# Advances in research on the intestinal microbiota in the mechanism and prevention of colorectal cancer (Review)

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**Abstract.** The intestinal microbiota represents a diverse population that serves a key role in colorectal cancer (CRC) and its treatment outcomes. Advancements in sequencing have revealed notable shifts in microbial composition and diversity among individuals with CRC. Concurrently, animal models have elucidated the involvement of specific microbes such as *Lactobacillus fragilis*, *Escherichia coli* and *Fusobacterium nucleatum* in the progression of CRC. The present review aimed to highlight contributions of intestinal microbiota to the pathogenesis of CRC, the effects of traditional treatments on intestinal microbiota and the potential for microbiota modulation as a therapeutic strategy for CRC.

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*Abbreviations:* CRC, colorectal cancer; ETBF, enterotoxigenic *Bacteroides fragilis*; ROS, reactive oxygen species; RNS, reactive nitrogen species; CoPEC, colibactin-associated *E. coli*; BFT, *B. fragilis toxin*; SMO, spermine oxidase; MMR, mismatch repair; MUC, mucin; LTA, lipoteichoic acid; NK, natural killer; COX-2, cyclooxygenase-2; MeIQ, 2-amino-3,4-dimethylimidazo (4,5-f) quinoline; CLA, conjugated linoleic acid; GPR, G-protein-coupled receptor; HDAC, histone deacetylase; PPARγ, peroxisome proliferator-activated receptor γ; IGF, insulin-like growth factor; *EcN*, *E.coli* Nissle 1917; SOD, superoxide dismutase; GST, glutathione S-transferase; DMH, 1,2-dimethylhydrazine; GPx, glutathione peroxidase; CAT, catalase; EPS, exopolysaccharide; FMT, fecal microbiota transplantation; ICI, immune checkpoint inhibitor; PD-1, cell death protein 1; APC, adenomatosis polyposis coli; ZO-1, tight junction protein 1; TLR, Toll-like receptor

*Key words:* intestinal microbiota, colorectal cancer, intestinal barrier

**Contents**



## 1. Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, accounting for ~10% of all tumour-related deaths, and its multifaceted etiology involves genetic and environmental factors (1). The majority of CRC cases (90%) develop sporadically over time, with multiple risk factors contributing to its onset (2,3). Notably, environmental factors such as pro-inflammatory environments induce changes in the composition and structure of intestinal microbiota (4,5).

The human intestinal microbiota is key for numerous functions, including energy acquisition, intestinal epithelial repair, defense against pathogens and immune regulation (6). Certain probiotics and their metabolites exhibit anti-CRC effects by utilizing short-chain fatty acids (SCFAs) to modulate $CD8^+$ T cell activity (7). In CRC treatment, probiotics enhance the effectiveness of radiotherapy and other therapeutic modalities, mitigate side effects and improve therapeutic outcomes (8). In a recent study, the probiotic strain *E.coli* Nissle 1917 (*EcN*) demonstrated the ability to enhance the drug efficacy and overcome resistance to prodrugs, including CB1954 and fludarabine phosphate. When administered in combination with these prodrugs to BALB/c mice with CT26 tumors, *EcN* exhibits considerable antitumor effects (9). Conversely, disruption of intestinal microbiota equilibrium disrupts normal physiological functions and contributes to the onset of diseases such as inflammatory bowel disease and CRC (10). The gut microbiota produces pathogenic metabolites that trigger the release of genotoxic disease-causing agents, potentially fostering the development of CRC (11). Recent findings have revealed decreased diversity and abundance of bacterial populations in fecal samples and intestinal mucosa from patients with CRC compared with those of healthy individuals (12,13). Notably, alterations in specific bacterial populations within CRC may affect the mucosal immune response, potentially

leading to an increase in pro-inflammatory pathogenic bacteria and a decrease in probiotics. This microbial imbalance, known as dysbiosis, contributes to the development of CRC (14,15). Therefore, investigating the oncogenic roles of detrimental bacteria provides a foundation for use of intestinal microbiota and their metabolites as potential biomarkers for CRC. Intestinal microbiota hold promise as a tool for screening, diagnosing, treating and predicting outcomes in CRC. Furthermore, prior research has emphasized the potential of modulating the intestinal microbiota in conjunction with conventional therapeutic strategies to manage CRC, highlighting microbiota research as a potential avenue for prevention and therapy for patients with CRC (16,17).

## 2. Microbial mechanisms in CRC

Mechanisms through which the intestinal microbiota contribute to the onset of CRC include inflammatory pathways, intestinal microbial metabolic products, gene toxins and virulence factors, oxidative stress and regulation of antioxidant defenses (Fig. 1).

*Inflammatory pathways*. Chronic inflammation poses a key risk to CRC (18). This persistent inflammatory state may lead to mutations, suppress apoptosis and promote angiogenesis as well as cellular proliferation, thus increasing the risk of CRC (19). An imbalance in the intestinal microbiota, favoring opportunistic pathogens, can enhance mucosal permeability, facilitate bacterial translocation and activate both innate and adaptive immune responses, thereby perpetuating chronic inflammation (20).

The chronic inflammatory response within the colorectal region, mediated by the intestinal microbiota, recruits inflammatory cells and triggers the release of multiple mediators of inflammation such as IL-6 and IL-1β. This process is exacerbated by direct interactions with the intestinal epithelium, leading to recurrent damage and regenerative inflammation. Such an environment fosters the proliferation of genotoxic microorganisms in the gut, causing oxidative stress and, as a result, accumulating DNA damage within the intestinal epithelium, culminating in tumorigenesis (21,22). Key inflammatory mediators implicated in this process include TNF-α, IL-6, IL-11, IL-10 and TGF-β. IL-21 has been proven to facilitate the progression of inflammation-associated CRC in murine models of CRC (23). In experiments involving dextran sulfate-induced chronic colitis, an increase in expression of IL-21 was observed in the colon of affected mice; conversely, mice deficient in IL-21 exhibit mitigated colitis and a notable decrease in colonic tumor formation (24). Notably, the down-regulation of IL-21 is associated with increased levels of IFNγ and diminished IL-6 and IL-17 in colon tumors, underscoring the anti-tumor effects of IFNγ and the pro-tumor properties of IL-6 and IL-17 (25). IL-22, belonging to the IL-10 cytokine family, has key roles in warding off pathogens and repairing enterocytes (26,27). IL-22 facilitates CRC progression through the activation of STAT3 in tumor cells (28-30) and signals epithelial cells to produce nitric oxide, which contributes to the accumulation of genetic modifications (31).

*Helicobacter* species have also been linked to inflammatory processes in the gastrointestinal tract, leading to the upregulation of pro-inflammatory cytokines such as IL-1α, IL-1β, IFN-γ and TNF-α (32-34). In the Adenomatous Polyposis Coli minus (ApcMIN) murine model of spontaneous CRC, Wu *et al* (35) demonstrated that infestation by enterotoxigenic *Bacteroides fragilis* (ETBF) induces colitis and accelerates the cancerous process of tumors, primarily mediated by the induction of IL-17A.

