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REVIEW

Advances in gut microbiota-related treatment strategies for managing colorectal cancer in humans

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ABSTRACT Colorectal cancer (CRC) is a major contributor to global cancer-related mortality with increasing incidence rates in both developed and developing regions. Therefore, CRC presents a significant challenge to global health. The development of innovative tools for enhancing early CRC screening and diagnosis, along with novel treatments and therapies for improved management, remains an urgent necessity. CRC is intricately associated with the gut microbiota, which is integral to food digestion, nutrient generation, drug metabolism, metabolite production, immune enhancement, endocrine regulation, neurogenesis modulation, and the maintenance of physiologic and psychological equilibrium. Dysbiosis or imbalances in the gut microbiome have been implicated in various disorders, including CRC. Emerging evidence highlights the critical role of the gut microbiome in CRC pathogenesis and treatment, which presents potential opportunities for early detection and diagnosis. Despite substantial advances in understanding the relationship between the gut microbiota and CRC, significant challenges persist. Gaining a deeper and more detailed understanding of the interactions between the human microbiota and cancer is essential to fully realize the potential of the microbiota in cancer management. Unlike genetic factors, the gut microbiome is subject to modification, offering a promising avenue for the development of CRC treatments and drug discovery. This review provides an overview of the interactions between the human gut microbiome and CRC, while examining prospects for precision management of CRC.

KEYWORDS Gut microbiome; colorectal cancer; microbial biomarkers; precision medicine

Introduction

Colorectal cancer (CRC) ranks as the third most common cancer and the fourth leading cause of cancer-related deaths worldwide. CRC originates in the epithelial cells of the colon and rectum. Between 60% and 65% of CRC cases occur sporadically, while approximately 25% of patients have a family history of CRC without an identifiable genetic cause. Only 5% of cases are linked to hereditary cancers, such as hereditary non-polyposis CRC[1]. Approximately 1.2 million new CRC cases are diagnosed globally each year. Without advances in diagnosis, screening, and treatment, the CRC incidence is anticipated to rise significantly with projections exceeding 2.2 million new cases and 1.1 million deaths by 2030[2]. These statistics underscore the substantial global health burden posed by CRC. The current 5-year survival rate for CRC is 64%. CRC patients in China account for approximately 25% of global cases. The CRC incidence rates are gradually declining in developed countries, primarily due to improved early diagnosis and screening measures[3]. The human intestine contains approximately 10^{14} bacteria for multifunctional activity; the bacterial cell number is 10-fold greater than the number of human cells[4]. Imbalances in the gut microbiome are associated with various pathogenic factors, including inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), CRC, metabolic disorders, metabolic diseases[5] (obesity, diabetes, and cardiovascular disease)[6], immune disorders (infection and autoimmune disease), Parkinson's disease, schizophrenia disease, autism spectrum disorder (ASD)[7], Alzheimer's disease (AD)[8], bone homeostasis disorders[9], and bacterial vaginosis[10]. The gut also directly influences behavior, mood control, and mental health[11]. Nearly all of these factors contribute to the

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development of CRC. The extraordinary microbiome biodiversity is increasingly disrupted by antibiotics, dietary factors, lack of breast feeding[12], environmental exposures, and distinct microbiomes of different organs within the body[13]. Gut microbiome activity in CRC is incompletely understood. Indeed, scientists are still uncertain how microbiomes function in CRC. Some studies have suggested that a link exists between diet and the influence of microbiota metabolism on CRC risk[14]. Several reports link CRC development to factors, such as unhealthy diets, alcohol consumption, antibiotic treatment, hospitalization, chemical exposures, cigarette smoking, lifestyle choices, genetic predispositions, and even the vaginal microbiota during childbirth, collectively accounting for approximately 90% of CRC cases[15]. Obesity and inadequate physical activity have also been shown to contribute to CRC. Consumption of red meat and diets low in fiber, calcium, folic acid, and vitamin D have been reported to increase CRC risk. Additionally, several studies have reported that the gut microbiota is influenced by diet, with high-fat diets in particular increasing CRC risk[16]. This review illustrates how the microbiome interacts with common risk factors in CRC development (**Figure 1**).

