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Colorectal cancer and probiotics

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The colorectal cancer (CRC) ranks as the third most common cause of death among various cancer types globally, with the highest occurrence observed in developed nations. In recent times, there has been an acknowledgment that the composition of the intestinal microbiota serves as a risk factor in the onset of CRC. The intestinal microbiota exerts influence over various facets of intestinal health, encompassing cellular characteristics, physiology, metabolism, development, and immune homeostasis. The aim of this review is to explore the potential mechanisms by which probiotics act in preventing colorectal cancer. Research indicates that consistent probiotic consumption has the potential to thwart the onset of colorectal cancer.

Keywords: colorectal cancer, intestinal microbiota, probiotics.

INTRODUCTION

The intestinal microbiota plays a crucial role in facilitating the absorption of nutrients, bolstering the host's resilience against infections, fortifying the immune system within the intestines, and regulating the host's metabolic processes [1]. The alteration or dysbiosis of the gut microbiota is widely acknowledged for its significant role in triggering and promoting chronic inflammatory pathways. Moreover, it is implicated in profound genetic and epigenetic alterations that culminate in dysplasia, clonal expansion, and malignant transformation. Probiotic bacteria exhibit antitumor activity through diverse mechanisms, including nonspecific physiological and immunological pathways [2].

The term 'probiotic' is derived from the literal meaning 'for life.' According to the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) of the United Nations, probiotics are living microorganisms that, when applied in appropriate quantities, confer health benefits to the host [3]. Primarily belonging to the genera *Lactobacillus, Bifidobacterium*, and *Streptococcus*, they contribute to the restoration and maintenance of the balance of the human gut microbiome [4].

Probiotics can exert a range of favorable effects on the human body when consumed in the form of functional foods and dietary supplements containing high levels of viable bacteria, denoted by at least 10^6–10^7 CFU per gram of the product at the time of consumption. The efficacy of probiotics is also contingent on their ability to reach the small intestine of the human gastrointestinal tract in an active state [5]. Numerous investigations, both in animal models and human populations, have underscored the efficacy of probiotic consumption in addressing diverse medical conditions such as gastroenteritis, lactose intolerance, constipation, antibiotic-induced diarrhea and genitourinary tract infections [6]. Furthermore, many studies indicate the anti-tumor effect of probiotics and their capacity to inhibit the progression of cancerous conditions, particularly highlighting a specific correlation between colorectal cancer and probiotics [7].

Colorectal cancer ranks as the second most prevalent cause of cancer-related morbidity and mortality on a global scale. The incidence rates are notably increasing among younger populations, underscoring the imperative for enhanced and cost-effective interventions and adequate treatment [8].

This review aims to offer a broad overview of the potential mechanisms through which probiotics might exert their positive effects in preventing colorectal cancer.

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Intestinal microflora

From the moment of birth, an individual's gastrointestinal tract becomes a habitat for a diverse array of microorganisms that persists throughout their lifetime. This assemblage of microorganisms, commonly referred to as the 'normal' gut microflora, comprises bacterial species endowed with genetic, physiological and morphological characteristics that enable them to establish and proliferate under specific conditions at designated sites. These microbes coexist harmoniously with other colonizing microorganisms and exert a competitive influence, impeding the growth of potentially harmful bacteria [9].

Each person possesses a distinct microbiota, and the specific counts of bacterial phyla and species differ among individuals. The intestinal microbiota encompasses a diverse community of viruses, bacteria, archaea, fungi, helminths and protists that symbiotically inhabit the human digestive system. Among these, the predominant microorganisms in the gut belong to five bacterial phyla: *Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria* and *Verrucomicrobia* [10]. The term "microbiome" collectively refers to the entire genome of these microbes.

Remarkably, the colon contains one million times more bacteria than the small intestine, and intriguingly, it encounters around 12 times more malignancies than the latter. This proves the possibility that the gut microbiota may play a significant role in the initiation of colorectal carcinogenesis [11, 12].

However, the equilibrium of this complex microbial community is susceptible to alterations induced by various environmental factors, including but not limited to diet and medications. Such external influences can lead to shifts in the composition of the resident microbiota, giving rise to a state of dysbiosis [13]. Nutrition is the primary controller of intestinal microbial function. Typically, individuals adhering to a Western-style diet exhibit a higher *Firmicutes/Bacteroidetes* phyla ratio, while those on a subsistence diet show an increased quantity of the Prevotella genus, which is part of the *Bacteroidetes* phylum [14]. This imbalance carries adverse implications for the individual's health, emphasizing the intricate interplay between environmental factors and the delicate symbiosis within the gastrointestinal ecosystem [13].