The aforementioned immune mediators influence CRC development by directly or indirectly modulating signaling pathways within tumor cells. Key transcription factors are NF-κB and STAT3, both of which serve key roles in promoting cancer through inflammatory mechanisms (36-39). The NF-κB pathway is activated by cytokines such as TNF-α and IL-17, while STAT3 activation occurs in response to IL-6, IL-11 and IL-23, with studies confirming its tumor-promoting roles. NF-κB signaling is implicated in cancer progression through its activity in both neoplastic and tumor-infiltrating immune cells (40,41). In murine models, NF-κB activation in immune cells leads to the generation of pro-inflammatory cytokines such as TNF-α, IL-17 and IL-23, thereby facilitating cancer development (42,43). Additionally, genes involved in cell survival and proliferation, including Bcl-xL, Bcl-2, cellular inhibitor of apoptotic protein 2, myeloid cell leukemia 1 and survivin, are upregulated by STAT3, enhancing cancer cell proliferation and viability (44). Activated STAT3 promotes the progression of the cancer cell cycle by driving the expression of genes encoding c-Myc and cyclins B and D (45,46). In summary, the intra-tumoral inflammatory microenvironment promotes cancer development through the activation of NF-κB and STAT3 signaling pathways, leading to the upregulation of pro-survival and cell cycle-promoting genes.

*Production of cancer-associated metabolites*. Gut microbiota are instrumental in the production and degradation of intestinal contents, particularly in the metabolism of dietary components and pharmaceuticals. They regulate numerous products of metabolism, including secondary bile acids, $H_2S$ and reactive oxygen species (ROS) derived from high-fat diet, impacting the incidence and progression of CRC by regulating DNA damage, inflammatory levels, apoptosis and the activity of carcinogens (41).

*$H_2S$*. $H_2S$ is primarily involved in colon cancer etiology via its capacity to induce DNA damage, release free radicals, promote colonic mucosal inflammation and stimulate hyperproliferation of colonic mucosa. $H_2S$ inhibits key metabolic functions such as cytochrome oxidase activity and butyrate use, as well as mucus synthesis and DNA methylation.

*ROS*. Prolonged exposure to oxidative damage induced by ROS is a notable factor contributing to DNA mutations, which is a key element in colon cancer development. ROS also facilitate colon cancer cell invasion and proliferation (47).

*Secondary bile acids*. Elevated concentrations of fecal bile acids are associated with increased colon cancer incidence in humans (48). In the intestine, unabsorbed bile acids in the enterohepatic circulation undergo conversion to secondary bile acids such as deoxycholic and lithocholic acid through microbial action, particularly by bile salt hydrolase-positive

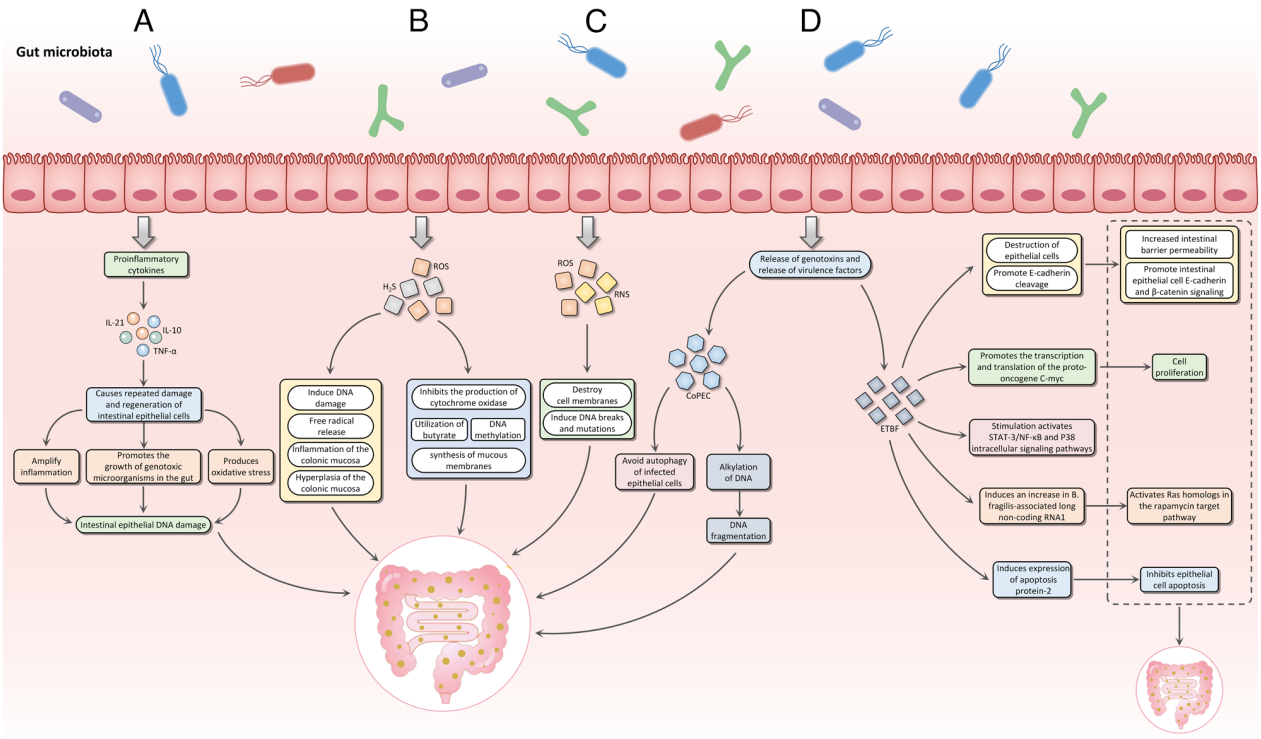


Figure 1. Key mechanisms of gut microbiota-induced CRC. (A) Imbalance of the gut microbiota is positively associated with the development of chronic inflammation, which triggers the release of inflammatory factors and exacerbates intestinal epithelial DNA damage, thus perpetuating chronic inflammation. (B) Gut microbiota promotes the occurrence and progression of CRC by regulating the production of metabolites such as ROS and $H_2S$ that disrupt mucosal homeostasis and induce DNA damage. (C) Overexpression of ROS and RNS disrupts cell membranes and induces DNA breaks and mutation. (D) Multiple types of pathogenic bacteria release genotoxic substances that induce DNA damage or chromosomal instability and virulence factors that damage the intestinal epithelial mucosal barrier, thereby promoting malignant transformation of intestinal epithelial cells and tumor development. ROS, reactive oxygen species; RNS, reactive nitrogen species; CRC, colorectal cancer; CoPEC, *Escherichia coli*; ETBF, enterotoxigenic Bacteroides fragilis.

species such as *Clostridium* spp (49). Administering secondary bile acids to mice exacerbates inflammatory damage and tumor promotion, with underlying mechanisms involving the stimulation of ROS and reactive nitrogen species (RNS), DNA damage, mutation induction and apoptosis resistance (50).

Overall, the interplay of gut microbes, such as sulfidogenic bacteria (*Fusobacterium*, *Desulfovibrio* and *Bilophila wadsworth*), leads to the production of $H_2S$, which shows notable genotoxic potential, causing DNA damage that results in genomic instability (51,52). In CRC cells, $H_2S$ inhibits mitochondrial functionality, elevates adenosine triphosphate turnover and enhances glycolytic activity (53-55). Furthermore, $H_2S$ exposure has been associated with the modulation of pro-angiogenic pathways, implicated in endothelial cell dynamics and promotion of tumorigenesis through pathways involving AKT and ERK1/2 (56-59).

