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REVIEW

Probiotics in colorectal cancer: mechanisms, biomarkers, and adjunct strategies

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ABSTRACT Colorectal cancer (CRC) is among the most common malignant tumors and remains a leading cause of cancer-related mortality worldwide. The gut microbiota and metabolites, which are modulated by host genetics and environmental exposures, have emerged as key contributors to the pathogenesis of CRC. A key feature of gut dysbiosis in CRC is the enrichment of pathogenic bacteria alongside the depletion of beneficial commensals. Probiotic supplementation has been shown to counteract this imbalance and suppress tumor progression. Mechanistically, probiotics suppress CRC development through multifaceted actions, including directly inhibiting tumor cell growth, reducing inflammation, reinforcing the intestinal barrier, and reprogramming host immunity. This review summarizes evidence on the inhibitory role of probiotics in CRC, evaluates the potential of probiotics as predictive biomarkers, and discusses microbiome-modulation strategies designed to enhance immunotherapy and chemotherapy, thereby offering a complementary paradigm for CRC prevention and treatment.

KEYWORDS Colorectal cancer; probiotics; mechanism; biomarker; therapy

Introduction

Colorectal cancer (CRC) remains a leading cause of global cancer morbidity and mortality. This malignancy arises from a complex interplay of intrinsic and extrinsic factors. Intrinsic drivers include genetic mutations, immune dysregulation, and metabolic reprogramming within cells, while extrinsic influences encompass diet, obesity, lifestyle, and environmental exposures[1-3]. Central to this paradigm is the gut microbiota, a complex community of bacteria, fungi, archaea, viruses, and parasites that is fundamental to intestinal homeostasis. The gut microbiota consists of commensals (symbiotic, beneficial species), pathobionts (which become harmful in dysbiosis), and transient microbes[4]. This ecosystem undergoes profound dysbiosis in CRC. Despite population-level variations in baseline microbiota due to genetics and diet, consistent patterns emerge across cohorts. Specifically, a marked depletion of commensal, potentially protective species is accompanied by a selective enrichment of microorganisms with pro-carcinogenic functions[5-7]. Given the established role of dysbiosis as a driver of carcinogenesis, therapeutic strategies focused on restoring microbial equilibrium have become a major research focus. These approaches aim to reconstitute beneficial taxa and precisely modulate pathogenic host–microbe interactions[8]. Within this framework, the investigation of probiotics, both for CRC prevention and as potential adjuvants to conventional therapy, represents a critical and timely translational pursuit.

Alterations in the gut microbiota are detectable from the earliest stages of colorectal carcinogenesis, spurring interest in non-invasive screening that uses microbial abundance as an early diagnostic indicator[9,10]. In addition to diagnosis, the presence of specific probiotic species has emerged as a biomarker for predicting patient responsiveness to immune checkpoint inhibitor (ICI) therapy and long-term prognosis[11]. Notably, the depletion of these beneficial bacteria may represent a critical tipping point in tumor progression. In support of this notion, studies in animal models have consistently shown

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that probiotic supplementation can significantly suppress colorectal cancer development[12,13]. Mechanistically, probiotics exert antitumor effects by generating beneficial metabolites, strengthening the intestinal barrier, restoring microbial homeostasis, and potentiating antitumor immune responses[13-15]. Together, these findings highlight the dual promise of probiotics in colorectal cancer as both predictive biomarkers and therapeutic agents.

Despite the growing evidence, several challenges hinder the clinical translation of probiotics. Achieving robust therapeutic efficacy while minimizing microbial toxicity, as well as developing strategies that precisely target the specific microbes, remain critical and underexplored avenues. Indeed, the rational design of microbiota-based combination therapies warrant greater attention in future research given the dynamic nature and individual variability of the gut microbiome. In this review we summarize current knowledge on the molecular mechanisms through which probiotics and metabolites influence cancer therapy. We discuss strategies for targeting the gut microbiota in CRC intervention, evaluate the potential of the gut microbiota as diagnostic and prognostic biomarkers, and explore emerging microbiota-based therapies centered on probiotics for CRC prevention and management. By integrating these perspectives, we aim to provide a comprehensive framework for future clinical translation.

Mechanisms underlying probiotics in suppressing CRC

Probiotics are live microorganisms that improve gut health and immunity by balancing the gut microbiome. Supplementation with specific beneficial bacteria has shown promise in suppressing tumorigenesis. This supplementation includes classic probiotics (*Lactobacillus* and *Bifidobacterium* spp.), as well as other beneficial commensals recently identified for antitumor potential. These organisms exert the effects through key mechanisms: reversing dysbiosis; restoring the intestinal barrier; and modulating immune responses (**Figures 1 and 2**).

Restoring the intestinal mechanical barrier

The intestinal barrier is comprised of mechanical and chemical components that work in concert to protect the host from luminal threats. Mechanical barriers physically block and remove pathogens (e.g., mucus and epithelial tight junctions), while chemical barriers (antimicrobial peptides and enzymatic mediators) kill or inhibit pathogens using specialized molecules (e.g., α/β-defensins, cathelicidin, and lysozyme). The intestinal epithelial barrier, as the primary mechanical defense, functions as a selectively permeable interface by restricting the passage of harmful substances while supporting epithelial regeneration. Bacterial endotoxins [e.g., lipopolysaccharide (LPS)], food antigens, and microbial metabolites translocate into the systemic circulation when this barrier is compromised, triggering a cascade of chronic inflammation. This persistent inflammatory state promotes local immune dysregulation and inflicts damage on epithelial cells, thereby driving malignant transformation[16]. Key barrier components are essential for this protective function. For example, the tight junction (TJ) protein, claudin-7, is crucial for tissue integrity. In fact, claudin-7 deficiency in mice disrupts cell junctions, exacerbates inflammation, and promotes severe colitis and colon cancer[17]. Similarly, mucin-2 (Muc2), the primary secreted gastrointestinal mucin, is vital for maintaining normal intestinal architecture. Mice lacking Muc2 frequently develop invasive adenocarcinomas, underscoring the critical role in suppressing CRC[18].

Several probiotic strains can repair and reinforce the intestinal epithelium (**Table 1**). For example, *Lactobacillus acidophilus* (*L. acidophilus*) upregulates occludin[20], *Lactobacillus plantarum* (*L. plantarum*) upregulates ZO-1 and ZO-2[14], *Lactobacillus rhamnosus* (*L. rhamnosus*) upregulates claudin-3[21]; *Bifidobacterium infantis* (*B. infantis*) upregulates claudin-4[24]; and *Escherichia coli Nissle* (*E. coli Nissle*) *1917* upregulates ZO-2[26]. Other strains, including *Bacillus subtilis (B. subtilis) CW14* and *L. plantarum ZLP001*, prevent ZO-1 degradation and alleviate damage from increased intestinal permeability[19,27]. Probiotics also support the epithelial barrier by increasing goblet cell populations [*Faecalibacterium prausnitzii* (*F. prausnitzii*)[30]] and elevating mucin (MUC-2) expression [*Clostridium butyricum* (*C. butyricum*)[31]]. Mechanistically, probiotic-mediated intestinal barrier repair frequently involves activation of toll-like receptor (TLR) signaling pathways. Strains, such as *Bacillus amyloliquefaciens SC06*[32], *B. subtilis CW14*[27], and *Lactobacillus reuteri* (*L. reuteri*)[22], modulate TLR signaling pathways to improve mucosal structure and TJ integrity. For example, *Bifidobacterium bifidum* (*B. bifidum*) activates the TLR-2/TLR-6 receptor complex on intestinal epithelial cells, thereby inducing IRAK-1 phosphorylation and recruitment of the anti-inflammatory adapter protein, TOLLIP, to the apical membrane, which results in the downstream upregulation of occludin[25]. *L. acidophilus* enhances barrier function through a TLR-2-dependent pathway involving PI3K-mediated inhibition of TNF-α-induced NF-κB activation, thereby protecting against inflammation-induced barrier disruption[33]. Another critical pathway involves the suppression of pro-inflammatory signaling cascades. For example, *B. bifidum* prevents TNF-α-induced barrier disruption[34], while *B. infantis* and *L. acidophilus* normalize occludin and claudin-1 expression, and suppress NF-κB activation under IL-1β stimulation[23]. Furthermore, *L. rhamnosus CY12* can alleviate colitis by inhibiting the TLR-4/MyD88/NF-κB signaling pathway, thereby reducing pro-inflammatory cytokine (IL-6, IL-1β, and TNF-α) expression, while promoting production of the anti-inflammatory

