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IMPACT OF GUT MICROBIOTA ON COLORECTAL CARCINOGENESIS AND OPPORTUNITIES FOR THERAPEUTIC MODULATION

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ABSTRACT

Background: Colorectal cancer is a significant global health concern, characterized by increasing incidence and mortality rates, including among younger demographics. Emerging evidence highlights the role of gut microbiota in CRC development, progression, and response to the therapy.
Methodology: A narrative review was conducted, incorporating recent preclinical studies, clinical trials, cohort studies, and meta-analyses to examine the relationship between gut microbiota composition, metabolites, and colorectal cancer, as well as microbiota-targeted therapeutic strategies.
Results: Colorectal cancer is linked to intestinal dysbiosis, where pro-carcinogenic bacteria (Fusobacterium nucleatum, Bacteroides fragilis) are enriched and beneficial butyrate-producing bacteria (Faecalibacterium, Roseburia, Bifidobacterium) depleted. This leads to impaired short-chain fatty acid production, chronic inflammation, epithelial barrier disruption, and immune and oncogenic pathway modulation. Metagenomic and metabolomic analyses have identified microbial and metabolite signatures that could be useful for early detection, prognosis and predicting therapy response. A plethora of microbiota-targeted interventions have demonstrated promising preclinical and early clinical results, including dietary modulation, probiotics, prebiotics, postbiotics, fecal microbiota transplantation, and emerging strategies such as bacteriophage therapy. These interventions have been shown to improve antitumor immunity, reduce treatment-related toxicity, and potentially enhance therapeutic efficacy. Nevertheless, the presence of inter-study heterogeneity and the paucity of large-scale clinical validation currently serve as significant constraints on their routine implementation.
Conclusions: The gut microbiota represents a promising avenue for precision oncology in colorectal cancer. While preclinical and translational studies suggest potential for microbiota-based diagnostics, prognostics, and therapeutic modulation, well-designed, large-scale clinical trials are required to establish efficacy, safety, and standardized implementation.

KEYWORDS

Colorectal Cancer, Dysbiosis, Fecal Microbiota Transplantation, Gut Microbiota, Microbiota-Targeted Therapy

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Introduction

Colorectal cancer (CRC) is the third most prevalent form of cancer globally and the second leading cause of cancer deaths worldwide. In 2020, the global incidence of CRC exceeded 1.9 million cases, with nearly 0.9 million deaths attributable to this condition. According to GLOBOCAN 2020 estimates, the number of new cases of CRC is projected to increase from 1,931,590 in 2020 to 3,154,674 in 2040 worldwide, suggesting a 63.3% increase in the number of new cases of CRC (Roshandel et al., 2024). Alterations in the age structure of CRC have been observed, with an increase in incidence among young people, particularly in developed countries (Eng & Hochster, 2021). These data emphasize the importance of gaining a better understanding of the factors that contribute to its development, as well as developing effective prevention strategies. Recent years have seen a surge of interest in research investigating the correlation between colorectal cancer and the composition of gut microbiota. The gut microbiota is defined as a complex, dynamic ecosystem of microorganisms (including bacteria, fungi, viruses and archaea) inhabiting the human digestive tract. The composition of this ecosystem is variable and is shaped by genetic, dietary and environmental factors. It has been determined that the total quantity of intestinal microbial genes in a given individual exceeds that of the human genome by more than one order of magnitude (Fan & Pedersen, 2021). The gut microbiome plays a pivotal role in the maturation of the immune system, the process of digestion, the regulation of gut endocrine function and neurological signaling, the modification of drug action and metabolism, the elimination of toxins and the production of a variety of compounds that influence the host (Lynch & Pedersen, 2016). Microbiota imbalances, otherwise known as dysbiosis, are characterized by alterations in species composition, a reduction in microbial diversity, and a loss of metabolic and immune functions. The condition has been linked to a wide range of pathological conditions, potentially including gastrointestinal disorders, neurological conditions, respiratory, metabolic dysfunction, hepatic pathologies, cardiovascular conditions, and stomach and colon cancers (Carding et al., 2015). It has been demonstrated that individuals diagnosed with colorectal cancer exhibit distinct changes in their gut microbiota compared to those who are deemed healthy (Herlo et al., 2024). Colorectal cancer has been observed to be related to microbial dysbiosis involving particular bacterial species, including *Fusobacterium nucleatum*, *polyketide synthases (pks^{+}) Escherichia coli*, and *Bacteroides fragilis*, with virome commensals also being shown to be disrupted in patients. Furthermore, a decline in the population of the preventative species *Clostridium butyricum*, *Roseburia*, and *Bifidobacterium* has been observed in patients diagnosed with CRC. A correlation has been observed between Clostridium infection and CRC. *Fusobacterium nucleatum* has been found to be particularly associated with CRC, where it has been linked to therapeutic resistance and poor patient outcomes (Garvey, 2024).

The present literature review has been undertaken with the aim of systematizing the latest knowledge on the relationship between changes in the composition of the gut microbiota and the development of colorectal cancer, and of assessing its potential for use in prevention and treatment support. This issue is of key importance from both the perspectives of public health and the further development of medicine. The growing incidence of colorectal cancer and the increasing evidence of the role of the microbiome in carcinogenesis make this topic extremely important. A comprehensive understanding of these relationships may contribute to the development of more effective diagnostic, preventive and therapeutic strategies in the future, which highlights the need for further research on this issue.

