis of short-chain fatty acids contributing to intestinal health.

B. Anti-Cancer metabolite production

The short-chain fatty acids (SCFAs) such as butyrate, propionate, acetate etc. induce apoptosis in cancel cells. They also support mucosal healing and suppress the pro-tumorigenic pathways and oncogenic signaling.

C. Immune modulations

Bifidobacteria increases the production of interleukin-10, an anti-inflammatory cytokine and simultaneously suppresses the production of pro-inflammatory cytokine interleukin-6 and the tumor necrosis factor-alpha. This regulation shift promotes the development of regulatory T cells and macrophages. This results in the improvement of gut environment and controls the chronic inflammation playing a dual role.

D. Inhibition of Oncogenic Signaling

Research supports the ability of Bifidobacteria to suppress major oncogenic signaling pathways specifically NF-κB and β-catenin. The NF-κB pathway is usually activated during inflammation and plays a major role in cell survival and resistance to apoptosis. The bacteria reduce the expression of the pro-inflammatory and anti-apoptotic genes. The Wnt pathway is generally required for maintaining cancer stem cell proliferation. The decreased accumulation of Wnt and the reduced transcription of genes leads to a control in the cellular proliferation. In addition to this is the induced apoptosis in cancerous cells which highlights the potential of the bacterium as a microbiota based therapeutic agent.

IV. CONVENTIONAL THERAPIES

- Enhancement of chemotherapy- the bacteria is known to control the various adverse effects caused by chemotherapy such as mucositis and the mucosal disruption. This protective effect permits the improved tolerance to chemotherapeutic agents leading to a better efficacy.
- Augmentation of immunotherapy response- the bacterium increases infiltration of cytotoxic CD8+ T cells into tumor cells and tissues promoting the maturation of dendritic cells. These are necessary for antigen improvement helping the targeted attack of immune cells on tumor cells. These bacteria can support immunotherapy effectively.

V. FUTURE SCOPE

A. Strain specific clinical trials

The clinical validation remains limited for the Bifidobacterium strains. Controlled trials are essential to determine the efficacy of specific strains in the patients diagnosed with colorectal cancer. These trials should include patient-reported outcomes for better understanding.

B. Optimal delivery formats

The administration route has a notable effect on viability, ability to colonize and their functional activity. A detailed study should be conducted to determine the ideal mode of delivery like synbiotics, capsules, gelatin coats, bioengineered vehicles etc. This helps in the accurate and targeted delivery to the colon and the tumor microenvironment.

C. Personalized microbiome modulation

The composition and functional needs of the microbiota vary from individual to individual. Therefore, the one-size-fits-all strategy will not be the right approach. Personalized treatments based on sequencing of obtained individual samples might help to achieve maximal efficacy and reduced side effects.

D. Safety and drug interactions

These are generally considered safe, but long-term consequences of Bifidobacterium supplementation, especially in immunocompromised cancer patients. Future tests must sample the interactions with chemotherapeutic drugs, immunotherapies and other medications. The horizontal gene transfer risks must also be checked.

VI. CONCLUSION

Gut microbiota dysbiosis plays a critical role in the colorectal cancer pathogenesis through the interruption of intestinal homeostasis and the initiation of pro-inflammatory, tumor-promoting microenvironment. This disruption in microbial balance results in an increase of pathogenic bacteria, diminished commensals and increased production of microbial toxins and inflammatory cytokines, all of which contribute to DNA damage, immune cells dysfunction and tumor initiation. Of all the beneficial microbes, Bifidobacterium species have been identified as important modulators of gut health. These probiotics restore microbiological ratios and strengthen the epithelial barrier function and generating SCFAs such as butyrate, and modulating immune responses to anti-tumorigenic mechanisms. Additionally, Bifidobacterium is able to upregulate anti-inflammatory cytokines like IL-10 while downregulating the pro-inflammatory mediators like IL-6 and TNF-α, making the host less favorable to tumor growth. Proper dietary interventions provide a non-surgical and a potentially revolutionary strategy for prevention and management of colorectal cancer. Yet, to maximize their benefit and therapeutic effect, rigorous clinical and medical testing must be made to ensure strain-specific effectiveness, to determine dosing regimens, and learn about long-term effects across various patient populations.

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