Factors Potentially Contributing to Colon Cancer Development

Colorectal cancer does not seem to have a specific, singular cause. Instead, there are multiple risk factors associated with its development. The mechanisms underlying how these risk factors contribute to colorectal cancer carcinogenesis remain unclear. Exceptions to this general pattern include Lynch Syndrome and familial adenomatous polyposis, both genetic conditions, although they represent a minority of global colorectal cancer cases [15].

Specific bacterial strains and an imbalance in gut microbiota, known as dysbiosis, have been linked to the onset of colorectal cancer [16]. Dysbiosis in the gastrointestinal tract has the potential to disturb the balance of the immune system and the homeostasis of the mucosal barrier, triggering inflammation and heightened mucosal barrier permeability. This persistent state of inflammation can activate cytokines and some growth factors, including vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF), tumor growth factor beta (TNF-β) and IL-6. This cascade of events may contribute to the proliferation and viability of abnormal cells [17].

There are suspicions that *Bacteroides fragilis, Enterococcus faecalis, Streptococcus bovis, Escherichia coli* and *Fusobacterium spp*. may play a role in colorectal carcinogenesis. The disruption in microbial phyla balance is frequently heightened by oxidative stress driven by leukocytes, the secretion of bacteriocins by harmful bacteria, and the prevalence of bacteriophages in the population [18]. In a comprehensive review, Song *et al.* explored the intricate relationship between the occurrence of colorectal cancer and environmental factors, dietary habits, and the composition of the gut microbiome [19].

Prolonged use of antibiotics is connected to a heightened risk of colorectal cancer, establishing a link between gut microbiota and CRC [20]. As individuals age, there is a decline in CD4 T-cells and a transition in the microbiota towards a pro-inflammatory profile. This diminishes the capacity of immune cells to restrain inflammation in the colon. Moreover, there is a decrease in butyrate-producing bacteria, leading to an elevation in intracolonic pH. This, combined with dysbiosis and inflammation, contributes to CRC [21]. Additionally, smoking has been identified to alter the composition of the gut microbiota.

Moreover, the potential exposure of colon mucosa to toxins from *Bacteroides fragilis* has been proposed as a risk factor for the development of colorectal cancer [22]. The *B. fragilis* toxin induces tumorigenesis in colonic epithelial cells through mechanisms reliant on signal-transducer-and-activator-of-transcription 3 (STAT3) and interleukin-17 (IL-17) activity [23]. Oxidative stress is

pivotal in the onset of colorectal cancer. Reactive oxygen species (ROS), generated as by-products of normal cell metabolism in the gastrointestinal tract, are implicated in this process. The toxin produced by *Bacteroides fragilis* stimulates the generation of ROS in intestinal epithelial cells (IECs) and dendritic cells [24].

Peptostreptococcus and *Fusobacterium* contribute to colorectal cancer pathogenesis and, as such, can serve as biomarkers for the early detection of the disease [25]. Notably, *F. nucleatum* has recently surfaced as a potential contributor to colorectal cancer susceptibility, acting during the initial stages of promoting colorectal carcinogenesis [26]. The heightened presence of *Fusobacterium nucleatum* in individuals with CRC appears to play a potential role in the progression from adenoma to cancer [27]. Castellarin *et al.* documented the over-representation of these microbes in colorectal tumor tissue, establishing their invasive nature [28]. Additionally, Kostic *et al*. provided further evidence by demonstrating the presence of these species in human colonic adenomas [29]. Regarding the mechanisms through which *Fusobacterium* contributes to carcinogenesis, it has been suggested that its interaction with E-cadherin enhances the malignant potential of CRC by increasing inflammation and antagonizing the immune function of T cells. Another proposed mechanism is that Fusobacteria may promote colorectal cancer by activating Wnt/β-catenin signaling, inducing DNA damage through ROS production, and activating oncogenes [30].

Boleij *et al*. demonstrated that the distinct association of *S. gallolyticus* with colonic malignancy is attributed to tumor cell metabolites that support the survival of *S. gallolyticus*. This bacterium produces virulence factors, such as a pilus protein featuring a collagen-binding domain, enabling its growth in the microenvironment of colon tumors. Additionally, it exhibits heightened inflammatory signals, including Ptgs2 (COX-2) [31].

In the context of colonic polyp carcinogenesis (CPC), scientific evidence points to the involvement of *Clostridium perfringens* and species within the *Atopobium* cluster, notably *Enterobacteriaceae* and *Staphylococcus sp*., highlighting their association with colon tumorigenesis [27].