The interplay between *F. nucleatum* and CRC further elucidates these mechanisms: FadA, a surface virulence factor of *F. nucleatum*, facilitates the binding to E-cadherin, inducing pro-inflammatory cytokine production while inhibiting the tumor-suppressive functions of E-cadherin. This promotes activation of β-catenin signaling pathways, resulting in inflammatory and pro-oncogenic cascades (60). Additionally, nitrogen-containing compounds, particularly N-nitroso compounds generated by nitroreductase activity, promote DNA alkylation and chromosomal mutations within intestinal cells (61,62). Polyamines originating from arginine metabolism by gut microbes exert toxic influences at high concentrations and are associated with various diseases, including cancer (63,64).

In conclusion, microbial activity within the gastrointestinal tract notably influences risk of CRC and progression through the disruption of mucosal homeostasis and the induction of DNA damage.

*Release of genotoxins and virulence factors*. Pathogenic bacteria promote carcinogenic effects through the production of virulence factors. These virulence factors primarily fall into two categories. The first category includes genotoxic agents, which directly induce DNA damage or chromosomal instability. These genotoxins may also compromise the DNA repair mechanisms, giving rise to the accumulation of mutations that result in cell proliferation disorders and tumor development. For example, certain strains of *Escherichia coli* possess genotoxins such as cytotoxic necrotizing factor, cycle-inhibiting factor and colibactin. Colibactin is a secondary metabolite that damages DNA, produced via its pks island. In addition, members of the *Enterobacteriaceae* family, including *Citrobacter koseri, Klebsiella pneumoniae* and *Enterobacter aerogenes*, produce colibactin (65,66). Colibactin-associated *E. coli* (CoPEC) can avoid autophagic degradation within infected epithelial cells, giving rise to DNA alkylation, which results in double-stranded DNA breaks. Colibactin interferes with the human cell cycle and contributes to genome

lability. Furthermore, the internalization of CoPEC strains is associated with increased production of ROS, which further exacerbates the incidence of double-strand DNA breaks (67). Notably, CoPEC infection is associated with a decrease in tumor-infiltrating T lymphocytes, giving rise to increased resistance to immunization therapy in both human and mouse models (68,69).

The second category encompasses more aggressive virulence factors that stimulate epithelial cell proliferation and foster malignant transformations by modulating gene expression, thereby compromising the intestinal epithelial mucosal barrier. ETBF strain produces the *B. fragilis* toxin (BFT) (70). BFT has been implicated in disrupting the protective layer of the epidermis and promoting the cleavage of E-cadherin via γ-secretase-dependent mechanisms (71). This cleavage not only increases intestinal barrier permeability but also enhances signaling associated with E-cadherin and β-catenin in enterocytes (72). Additionally, BFT stimulates the transcription and translation of the proto-oncogene c-Myc in CRC cells, leading to enhanced cell multiplication (73).

BFT can activate intracellular signalling pathways, including STAT-3, NF-κB and p38 mitogen-activated protein kinase (74). Another mechanism fostering increased proliferation is the induction of *B. fragilis*-associated long non-coding RNA, which activates the RAS homolog in the mammalian target of rapamycin signaling pathway, thus promoting tumor growth in CRC (75). Furthermore, BFT inhibits apoptosis in epithelial cells by upregulating cellular inhibitors of apoptosis protein-2 (76).

In mouse models, purified BFT upregulates the enzyme spermine oxidase (SMO) in colonic epithelial cells. SMO, which is highly expressed in inflammatory conditions, results in elevated ROS production and DNA damage (77,78). In a colonic adenoma-carcinoma progression model involving somatic APC inactivation, BFT-induced disruption of the intestinal barrier leads to inflammatory responses mediated by IL-23 and IL-17. This inflammation results in DNA damage within epithelial cells, facilitating tumor formation (79). BFT promotes the release of pro-inflammatory signals that drive regulatory T cell/T helper cell 17 responses from the colonic epithelium, promoting inflammatory pathways and resulting in the transformation of enterocytes into cancerous entities.

*Oxidative stress*. Oxidative stress arises from a disequilibrium between ROS, RNS and antioxidant defenses (80). This adversely impacts cellular biomolecules, disrupts cytomembrane and induces DNA fission and damage (81). Oxidative stress activates the NF-κB pathway and upregulates the expression of pro-inflammatory cytokines and anti-apoptotic signals (82,83).

ROS production can occur due to the activity of intestinal microbiota and immune cells, such as macrophages and neutrophils, in response to inflammatory stimuli from pathogenic bacteria or other environmental cues (17,84). Certain bacteria, including *Lactobacillus* and *Bifidobacterium*, generate RNS, while *Enterococcus faecalis* promotes the progression of CRC by producing hydroxyl radicals that induce gene saltation and chromosome fissions (85).

The body uses various antioxidative mechanisms to restore balance during oxidative stress, including DNA repair pathways. Key DNA repair proteins, which include endo- and exonuclease, glycosylases, DNA ligases and DNA polymerases, are key for maintaining genomic stability (86). For example, DNA glycosylases have key roles in repairing and removing oxidized bases from DNA, predominantly through base excision repair (87). Additional oxidative damage is managed by nucleotide excision repair and mismatch repair (MMR) systems (88). Certain enteropathogenic *E. coli* strains inhibit the MMR system, as observed in colitis-induced CRC models (89,90). Furthermore, in APCmin/+ MMR-deficient mice, gut microbiota could induce CRC in epithelial cells deficient in MMR, underscoring the interactions between microbial communities and host genomic integrity (91).

In summary, pathogenic bacteria contribute to CRC through multifaceted mechanisms, including the release of genotoxins and aggressive virulence factors that impair cellular function and genomic integrity. By systematically studying the carcinogenic potential of gut microbiota and their distribution, specific microbial profiles associated with heightened cancer risk may be identified, leading to early clinical interventions for CRC. Moreover, non-invasive tests that detect oncogenic gut bacteria may serve as valuable tools for assessing CRC risk, fostering improvements in preventive screening strategies for emerging forms of intestinal malignancy.

## 3. Mechanism of probiotics in cancer prevention and therapy

*Modification of the intestinal microbiota composition*. Healthy gut microbiota typically exhibit a higher proportion of beneficial bacteria than pathogenic organisms. An imbalance between these can lead to chronic inflammation and dysbiosis, markedly increasing the risk of developing CRC (92,93).

Regular probiotic consumption positively influences both the quantity and diversity of gut microbial populations (94-97). Notably, strains such as *Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *B. infantum* effectively modulate the gut microbiota by decreasing the prevalence of pathogenic bacteria, including *Escherichia*, *Pseudomonas*, *Helicobacter* and *Chlamydia*, while promoting beneficial probiotic populations such as *Lactobacillus*. This shift in microbiota composition is associated with a decreased risk of colon cancer, manifesting as decreased tumor incidence, multiplicity and growth (98).