Various types of bacteria have significant roles in developing both early- and late-stage CRC. A study conducted by Zeng[17] showed that mucosal adherent bacterial dysbiosis is linked to the early stages of CRC. The study identified eight phyla of gut microbiota associated with colorectal adenomas (Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, Chloroflexi, Cyanobacteria, Candidate-division TM7 and Tenericutes). A 2019 study reported notable changes in the microbiota in patients with multiple colorectal adenomas and intramucosal carcinomas[18]. *Fusobacterium nucleatum* and *Solobacterium moorei* spp. were more enriched in the early and late stages of carcinogenesis, while *Atopobium parvulum* and *Actinomyces odontolyticus* were highly abundant in the early stage of carcinogenesis. Some toxic bacteria, such as *Clostridium difficile* and *Enterococcus faecalis*, have also been implicated in CRC development[19]. Another study showed that CRC patients have enhanced gut microbiomes with altered choline metabolism potential, gluconeogenesis enrichment, and increased amino acid putrefaction and fermentation pathways, which are all associated with CRC[18]. Fecal samples from CRC patients also have a higher prevalence of *Bacteroides fragilis*, *Escherichia coli*, *Streptococcus bovis/gallolyticus*, *E. faecalis*, and *F. nucleatum*[20]. Recently, *Fusobacterium* has been increasingly detected in tumor samples compared to adjacent non-tumor tissues and is associated with later stages of CRC[21]. Further studies

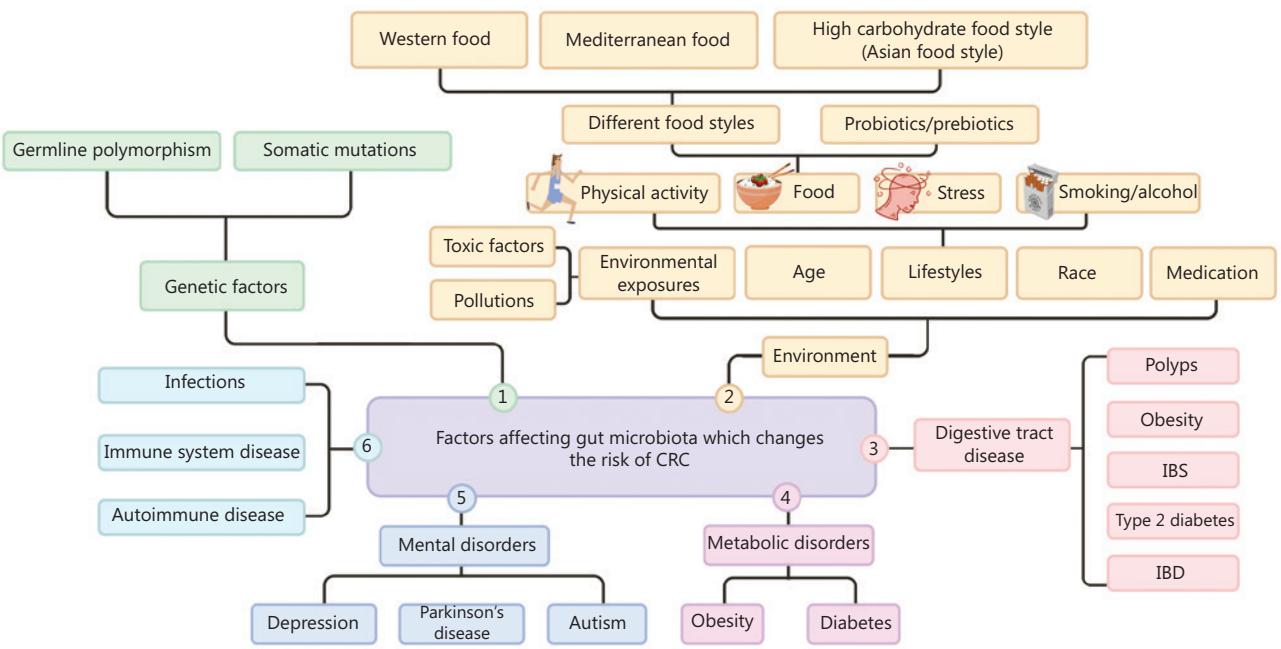


Figure 1 Risk factors for the development of colorectal cancer. The gut microbiome has a crucial role in influencing various risk factors associated with colorectal cancer development. These major factors are genetic, environmental influences, digestive tract disease, immune system diseases, autoimmune diseases, and infections. IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; CRC, colorectal cancer.

have suggested that *Bacteroides*, *Proteobacteria*, *Roseburia*, and *Eubacterium* are also present in CRC[22]. While gut microbiome biomarkers for CRC have not always been validated across diverse populations, these findings hold promise for predicting biomarkers that could guide CRC therapies. This review article explored the associations between commensal gut microbes and CRC in humans (**Table 1**). The relationship between the microbiome and the host is multifaceted, encompassing both beneficial and detrimental effects. With respect to benefit, the microbiome supports nutrition, vitamin synthesis, and metabolism, which contributes to overall health. Conversely, some bacteria have toxin genes that produce harmful metabolites, which can adversely affect the host. Microorganisms interact with the human genome and have essential roles in maintaining health. For example, C-type lectins serve as mediators between host genetics, diet, and the microbiome, which influences gut homeostasis and immune system functionality. Interestingly, microbiomes are partly hereditary, but there is still a limited understanding of the host genes that shape the microbiome[47]. Despite considerable progress, we still lack a complete understanding of how microorganisms influence CRC development.