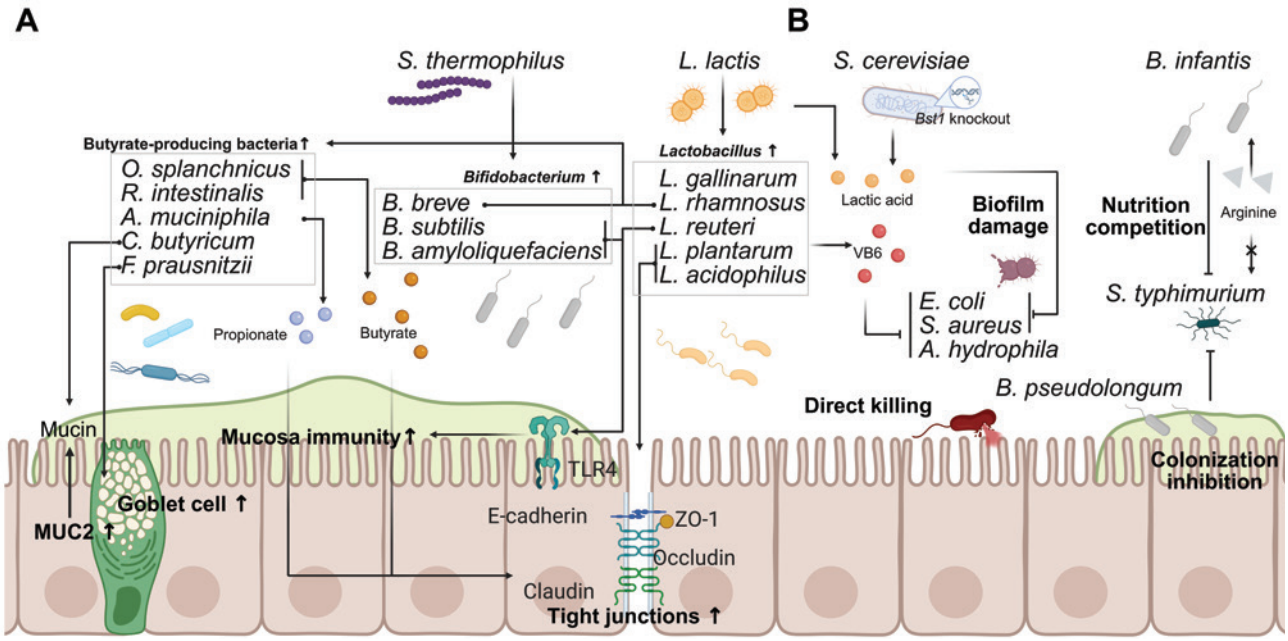


Figure 1 Proposed mechanisms for the beneficial effects of probiotics on gut homeostasis. (A) Enhancement of intestinal barrier function. Probiotics and their metabolites (e.g., short-chain fatty acids) strengthen the gut barrier through multiple pathways: (i) upregulating the expression of tight junction proteins (ZO-1, occludin, and claudin) and the adherens junction protein, E-cadherin; (ii) increasing the number of goblet cells and stimulating the production of the mucin protein, MUC2; and (iii) modulating mucosal immunity. Collectively, these actions improve barrier integrity and restore mucosal homeostasis. (B) Inhibition of pathogenic bacteria. Probiotics counteract pathogens *via* several mechanisms: (i) direct antagonism and competition for adhesion sites and nutrients; (ii) production of antimicrobial metabolites (e.g., bacteriocins and organic acids) that kill or inhibit pathogens; (iii) disruption of pathogenic biofilm formation and restoration of a balanced gut microbiota; and (iv) occupying colonization sites to prevent pathogen colonization. *A. hydrophila, Aeromonas hydrophila; A. muciniphila, Akkermansia muciniphila; B. infantis, Bifidobacterium infantis; B. pseudolongum, Bifidobacterium pseudolongum; C. butyricum, Clostridium butyricum; E. coli, Escherichia coli; F. prausnitzii, Faecalibacterium prausnitzii; L. lactis, Lactobacillus lactis; O. splanchnicus, Odoribacter splanchnicus; R. intestinalis, Roseburia intestinalis; S. aureus, Staphylococcus aureus; S. cerevisiae, Saccharomyces cerevisiae; S. thermophilus, Streptococcus thermophilus; S. typhimurium, Salmonella typhimurium;* TLR, Toll-like receptor. Figure created using BioRender (www.biorender.com).

cytokine, IL-10[35]. Suppression of NF-κB can also prevent activation of myosin light chain kinase (MLCK), which induces actomyosin contraction and TJ opening by phosphorylating the myosin II regulatory light chain (MLC2)[36].

In addition to direct regulation of host proteins, the protective metabolites produced by these probiotics have a critical role. For example, propionate secreted by *Akkermansia muciniphila* (*A. muciniphila*) activates the GPR43 receptor to enhance the expression of occludin, ZO-1, and mucins[28]. In a more complex interaction, conjugated linoleic acid (CLA) produced by *Bifidobacterium breve* (*B. breve*) promotes the growth of *Odoribacter splanchnicus*, which in turn increases butyrate production. This cascade upregulates TJ proteins and modulates inflammatory cytokines[12]. *Roseburia intestinalis* also directly improves intestinal permeability in $Apc^{Min/+}$ mice *via* butyrate production[29]. Collectively, these mechanisms demonstrate that probiotics maintain intestinal barrier integrity through direct protein upregulation, immune modulation, and metabolite-mediated protection, thereby counteracting inflammatory and pathogenic insults and highlighting the therapeutic potential in CRC (**Figure 1A**).

Inhibition of pathogenic bacteria growth and colonization

CRC is marked by severe gut microbiota dysbiosis, in which pathogenic bacteria become enriched and actively contribute to disease progression[7]. Stool transplants from CRC patients can directly induce carcinogenesis in mice, leading to increased dysplasia, proliferation, and pro-tumorigenic inflammation[37]. Pathogens, such as *Fusobacterium nucleatum* (*F. nucleatum*), *Peptostreptococcus anaerobius*, and *Bacteroides fragilis* (*B. fragilis*), drive tumorigenesis through multiple mechanisms, including enhanced mucosal adhesion[38], production of harmful metabolites[39], induction of damage *via* virulence factors[40], and conferring resistance to chemotherapy[41,42]. While targeted strategies, like selective antibiotics or phage therapy, have been explored, the limitations are significant. Antibiotic overuse