Probiotic microorganisms decrease harmful bacterial populations through several mechanisms, including competition for nutrients, growth factors and adherence sites. Certain probiotics produce antibacterial compounds, such as bacteriocins, reuterin, hydrogen peroxide and lactic acid, which inhibit or eliminate the growth of pathogenic organisms in the gut (99). Thus, the favorable alteration of the intestinal microbiota composition is associated with a lower risk of developing CRC.

Thus, probiotics enhance the intestinal microbiota composition by increasing the abundance of commensal and protective bacteria, while decreasing the prevalence of pathogenic strains. This modulation serves a key role in the prevention and management of CRC.

*Changes in metabolic activity of the intestinal microbiota*. Modifying microbial metabolism via the intake of probiotics can affect the risk of CRC by changing the activity of enzymes. Certain enzymes, involving β-glucosidase, β-glucuronidase, nitrate reductase, azoreductase and 7-α-dehydroxylase, convert polycyclic aromatic hydrocarbons, heterocyclic aromatic amines and primary bile acids into active carcinogens (100). *In vitro* (101-104), *in vivo* (105-108) and clinical investigations (109) have proved that the intake of selected probiotic strains decreases activity of these harmful enzymes, most notably β-glucuronidase and nitrate reductase. By decreasing the populations of pathogenic bacteria within the gut microbiota, probiotics decrease production of intestinal carcinogenic compounds (110). For example, certain strains of *Lactobacillus* inhibit the enzymatic activity associated with the dehydroxylation of primary bile acids, and *L. rhamnosus* GG can decrease β-glucuronidase activity (111). Additionally, oral intake of *L. acidophilus* and *B. bifidum* for >3 weeks decreases nitroreductase activity in stool samples (112).

Consequently, probiotics serve a key role in regulating enzyme activity associated with carcinogenic pathways, thus preventing the generation of carcinogens and facilitating both the prevention and therapy of CRC.

*Improvement of the intestinal barrier*. Probiotics serve a considerable role in CRC prevention by modifying the properties of the intestinal barrier, which includes factors such as colonic pH, mucin (MUC) production and the expression of cellular junction proteins. These modifications restore the integrity of the intestinal barrier and prevent excessive enterocyte proliferation and adhesion (113,114).

Metabolism of probiotics leads to the production of organic acids such as lactic, acetic and propionic acid. These organic acids serve to lower intestinal pH (115). An acidic environment in the colon inhibits the proliferation of putrefactive and pathogenic microorganisms, as well as the activity of bacterial enzymes responsible for generating carcinogenic compounds (116). For example, *Bifidobacterium* species produce notable amounts of organic acids through glucose fermentation, effectively lowering intestinal pH and suppressing the proliferation of pathogenic bacteria and fungi, including *Shigella*, *Typhi*, *Proteus* and *Pseudomonas aeruginosa* (117). Furthermore, a low pH environment prevents the adhesion of these pathogens and their toxins to enterocytes (118,119). *In vitro* studies have corroborated that *Lactobacillus bulgaricus* inhibits the proliferation of clinical isolates of *H. pylori*, while *Lactobacillus casei* subsp. *rhamnosus Lcr35* decreases proliferation of enteropathogenic and enterotoxigenic *E. coli* and *K. pneumonia* (120-122). The inhibition effect is predominantly noted under acidic pH conditions, implying that probiotics modulate pH levels to enhance their survival and maintain metabolic activity in a relatively low pH environment.

Furthermore, probiotics stimulate the expression of specific adhesive proteins, including MUCs. MUCs are classified as either secretory or transmembrane glycoproteins, with the gel-forming secretory MUCs (MUC-2, MUC-5AC, MUC-5B and MUC-6) forming the primary components of the mucosal layer. These MUCs are synthesized by specialized mucus-secreting cells, known as goblet cells, which are distributed throughout the gastrointestinal epithelium (123). MUC genes, including MUC1, MUC2, MUC3, MUC4 and MUC5AC, are expressed in the human colon (124), and abnormal MUC expression is associated with numerous types of gastrointestinal disease, such as inflammatory bowel disease and CRC, which are characterized by dysregulated intestinal barrier (125). Probiotic intervention can enhance the gastrointestinal mucosal barrier, impeding pathogenic bacteria adhesion (126). For example, the administration of *L. plantarum* and *L. rhamnosus* notably increases the expression of MUC-2 and MUC-3 in enterocytes, thereby fortifying the mucosal barrier and decreasing sensitivity to pathogen invasion (127). The effects of these *Lactobacilli* species have been validated in an HT-29 cell culture model, where they inhibited the adhesion of enteropathogenic *E. coli* and subsequent infection of the intestinal epithelium (128).

Inflammation and carcinogenesis increase intestinal permeability, primarily by altering the components and expression of cellular junction proteins that facilitate adhesion between colonocytes. These proteins, located at the apical junction between cells, form tight junctions through membrane-spanning proteins that are associated with the cytoskeleton of colonocytes (129).

Lipoteichoic acids (LTA) produced by probiotics regulates extracorporeal epithelial barrier function (130). Treatment with LTA from *Lactobacilli* increases the expression of tight junction protein 1 (ZO-1) through a toll-like receptor (TLR)-2 dependent pathway (131). Furthermore, pretreatment with LTA from *Bacillus subtilis* improves barrier integrity and increases tight junction protein levels, including ZO-1 and claudin-3 (132). Additionally, peptidoglycan secreted by *Lactobacillus* and *Bifidobacterium* species elevates the levels of tight junction proteins, such as claudins, occludin and ZO-1, thus improving both permeability and integrity of the intestinal barrier via TLR2 signaling (133). Notably, *Lactobacillus* and *Bifidobacterium* also enhance the production of secretory IgA and increase levels of ZO-1 and occludin in the Caco-2 cell line (134).

In conclusion, leveraging the barrier-repairing functions of probiotics offers prospective tactics for the prevention of CRC by maintaining the integrity of the intestinal barrier and attenuating the risks associated with pathogenic invasion.

*Immunomodulation*. Immunomodulation has a key part in preventing the immune evasion of CRC cells (135). Probiotics influence the proliferation and differentiation of T cells, particularly by enhancing the ratio of effector to regulatory T cells (136).

Beyond their general immunomodulatory effects, probiotics activate the immune system by increasing the production of immunoglobulins, enhancing the activity of macrophages and lymphocytes and boosting the production of IFN-γ (137). For example, probiotic supplementation stimulates macrophages while simultaneously inhibiting the proliferation of CRC cells (138). Similarly, therapy with the *L. casei* strain Shirota increases T cell-mediated cytotoxic activity against CRC cells (139) and activates natural killer (NK) cells, which are key in preventing tumorigenesis in C57Bl/6 mouse models (140,141). Enhancement of NK cell activity is associated with the production of IL-12, a cytokine integral to NK

cell function (142). Additionally, the combination of resistant starch and *B. lactis* markedly increases the apoptosis rate of rat CRC cells (143). In a clinical trial, administration of *B. polyfermenticus* in patients with CRC resulted in improved counts of circulating $CD4^+$ and $CD8^+$ T cells as well as elevated levels of IgG (144).