The pathogenesis of CRC has been linked to two strains of *E. coli*, characterized as genotoxic and tightly adherent. The prevalence of mucosa-associated *E. coli* was notably higher in colon tissue from individuals with adenocarcinomas compared to control samples. Furthermore, *E. coli* isolated from colon cancer patients demonstrated the ability to persist in the gut, triggering colon inflammation, causing epithelial damage, and promoting cell proliferation [32].

In cases of colorectal cancer, elevated oxidative and genotoxic levels have been noted in the gastrointestinal tract [16]. Notably, there were increased levels of bile acids in the aqueous phase of feces. Bile acids have the potential to induce cytotoxic effects on the colonic epithelium and enhance the proliferation of malignant cells [33].

Bacterial Influence and Defense Mechanisms in Colorectal Cancer Prevention

Eubiosis is characterized as the state of a well-balanced and harmonious gut microflora ecosystem [34]. Creating a eubiotic state holds potential in both preventing and treating colorectal cancer. Restoring balance to the gut ecosystem can be achieved through the administration of probiotics, prebiotics, and synbiotics. These interventions work to establish homeostasis by counteracting harmful pathogens, promoting the growth of beneficial indigenous bacteria, modulating immunological responses, and repairing the intestinal mucosa [35]. The composition of the intestinal microflora plays a pivotal role in influencing the response to treatments for colorectal cancer (Fig. 1).

Currently, research indicates that the normal microbiota consists of both beneficial and pathogenic bacteria. If pathogenic bacteria proliferate excessively, it can initiate an inflammatory process leading to the production of carcinogenic compounds. It is crucial to acknowledge the protective role that a healthy microbiota plays in preventing detrimental health conditions [15].

Probiotics present an appealing option as a potential adjunct to treatment due to their cost-effectiveness and minimal associated adverse effects. The existing evidence also indicates a substantial clinical impact of probiotics. For example, in a study involving 168 patients assessed post-colorectal cancer surgery, those who received probiotics demonstrated a significantly reduced rate of all major postoperative complications compared to the placebo group (28.6% vs. 48.8%, $p = 0.010$) [36].

Furthermore, probiotic microorganisms can diminish the population of pathogenic bacteria through various mechanisms, including competing for nutrients, growth factors, and adhesion receptors. Certain probiotics can generate antibacterial substances such as bacteriocins, reuterin, hydrogen

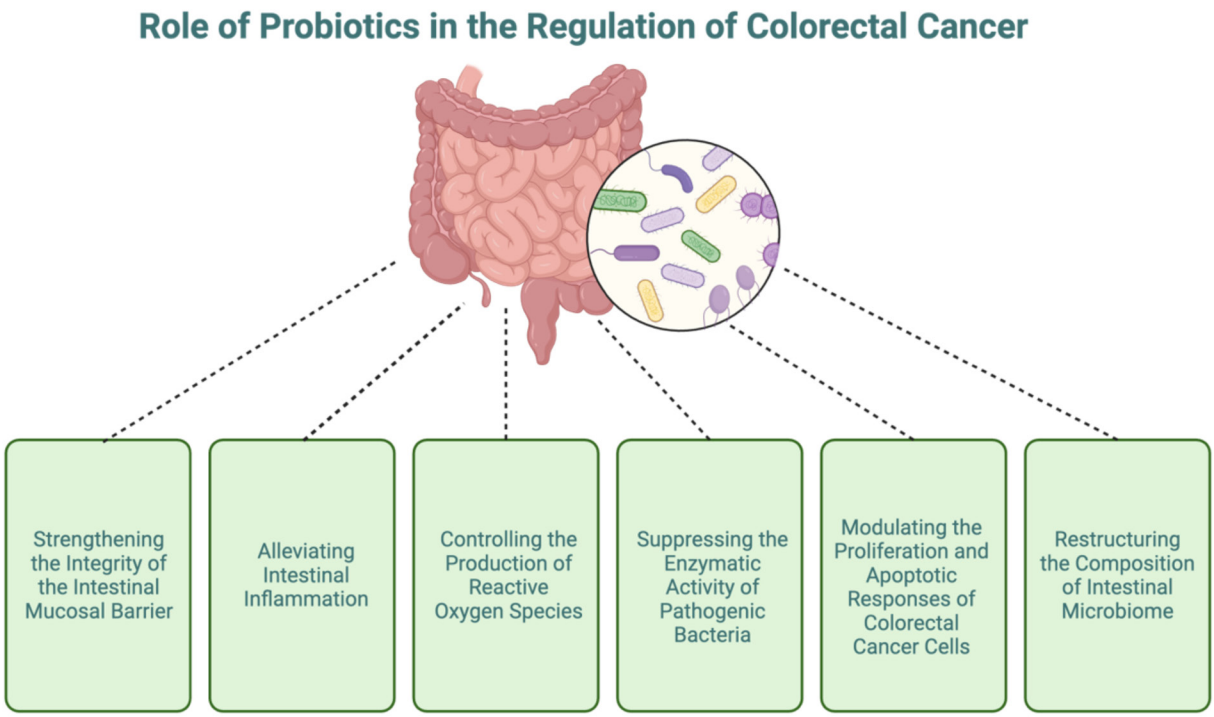

Fig. 1. Mechanisms Governing the Role of Probiotics in the Regulation of Colorectal Cancer. *Created with BioRender.com (accessed on 20 December 2023).*