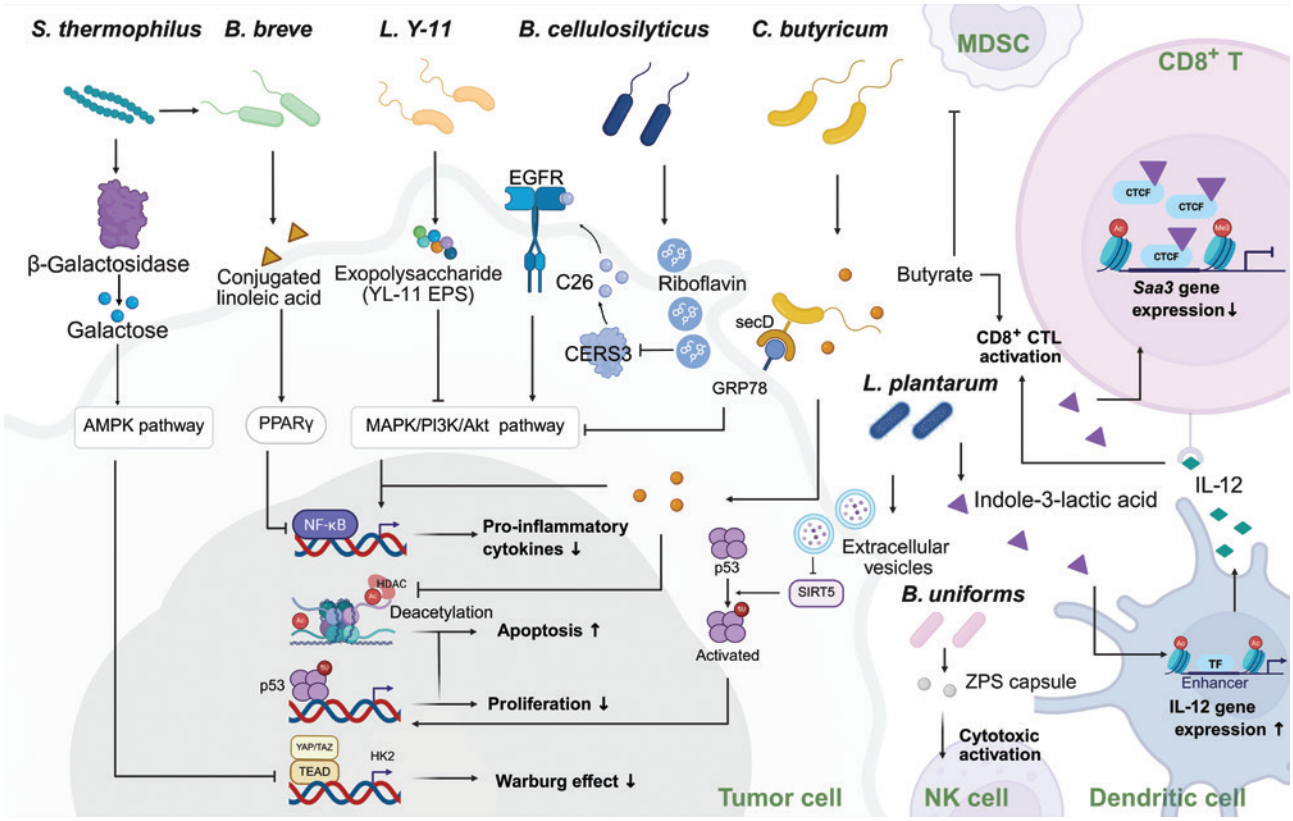


Figure 2 Regulation of the tumor microenvironment by probiotics and metabolites. Probiotics and derived metabolites suppress CRC through direct effects on tumor cells and indirect remodeling of the immune microenvironment. Direct mechanisms involve strain-specific signaling regulation. *S. thermophilus* produces β-galactosidase to modulate the Hippo pathway, whereas *B. breve* (*via* conjugated linoleic acid) and *L. Y-11* (*via* YL-11 EPS) inhibit NF-κB activity, thereby reducing tumor cell survival and proliferation. Indirectly, these metabolites promote antitumor immunity by enhancing NK cell recruitment (e.g., *B. uniformis* secretes ZPS capsule), $CD8^+$ T cell cytotoxicity (e.g., *C. butyricum* produces butyrate), and dendritic cell antigen presentation (e.g., *L. plantarum* secretes indole-3-lactic acid). *B. breve*, *Bifidobacterium breve*; *B. cellulosilyticus*, *Bacteroides cellulosilyticus*; *B. uniformis*, *Bacteroides uniformis*; *C. butyricum*, *Clostridium butyricum*; EGFR, epidermal growth factor receptor; GRP78, glucose-regulated protein 78; *L. plantarum*, *Lactobacillus plantarum*; *L. Y-11*, *Lactobacillus. YL-11*; MDSC, myeloid-derived suppressor cell; NK, natural killer; *S. thermophilus, Streptococcus thermophilus*. Figure created using BioRender (www.biorender.com).

risks driving bacterial resistance and further disrupts microbial balance. Indeed, the elimination of a single species often fails to restore overall community homeostasis. Consequently, there is a compelling rationale for more systematic microbiota modulation, such as can be achieved with probiotic supplementation. For example, a clinical study in CRC patients demonstrated that oral administration of a probiotic mixture containing *Lactobacillus lactis* (*L. lactis*) and *L. acidophilus* significantly increased beneficial butyrate-producers, while reducing CRC-associated taxa, like *Clostridium* and *Peptostreptococcus*[43]. This finding underscores the potential of probiotics to simultaneously reconfigure microbial populations and ameliorate dysbiosis.

Probiotics can significantly reshape the gut microbial community structure and exert broader modulatory effects on the intestinal ecosystem (**Table 2**). For example, administration of *L. rhamnosus* GG or *B. breve* CCFM683 significantly increase the abundance of key butyrate producers, such as *Faecalibacterium*, *Roseburia*, and *Akkermansia*[12,46,47]. This shift is particularly relevant for CRC prevention because butyrate reinforces the intestinal barrier, exhibits anti-inflammatory properties, and supports colonocyte health. Another consistent pattern is the suppression of pro-inflammatory and potentially pathogenic taxa. Probiotic interventions often reduce the relative abundance of genera associated with mucosal inflammation and tumor promotion. For example, *L. plantarum* L168 inhibits the overgrowth of *Oscillibacter* and *Alistipes*, while simultaneously increasing the abundance of *Faecalibaculum* and *Bifidobacterium*[50]. In addition to single-strain interventions, rationally designed

Table 1 List of tight junction proteins regulated by probiotics

Probiotics	ZO-1	ZO-2	Occludin	Claudin-3	Claudin-4
L. plantarum	Upregulation[14] Prevent degradation[19]	Upregulation[14]	-	-	-
L. acidophilus	-	-	Upregulation[20]	-	-
L. rhamnosus	-	-	-	Upregulation[21]	-
L. reuteri	Upregulation[22]	-	-	-	-
B. infantis	-	-	Upregulation[23]	-	Upregulation[24]
B. bifidum	-	-	Upregulation[25]	-	-
B. breve	Upregulation[12]	-	-	-	-
E. coli Nissle 1917	-	Upregulation[26]	-	-	-
B. subtilis	Prevent degradation[27]	-	-	-	-
A. muciniphila	Upregulation[28]	-	Upregulation[28]	-	-
R. intestinalis	Upregulation[29]			Upregulation[29]	

A. muciniphila, Akkermansia muciniphila; *B. subtilis,* Bacillus subtilis; *B. bifidum,* Bifidobacterium bifidum; *B. breve,* Bifidobacterium breve; *B. infantis,* Bifidobacterium infantis; *E. coli Nissle 1917,* Escherichia coli Nissle 1917; *L. acidophilus,* Lactobacillus acidophilus; *L. plantarum,* Lactobacillus plantarum; *L. reuteri,* Lactobacillus reuteri; *L. rhamnosus,* Lactobacillus rhamnosus; *R. intestinalis,* Roseburia intestinalis.

Table 2 Effects of probiotics on gut microbial communities in CRC

Functional features	Probiotics	Enriched probiotics	Inhibited CRC-associated pathogens	Model
Lactobacillus enrichment	*Lactococcus lactis* HKyuLL10[15]	*L. intestinalis* *L. johnsonii*	*Aeromonas hydrophila* *Streptococcus*_sp_LYSM12	AOM/DSS *Apc*$^{min/+}$
	Streptococcus thermophilus[44]	*L. reuteri* *L. animalis* *L. acidophilus* *L. gallinarum*	-	*Apc*$^{min/+}$
	L. gallinarum[45]	*L. reuteri* *L. harmsterl*	*Alistipes* *Allobacullum*	*Apc*$^{min/+}$
Butyrate-producing bacteria enrichment	*Lactobacillus rhamnosus* GG[46-48]	*Blautia* *Roseburia* *Coprococcus*	*Clostridium perfringens*	*Apc*$^{min/+}$
	Lactobacillus rhamnosus LS8[49]	*Faecalibaculum Akkermansia*	-	AOM/DSS
	Bifidobacterium breve CCFM683[12]	*Odoribacter splanchnicus*	-	*Apc*$^{min/+}$
	Lactobacillus plantarum L168[50]	*Faecalibaculum*	*Oscillibacter* *Alistipes*	AOM/DSS

CRC, colorectal cancer; *L. acidophilus,* Lactobacillus acidophilus; *L. animalis,* Lactobacillus animalis; *L. gallinarum,* Lactobacillus gallinarum; *L. reuteri,* Lactobacillus reuteri.

multi-strain consortia can further enhance the precision of microbial modulation. A synthetic community (SynCom) composed of seven strains successfully eradicated *F. nucleatum* and suppressed *F. nucleatum*-associated CRC in mice[51]. Similarly, larger microbial consortia have been shown to enhance resistance to enteric pathogens or alleviate intestinal inflammation[52,53].