Methodology

This review was based on articles sourced from PubMed, Scopus, and Google Scholar databases, with a particular focus on recent original studies, systematic reviews, and meta-analyses investigating the role of gut microbiota in CRC. The selection criteria included studies evaluating changes in gut microbial composition and function in CRC patients or experimental models, as well as research assessing microbiota-targeted interventions such as probiotics, prebiotics, postbiotics, fecal microbiota transplantation (FMT), dietary modulation, and engineered microbial therapies. Both human and preclinical studies were considered to provide mechanistic and translational insights. The literature search was conducted using the following keywords: colorectal cancer, gut microbiota, dysbiosis, short-chain fatty acids, fecal microbiota transplantation, probiotics, prebiotics, postbiotics, and microbiota-targeted therapy. Studies were selected based on relevance to CRC pathogenesis, diagnostic and prognostic potential of microbial or metabolite biomarkers, and evidence supporting therapeutic modulation of the microbiota. Articles without original data, non-English publications, or studies lacking sufficient methodological detail were excluded.

Results

1. The relationship between microbiota and colorectal cancer

CRC develops through a multistep process initiated by molecular alterations in epithelial cells and culminating in invasive malignancy. This sequence is typically categorized into four stages: initiation, promotion, malignant conversion, and progression (Weston Ainsley & Harris Curtis C., 2003). A broad spectrum of environmental and lifestyle factors has been identified as contributing to CRC risk. Increased consumption of processed and red meat, alcohol intake, smoking, physical inactivity, obesity, and adult weight gain have consistently been associated with elevated risk. Conversely, higher dietary intake of fiber, calcium, and vitamin D is linked to a reduced incidence of CRC (Genua et al., 2021). An expanding body of evidence highlights the crucial role of the gut microbiota in modulating colorectal carcinogenesis. Microbial dysbiosis has been shown to facilitate both the initiation and progression of neoplastic lesions, primarily through disruption of the intestinal barrier, promotion of inflammation, altered metabolite production, and induction of DNA damage (Karam et al., 2025). Consequently, elucidating host–microbiota interactions remains essential for advancing prevention, early detection, and therapeutic strategies in CRC (Fusco et al., 2024). It is important to note that alterations in gut microbiota observed in colorectal cancer may partly represent a consequence of tumor-associated inflammation and metabolic reprogramming rather than a purely initiating factor. Therefore, distinguishing causal microbial drivers from secondary microbial shifts remains a central challenge in current CRC–microbiota research. In this context, the study conducted by Jingjing Liu investigated the effects of inflammation-induced carcinogenesis on the composition of the intestinal microbiota in a murine model using 16S rRNA sequencing. The researchers observed marked shifts in microbial diversity during both inflammatory and neoplastic phases, notably an increased abundance of *Bacteroidaceae* accompanied by a reduction in *Muribaculaceae*. These changes were hypothesized to impair pathways associated with DNA repair and replication while enhancing microbial metabolic activity, thereby fostering a microenvironment conducive to tumor development (J. Liu et al., 2022). The findings underscore the regulatory role of the gut microbiota in modulating inflammatory responses and driving tumor progression. However, it is imperative to emphasize that, despite the invaluable mechanistic insights provided by murine models, their translational relevance is constrained by substantial disparities in host physiology, immune system architecture, and baseline microbial composition between mice and humans. Furthermore, experimental procedures such as antibiotic pretreatment, germ-free rearing, or chemical induction of tumors have the capacity to modify the microbial landscape, thereby rendering the interpretation of causality more complex.

Further support for the functional significance of microbiota modulation comes from studies examining FMT (H. Yu et al., 2023). One investigation demonstrated that FMT from healthy donors to mice with CRC and dysbiosis effectively restored microbial balance, limited tumor growth, reducing both lesion number and diameter, and improved survival. These effects were accompanied by enhanced antitumor immunity, characterized by increased infiltration of CD8+ T cells and NK cells, and reduced levels of Tregs. FMT also modulated cytokine profiles by lowering proinflammatory mediators (e.g. IL-6, IL-17A) and elevating IL-10. Additional research corroborates these outcomes, indicating that FMT not only restores microbial diversity but also reduces pathogenic taxa and strengthens antitumor immune responses. Collectively, these findings suggest that targeted manipulation of the gut microbiota may offer a promising adjunctive approach to CRC therapy (Song et al., 2024). A complementary line of evidence highlights the tumor-promoting potential of obesity-associated microbiota. A recent study demonstrated that the transfer of fecal microbiota from obese human donors to mice significantly accelerated tumor development, as reflected by increased number and size of neoplastic lesions, impaired barrier integrity, enhanced epithelial proliferation, and activation of proinflammatory genes and Wnt signaling. Microbiota profiling revealed an increased abundance of potentially pathogenic species, including *Alistipes finegoldii*, and a reduction in beneficial taxa such as *Bacteroides vulgatus* and *Akkermansia muciniphila*. These findings suggest that obesity-related dysbiosis generates a pro-carcinogenic intestinal milieu by disrupting mucosal homeostasis, intensifying inflammation, and modulating key oncogenic pathways (Kang et al., 2023). In line with these observations, another study demonstrated that FMT from healthy, physically active mice to obese, high-fat-diet–fed animals treated with azoxymethane resulted in a marked reduction in polyp and tumor burden. This intervention also shifted microbial composition and metabolite profiles, including an increase in short-chain fatty acids and favorable bile acids. Taken together, these results highlight the protective effects of a “healthy” and physically active microbiota and further emphasize the mechanistic interplay between microbial ecology, host metabolism, and colorectal tumorigenesis (Matsumoto et al., 2025). It should be emphasized that most current findings derive from murine studies or early-stage translational research, and robust clinical validation in human populations is still lacking. Large, controlled trials are needed to determine whether microbiota-targeted interventions can meaningfully influence CRC risk or treatment outcomes in patients.