peroxide, and lactic acid, effectively inhibiting the growth or eliminating pathogenic bacteria from the intestinal lumen. The positive alterations in the composition of the intestinal microbiota are directly linked to a reduced risk of developing colorectal cancer [37].

The anticancerous (ACA) and antimutagenic activity (AMA) of probiotics stems from specific mechanisms, including their capability for [33, 38]:

A) Inhibiting mutagenesis and binding or degrading of mutagens by probiotics.

B) Inhibition of the transformation of non-toxic procarcinogens into potent carcinogens is achieved by probiotics.

C) Acidification of the intestinal environment through the generation of short-chain fatty acids (SCFA) during the breakdown of non-digestible carbohydrates.

D) Augmentation and adjustment of the host's innate immune response through the secretion of anti-inflammatory molecules.

Probiotics boost the integrity of the intestinal barrier by influencing the expression of tight junction proteins, for example, claudin-1 and occludin. Additionally, they stimulate intestinal cells to produce mucin [24]. *Bifidobacterium infantis* and *Lactobacillus acidophilus* were identified as agents that safeguard intestinal permeability. They achieve this by controlling the expression of occludin and claudin-1 proteins while shielding against the activation of nuclear factor kappa-B (NF-kB) induced by IL-1β in Caco-2 cells [39]. One potential mechanism through which probiotics enhance the stability of the colonic environment is by influencing colonic macrophages. They engage in probiotic phagocytosis, mitigating deep tissue damage following infection by secreting anti-inflammatory mediators [2].

Evidence indicates a substantial decrease in the abundance of fecal putrefactive bacteria, such as coliforms, alongside an increase in commensal bacteria like *Lactobacillus* and *Bifidobacteria.* This shift has been linked to a reduced occurrence of colonic adenocarcinoma [40]. Several bacterial enzymes, including β-glucuronidase and nitroreductase, exert a pivotal role in cancer development by hydrolyzing carcinogenic compounds. Insights from animal studies suggest that the intake of yogurt starter bacteria has the potential to diminish the activity of these enzymes. This observation points towards a plausible mechanism through which probiotics may act to prevent colorectal cancer [41].

Beyond their implicated role in CRC prevention, probiotics exhibit anti-tumorigenic activity, hinting at a potential application in treating established tumors. A conceivable mechanism involves the modulation of both mucosal and systemic immune responses. Research has highlighted instances of probiotics enhancing anti-tumor immunity through processes such as cytokine production and the alteration of T-cell function [40].

The gut microbiota is pivotal in promoting the development of the immune system and establishing immune tolerance — a mechanism that modulates the immune system to safeguard the host organism against pathogens. Supplying an adequate amount of probiotics and cultivating a favorable microbiota for immune system support represents an approach to immunomodulation for the benefit of the host organism. The utilization of probiotics for immunomodulation is a widespread and expanding practice, facilitated through the interaction between immune cells in the gastrointestinal tract and probiotic microorganisms or their metabolites [42].

A newly identified protein, P8, derived from probiotics, demonstrates the ability to inhibit the progression of colorectal cancer. P8 exhibits the capacity to enter cell membranes through endocytosis, leading to the arrest of the cell cycle in DLD-1 cells. This effect is achieved by down-regulating CDK1/Cyclin B1 [43]. An *et al*.'s investigation unveiled the anti-cancer mechanisms underlying the actions of P8. Firstly, endocytosed P8 in the cytosol was observed to undergo translocation into the nucleus facilitated by KPNA3 and importin. Once in the nucleus, P8 directly bound to GSK3β introns, causing disruption in its transcription. Secondly, cytosolic P8 demonstrated a specific binding affinity to GSK3β, preventing its inactivation by protein kinases AKT/CK1ε/PKA. This active GSK3β, in turn, exhibited robust phosphorylation of β-catenin, leading to its degradation [44].