Probiotics prevent pathogenic colonization and expansion through several strategies: (1) secretion of direct antimicrobial compounds; (2) sequestration of essential nutrients; (3)

blockade of mucosal adhesion; and (4) interference with pathogen quorum sensing (QS) (**Figure 1B**). Direct antibacterial activity could be mediated by secreted molecules. For example, nisin from *L. lactis* forms pores in the membrane of pathogens, particularly, gram-positive bacteria, leading to rapid bacteria death, while *L. lactis* self-protects from nisin by expressing NisI (a membrane-anchored lipoprotein capturing nisin before reaching the membrane) and NisFEG (an ABC transporter expelling nisin)[54]. Organic acids, such as lactic and acetic acids, penetrate bacterial membranes, acidify the cytoplasm, and impair the proton motive force, thereby inhibiting growth. Engineered *Saccharomyces cerevisiae* with a BTS1 gene knockout produces lactic acid, lowering the environmental pH to inhibit *E. coli* and *Staphylococcus aureus* (*S. aureus*) growth, and disrupt biofilm formation[55]. These pathogens are often more vulnerable than commensal bacteria to environmental stresses, such as acidification, metabolic strain, and membrane disruption. In addition, vitamin B6 produced by *Lactobacillus* spp. can compromise pathogenic cell membrane integrity, leading to leakage of intracellular contents and bacterial death[56]. Competitive exclusion through nutrition limitation represents another critical mechanism. For example, *B. infantis* suppresses host apoptotic pathways, activates anti-inflammatory signaling, and competes with *Salmonella typhimurium* (*S. typhimurium*) for arginine, thereby limiting growth[57]. Iron is another nutrient for which strains compete. The probiotic strain, *E. coli Nissle* 1917, produces high-affinity siderophores, such as salmochelin, enabling efficient iron acquisition and thereby outcompeting and reducing *S. typhimurium* colonization in mouse models of acute colitis and chronic persistent infection[58]. Similarly, *Bifidobacteria* with strong iron-chelating capacity can inhibit the growth and adhesion of enterohemorrhagic *E. coli* and *Salmonella in vitro*[59]. Blocking mucosal adhesion establishes an additional physical barrier that limits colonization by opportunistic pathogens. Probiotics facilitate this effect by competing for glycan receptors on intestinal epithelial cells, typically through surface-layer proteins or pili. For example, *Bifidobacterium pseudolongum* (*B. pseudolongum*) PV8-2 exhibits high affinity for mucins and significantly reduces *S. typhimurium* adhesion to epithelial cells *in vitro*[59]. QS allows individual bacteria to coordinate colony-wide functions, making QS a promising target for intervention. Probiotics can disrupt this process by secreting enzymes or metabolites that degrade or mimic QS signaling molecules and reducing virulence without exerting direct killing. For example, *Bacillus* strains produce fengycins, a class of lipopeptides that inhibit the *S. aureus* agr QS system, reducing toxin production and biofilm formation[60]. In addition, certain *Lactobacillus* strains degrade autoinducer-2 (AI-2), a signal molecule widely used by gram-negative bacterial pathogens to coordinate virulence[61]. While these mechanisms are promising, corollary human studies are needed. Ultimately, exploiting such microbial antagonism to identify targeted antimicrobial molecules could offer novel avenues for microbiota-based CRC therapies.

Probiotic metabolites target cancer signals

Probiotic-derived metabolites are central to the therapeutic benefits against CRC. These microbial molecules, encompassing carbohydrates, lipids, proteins, and small compounds, directly reprogram oncogenic signaling, modify epigenetic pathways, and enhance antitumor immunity to suppress tumor growth. Probiotic-derived metabolites could promote the accumulation of reactive oxygen species (ROS) in tumor cells to trigger mitochondrial apoptotic pathways. For example, *Bifidobacterium longum* D42 elevates intracellular ROS in HT-29 cells, disrupts mitochondrial membrane potential, promotes cytochrome c release, and activates downstream caspase cascades, ultimately inducing CRC cell apoptosis *via* the intrinsic mitochondrial pathway[62]. In contrast, probiotic metabolites could directly interfere with core oncogenic networks to halt proliferation and induce apoptosis. The well-studied metabolite, butyrate, inhibits pro-survival pathways, like NF-κB and STAT3, downregulating cyclins, and activating apoptosis genes[63]. Moreover, butyrate has been reported to suppress vascular endothelial growth factor (VEGF) expression by blocking the transactivation of the key transcription factor [specificity protein 1 (Sp1)], thereby reducing tumor angiogenesis and migration[64,65]. Riboflavin from *Bacteroides cellulosilyticus* binds to ceramide synthase (CERS3), blocking the synthesis of very long-chain ceramide (C26) and the interaction with epidermal growth factor receptor (EGFR), thereby attenuating proliferation[66]. Conjugated linoleic acid (CLA) from *B. breve* activates PPAR-γ to promote tumor cell apoptosis[12]. Furthermore, gut microbiota-derived N-acetylmuramic acid inhibits AKT1 phosphorylation, suppressing the AKT1-FOXO3a pathway to suppress cancer cell proliferation and induce apoptosis[67]. In addition to small molecules, probiotic macromolecules exert antitumor effects. β-galactosidase from *Streptococcus thermophilus* generates galactose, impairing glucose utilization and activating oxidative phosphorylation to inhibit tumor growth[44]. The extracellular polysaccharide, YL-11 EPS, from *Lactobacillus YL-11* blocks the PI3K/AKT pathway, arresting the cell cycle at G1 phase, thereby suppressing colorectal carcinogenesis[68]. In addition, extracellular vesicles from *L. plantarum* can be internalized by CRC cells, downregulating the desuccinylase (SIRT5) to enhance succinylation of p53, inhibiting glycolysis and proliferation while inducing apoptosis[69]. Probiotic metabolites can also function as epigenetic regulators, reversibly altering chromatin states to reshape transcriptional programs. For example, butyrate acts as an endogenous histone deacetylase (HDAC) inhibitor that increases histone acetylation by suppressing HDAC activity, thereby opening chromatin

structure to activate the transcription of tumor suppressor and apoptosis-related genes, while simultaneously repressing oncogene expression[70,71]. Together, probiotic-derived metabolites combat CRC through diverse mechanisms, including oxidative stress induction, modulation of oncogenic signaling pathways, suppression of angiogenesis, and epigenetic reprogramming *via* HDAC inhibition. These findings underscore the therapeutic potential of these bioactive molecules as mechanism-based adjuncts to conventional CRC therapy.

Probiotic metabolites remodeling the tumor immune microenvironment (TIME)

While ICI therapy targeting PD-1 is approved for microsatellite instability (MSI) CRC, the efficacy remains restricted in the majority of microsatellite stable (MSS) tumors[72]. MSS CRC is typically considered an immunologically "cold" tumor that is characterized by limited infiltration of cytotoxic T cells within the TIME, and enrichment of immunosuppressive populations, such as myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and M2-type tumor-associated macrophages (TAMs)[73]. This immunosuppressive milieu leads to intrinsic resistance to ICI therapy. A key mechanism by which probiotics and metabolites may overcome this limitation is by reprogramming the immunosuppressive tumor microenvironment, converting "cold" tumors into "hot" immunologically active tumors to synergize with ICIs. For example, among patients resistant to ICIs, *C. butyricum* can colonize tumors and locally produce butyrate to suppress the IL-6/JAK2/STAT3 pathway, subsequently reducing immunosuppressive cell infiltration and boosting cytotoxic $CD8^+$ T cell function to restore tumoral sensitivity to anti-PD-1 therapy[13]. Furthermore, *L. plantarum*-derived indole-3-lactic acid (ILA) orchestrates a multi-layered epigenetic attack. ILA promotes IL-12 secretion in dendritic cells (DCs) to prime T-cell immunity, while ILA remodels chromatin in $CD8^+$ T cells to enhance infiltration and cytotoxic activity[50]. Capsular polysaccharides derived from *Bacteroides uniformis* bind to Lag-3 molecules on the cell surface of natural killer (NK) cells, activating cytotoxic function and enhancing tumor cell killing[74]. Importantly, this pathway synergizes with anti-PD-1/PD-L1 therapy to further strengthen immune responses against the immunologically "cold" tumors[74]. Moreover, short-chain fatty acids (SCFAs), such as acetate and butyrate, have been reported to directly enhance antitumor NK cell activity *in vitro*. SCFAs promote the release of NK-derived extracellular vesicles, which can carry cytotoxic cargo, while reducing secretion of the immunosuppressive cytokine, IL-10[75].