2. The composition of the gut microbiota in patients with CRC

In recent years, the identification of microbial patterns that distinguish cancer-related gut communities from those of healthy individuals has become possible. This is attributable to the recent advancements in metagenomic sequencing, which have facilitated comprehensive comparisons between CRC patients and healthy individuals (C. Chen et al., 2025). Nonetheless, it is crucial to acknowledge the inherent limitations of this method, which are intricately linked to two fundamental factors. Firstly, there exists a considerable degree of internal variability within the microbiota of healthy individuals. Secondly, a significant degree of heterogeneity within the population is attributable to a variety of factors, including dietary habits, lifestyle choices, geographical location and exposure to antibiotics (Keohane et al., 2020). Furthermore, the technical aspects of conducting the study may influence the results obtained, which complicates the comparison of studies (Bartolomaeus et al., 2021). Despite the limitations previously outlined, it has been demonstrated that in patients diagnosed with CRC, there is a significant change in gut microbiome composition, characterized by a reduction in bacterial diversity and the proliferation of pathogenic species (Y. Yang et al., 2021). In this meta-analysis, 536 fecal shotgun metagenomes were compared, and it was demonstrated that the species *Fusobacterium nucleatum*, *Bacteroides fragilis*, *Parvimonas micra*, *Porphyromonas asaccharolytica*, *Prevotella intermedia*, *Alistipes finegoldii*, and *Thermanaerovibrio acidaminovorans* were more abundant in patients diagnosed with CRC (Dai et al., 2018). Furthermore, a decline in the prevalence of the potentially probiotic species *Clostridium butyricum*, *Roseburia*, and *Bifidobacterium* has been observed in the microbiota of patients diagnosed with CRC (Ternes et al., 2020). An analysis of tissue biopsies collected at various stages of colorectal cancer further underscores the role of gut dysbiosis in adenoma formation. This indicates the functional significance of the gut microbiome in the initiation and progression of CRC (Nakatsu et al., 2015).

Dysbiosis observed in CRC includes important functional shifts in the microbiome, such as reduced production of beneficial short-chain fatty acids, particularly butyrate. Butyrate depletion is of particular significance, given that this metabolite serves as a primary energy source for colonocytes and demonstrates anti-inflammatory, pro-apoptotic, and anti-tumorigenic properties. These changes result in a weakened intestinal barrier, modulation of inflammation and potential epigenetic effects on intestinal epithelial cells (Alvandi et al., 2022). Furthermore, the distribution of microflora in left-sided colorectal cancer (LCC) and right-sided colorectal cancer (RCC) is significantly different in terms of both type and abundance. Some studies suggest that the higher incidence of LCC may partly reflect differences in microbial distribution, including a greater abundance of certain pathogenic taxa in the left colon. The discrepancy in microbiota between samples obtained from the left and right sides of the colon may prove advantageous in the context of VEGF- and EGFR-targeted therapy. However, it should be emphasized that, due to the limited sample size employed in this study, further research is necessary to validate these findings (Zhong et al., 2020).

In patients diagnosed with CRC, in addition to the previously described alterations in bacterial communities, numerous viruses, such as CMV (Bender et al., 2009) and HPV (J. Y. Cheng et al., 1995), have also been detected, although conclusive evidence supporting their causal involvement is lacking. Furthermore, the role of the mycobiome in CRC remains poorly defined, largely due to the low abundance of fungal species and the considerable inter- and intra-individual variability observed across studies (Lin et al., 2022). Although evidence for a causal role of viral or fungal communities remains limited, their presence suggests that CRC-associated dysbiosis extends beyond bacteria and may involve complex multi-kingdom interactions.

The resulting alteration in the equilibrium between pro-carcinogenic and anti-carcinogenic microorganisms within the gut microbiota may, in turn, contribute to the modulation of pathogenic pathways. Understanding these microecological shifts provides an opportunity to identify reliable microbial biomarkers and to develop microbiome-targeted therapeutic interventions, including probiotics, prebiotics, and personalized modulation of microbial communities.

3. Gut microbiota as a diagnostic and prognostic biomarker in colorectal cancer

The importance of the gut microbiota in the development and progression of colorectal cancer is becoming increasingly evident, as is its potential as a clinical biomarker. The gut microbiota is an attractive candidate for a CRC biomarker due to its relative accessibility (e.g. stool samples), high-resolution analysis capabilities (e.g. metagenomics, 16S rRNA sequencing and shotgun metagenomics) and significant impact on metabolism, immunology and the intestinal microenvironment. Analysis of changes in the composition and functioning of the microbiome can not only serve as a tool for early diagnosis, but also allows for disease progression prediction and personalized therapy, making it a promising direction for translational research. In a systematic review of 28 studies that utilized stool samples as the basis for screening tests for CRC and