Furthermore, probiotics downregulate the expression of enzymes involved in the production of pro-inflammatory prostaglandins, thereby decreasing cellular proliferation and the inflammatory response. Purified exopolysaccharides from *L. acidophilus* exhibit modulatory effects on apoptosis and NF-κB signaling pathways in human CRC (145). Moreover, *L. reuteri* inhibits NF-κB signaling, which leads to decreased expression of cyclooxygenase-2 (COX-2), cyclin D1 and Bcl-2, while inducing the expression of pro-apoptotic factor Bax (146). COX-2 is a key enzyme in the synthesis of prostaglandin E2, a compound known to promote inflammatory responses (147). Therefore, downregulating COX-2 expression exerts substantial effects on inflammatory activity (148).

The integration of immunotherapy and radiotherapy that uses gut microbiota immunomodulation has shown promising initial results in treating CRC (149). However, further research into the role of intestinal microbiota in CRC is key for developing personalized interventions that enhance anticancer efficacy while minimizing adverse effects.

*Binding and degradation of carcinogenic compounds in the intestinal lumen*. The presence of toxic compounds in the intestinal lumen creates a conducive environment for cancer cell proliferation. By contrast, probiotics can interact with these carcinogenic compounds through mechanisms such as cation exchange, effectively binding to them and facilitating their excretion from the body. This binding process decreases risk of cancer cell proliferation (150).

Several strains of probiotics disintegrate and inactivate cancer-causing substances, particularly N-nitroso compounds and heterocyclic aromatic amines. Strains such as *B. longum*, *L. acidophilus* and *Streptococcus salivarius* can bind to and promote the excretion of heterocyclic aromatic amines and mutagenics, including 2-amino-3,4-dimethylimidazo (4,5-f) quinoline (MeIQ) and 2-amino-3-methyl-3H-imidazo (4,5-f) quinoline in feces (151). Zhang and Ohta (152) investigated the binding capacity of heterocyclic amines {Trp-P1 (3-amino-1,4-dimethyl-[5H]pyridine[4,3-b]indole)}, Glu-P-1 (pyrolyzates of glutamic acid), Phe-P-1 (isolated from a phenylalanine pyrolyzate), MeIQ [2-amino-3,4-dimethylimida zo(4,5-f)quinoline], IQ [2-amino-3,4-dimethylimidazo (4,5-f) quinoline] and MeIQX [2-amino-3,8-dimethylimidazo(4,5-f) quinoxaline] with both whole cells and cell wall skeleton components of *L. acidophilus* IFO (Institute for Fermentation, Osaka) 13951 and *B. bifidum* IFO 14252, indicating that the intact peptidoglycan of cell walls contributes to the xenobiotic-binding activity of these bacteria (153). Similarly, studies have reported the binding capacity of heterocyclic amines by various human intestinal and lactic acid bacteria (154,155). The capacity for binding and degrading carcinogenic compounds depends on the specific bacterial strain, microbial viability, type of carcinogenic compound, probiotic dosage and environmental factors such as pH, bile salt presence and gastrointestinal enzymes (156,157).

Probiotics may exert detoxifying abilities against mycotoxins, which are carcinogenic substances (158,159). Mycotoxins, produced by fungi, contaminate food products made for human consumption or animal feed. Certain dairy probiotics, such as *Propionibacteria*, effectively remove mycotoxins from aqueous solutions *in vitro* (160,161). Additionally, dairy *Propionibacteria* bind to cyanotoxins such as microcystin-leucine-arginine, as well as heavy metals such as lead and cadmium (162,163).

Thus, future studies should investigate the ability of probiotics to degrade and detoxify carcinogenic compounds to provide novel insights into CRC prevention.

*Inhibition of proliferation and induction of apoptosis in cancer cells*. Apoptosis, or programmed cell death, is a mechanism in regulating cellular equilibrium and eliminating cancer cells. This process involves three interrelated pathways: The perforin/granzyme, mitochondrial/intrinsic and death receptor/extrinsic pathways (164-166). Key genes involved in apoptotic regulation include TNF, inhibitors of apoptosis proteins, caspases, Bcl-2 and p53 (167).

For example, Chen *et al* (168) revealed that the apoptosis in SW620 tumor cells induced by probiotics is associated with increased expression of Caspase-3 and decreased expression of Bcl-2. The Bcl-2 family comprises both antiapoptotic, such as Bcl-2, and proapoptotic proteins, such as Bax. The balance between these proteins is key for regulating the intrinsic apoptotic pathway. An elevated Bax/Bcl-2 ratio is associated with heightened levels of activated caspase-3, resulting in the increased sensibility of cancer cells to fade out. Probiotics have significant apoptosis-inducing effects on cancer cells, but they do not affect normal colonic epithelial cells. If probiotics have apoptosis-inducing effects on normal cells, they may disrupt the integrity of the intestinal barrier and thus impair intestinal defenses, thus creating favourable conditions for the development and progression of CRC. Therefore, when using probiotics for therapeutic purposes, their potential effects on normal cells need to be carefully assessed to ensure the safety and efficacy of the treatment.

Probiotics abduct fadeout in cancer cells through mechanisms involving the modulation of Bax/Bcl-2 ratio and caspase activation (169-171) (Fig. 2). Konishi *et al* (172) investigated a probiotic-derived tumor suppressor molecule known as iron-chromium, which inhibits colon cancer progression via JNK-mediated pathways. An *in vitro* study revealed that strains such as *E. faecium* RM11 and *L. fermentum* RM28, both present in acidophilus milk, decrease the diffusion of Caco-2 colon cancer cells by 21 and 23%, respectively (173). Furthermore, *L. acidophilus* and *B. bifidum* display enhanced cytotoxic effects against colon cancer cell lines by upregulating Bax, IFN-γ and TNF-α expression, while downregulating Bcl-2 expression (174).

Alshuail *et al* (175) reported that apoptosis can occur through mitochondrial pore formation pathways, which facilitate caspase activation. Moreover, *Propionibacterium* induces apoptosis in CRC cells via short-chain fatty acids that act on mitochondria (176). Moreover, *L. acidophilus* has been shown to induce apoptosis by increasing the mRNA expression of survivin while decreasing the expression of second mitochondria-derived activator of caspases (177).