Probiotics contribute to the augmentation of dietary fiber fermentation, resulting in elevated levels of anti-tumor compounds, such as short-chain fatty acids (SCFAs), conjugated linoleic acids (CLAs), or phenols. These compounds have demonstrated potential therapeutic effects against colorectal cancer. SCFAs, in particular, serve as an energy source for colonocytes and contribute to the induction of acidosis and apoptosis in CRC cells [45]. Elevated concentrations of short-chain fatty acids in the colon appear to bring about several positive effects, including heightened synthesis of intestinal mucus, enhanced barrier function, diminished levels of pro-inflammatory mediators and stimulation of immunosuppressive cytokines like interleukin 10 (IL-10). Additionally, the increased presence of SCFAs appears to foster the preferential growth of beneficial bacteria while suppressing pathogenic strains [46]. The utilization of short-chain fatty acids derived from the gut microbiota holds promise for both the prevention and treatment of colorectal cancer [47].

In a clinical study involving patients with colorectal cancer, the oral intake of probiotics led to elevated levels of *Bifidobacterium, Lactobacillus*, and *Enterococcus,* while concurrently reducing the levels of *Escherichia coli* and *Staphylococcus aureus* [48].

Bifidobacterium longum has been documented to inhibit the incidence of colon cancer induced by the food mutagen 2-Amino-3-methylimidazo(4,5-f) quinoline [49].

Several other lactic acid bacteria (LABs) have demonstrated protective roles against colorectal cancer. These encompass *Lactobacillus rhamnosus, Lactobacillus acidophilus, Lactobacillus salivarius, Lactobacillus casei* and *Lactobacillus plantarum*. LABs inhibit CRC initiation and progression through various mechanisms, including the induction of metabolic antioxidant activity by producing antioxidants like glutathione, superoxide dismutase, and catalase. They also play a role in suppressing inflammation by activation of anti-tumor immune effectors, tumor cell apoptosis and reducing tumor size. LABs inhibit the expression of tumor-specific proteins and polyamine components and lead to anti-tumorigenic epigenetic modifications facilitated by metabolic products like short-chain fatty acids [50, 51].

The study of Budu *et al*. evidenced the distinctive antitumor properties of *Lacticaseibacillus rhamnosus* (LGG) against two colon cancer cell types, HCT-116 and HT29, elucidating the underlying mechanisms. The probiotic exhibited a targeted pro-apoptotic effect on mitochondria, inducing cytotoxicity in both colon cancer cell lines. Notably, HCT-116 displayed heightened sensitivity to LGG's anticancer activity. Nevertheless, the data presented implies that the use of probiotics, particularly LGG, either alone or in conjunction with 5FU, holds promise in triggering apoptosis in colon cancer cells. These findings may pave the path for the development of alternative chemopreventive and chemotherapeutic agents for diverse forms of colon cancer [52].

Bashir *et al.* prove in their study that the utilization of *Enterococcus faecium* strain as adjuvant

therapy alongside anticancer chemotherapy exhibits a dual benefit – it diminishes the proliferation of cancer cells and provides a protective effect against cancer [53].

Propionibacterium freudenreichii, a probiotic present in the human gut microbiota, has demonstrated the ability to suppress colorectal adenocarcinoma cells through apoptosis mediated by short-chain fatty acids. Specifically, butyric acid, one of the SCFAs, was identified as a preventive agent against colorectal cancer. It exerts its effects by modulating the cell cycle, differentiation, and apoptosis of colon cancer cell lines [24, 54].

It is logical to consider that various bacteria with anti-tumor effects might work synergistically when administered together. The use of probiotic strains with distinct and complementary mechanisms of action could potentially yield superior outcomes compared to any single strain alone. There could be additional cooperative mechanisms among commensal bacteria. Yet, it is equally plausible that combining specific probiotics may result in a scenario where their effectiveness is mutually constrained [51].

CONCLUSIONS

All the cited studies show the impact of probiotic administration on the modification of colonic microflora, influencing the intestinal environment and the development of preneoplastic or neoplastic lesions. Recent research indicates a noteworthy distinction in the microbiome composition between patients who have developed colorectal cancer and those who have not. These findings expand our understanding of the intricate interplay between gut microflora, the development of cancer, and the efficacy of cancer treatments. Researchers face the task of pinpointing strains with the most pronounced antitumoral characteristics. Subsequently, clinical investigators should develop studies that employ well-defined bacterial strains in predetermined quantities, carefully chosen for their specific characteristics. This approach is crucial for advancing our understanding of the potential clinical applications of probiotics in preventing or treating neoplastic conditions. Nevertheless, further research is imperative to ascertain whether the synergistic interplay between probiotics and anti-cancer drugs will indeed translate into enhanced oncologic outcomes.

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