advanced adenomas (precursor lesions), the authors report that the effectiveness of microbiome biomarkers varied significantly. The area under the ROC curve (AUC) values for precancerous lesions ranged from 0.28 to 0.98, while for early CRC cancers they ranged from 0.54 to 0.89. Models incorporating common metabolites, referred to as the "co-metabolome", attained AUC values ranging from approximately 0.69 to 0.84 for adenomas and from 0.65 to 0.93 for early CRC. Concurrently, the authors underscore the substantial heterogeneity inherent within the studies, which is characterized by discrepancies in cohort size, sampling methodology, sequencing, and bioinformatic analyses. This heterogeneity presently imposes significant limitations on the standardization and clinical application of these tests (Zwezerijnen-Jiwa et al., 2023). A subsequent review of 45 studies covering the period 2018–2024 indicated that certain bacterial species, including *Fusobacterium nucleatum*, *Bacteroides fragilis*, and *Parvimonas micra*, have relatively high reproducibility (AUC >80%) for CRC detection across diverse populations using non-invasive stool-based metagenomic approaches (Upadhyay et al., 2025). Furthermore, it has been observed that specific species, including *Ruminococcus bicirculans* and *Faecalibacterium prausnitzii*, have been found to be associated with advanced stages of CRC and subsequent disease progression (Piccinno et al., 2025). Zou et al., conducted a comprehensive analysis of fecal microbiota samples and tissue material (tumor and healthy mucosa) from 41 patients with CRC. The analysis was meticulously combined with genomic (somatic mutations) and transcriptomic analysis. A total of 22 bacterial species were identified as being closely correlated with the presence of cancer. Of particular significance were the associations identified between the presence of specific bacteria and mutations in key genes (including TP53, APC, KRAS, SMAD4) and differences in the expression of genes related to metabolism and immunology. Specifically, the presence of *Fusobacterium nucleatum* has been linked to alterations in the tumor's immune microenvironment (e.g., the regulation of the TNFSF9 gene) (Zou et al., 2024). This finding suggests that the microbiota might possess prognostic value, functioning not only as an indication of tumor presence, but also as a potential marker of biological tumor characteristics with the potential to influence disease progression, treatment response, or risk of recurrence. Another prospective study, conducted in 2023, analyzed tumor mucosal microbiota, tumor metabolome, and clinical data in patients following CRC resection. Groups of bacteria were identified whose presence or relative abundance was correlated with worse or better outcomes (e.g. time to recurrence). The results of this study suggest that the tumor microbiota itself, and not merely the fecal microbiota, can serve as a prognostic biomarker that can stratify patients in terms of risk of recurrence or tumor aggressiveness (Alexander et al., 2023). The gut microbiota has been identified as a potential predictive biomarker of response to therapy in patients with colorectal cancer, with the potential to inform the effectiveness of immunotherapy, chemotherapy, and chemoradiotherapy. The composition of the microbiota, particularly the presence of butyrate-producing bacteria (e.g., *Faecalibacterium*, *Eubacterium rectale*, *Roseburia*), has been shown to be associated with a more favorable response to neoadjuvant chemoradiotherapy and checkpoint inhibitor immunotherapy. Higher microbiota diversity and the predominance of bacteria from the *Ruminococcaceae*, *Lachnospiraceae*, *Akkermansia muciniphila*, and *Prevotellaceae* families have been shown to correlate with a favorable response to treatment. Conversely, the dominance of *Micrococcaceae* or *Rothia mucilaginosa* has been associated with a lack of response (Ajab et al., 2024; Sánchez-Alcoholado et al., 2021; Yi et al., 2021). The influence of the microbiota on therapeutic response is multifaceted, encompassing the modulation of drug metabolism, the regulation of immune responses, and the production of metabolites, such as short-chain fatty acids, that can enhance the anticancer effect. In cases of non-response to treatment, an increase in pro-inflammatory pathogens and oncogenic metabolites (e.g., polyamines) has been observed (Sánchez-Alcoholado et al., 2021; Yi et al., 2021). High levels of *Fusobacterium nucleatum* in tumor tissue have been demonstrated to be associated with diminished overall survival, an elevated risk of recurrence, and diminished chemotherapy efficacy, particularly in the context of treatment with oxaliplatin and fluorouracil (Borozan et al., 2022; Huangfu et al., 2021; Lee et al., 2018; Mima et al., 2016). The mechanisms in question involve the induction of chemotherapy resistance through the activation of autophagy, the inhibition of ferroptosis, and the modulation of immune pathways. This results in immunosuppression and reduced efficacy of immunotherapy (Dadgar-Zankbar et al., 2024; Incognito et al., 2025; B. Li et al., 2024). Patients with high levels of *Fusobacterium nucleatum* have an increased risk of recurrence following neoadjuvant chemoradiotherapy and no increase in CD8+ lymphocyte infiltration after treatment, indicating impaired cytotoxic response (Serna et al., 2020). Furthermore, the maintenance of elevated levels of *Fusobacterium nucleatum* post-therapy has been shown to be associated with a sevenfold elevated risk of recurrence in cases of locally advanced rectal cancer (Serna et al., 2020). *Fusobacterium nucleatum* has been found to be associated with the mesenchymal tumor

phenotype (CMS4/CRIS-B), which is characterized by a particularly poor prognosis and resistance to treatment (Salvucci et al., 2021).

Recent research findings suggest that potential biomarkers may not be limited to the microbiota composition itself, but could also encompass the functional consequences of the resulting metabolic products, interactions with the immune system, and effects on the intestinal microenvironment. Alterations in the profile of metabolites, including short-chain fatty acids, branched-chain amino acids, tryptophan derivatives, polyamines, bile acids and lipids, have been demonstrated to be closely related to the presence and stage of cancer. Specific panels of microbiome metabolites, both in serum and feces, have been shown to distinguish between healthy individuals, patients with adenoma, and patients with colorectal cancer with high sensitivity and specificity (AUC even >0.90), surpassing classic markers such as CEA (F. Chen et al., 2022; Coker et al., 2022; Gao et al., 2022). The metabolites produced by the microbiome are indicative of the metabolic activity of gut bacteria, which undergoes a process of reprogramming during carcinogenesis. These alterations manifest during the early stages of tumor development, thus facilitating non-invasive detection of preclinical changes and disease progression monitoring (Coker et al., 2022; Feng et al., 2023; Yachida et al., 2019). Furthermore, certain metabolites (e.g., norvaline, myristate, imidazolepropionate, serotonin) have been found to be associated with tumor aggressiveness and prognosis, thus serving as useful prognostic biomarkers (Avuthu & Guda, 2022; Coker et al., 2022; Gao et al., 2022). However, it should be noted that there are significant limitations in the use of biomarkers from the gut microbiota and its metabolites in patients with colorectal cancer, primarily due to the high heterogeneity of results between studies, populations, and analytical platforms, which hinders the standardization and clinical validation of these markers (Gao et al., 2022; Piccinno et al., 2025; Zwezerijnen-Jiwa et al., 2023). The composition of the microbiota and the metabolite profile are strongly modulated by environmental factors, diet, medications, comorbidities, and geographical differences. This results in variability in biomarker signatures and limits their universality (Avuthu & Guda, 2022; John Kenneth et al., 2023). A further limitation is the absence of clear, validated diagnostic thresholds, as well as an insufficient number of large, prospective studies with external validation to confirm the usefulness of microbiota and metabolite biomarkers in routine clinical practice. The majority of extant studies are predicated on cross-sectional or retrospective analyses, frequently comprising a modest number of cases and exhibiting an absence of consideration for confounding factors (Feng et al., 2023; L. Yu et al., 2022; Zwezerijnen-Jiwa et al., 2023). Furthermore, the technical aspects of sample collection, storage, and analysis (e.g. stool, serum) are not standardized, which has a detrimental effect on the reproducibility of results and their interpretation (Gao et al., 2022; Zwezerijnen-Jiwa et al., 2023). With regard to microbiota metabolites, concentrations are subject to variation depending on the time of sample collection, nutritional status, or metabolic activity of the patient (Cao et al., 2025; Coker et al., 2022; J. Li et al., 2022). In summary, despite the encouraging research results, the limitations mentioned above currently prevent the routine use of gut microbiota biomarkers and their metabolites in the diagnosis and monitoring of colorectal cancer therapy.