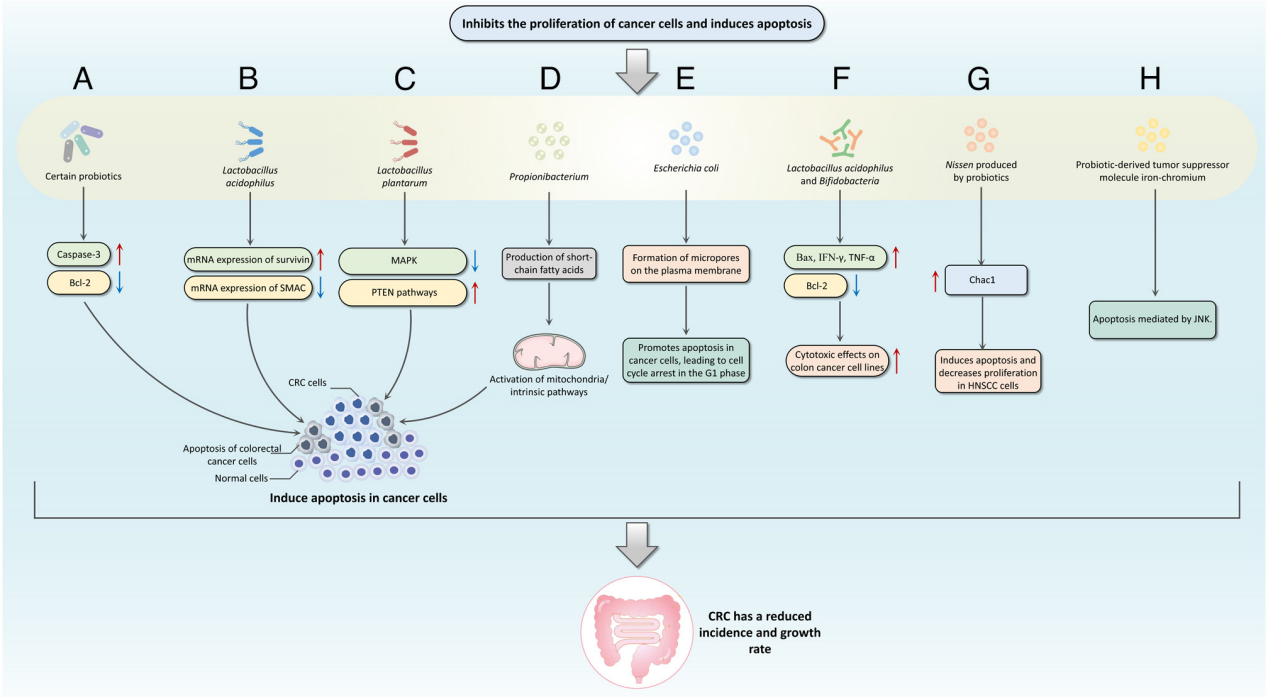


Figure 2. Inhibition of proliferation and induction of apoptosis in cancer cells. (A) Probiotics increase the expression of caspase-3 and inhibit the expression of Bcl-2, leading to a resurgence of reduced susceptibility of CRC cells. (B) *Lactobacillus acidophilus* induces apoptosis in CRC cells by increasing the mRNA expression of survivin while decreasing the expression of SMAC. (C) *Lactobacillus plantarum* increases the expression of MAPK and blocks PTEN signaling, inhibiting the proliferation of CRC cells. (D) *Propionibacterium* activates mitochondria and increases the production of short-chain fatty acids, thereby inducing apoptosis in CRC cells. (E) *Escherichia coli* induces apoptosis in CRC cells by forming micropores in the plasma membrane and leads to cell cycle arrest in $G_1$ phase. (F) *Lactobacillus acidophilus* and *Bifidobacterium bifidum* increase Bax, IFN-γ and TNF-α expression while inhibiting Bcl-2 expression, resulting in increased sensitivity of CRC cells to cytotoxic effects. (G) Nissen produced by probiotics inhibits the proliferation of cancer cells by increasing intracellular calcium levels, inducing cell cycle arrest and activating the expression of Chac1. (H) Probiotic-derived molecule known as iron-chromium blocks the JNK-mediated pathway to inhibit colon cancer progression. CRC, colorectal cancer; SMAC, second mitochondria-derived activator of caspase; Chac1, intracellular calcium levels, abducting cell cycle arrest and stimulating the cation transport regulator homolog 1; HNSCC, head and neck squamous cell carcinoma.

*L. casei* considerably increases expression of the human β-defensin 2 gene in the HT-29 colon cancer cell line (178). Małaczewska and Kaczorek-Łukowska (179) further demonstrated that nisin, a bacteriocin, abducts fadeout and decreases multiplication in head and neck squamous cell carcinoma cells by increasing intracellular calcium levels, abducting cell cycle arrest and stimulating the cation transport regulator homolog 1.

Overall, there is an ongoing effort in research to clarify the fadeout of potential of probiotics against cancer (180,181). As research on probiotics continues, the ability of probiotics to induce apoptosis is gradually being uncovered, presenting the opportunity to use probiotic-based regimens as adjuvant therapy alongside conventional anticancer chemotherapy (182,183). Despite the identification of numerous apoptotic proteins, the precise molecular mechanisms by which they exert their effects remain to be fully elucidated.

*Production of biological substances with anticarcinogenic activity [SCFAs and conjugated linoleic acid (CLA)].* SCFAs and CLA are bioactive compounds generated by intestinal probiotics, which exhibit notable anticarcinogenic properties (184,185). SCFAs are effective in promoting apoptosis in cancer cells and inhibiting the formation of high levels of secondary bile acids, thereby serving as a preventive measure against CRC (186). CLA exerts its anticancer effects through unique anti-proliferative and pro-apoptotic mechanisms (187).

*Role of SCFAs.* SCFAs have a notable impact in maintaining intestinal barrier integrity. They enhance the secretion of IL-18, MUC2 and antibacterial peptides, while also increasing the expression of tightly linked proteins in intestinal epithelial cells (188,189). SCFAs are conducive to the improvement of the lining of gut function by regulating pH levels within the gut (190).

SCFAs influence immune responses by modulating T cell function through G-protein-coupled receptors (GPRs), such as GPR41, GPR43 and GPR109A, as well as Olfactory receptor 78 receptor signaling. They also inhibit histone deacetylase (HDAC), which impacts the inhibition of NF-κB (191,192). Notably, butyrate inhibits HDAC activity, leading to histone hyperacetylation, which results in changes to the expression of genes involved in cell cycle regulation, differentiation, apoptosis and cancer progression (193-195). For example, hyperacetylation can activate the p21 gene, contributing to $G_1$ cell cycle arrest (196).

SCFAs promote the migration of neutrophils to the site of cellulitis and enhance their phagocytic ability. They inhibit the secretion of pro-inflammatory cytokines such as IL-6, IL-8, IL-1β and TNF-α by intestinal macrophages and may promote intestinal IgA production by B cells (197,198). SCFAs have

been revealed to regulate the production of regulatory T and T helper cell subsets in response to different cytokine environments (199,200).

SCFAs accelerate programmed cell death and restrain the proliferation of tumor cells, effectively hindering tumor development. For example, butyrate regulates Bcl-2 family proteins and induces apoptosis by upregulating BAK and downregulating Bcl-xL (201,202). It also decreases the levels of cyclin D1 and c-myc, which are key for intestinal tumor development, via transcriptional suppression in human colorectal adenocarcinoma cells (203,204). Moreover, both propionate and butyrate are associated with the modulation of autophagy and type II programmed cell death in CRC cells (205,206).

*Role of CLA*. CLA, an important metabolin synthesized by probiotics such as *Lactobacillus* and *Bifidobacterium*, has been recognized for its anticancer effects (207). The antiproliferative and apoptosis-promoting activity associated with CLA arises from its capacity to activate peroxisome proliferator-activated receptor γ (PPARγ), which has a key role in adjusting lipid elimination, apoptosis and immunological system functions (208). Various species of probiotic, such as *Lactobacilli* and *Bifidobacteria*, transform LA into CLA, with strains such as *L. bulgaricus* and *Streptococcus thermophilus* demonstrating higher conversion efficiency (209).