Probiotic-derived metabolites can alleviate the immunosuppressive state of the TIME. For example, metabolites from *L. plantarum* can reprogram tumor-associated macrophages from a pro-tumor M2 phenotype to an anti-tumor M1 state by activating the NLRP3 inflammasome[76]. Lysates of *L. acidophilus*, when combined with anti-CTLA-4 therapy, can increase the number of $CD8^+$ T cells, while reducing $CD4^+CD25^+Foxp3^+$ regulatory T cells and the M2 phenotype of macrophages within the TIME[77]. *Lactobacillus gallinarum* secretes indole-3-carboxylic acid that diminishes recruitment of $Foxp3^+CD25^+$ regulatory T cells and enhances $CD8^+$ T cell function, synergistically augmenting the inhibitory effect of anti-PD-1 antibodies on tumor growth[45]. In addition, SCFAs suppress the accumulation of MDSCs in tumor tissues, which alleviates MDSC-mediated immunosuppression and promotes $CD8^+$ T cell infiltration and activation[78]. Notably, tyrosine kinase inhibitors can also increase the abundance of *Muribaculum* and the metabolite, urocanic acid (UCA), to potentiate cancer immunotherapy efficacy. Increased UCA inhibits p65 signaling in tumor endothelial cells to reduce MDSC recruitment *via* the CXCL1-CXCR2 axis, ultimately suppressing colorectal tumorigenesis[79]. Collectively, these findings demonstrate how microbial metabolites can reshape the TIME at cellular, metabolic, and epigenetic levels to potentiate anticancer immunity (**Figure 2**).

Probiotic signatures as biomarkers in CRC

The diagnosis and prognosis of CRC currently depend on biomarkers derived from host genetics and gene expression profiles, which often lack sufficient sensitivity for early detection. In contrast, the gut microbiota constitutes a dynamic ecosystem deeply implicated in CRC development, representing a vast reservoir of untapped biomarker potential. Specifically, defined shifts in probiotic communities are increasingly associated with disease status. Therefore, a biomarker platform that combines these CRC-specific microbial alterations with established clinical markers could revolutionize diagnostic sensitivity and provide a novel means of monitoring therapeutic efficacy.

Probiotic signatures as diagnostic markers

Current diagnostic research into gut microbiota for CRC and colorectal adenomas (CRAs) has predominantly focused on pathogenic bacteria (e.g., *F. nucleatum*), metabolites, or a combination with host genetic markers. While these microbial features are often examined as auxiliary tools, a parallel and compelling diagnostic signal lies in the progressive depletion of probiotic taxa during CRC progression. This decline is driven by multiple interrelated factors, including elevated oxidative stress within the tumor tissues that inhibits survival of strict anaerobes[80,81], tumor-associated metabolic alterations

that lead to ecological niche loss[82], and remodeling of the host immune microenvironment that excludes some probiotics and impedes stable colonization[83,84]. Such antagonistic ecological dynamics suggest that the loss of beneficial microbes represents a potent yet underexploited biomarker class. The diagnostic power of this ecological shift is evident when probiotic signatures are formally quantified. For example, a simple abundance ratio of *F. nucleatum*-to-beneficial taxa (*F. prausnitzii*, *Bifidobacterium*, and *Lactobacillus*) can significantly improve diagnostic specificity over single-pathogen assays[85]. More sophisticated, multi-taxa classifiers that incorporate probiotic genera have demonstrated strong performance. Specifically, a seven-genus panel, including *Lactobacillus*, achieved an AUC of 0.84 for CRC detection[86], while a six-taxon panel containing *Roseburia inulinivorans* differentiated CRA from CRC with an AUC of 0.93[9]. In specific contexts like obesity-associated CRC, the marked reduction of *F. prausnitzii* has been a key discriminative feature, reinforcing the broader role as a biomarker for intestinal health[87,88].

Despite this promise, probiotic signatures remain underrepresented in diagnostic models. A primary challenge is the inconsistent loss across CRC stages, complicating the development of universal single-taxon biomarkers. Furthermore, gut microbiota composition is profoundly confounded by host-specific factors, including environment, genetics, medication history, and demographic variables, like gender, as illustrated by the hormone-dependent colonization of *Carnobacterium maltaromaticum*[89]. Another key limitation is the lack of disease specificity because the reduction of probiotic taxa is not unique to CRC. For example, depletion of *F. prausnitzii* is commonly observed in inflammatory bowel disease (IBD) and other metabolic disorders[90]. Such overlapping dysbiosis patterns may undermine the diagnostic specificity of probiotic signatures and increase the risk of false positives. Nevertheless, CRC and IBD exhibit quantifiable differences in microbial structure[90,91], suggesting that diagnostic accuracy could be improved through multi-feature microbial profiling rather than reliance on single taxa. Therefore, these observations highlight a critical diagnostic strategy in which probiotic signatures ae integrated into composite multi-marker classifiers. Such models can account for ecologic dynamics (pathogen rise and probiotic decline), stage-specific variability, and host confounders, moving beyond auxiliary use to establish a robust, ecology-informed framework for CRC and CRA detection. From a translational perspective, routine clinical implementation of probiotic signatures faces ongoing challenges in standardization, cost-effectiveness, and analytic reproducibility, despite the encouraging feasibility demonstrated by fecal microbiome analysis using quantitative PCR and metagenomic sequencing. Future efforts should therefore focus on establishing standardized testing workflows and diagnostic thresholds, as well as validating the robustness, alone or in combination with existing biomarkers, across diverse populations through large-scale prospective studies to facilitate clinical adoption.

Probiotic signatures as predictive markers

In addition to diagnostics, fecal microbial signatures are emerging as valuable predictors of therapeutic response and clinical outcomes in CRC. The predictive relevance is particularly pronounced in the context of immunotherapy, in which the composition of the gut microbiota can critically influence efficacy. A growing body of evidence indicates that favorable responses to ICIs and prolonged survival are strongly associated with the enrichment of specific probiotic taxa and the metabolic byproducts, rather than solely the depletion of pathogens. Pan-cancer analyses have consistently shown that ICI responders harbor increased abundances of bacteria, such as *A. muciniphila*[92], *F. prausnitzii*[11], and *L. reuteri*[93], as well as fungi with probiotic-like functions (e.g., *Schizosaccharomyces*[94] and *Nemania serpens*[11]). In parallel, elevated levels of related metabolites, such as indole-3-aldehyde (I3A)[93], galanthamine ketone[95], and hippuric acid[79] are significantly associated with improved prognosis. Butyrate-producing strains (*Agathobacter M104/1* and *Blautia SR1/5*) have been identified as potential prognostic indicators for combined cetuximab and avelumab therapy in CRC[96]. These findings highlight a key insight, i.e., therapeutic success may depend more on the active presence of beneficial microbes than on the absence of harmful microbes.

Probiotic signatures also hold promise in predicting susceptibility to immune-related adverse events (irAEs) during immunotherapy[97]. In patients with metastatic melanoma receiving anti-CTLA-4 therapy, those with higher baseline abundances of *Bacteroidetes* exhibited greater resistance to ICI-induced colitis[98]. In contrast, microbial profiles enriched in *Firmicutes* were associated with treatment-related colitis[99]. Therefore, observations suggest that incorporating microbial signatures into risk stratification models may enable early detection and preventive interventions, thereby expanding the therapeutic window of ICIs.