4. Therapies targeting the gut microbiota in colorectal cancer

Interventions targeting the gut microbiota are an increasingly important component of translational research on the prevention and treatment of CRC. These approaches encompass dietary modifications and prebiotics, probiotics and bacterial consortia, postbiotics (microbiota metabolites), microbiota transplantation, pharmacological modulation, and novel technologies, including phage therapy and bacterial genetic engineering (tab. 1). In recent years, there has been an increase in the number of preclinical studies and systematic reviews in the literature that indicate the potential of such interventions. However, these studies have also highlighted the limitations associated with the heterogeneity of the studies and the lack of broad clinical validation (Bohm et al., 2024; Brusnic et al., 2024; L.-Y. Zhao et al., 2023).

Table 1. Therapies targeting the gut microbiota in colorectal cancer

Therapy	Mechanism of Action	Clinical Status	Benefits	Limitations / Risks	References
Dietary interventions	Modulation of microbiota via fiber, polyphenols, plant-based diets	Observational & interventional studies	Increases SCFA-producing commensals, anti-inflammatory, antineoplastic effects, supports therapy	Effects depend on baseline diet/microbiota, adherence, lack of standardized protocols	(García Mansilla et al., 2025; Madrigal-Matute & Bañón-Escandell, 2023; Sánchez-Alcoholado et al., 2020; Zhang et al., 2025)
Probiotics	Restoration of microbial balance, immunomodulation	Clinical trials, adjuvant use	Improves barrier function, reduces inflammation, may enhance therapy tolerance	Strain-specific effects, safety in immunosuppressed, lack of standardization	(Bai et al., 2025; Fong et al., 2020; García Mansilla et al., 2025; Kvakova et al., 2022; Y. Wang & Li, 2022)
Prebiotics	Stimulation of beneficial bacteria growth	Clinical trials	Increases SCFA (e.g., butyrate), supports commensals	Variable efficacy, dependent on host microbiota	(Fong et al., 2020; García Mansilla et al., 2025; Taghinezhad-S et al., 2021; Y. Wang & Li, 2022; Zhang et al., 2025)
Synbiotics	Combined effect of probiotics and prebiotics	Clinical trials	Synergistic modulation, improved diversity	Limited long-term data, formulation variability	(Fong et al., 2020; García Mansilla et al., 2025; Kvakova et al., 2022; Taghinezhad-S et al., 2021; Y. Wang & Li, 2022; Zhang et al., 2025)
Postbiotics	Administration of bacterial metabolites (e.g., SCFA)	Early clinical studies	Anti-inflammatory, supports barrier function	Lack of standardization, limited clinical data	(Kvakova et al., 2022; Taghinezhad-S et al., 2021; Zhang et al., 2025)
Fecal microbiota transplantation (FMT)	Restoration of whole microbiota composition	Clinical trials, off-label	Potential to improve immunotherapy response, restores diversity	Infection risk, lack of standardization, limited CRC-specific data	(Bai et al., 2025; M. Chen et al., 2022; Fong et al., 2020; García Mansilla et al., 2025; Perillo et al., 2020; Taghinezhad-S et al., 2021; Y. Wang & Li, 2022; Wong & Yu, 2023)
Bacteriophage therapy	Selective elimination of pathogenic bacteria	Preclinical/early clinical	Targeted action, minimal dysbiosis	Limited clinical data, resistance potential	(Bai et al., 2025; Zhang et al., 2025)
Engineered microbiota (e.g., genetically modified bacteria)	Targeted metabolite production, cytotoxicity	Preclinical	High specificity, potential for precision therapy	Safety concerns, unpredictable effects, no clinical data	(Kvakova et al., 2022; Zhang et al., 2025)