Studies have indicated that CLA decreases cell proliferation and induces apoptosis in cancer cells by downregulating key pathways. For instance, CLA diminishes ErbB3 gene expression and inhibits the PI3K/Akt pathway, in addition to upregulating caspases 3 and 9 while decreasing Bcl-2 expression (210-212). In the context of HT-29 human CRC cells, CLA induces apoptosis by suppressing insulin-like growth factor (IGF)-II synthesis and downregulating IGF-I receptor signaling (213). Furthermore, CLA promotes $G_1$ cell cycle arrest in CRC cells and inhibits the production of eicosanoids through two mechanisms: Replacing arachidonic acid in the cytomembrane and interfering with the activity of epoxidase and fatty acid oxidase, enzymes primarily in charge of eicosanoid synthesis (214,215). CLA produced by probiotics upregulates the PPARγ gene, which participates in biological processes, including the control of apoptosis. As a result, CLA induces apoptosis and decreases viability in cancer cells (216,217).

Previous research has highlighted a strain derived from the human intestine, *B. breve* CCFM683, which demonstrates notable isomerase activity for free LA and is effective in ameliorating inflammatory bowel disease in mouse models through the accumulation of CLA and modulation of gut microbiota (218,219). Similar effects have been reported in other bifidobacterial strains, such as *B. bifidum* S17 and *B. longum* subsp.

In conclusion, SCFAs and CLA generated by probiotics serve essential roles in cancer prevention through mechanisms including apoptosis induction, modulation of inflammation and enhancement of intestinal barrier functions. To capitalize on the potential of probiotics in the prevention and therapy of CRC, further study is warranted to identify mechanisms of action on human colon cancer cells.

*Effects on other mutagenic and carcinogenic factors*. Probiotics may affect mutagenic and carcinogenic agents, thereby serving a role in cancer prevention. They can modify the activity of enzymes involved in expelling toxin processes from cells, preventing the accumulation of toxins within the cells and thereby mitigating the effects of free radicals and potential carcinogens. Furthermore, probiotics exert their antitumor effects through mechanisms such as competitive adhesion mechanisms, increasing the diversity of the intestinal flora, and inhibiting the activity of harmful enzymes in the gut (220,221).

Imbalances in intestinal microbiota give rise to an increased release of harmful enzymes such as β-glucuronidase, β-glucosidase, azoreductase and nitroreductase, resulting in the generation of carcinogenic substances (222). These enzymes can generate toxic metabolites, including $H_2S$, aromatic amines, carcinogenic aglycones and acetaldehyde (223). For example, the bacterium *Clostridium perfringens* produces IQ from dietary components by secreting β-glucuronidase (224). Similarly, azoreductase enzymes, commonly synthesized by bacteria such as *Staphylococcus*, *Salmonella*, *Clostridium* and *Enterococcus*, metabolize mixtures such as dyes and pharmaceuticals, leading to the generation of toxic aromatic amines (225,226). The intake of probiotics decreases activity of these harmful enzymes through multiple mechanisms. *Lactobacillus* strains inhibit the enzymes responsible for the primary bile acid dehydroxylation, while *L. rhamnosus* GG specifically reduces β-glucuronidase activity (227). Additionally, oral supplementation of *L. acidophilus* and *B. bifidum* for 3 weeks decreases nitroreductase activity in stool samples (228).

Lactic acid bacteria bind to and degrade carcinogenic compounds such as nitrosamines and heterocyclic amines, as well as produce antioxidant enzymes such as superoxide dismutase (SOD), glutathione S-transferase (GST) and glutathione reductase. These enzymes absorb reactive intermediates, thus decreasing the activity of several carcinogenic compounds, including 1,2-dimethylhydrazine (DMH) and N-methyl-N'-nitro-N-nitrosoguanidine (113,229). A study revealed that administering DMH to rats results in decreased activities of glutathione peroxidase (GPx), GST, SOD, catalase (CAT) and glutathione (230). Conversely, co-administration of probiotics such as *L. plantarum* and *rhamnosus* GG with chemotherapy notably elevates the activities of these enzymes, suggesting that probiotics alleviate oxidative stress during colon cancer treatment (231).

Furthermore, studies indicate that probiotics not only reduce free radicals but also upregulate antioxidant-associated genes and stimulate the production of antioxidative enzymes to increase overall antioxidative activities (232-234). The presence of selenium may support the selective enhancement of antioxidative activities by certain probiotics (235). *L. brevis LSe*, when cultured in selenium-enriched conditions, demonstrated greater radical scavenging capability compared with culture in selenium-free media (236).

Exopolysaccharides (EPSs) extracted from probiotic sources, such as *E. faecium*, *L. plantarum* RJF4 and *Weissella cibaria* GA44, exert promising antioxidative effects by scavenging free radicals. The efficacy of these EPS primarily hinges upon their saccharide constitution, formula weight and branched chain structures. Additionally, fermented products from probiotics, such as peptide extracts, exhibit notable

antioxidant potential (237-239). For example, glycine-rich antimicrobial peptide YD1, derived from *B. amyloliquefaciens* has been reported to increase the mRNA and protein levels of antioxidant enzymes such as SOD1, CAT and GPx-1 while decreasing nitric oxide and ROS levels (240).

In summary, probiotics inhibit development of CRC through multiple pathways, presenting potential avenues for clinical exploration of the treatment of CRC.

## 4. Gut microbiota in CRC treatment

Traditional approaches for managing CRC primarily involve chemotherapy and radiotherapy. However, these treatments often disrupt intestinal microbiota, potentially exacerbating the condition of the patient. Studies indicate that probiotics complement modern therapy by enhancing efficacy and minimizing toxic side effects (241-243).

*Chemotherapy*. Chemotherapy is the standard treatment for CRC. However, this therapeutic approach often leads to disruptions in the intestinal microbiota, which exacerbates adverse effects and diminishes therapeutic efficacy. One potential strategy to counteract these negative effects is restoration of the gut microbiota (244).

The gut microbiota has a notable influence on the pharmacological actions of chemotherapeutics, including cyclophosphamide, irinotecan, oxaliplatin and gemcitabine (245). The administration of these chemotherapy drugs results in an imbalance of gut microbiota, such as decreased levels of *Lactobacilli*, *Bacteroides* and butyric acid-producing bacteria. Concurrently, there is often an increase in pathogenic bacteria, including *F. nucleatum*, *E. coli* and sulfate-reducing bacteria (246). This ecological imbalance leads to decreased chemotherapy efficacy, heightened toxicity, emergence of drug resistance and potentially the progression of CRC (247). For example, studies have revealed an increase in the number of pathogen types, such as *Enterobacteriaceae*, *Fusobacteria* and *Proteobacteria,* following irinotecan treatment in tumor-bearing rats (248-250).