Outside of immunotherapy, the direct predictive role of probiotics is less clear. Probiotics are primarily documented for their role in mitigating treatment-related side effects in chemotherapy[100] with limited evidence supporting a substantial direct impact on chemotherapeutic efficacy or overall survival. Nonetheless, certain probiotic signatures may hold broader prognostic value, as illustrated by the association between higher abundance of *Carnobacterium maltaromaticum* and improved outcomes, particularly in female patients[89]. Overall, probiotic signatures and the metabolic products represent a promising, yet underdeveloped, component of predictive oncology. Integrating these features into models of therapeutic responsiveness, especially for immunotherapy, offers a feasible strategy to refine patient stratification and personalize treatment. However, as with diagnostic applications, research in this area remains nascent. Translating these insights into clinical practice will require more comprehensive, longitudinally designed studies and multi-omics integration

to validate and standardize microbial predictors across diverse patient populations and treatment regimens.

Strategies for microbiota-based combination therapies

The gut microbiota functions as a dynamic and resilient ecosystem, the composition of which is continually shaped by host genetics, immune activity, and environmental exposures. Although specific probiotic supplementation represents a validated approach for modulating microbial populations, conventional single-strain interventions frequently overlook the ecologic diversity and functional redundancy inherent to the native community. To achieve durable and clinically meaningful outcomes, therapeutic strategies must advance beyond monotherapy toward precisely designed, multifaceted interventions that engage the microbiota as an integrated system. The design of such consortia should be guided by the complementary mechanisms of action and the natural co-occurrence relationships among the selected strains.

Modulating microbiomes to enhance immunotherapy

The gut microbiota is a critical determinant of immunotherapy efficacy in CRC. A compelling illustration of this is the finding that fecal microbiota transplantation (FMT) from healthy donors restores anti-PD-1 responsiveness in murine CRC models, whereas FMT from non-responding CRC patients fails to do so[101]. This finding highlights the therapeutic potential of modulating the microbiome with probiotic supplementation emerging as a promising strategy to overcome resistance to ICIs (**Table 3**). Probiotics exert direct antitumor effects and reprogram the TIME. For example, *Lactobacillus paracasei* sh2020, which has been isolated from healthy human feces, upregulates the chemokine, CXCL10, within tumors and enhances recruitment of cytotoxic $CD8^+$ T cells and synergizing with anti-PD-1 therapy[101]. Similarly, the surface protein, SecD, of *C. butyricum* binds to glucose-regulated protein 78 (GRP78) on CRC cells, inactivating the downstream PI3K-AKT-NF-κB pathway[13]. This interaction suppresses the production of the immunosuppressive cytokine, IL-6, which alleviates the functional inhibition of $CD8^+$ T cells and reduces the infiltration of TAMs, thereby creating a more permissive environment for immunotherapy[13].

In addition to direct cellular interactions, probiotic-derived metabolites systemically potentiate antitumor immunity. SCFAs, like butyrate, produced by genera (*Roseburia* and *Clostridium*) directly enhance the cytotoxic function of $CD8^+$ T cells, thereby synergizing with anti-PD-1 therapy[13,29]. Mechanistically, butyrate modulates T-cell receptor (TCR) signaling and engages Toll-like receptor 5 (TLR-5) to activate NF-κB, amplifying T-cell effector capacity[29,107]. Other microbial metabolites also fine-tune immune responses. Specifically, indole derivatives (e.g., indole-3-propionic acid

Table 3 Microbiome strategies to improve immunotherapy

Approach	Targets	Key enriched probiotic/ metabolite	Primary function	Outcomes
Lactobacillus paracasei sh2020 oral administration[101]	Tumor cells (CXCL10)	*Lactobacillus paracasei*	Directly recruits $CD8^+$ T cells	Enhances anti-PD-1 efficacy
Oral administration of *C. butyricum* (*via* SecD protein)[13]	Tumor cells (PI3K-AKT-NF-κB pathway)	*C. butyricum/butyrate*	Blocks oncogenic signaling and reduces IL-6	Enhances anti-PD-1 efficacy
Roseburia intestinalis[29]	$CD8^+$ T cells	Butyrate	Directly enhances cytotoxic function of $CD8^+$ T cells	Enhances anti-PD-1 efficacy
Enrichment of bacteria producing indole derivatives	T cells	Indole-3-propionic acid[102], indole-3-carboxylic acid[45], and indole-3-aldehyde[103]	Modulates T-cell differentiation and stemness	Enhances anti-PD-1 efficacy
Utilization of LIPOAF protein from *Alistipes fingoldii*[104]	Dendritic cells (TLR-2-NF-κB pathway)	LIPOAF protein	Activates dendritic cells	Drives tumor infiltration of $CD8^+$ T cells
Utilization of outer membrane vesicles from *A. muciniphila*[105]	Dendritic cells	*A. muciniphila*	Induces dendritic cell maturation	Activates cytotoxic T-cell responses
Co-administration of *C. butyricum* and *A. muciniphila*[106]	Gut microbiota ecosystem/Systemic inflammation	*C. butyricum*, *A. muciniphila*	Synergistically reshapes microbiota and reduces inflammation	Enhances anti-PD-L1 efficacy

A. muciniphila, Akkermansia muciniphila; *C. butyricum,* Clostridium butyricum.

and indole-3-carboxylic acid) influence T-cell stemness and differentiation[45,102,103], while *B. pseudolongum* utilizes the L-arginine pathway to drive the generation of tissue-resident memory $CD8^+$ T cells, boosting anti-CTLA-4 efficacy[108]. Notably, SCFAs, like butyrate and valerate esters, have also been shown *in vitro* to enhance the antitumor activity of engineered cell therapies, including chimeric antigen receptor (CAR)-T cells[109].

Probiotics further bridge innate and adaptive immunity by activating antigen-presenting cells. For example, the membrane protein, LIPOAF, from *Alistipes fingoldii* activates DCs *via* the TLR-2-NF-κB pathway, stimulating CXCL16 secretion and promoting $CD8^+$ T-cell tumor infiltration[104]. Similarly, outer membrane vesicles from *A. muciniphila* induce DC maturation, leading to more robust cytotoxic T-cell priming[105]. At an ecologic level, probiotics can durably reshape the gut microbial community to sustain a pro-inflammatory, immune-active state. Synergistic effects are observed with combination approaches. Co-administration of *C. butyricum* and *A. muciniphila* more effectively restores a favorable microbiota composition, reduces systemic inflammation, and sensitizes tumors to anti-PD-L1 therapy than either probiotic alone[106].

Together, probiotics enhance ICI efficacy in CRC through the following multifaceted network of mechanisms: direct tumor targeting; metabolic reprogramming; innate immune activation; and ecologic restoration. This coordinated action helps convert immunologically "cold" tumors into "hot" tumors, offering a viable strategy to break immunotherapy resistance.

Modulating microbiomes to overcome chemoresistance

Chemotherapy, using agents, such as 5-fluorouracil (5-FU), oxaliplatin, and irinotecan, remains a cornerstone of CRC treatment. However, the long-term success is frequently compromised by intrinsic or acquired chemoresistance. Emerging research has established the gut microbiome as a critical modulator of therapeutic efficacy, influencing resistance through diverse mechanisms (**Table 4**). Key insights have been derived from model systems and clinical observations. Studies involving *Caenorhabditis elegans* fed a bacterial diet revealed that microbial genetics directly alter host responses to chemotherapeutics[114]. For example, bacterial nucleotide metabolism genes have been shown to widely modulate the efficacy of drugs, like 5-FU, with cytotoxicity surprisingly mediated through bacterial ribonucleotide metabolism rather than solely through canonical host pathways[114]. An intact microbiota is essential for optimal therapy in mammalian systems. Depletion of commensal bacteria in mouse models impairs the response to both platinum-based chemotherapy and immunotherapy[115]. This finding is linked to dysfunctional tumor-infiltrating myeloid cells, which exhibit reduced cytokine production and cytotoxic activity. Clinical data further underscore this relationship, revealing significant differences in gut microbial composition between chemotherapy responders and non-responders. Specific pathogens, such as *F. nucleatum* and enterotoxigenic *B. fragilis* (ETBF), have been directly implicated in promoting chemoresistance[41,42]. Targeted modulation of the microbiome presents a promising therapeutic strategy. Phage-based targeting of ETBF successfully reverses chemoresistance in murine CRC models[42]. Furthermore, the administration of beneficial microbes, such as *B. bifidum*, in combination with 5-FU has been shown to enhance therapeutic efficacy significantly compared to chemotherapy alone[110]. Collectively, these results indicate that modulation of the gut microbiota represents a potential strategy to improve chemotherapy outcomes.