4.1. Probiotics

Probiotics have been shown to play a supportive role in the treatment of CRC, mainly by modulating the gut microbiota, reducing inflammation, improving the integrity of the intestinal barrier, and alleviating the complications of cancer treatment (Dikeocha et al., 2021; Kvakova et al., 2022). Randomized clinical trials have demonstrated that probiotic supplementation (most commonly *Lactobacillus* and *Bifidobacterium* strains) in patients diagnosed with CRC improves quality of life, reduces the incidence of postoperative complications (e.g. infections, diarrhea), shortens hospital stays, and reduces the side effects of chemotherapy, such as diarrhea and mucositis (Dikeocha et al., 2021; Wierzbicka et al., 2021). Probiotics have been shown to inhibit the production of pro-inflammatory cytokines, support the anti-cancer immune response, and limit the colonization of pathogens and the production of carcinogens in the intestinal lumen (Ghorbani et al., 2022; Q. Li et al., 2024). A beneficial effect on reducing tumor progression and improving immune and biochemical parameters has also been observed in preclinical and clinical studies (Niechcial et al., 2025). A meta-analysis of 18 randomized trials (n=1526) demonstrated that probiotics significantly reduce the risk of developing diarrhea after chemotherapy (RR=0.51; 95% CI: 0.40–0.64) and shorten the duration of the condition. Probiotics have been demonstrated to alleviate a range of gastrointestinal symptoms, including flatulence, nausea, loss of appetite, and abdominal pain (M. Yang et al., 2025). These benefits are achieved without significant adverse effects. The efficacy of probiotic supplementation in reducing symptoms of gastrointestinal disorders, such as nausea, vomiting, and diarrhea, has been corroborated by systematic reviews and meta-analyses. These studies have also demonstrated that probiotic supplementation can enhance the diversity and abundance of beneficial bacteria within the gut microbiota, thereby modulating the intestinal environment. Specifically, probiotics have been observed to increase the levels of *Bifidobacterium* and *Lactobacillus*, while concomitantly reducing the levels of *Escherichia coli* (Wierzbicka et al., 2021; Yao et al., 2025). In the context of immunotherapy, quasi-experimental studies have demonstrated that the incorporation of probiotics into immune checkpoint inhibitors (ICI) and chemotherapy regimens results in enhanced survival outcomes, augmented intestinal barrier function, elevated percentages of CD4+ and CD3+ lymphocytes, and a reduction in treatment-related complications (X. Wang et al., 2025). It is hypothesized that probiotics may also support the production of SCFAs, which in turn promote immune response (Huang et al., 2023). Future research directions include the personalization of probiotic therapy according to individual microbiota profiles, the employment of next-generation probiotics, and the combination of these with prebiotics or postbiotics to achieve synergistic effects (Ha et al., 2024; Kvakova et al., 2022). It is evident that large, randomized clinical trials are required to ascertain the most effective strains, doses, and administration regimens, in addition to confirming the safety and efficacy of these interventions in the colorectal cancer population.

4.2. Prebiotics and synbiotics

Prebiotics are defined as indigestible food components, typically oligosaccharides or polysaccharides, such as inulin, fructooligosaccharides and resistant starch. These prebiotics have been shown to stimulate the growth and activity of beneficial gut bacteria, particularly *Bifidobacterium* and *Lactobacillus* species. In the context of CRC, prebiotics have been demonstrated to stimulate the production of SCFAs, notably butyrate, which exerts anti-inflammatory, anti-proliferative and pro-apoptotic effects on colonic epithelial cells. A body of clinical evidence suggests that prebiotic supplementation can increase the abundance of beneficial bacteria and reduce inflammatory markers, such as TNF-α, while increasing anti-inflammatory cytokines, such as IL-10, in patients with colorectal adenomas, who are at high risk of CRC (Meng et al., 2025). Prebiotics have been shown to help mechanistically restore microbial homeostasis, improve epithelial barrier integrity and potentially reduce CRC risk by modulating the local immune microenvironment (Mahdavi et al., 2021).

Synbiotics are formulations combining prebiotics and probiotics, which are designed to enhance the survival and activity of beneficial microbes in a synergistic manner. In patients diagnosed with CRC, the administration of synbiotics has been shown to engender improvements in the composition of the gut microbiota, characterized by an increase in beneficial bacteria and a concomitant reduction in pathogenic taxa. Synbiotics have been demonstrated to enhance gut barrier function, reduce systemic and local inflammation, and improve postoperative outcomes and tolerance to conventional therapies (Cruz et al., 2020; Wierzbicka et al., 2021). A body of research in the field of preclinical and translational studies has demonstrated the potential of synbiotics to modulate procarcinogenic pathways, reduce oncometabolite production, and diminish tumor cell self-renewal capacity (Greenhalgh et al., 2019). The findings of clinical trials have indicated that patients suffering from CRC who have been administered synbiotics have demonstrated enhanced tight junction function and a reduction in inflammatory parameters (García Mansilla et al., 2025).