Gut microbiota mitigate the adverse side effects associated with chemotherapy in patients with CRC. For example, polysaccharides derived from *Calothrix hongkongensis* modulate the intestinal microbiota by increasing the populations of propionic and butyric acid-producing microorganisms and decreasing the abundance of *Lactobacillus*, *Prevotella*_UCG-001 and *Rikenellaceae*_RC9_gut_group. This modulation positively affects the TLR signaling pathway, which leads to improved outcomes concerning 5-fluorouracil (5-FU)-induced intestinal mucositis and malnutrition (251). Furthermore, probiotic transplantation considerably alleviates symptoms such as weight loss and diarrhea in a CRC mouse model treated with irinotecan, while also decreasing intestinal mucosal damage (249). Additionally, a study involving 150 patients with CRC undergoing treatment with 5-FU revealed that intervention with *L. rhamnosus* GG during chemotherapy markedly decreased patient mortality, improved gastrointestinal symptoms such as diarrhea and decreased the necessary chemotherapy dosage (252).

Gut microbial metabolites can also improve the anti-tumor effect of drugs in colorectal cancer treatment. Previous studies indicate that butyric acid, a metabolite produced by gut microbiota, enhances the anti-tumor cytotoxicity of $CD8^+$ T cells both *in vitro* and *in vivo* by promoting the IL-12 signaling pathway in an inhibitor of DNA binding 2-dependent manner. Butyric acid has also been associated with increased the anti-tumor efficacy of oxaliplatin (253,254).

Further research on intestinal microbiota may offer novel insight and strategies for improving chemotherapy modalities in CRC.

*Radiation therapy*. Numerous studies have highlighted alterations in intestinal microbiota in patients undergoing radiation therapy, with dysbiosis linked to the emergence of complications associated with radiation treatment (255,256). Analysis of the intestinal microbiota following radiotherapy has identified a decrease in beneficial commensal bacteria such as *Bifidobacterium*, *E. faecalis* and certain *Clostridium* species, accompanied by an increase in *Lactobacillus* spp. and *Enterococcus* spp (257). These changes indicate severe side effects, dysbiosis of the intestinal microbiota and disruption to the overall microbial composition (258).

Specific gut microorganisms, such as *Bifidobacteria*, *Lactobacillus acidophilus*, *Streptococcus* and *L. casei*, alleviate the severity of radiation enteritis and associated diarrhea (259). Although there are fewer studies directly addressing the influence of gut microbiota on the efficacy of radiation therapy in patients with CRC, previous findings suggest that oral microbiota impact both the effectiveness and prognosis of radiation treatment for CRC. Notably, *F. nucleatum* can migrate to and colonize the intestinal tract, where it heavily populates the intestinal mucosa of patients with CRC, thereby negatively affecting the efficacy and outcomes of radiotherapy. Treatment with metronidazole has been shown to counteract this adverse effect (260-262).

Fecal microbiota transplantation (FMT) is a potential therapeutic strategy for improving gastrointestinal function and maintaining enterocytes following tumor radiotherapy. This approach decreases radiation-induced gastrointestinal toxicity and enhances the prognosis of patients undergoing radiation treatment for tumors (263).

In summary, both chemotherapy and radiation therapy notably affect gut microbiota, potentially impacting treatment outcomes. As understanding of these interactions increases, integrating probiotics and FMT into cancer care regimens may offer valuable avenues for enhancing the efficacy and tolerability of standard cancer treatments.

*Immune checkpoint inhibitors (ICIs)*. Immunotherapy has emerged as a promising treatment for various types of cancer, including CRC (264). The US Food and Drug Administration has approved the use of immunotherapy as a second-line treatment specifically for tumors that are deficient in MMR or exhibit high microsatellite instability (265). ICIs are key components of immunotherapy that activate T cells, enabling them to mount an effective antitumor response (266).

ICIs, which are typically monoclonal antibodies, work by blocking the interaction between programmed cell death protein 1 (PD-1) and its ligand PD-L1 or by targeting cytotoxic T lymphocyte antigen 4. This blockade facilitates the

activation of cytotoxic T lymphocytes, enhancing their ability to attack tumor cells (267).

Recent research has indicated that specific intestinal microbiota enhance the therapeutic effects of ICIs. For example, isolated strains such as *L. testosterone*, *B. pseudopodium* and *Bacteroides europaeus* from mice potentiate the effects of immune checkpoint blockade in CRC models. Notably, inosine, a metabolite produced by *B. pseudopodium*, promotes the activation of antitumor T cells when co-stimulatory signals are present (268-270). This indicates microbial metabolite-immunity pathways may enhance immunotherapy, providing valuable insight for the development of microbe-assisted therapy (271).

Specifically, oral administration of *B. bifidum* influences the immune response in CRC by maturing dendritic cells, enhancing their function, increasing cytokine secretion and activating tumor-specific T cells (272). The intestinal microbiota is implicated in ICI-induced colitis: Administration of probiotics, including strains from *Bacteroides* and *Burkholderia*, as well as FMT, alleviate ICI-induced colitis (273).

*FMT.* FMT is an emerging biological therapy that involves transferring stool from healthy donors to patients with altered microbiota suspected of contributing to disease (274). This approach aims to restore a healthy, diverse microbiome in the gastrointestinal tract, thereby promoting eubiosis and ameliorating gastrointestinal disorders (275). FMT is an established treatment for recurrent and refractory *Clostridioides difficile* infection, demonstrating success rates of 80 to 90% (276,277).

In animal studies involving CRC, FMT markedly increases the abundance of beneficial gut bacteria, such as *Muribaculaceae*, *Lachnospiraceae*, *Prevotellaceae*, *Ruminococcaceae* and *Erysipelotrichaceae*, effectively alleviating intestinal dysbiosis (278-280). Additionally, FMT is associated with the augmentation of immune cells, including $CD4^+$ and $CD8^+$ T and CD49b NK cells, and it increases expression levels of cytokines such as IFN-γ and IL-10 while decreasing levels of IL-17 and STAT3. These changes create a microenvironment that hinders the progression of CRC (281).

FMT is effective in reversing microbial dysbiosis associated with CRC (282). Restoring gut microbiota balance inhibits progression of CRC by suppressing intestinal inflammation and enhancing anti-cancer immune responses mediated by immune cells and inflammatory factors (283). This highlights the importance of understanding the interactions between intestinal microbiota and CRC, especially when considering FMT as a potential therapeutic intervention in clinical practice.

## 5. Conclusion

Intestinal microbiota serve a key role in the pathogenesis and modulation of CRC. Although pathogenic bacteria and their oncogenic mechanisms require further investigation, identifying the risk factors associated with CRC by detecting specific intestinal bacteria offers novel avenues for preventive strategies. Analyzing the distribution and composition of the gut microbiota provides insight into microbial profiles that indicate an increased cancer risk, aiding in early intervention and treatment efforts for CRC.

Furthermore, a growing body of evidence supporting the role of probiotics in CRC prevention and therapy underscores their potential for clinical applications. The negative effect of traditional treatments on the gut microbiota highlights the need for strategies that leverage probiotics to enhance efficacy while minimizing toxic side effects. However, resistance to chemotherapy drugs is a key factor affecting traditional therapy and the mechanisms of reversal of resistance to chemotherapy drugs in the gut microbiota are rarely reported. Future studies should further explore the mechanisms of different intestinal microbes regulating drug resistance in CRC, providing a new window for the treatment of CRC. The association between the intestinal microbiota and CRC holds promise for personalized approaches to the diagnosis, prevention and management of CRC.

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## Authors' contributions

WS, SM and DM wrote and edited the manuscript. SM conceived the study. CW and JZ edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

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Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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