Despite promising data, few large-scale clinical trials have directly validated the ability of probiotics to enhance the anticancer efficacy of chemotherapy in humans, as most evidence still relies on animal models. Moreover, current research largely focuses on mitigating adverse effects rather than directly enhancing anticancer efficacy. Oral probiotics significantly reduced the risk and severity of chemotherapy-induced diarrhea and oral mucositis in a meta-analysis of 12 randomized controlled trials (1,013 patients) with benefits notably observed in Asian patients and linked to greater bacterial species diversity[116]. Another meta-analysis involving 8 studies (633 patients) demonstrated that probiotics significantly reduced chemoradiotherapy-induced diarrhea and improved pain, dyspnea, and insomnia[117]. Moreover, supplementation with *L. rhamnosus* GG or *Lactobacillus casei (L. casei)* has been shown to reduce chemotherapy-induced intestinal mucosal injury and diarrhea[111,112]. Similarly, probiotic

Table 4 Microbiome strategies to improve chemotherapy

Approach	Targets	Key enriched probiotic/ metabolite	Primary function	Outcomes
Administration of *B. bifidum*[110]	Tumor cells	*B. bifidum*	Acts synergistically with the chemotherapeutic agent	Potentiates 5-fluorouracil efficacy
Supplementation with *L. rhamnosus GG/L. casei*[111,112] and *Bifidobacterium*[113]	Intestinal barrier/microbial homeostasis	*Lactobacillus* spp.	Fortifies the intestinal barrier and restores homeostasis	Alleviates chemotherapy-induced mucositis and diarrhea

B. bifidum, Bifidobacterium bifidum; *L. casei,* Lactobacillus casei; *L. rhamnosus,* Lactobacillus rhamnosus.

mixtures containing *Lactobacillus* and *Bifidobacterium* spp. have been reported to alleviate severe diarrhea associated with irinotecan treatment[113]. The protective mechanisms likely involve probiotic-derived metabolites that help strengthen the intestinal barrier and restore microbial homeostasis. Thus, clinical evidence strongly supports the use of probiotics for maintaining intestinal integrity and improving patient tolerance to chemotherapy. However, whether probiotics can directly potentiate chemotherapy and overcome tumor resistance in patients remains an open question. The molecular and immunologic mechanisms underlying such potential synergy are not well-defined and warrant focused investigation. It is worth noting that chemotherapy-induced neutropenia could substantially increase systemic infections and the risk of sepsis caused by microbial pathogens. Under such conditions, even bacteria traditionally regarded as probiotics, such as *Bifidobacterium* and *Lactobacillus*, may cause opportunistic infections in immunocompromised hosts[118]. Future efforts should therefore prioritize well-designed prospective studies to define risk stratification for live microbial therapies under varying degrees of chemotherapy intensity and neutropenia, enabling the development of clearer and safer clinical guidelines.

Dietary and lifestyle modulation of the microbiome

Unhealthy lifestyle patterns are a major source of gut microbial dysbiosis and chronic, low-grade inflammation are key drivers of CRC pathogenesis. Factors, such as high-fat diets[119], smoking[120], and disrupted circadian rhythms[121] can drive the enrichment of pathogenic bacteria, undermine intestinal barrier function, and establish an immunosuppressive tumor niche, which collectively accelerate disease progression. Conversely, positive lifestyle modifications can restore microbial homeostasis and support cancer therapy[122]. For example, regular physical activity is associated with a reduced risk of CRC, in part by enriching SCFA-producing bacteria and enhancing overall microbial diversity[123].

A meta-analysis of over 2.2 million individuals showed that adherence to the Mediterranean diet is associated with a 16% reduction in CRC risk[124]. Similarly, high-fiber diets have shown a consistent inverse association with CRC incidence across multiple international studies[125]. These protective effects are primarily attributed to increased dietary fiber intake, which promotes the production of SCFAs, such as butyrate, by the gut microbiota, thereby exerting anti-inflammatory and anti-tumor effects[126]. Thus, targeted dietary strategies offer a more direct route to modulate the microbiome for therapeutic benefit. A ketogenic diet (KD) can suppress CRC tumorigenesis by shifting microbial communities to increase the production of stearic acid[127]. This effect can be mimicked by the ketone body, β-hydroxybutyrate (BHB), which activates the receptor Hcar2 on colonic cells, induces Hopx expression, and subsequently inhibits crypt proliferation and tumor growth[128]. Similarly, fasting-mimicking diets (FMDs) have emerged as a potent adjunct to immunotherapy[108,129]. Combining FMD with anti-PD-1 therapy has been shown to inhibit CRC progression in preclinical models by increasing *Lactobacillus* abundance, reducing proliferation and angiogenesis, and boosting intratumoral $CD8^+$ T-cell infiltration[129]. Another mechanism involves FMD-induced enrichment of *B. pseudolongum*, which enhances the efficacy of anti-CTLA-4 therapy by producing the metabolite, L-arginine, and promoting tissue-resident memory $CD8^+$ T cells[108]. These findings underscore that dietary and lifestyle interventions are powerful tools for reshaping the gut microbiome (**Table 5**).

Carcinogens in food pose a significant health risk. Lactic acid bacteria (LAB), probiotic microorganisms that ferment lactose into lactate, have gained attention as food additives capable of counteracting carcinogenic compounds. Some LAB strains do so through direct physical binding, thereby avoiding the re-pollution associated with toxic degradation byproducts[131]. This binding primarily involves cell wall components with peptidoglycan serving as the main site and is strain-specific. For example, *Lactobacillus* and *Bifidobacterium* spp. show potential against common carcinogens, such as mycotoxins, polycyclic aromatic hydrocarbons, heterocyclic amines, and

Table 5 Leveraging diet and lifestyle to modulate the CRC microbiome

Approach	Targets	Key enriched probiotic/ metabolite	Primary function	Outcomes
Fasting-mimicking diet combined with immunotherapy[108]	Tissue-resident memory T cells	Enrichment of *B. pseudolongum*, L-arginine	Promotes the generation and activation of tissue-resident memory $CD8^+$ T cells	Enhances anti-CTLA-4 therapy
Ketogenic diet[127]	Colonic crypt cell proliferation (*via* Hcar2)	Stearic acid, β-ydroxybutyrate	Generates metabolites that inhibit cell proliferation	Suppresses CRC growth
Regular exercise[123,130]	Gut microbiota diversity/ SCFA production	SCFA-producing bacteria	Increases microbial diversity and beneficial metabolites	Lowers CRC risk

B. pseudolongum, Bifidobacterium pseudolongum; CRC, colorectal cancer; SCFA, short-chain fatty acid.

phthalic acid esters[132]. However, it is noteworthy that the gut microbiota can also contribute to metabolic activation of some pro-carcinogens. Roje et al.[133] reported that the gut microbiota can metabolize environmental nitrosamine carcinogens, such as N-butyl-N-(4-hydroxybutyl)-nitrosamine and its derivatives, *via* bacterial β-glucuronidase-mediated deconjugation and oxidation, converting environmental nitrosamine carcinogens into more toxic metabolites. These metabolites accumulate systemically, reach distal organs, such as the urinary bladder, and drive tumor formation. This effect is causally linked to specific bacterial strains (e.g., *Lactobacillus*), varies across human donor microbiomes, and extends to related nitrosamines[133]. Together, the interactions between the gut microbiota and dietary/environmental carcinogens are complex, underscoring the importance of developing novel microbiome-targeted prophylactic approaches.