4.3. Postbiotics

Postbiotics, defined as preparations of inanimate microorganisms and/or their components (including metabolites such as short-chain fatty acids, exopolysaccharides, and cell wall fragments), are increasingly recognized as promising adjuncts in the prevention and therapy of CRC due to their safety, chemical stability, and immunomodulatory properties (Xie et al., 2024). Mechanistically, postbiotics have been shown to exert anti-tumor effects through several pathways. The modulation of the gut microbiota, restoration of eubiosis and enhancement of the integrity of the intestinal barrier have been demonstrated to reduce chronic inflammation and the risk of carcinogenesis. Key metabolites such as butyrate have been shown to induce apoptosis and cell cycle arrest in CRC cells, in addition to suppressing pro-oncogenic signaling, notably the Wnt pathway, and selectively inhibiting tumor cell proliferation without affecting normal fibroblasts. It is evident that a number of bioactive components, including exopolysaccharides and tryptophan metabolites, contribute to anti-inflammatory and antioxidant effects. This further supports the host's anti-tumor immune response (Erfanian et al., 2023; Feizi et al., 2024; Rad et al., 2021; Vrzáčková et al., 2021; Xie et al., 2024). As demonstrated by preclinical studies, postbiotics derived from Lactobacillus acidophilus and other commensals have the capacity to downregulate Wnt pathway genes (e.g., SFRP1, SFRP2, SFRP4, MMP7), induce G1 cell cycle arrest, and inhibit migration and proliferation of CRC cell lines. The validity of these findings is further substantiated by the use of sophisticated models, including organoids and organ-on-chip platforms, which exhibit a high degree of similarity with respect to human tissue architecture and tumor microenvironment (D'Amore et al., 2025; Erfanian et al., 2023). In comparison with probiotics, postbiotics offer a superior safety profile, particularly in immunocompromised or chemotherapy-treated patients, as they do not carry the risk of translocation or infection. Their chemical stability and ease of formulation further enhance their translational potential. However, the clinical evidence remains limited, with the majority of human data restricted to vitamin K molecules and early-phase trials. It is therefore imperative that robust, well-designed clinical studies are conducted as a matter of urgency in order to establish efficacy, optimal dosing, and long-term safety in CRC populations (D'Amore et al., 2025; Kudra et al., 2023; Xie et al., 2024). The prevailing consensus in the field endorses the incorporation of postbiotics as complementary components to conventional CRC therapies, particularly in the context of microbiota modulation, inflammation reduction, and the promotion of epithelial barrier function. Precision approaches, tailored to individual host-microbiome interactions and metabolomic profiles, are likely to enhance therapeutic outcomes. Pending additional clinical validation, postbiotics ought to be regarded as ancillary rather than primary measures in the management of CRC (García Mansilla et al., 2025; Y.-C. Yang et al., 2025).

4.4. Dietary interventions

It has been demonstrated that diets comprising high concentrations of fiber and polyphenols have the capacity to modulate the composition of the gut microbiota, thereby increasing the abundance of beneficial bacteria such as *Bifidobacterium*, *Lactobacillus*, *Roseburia*, and *Clostridium*. These bacteria are key producers of SCFA, with butyrate being a particularly notable example (Celiberto et al., 2023; He et al., 2025; Hussain et al., 2025). Dietary fiber is subject to fermentation by the gut microbiota, resulting in an increase in the concentration of SCFAs. These have been shown to exert anti-inflammatory, pro-apoptotic, and anti-proliferative effects on colon cancer cells (Celiberto et al., 2023; He et al., 2025; Pedrosa & Fabi, 2024). Polyphenols, found in vegetables, fruits, tea, and wine, among other foods, selectively promote the growth of probiotic bacteria and increase SCFA production, while their metabolites exhibit antioxidant properties, strengthen the integrity of the intestinal barrier, and inhibit inflammatory processes and angiogenesis in the tumor microenvironment (B. Cheng et al., 2025; Y. Zhao & Jiang, 2021). The combined effect of fiber and polyphenols has been shown to result in enhanced microbiota diversity, a decrease in pathogenic and pro-inflammatory strains, and an increase in metabolites with anti-cancer properties (B. Cheng et al., 2025; García Mansilla et al., 2025). These effects are reflected in a reduced risk of developing colorectal cancer and may improve the response to cancer treatment, including chemotherapy and immunotherapy, by modulating the tumor microenvironment, reducing inflammation, and improving immune function (García Mansilla et al., 2025; He et al., 2025; Pedrosa & Fabi, 2024; Sánchez-Alcoholado et al., 2020).

4.5. Fecal microbiota transplantation

FMT is a procedure that involves the administration of a suspension of feces from a healthy donor to the recipient's gastrointestinal tract. This is most often achieved via colonoscopy, naso-intestinal tube, or oral capsules, with the aim of restoring normal intestinal microflora (Yadegar et al., 2024). FMT is not currently recognized as a standard treatment for colorectal cancer; however, it is a subject of ongoing investigation as a potential supplementary strategy to regulate gut microbiota, strengthen anti-tumor immune responses and, consequently, enhance therapeutic outcomes (H. Yu et al., 2023). The mechanism of action of FMT involves several key aspects. Firstly, the administration of FMT has been demonstrated to restore the diversity of the microbiota, thereby leading to a reduction in the number of pro-inflammatory and pathogenic bacteria and an increase in bacteria with anti-inflammatory and immunomodulatory properties (Song et al., 2024). Secondly, FMT modulates the immune response of the host, resulting in increased infiltration of cytotoxic cells (CD8+ T, NK) into tumor tissue and a concomitant reduction in immunosuppressive cells (Treg), thereby promoting tumor growth inhibition (Brusnic et al., 2024; Xu et al., 2022). Thirdly, FMT has been demonstrated to influence bacterial metabolism, including the production of SCFAs, which have been shown to possess antiproliferative and anti-inflammatory properties (Song et al., 2024). In the context of immunotherapy, FMT is under investigation for its ability to overcome resistance to immune checkpoint inhibitors, particularly in patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) metastatic colorectal cancer who are refractory to anti-PD-1 therapy. It is important to note that early-phase clinical trials are ongoing, but robust clinical efficacy data in colorectal cancer are not yet available (Brusnic et al., 2024; Eng et al., 2024). In summary, in preclinical and early clinical studies, FMT shows potential in inhibiting the progression of colorectal cancer, improving response to immunotherapy (especially in cases of resistance to checkpoint inhibitors) and alleviating treatment toxicity, e.g., intestinal inflammation after chemotherapy (Chang et al., 2020; Van Dingenen et al., 2023; Wekking et al., 2025; Xu et al., 2022; H. Yu et al., 2023). Nevertheless, the use of FMT as an oncological intervention is still considered to fall within the category of experimental therapies, necessitating further clinical investigations to ascertain its effectiveness and safety. This necessity for further study is compounded by the requirement to standardize the methods of administration and the selection criteria for donors (Brusnic et al., 2024; Y.-H. Liu et al., 2024; Yadegar et al., 2024).

4.6. Bacteriophage therapy and engineered microbes

The therapeutic modality known as bacteriophage therapy involves the administration of viruses that selectively target bacteria implicated in the pathogenesis of colorectal cancer, including *Fusobacterium nucleatum* and *Bacteroides fragilis*. It has been demonstrated that bacteriophages have the capacity to selectively eliminate bacteria, modulate tumor microbiota, reduce resistance to chemotherapy, and enhance the anti-tumor immune response. For instance, the use of VA7 phages against *Bacteroides fragilis* has been demonstrated to restore sensitivity to chemotherapy and inhibit tumor progression in animal models (Ding et al., 2025). Furthermore, bacteriophages can be engineered to transport drugs, genes, or antigens directly to tumor tissue, thereby increasing the precision of therapy and reducing toxicity (Hsu et al., 2026; Huh et al., 2022; Ooi & Yeh, 2024). The modified microorganisms, with a particular focus on probiotic strains of *Escherichia coli* Nissle 1917, are engineered to selectively colonize colon tumors and locally release cytokines, checkpoint-blocking nanobodies (e.g., PD-L1, CTLA-4), or other therapeutic agents. Clinical studies have demonstrated that the administration of such strains results in a reduction in tumor burden and facilitates non-invasive detection of neoplastic changes through the production of biomarkers detected in urine (M. Chen et al., 2025; Gurbatri et al., 2024). Furthermore, genetic engineering facilitates the programming of bacteria to detect inflammation or the presence of cancer, and to release drugs in a controlled manner (M. Chen et al., 2025; Hamidi Nia & Claesen, 2022). In summary, bacteriophage therapy and modified microorganisms are safe under experimental conditions and show potential in modulating the microbiota and response to colorectal cancer treatment. However, they do not currently exceed current therapeutic standards in terms of clinical efficacy. Further research, standardization, and evaluation of long-term safety and effectiveness are required for their use in clinical practice.

4.7. Future directions

Future research directions in the field of gut microbiota in colorectal cancer are focused on several translational and clinical advances. Firstly, there is an increasing emphasis on the development of microbiome-derived biomarkers for the early detection, risk stratification and surveillance of colorectal cancer. This is being achieved by leveraging multi-omics platforms and artificial intelligence driven analytics to identify microbial signatures associated with tumorigenesis and treatment response (Bai et al., 2025; Hu et al., 2025; Tudorache et al., 2025; Y.-C. Yang et al., 2025). Secondly, precision microbiome modulation is emerging, including the use of probiotics, prebiotics, synbiotics, postbiotics, and FMT as adjuncts to conventional therapies. restore microbial balance, enhance gut barrier integrity, and modulate immune responses. This field of research is undergoing significant development, with ongoing studies focusing on engineered microbial consortia and bacteriophage therapy (Bai et al., 2025; Y.-C. Yang et al., 2025). Personalized approaches are being explored, in which microbiome profiles are matched to specific therapeutic regimens and longitudinal changes are monitored to optimize outcomes and minimize adverse effects (Fong et al., 2020; Y.-C. Yang et al., 2025). The integration of microbiome analysis into multi-omics frameworks is expected to facilitate precision oncology, thereby enabling individualized prevention and treatment strategies (Tudorache et al., 2025). Key challenges include standardization of interventions, regulatory oversight, and addressing interindividual variability in microbiome composition and function (Bai et al., 2025; Tudorache et al., 2025). In general, the field of colorectal cancer is progressing towards a paradigm of precision medicine informed by the microbiome. The overarching objective of this transition is to operationalize the complex biology of gut microbiota into practical tools for various applications, including diagnosis, therapy selection, and surveillance. The ultimate aim of this development is to enhance patient outcomes through the application of these novel methodologies.

Conclusions

The gut microbiota plays a pivotal role in the development and progression of CRC, and in determining the response to therapy. Dysbiosis, a condition characterized by an overgrowth of pro-carcinogenic bacteria such as *Fusobacterium nucleatum* and *Bacteroides fragilis*, and a simultaneous undergrowth of beneficial butyrate-producing bacteria (e.g. *Faecalibacterium*, *Roseburia*, *Bifidobacterium*), contributes to a state of chronic inflammation, impaired intestinal barrier function, and modulation of oncogenic pathways. Recent advancements in metagenomic and metabolomic analyses have led to the identification of microbial and metabolite signatures that have the potential to serve as diagnostic and prognostic biomarkers. Early-stage interventions targeting the microbiota, encompassing probiotics, prebiotics, synbiotics, postbiotics, FMT, dietary modulation, and engineered microbes or bacteriophage therapy, have demonstrated efficacy in restoring microbial balance, enhancing anti-tumor immunity, and improving treatment tolerance. Notwithstanding the encouraging preclinical and translational results, significant challenges persist. The routine clinical application of microbiota-based diagnostics and therapies is constrained by inter-study heterogeneity, a lack of standardization in sampling and analysis, and the limited number of large-scale clinical trials. Furthermore, the interpretation and generalization of findings are complicated by the influence of environmental factors, diet, medications and individual variability. It is recommended that future research endeavors concentrate on conducting large, controlled, multicenter trials. The objective of such trials should be to establish the safety, efficacy, and standardized protocols for microbiota-targeted interventions. The integration of microbiome profiling with multi-omics approaches and precision medicine frameworks holds considerable potential for the development of personalized prevention, diagnosis and therapy in CRC. It is evident that the gut microbiota represents a compelling avenue for precision oncology, with the potential to improve patient outcomes through targeted modulation and biomarker-driven strategies.

Ethics Approval: The study was a descriptive one. No humans or animals were a subject of examinations.

Conflicts of Interest: No conflicts of interest to declare.

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