Reshaping gut microbiota dysbiosis modulated by host genetics and gene expression

The composition of the gut microbiota is shaped by a complex interplay of exogenous factors and intrinsic host genetics. Integrated analyses using metagenomic sequencing of fecal samples with host genomic and transcriptomic profiling have established significant associations between specific microbial communities, host genetic variants, and gene expression patterns[134,135]. These genetic influences can define an individual's microbial landscape with direct consequences for health and disease. Specific host genotypes are powerful drivers of microbial community structure. For example, CRCs harboring a *KRAS p.G12D* mutation exhibit a distinct microbial niche enriched with *F. nucleatum* and *B. fragilis*, a combination that promotes tumorigenesis in murine models[136,137]. Furthermore, a host single nucleotide polymorphism (SNP rs2355016) within the *KCNJ11* gene correlates strongly with the abundance of *F. nucleatum*[138]. Carriers of the risk allele demonstrate reduced *KCNJ11* expression and enhanced mucosal adhesion of *F. nucleatum*, accelerating CRC progression[138]. In addition to oncogenes, genes regulating host defense also shape microbiota. Systemic or intestinal epithelial knockout of *Mettl9* impairs secretory functions, leading to pathologic over-colonization by *Candida albicans*, barrier disruption, and increased mortality[139]. Depending on the host context, inflammatory status, the presence of live *vs*. non-viable components, and strain specificity, *A. muciniphila* can exert protective or pathogenic effects[140,141]. Loss of group 3 innate lymphoid cells (ILC3s) triggers IL-22-dependent intestinal galactosylation, fostering the expansion of *A. muciniphila* within the mucus layer. This effect disrupts microbial equilibrium and heightens susceptibility to *S. typhimurium* infection[142]. Similarly, functional loss of the *Fut2* gene, which governs epithelial fucosylation, compromises gut homeostasis. Notably, fecal microbiota transfer from *Fut2*-deficient mice or inoculation with poorly fucosylated *B. fragilis* is sufficient to confer colitis susceptibility in recipients[143]. Such genetically influenced dysbiosis is a key driver in diseases, like early-onset CRC. This finding provides a compelling rationale for combining probiotics with genotype-targeted therapies. In *KRAS*-mutant settings, the probiotic, *Parabacteroides distasonis*, competitively excludes pro-tumorigenic *F. nucleatum*, and oral administration attenuates CRC progression in mice[136]. Advanced delivery systems are enhancing precision. Extracellular vesicles (EVs) from *L. acidophilus* loaded with TNF-α siRNA, enable colon-specific gene silencing, reshaping the microbiota and metabolite profile to restore homeostasis in IBD models[144]. In another approach, engineered *Pediococcus pentosaceus* was developed as a safe lactic acid bacterium delivery vehicle expressing the secreted anticancer protein, P8, which has been reported to downregulate cyclin B1 and Cdk1[145]. Oral administration of P8 suppresses tumor development in murine CRC xenografts and colitis-associated CRC and restores gut microbiota diversity[146]. Collectively, these strategies underscore the significant translational potential of precisely modulating the microbiota based on host genetic context to improve therapeutic outcomes (**Table 6**). However, the genotype-specific mechanisms governing host-microbe interactions in CRC require deeper characterization. Furthermore, the combined application of

Table 6 Microbiota remodeling based on host genetics

Approach	Targets	Key enriched probiotic/ metabolite	Primary function	Outcomes
P. distasonis oral administration[138]	*F. nucleatum*	*P. distasonis*	Inhibition of *F. nucleatum*	Suppress KARS-mutant CRC progression
Extracellular vesicles from *L. acidophilus* delivering TNF-α siRNA[144]	TNF-α	*L. acidophilus*	Colon-specific gene silencing and microbial remodeling	Suppress IBD
Co-delivery of the probiotic, EcN, and the TGF-β inhibitor, galunisertib, *via* microgels[147]	TGF-β pathway inhibition	*Escherichia coli* Nissle 1917	Synergistic modulation of the tumor microenvironment	Enhanced antitumor efficacy

CRC, colorectal cancer; *F. nucleatum,* Fusobacterium nucleatum; IBD, inflammatory bowel disease; *L. acidophilus,* Lactobacillus acidophilus; *P. distasonis, Parabacteroides distasonis*.

probiotics and gene-targeted agents demands rigorous optimization of dosing, safety, and delivery platforms to realize the full clinical promise.

Conclusions and future perspectives

Significant progress has been made in understanding the role of the gut microbiota in CRC pathogenesis. While recent studies have defined the functions of several key probiotics, the studies have captured only a fraction of the complex functional capacity of the microbiome. The advent of affordable high-throughput sequencing has dramatically expanded our catalog of microbial functions and large-scale population cohorts have identified structural signatures of CRC-associated dysbiosis. These microbial profiles are increasingly recognized as prognostic biomarkers, opening new avenues for microbiome-based therapeutics. Furthermore, technologies, such as nanopore sequencing[148,149] and microbial single-cell genomics[150,151], now enable strain-level resolution, allowing researchers to assemble genomes, annotate genes, and dissect the mechanisms of dysbiosis. This granular view facilitates the mapping of strain-level interactions, both cooperative and antagonistic, and paves the way for precisely targeted microbial interventions. However, the pharmacologic and toxicological safety of live probiotic therapies requires thorough clinical evaluation before widespread adoption.

A critical gap remains in understanding the dynamic nature of the gut microbiome, which is shaped by host genetics, ethnicity, geography, diet, and circadian rhythms. Conventional analyses often fail to capture the stable, long-term ecologic processes that truly determine clinical outcomes. Addressing this gap requires more comprehensive studies with longitudinal monitoring to distinguish transient noise from clinically meaningful signals and to identify robust biomarkers suitable for clinical practice[152,153]. Dynamic microbiome analysis that tracks changes in community structure and function during treatment may provide greater predictive value for therapeutic response and immune-related adverse events than single baseline measurements alone[154]. Notably, stable temporal patterns, such as the recovery of microbial diversity or sustained colonization by specific probiotics, could serve as real-time biomarkers to guide adaptive therapeutic strategies. However, most studies focus on individual strains, failing to adequately assess intervention efficacy within this variable ecologic context. A recent study on obesity and type 2 diabetes (T2D) demonstrated that the therapeutic efficacy of *A. muciniphila* supplementation depends entirely on the baseline abundance[155]. Similarly, circadian oscillations in microbiota can influence the tumor microenvironment, suggesting that time-specific administration may improve therapeutic outcomes[121]. Other underexplored dimensions include spatial heterogeneity, such as differences between tumor-associated microbiota and intestinal ecological niches, and the complex co-evolution of host and microbe during carcinogenesis. Techniques like multi-site sampling and spatial transcriptomic profiling[156] could elucidate these niche-specific patterns, guiding targeted modulation and potentially unlocking breakthroughs in cancer therapy.

Given the challenge of sustaining colonization by exogenous live probiotics and the associated risk of bacteremia, research has pivoted toward beneficial microbial metabolites and components from inactivated bacteria, which are collectively termed "postbiotics." In parallel, "prebiotics," host-indigestible substrates that selectively promote beneficial microbes, have gained prominence. Both strategies enhance intervention efficiency and have proven effective in regulating metabolic diseases. The stable structures and use of non-viable components offer practical advantages, including compatibility with concurrent antibiotic therapies. The synergistic combination of prebiotics and probiotics, known as "synbiotics," further improves probiotic viability and promotes long-term intestinal homeostasis more effectively than single-strain supplements. However, the specific utility in CRC prevention and treatment warrants deeper investigation. Importantly, it is necessary to critically acknowledge the inherent limitations of animal models, which are used in most studies cited in this review for mechanistic insights and preliminary translational evaluation. These limitations include, but are not limited to, substantial differences in immune system architecture, gut microbiota composition, metabolic pathways, and environmental exposures relative to humans. Such discrepancies may affect the translatability of findings and could lead to either overestimation or underestimation of probiotic effects in clinical contexts. Careful consideration of these limitations is therefore essential when interpreting preclinical data and designing subsequent human studies.

In summary, probiotic intervention represents a promising frontier in biotherapy for CRC. Future progress will hinge on integrating advanced bioinformatics with molecular biology to fully decipher the therapeutic potential of the gut microbiota. This knowledge will be crucial for refining gene-targeted therapies, chemotherapy, and immunotherapy, ultimately enabling the development of precise microbial biomarkers and more effective, personalized strategies for the prevention and treatment of CRC.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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