One of the major challenges in understanding the gut microbiome-CRC association is the production of toxins by some bacteria, such as *C. nucleatum*, *E. coli*, and *B. fragilis*. These toxins can reduce the effectiveness of treatments, increase the prevalence of multidrug-resistant organisms, impair metabolic activity, disrupt the epithelial barrier, produce pro-carcinogenic compounds, and change the intestinal microbiota. All of these factors are influenced by factors, such as diet, age, alcohol consumption, and nutritional status. Taken together, these disruptions can lead to chronic inflammation, increased cellular proliferation, and a high diversity of *Fusobacterium*[48], ultimately raising the risk of CRC. In addition to inflammation, mutations in intestinal microbiota also have an important role in CRC development. Earlier studies have suggested that normal intestinal microbiota may promote tumor growth more than an absence of microbiota, indicating that the microbiome contributes to tumorigenesis in CRC[49]. A 2019 review by Wong and Yu[50] in *Nature Reviews Gastroenterology and Hepatology* highlighted advances in understanding intestinal microecology and the clinical relevance to CRC. The intestinal microbiome metabolizes various substrates, producing metabolites like short-chain fatty acids (SCFAs) and secondary bile acids. These metabolites can accumulate in the gut, exerting toxic effects on intestinal epithelial cells, causing DNA damage and mutations, which often lead to CRC. The microbiome is also involved in CRC prevention and treatment. For example, specific microbial strains or metabolites can be targeted to inhibit tumor cell proliferation, while modulating interactions between the microbiome and host cells could enhance the anti-tumor immune response, thereby improving CRC therapy[50]. A 2015 study by Nakatsu et al.[51] in *Nature Communications* demonstrated that taxonomically defined microbial networks contribute to CRC development. Epigenetic factors, such as butyrate and hydrogen sulfide, can trigger inflammation and cancer-related signaling pathways, promoting genetic and epigenetic alterations in CRC[52].

Next-generation sequencing (NGS) technology, along with qPCR[53], digital PCR[54], and nano LC-MS/MS[55], has revolutionized the characterization of gut microbiomes, offering new insights into metagenomics and metaproteomics. These technologies have significantly enhanced our understanding of the gut microbiome role in the development and progression of CRC. Metagenomics and metaproteomics have emerged as powerful approaches for unraveling the intricate relationships between the microbiome and CRC. The five principal NGS platforms utilized in microbiome studies include 454 (Roche) GS FLX (+), Illumina (Solexa) GA/HiSeq/MiSeq/NextSeq, Applied Biosystems SOLiD, Ion Torrent Personal Genome Machine/Proton, and PacBio RS. A key future challenge is ensuring the delivery of standardized clinical microbiome services that are both cost-effective and capable of rapidly identifying microbiomes. Applications in this field include amplicon-based profiling, bacterial community profiling (16S rRNA amplicon sequencing), fungal community profiling (ITS, LSU, and SSU amplicon sequencing), metagenomics (shotgun DNA sequencing), meta-transcriptomics (RNA transcript sequencing), and shotgun proteomics. Open-source software systems are available to facilitate comprehensive analysis of NGS microbiome data. Advanced NGS technology enables targeted (qualitative) and non-targeted (quantitative) profiling of metabolites over time, helping to elucidate the interplay between diet, nutritional status, and microbiome composition among individuals. These advances have not only accelerated microbiome research but also made microbiome characterization increasingly accessible and affordable for the scientific community[56].

CRC remains a significant global health challenge with prevention heavily reliant on screening programs. However, such programs are often unavailable in developing countries, which contribute to rising disease rates[57]. The human body hosts

Table 1 Effects of the gut bacterial species/strains on CRC. These are some of the most common gut bacterial species/strains linked to CRC.

Bacterial species	Human CRC study	Mechanisms	Ref.
Enterococcus faecalis	High abundance in CRC patients	*E. faecalis* produces extracellular superoxide (O_2) and hydrogen peroxide (H_2O_2), resulting in DNA damage and genomic instability	23
Enterotoxigenic Bacteroides fragilis	*B. fragilis* is highly abundance in tumor tissue and fecal samples of CRC patients	ETBF (enterotoxigenic *Bacteroides fragilis*) binds to epithelial cell receptors and stimulates β-catenin, tyrosine kinases (TK), mitogen-activated protein kinases (MAPK), and NF-κB pathways, leading to increased c-Myc, cyclooxygenase-2 (COX-2), chemokines/cytokines, IL-8, TGF-β, and DNA damage	24
Fusobacterium nucleatum	*F. nucleatum* was associated with CRC and had an increased abundance in CRC	Adhesion to the epithelial cells *via* FadA, Fap2, and RadD by the E-cadherin signaling pathway leads to anti-cancer defense mechanism by T-cells and NK cells	25
Streptococcus bovis/ gallolyticus	*S. bovis* was strongly associated with CRC and found in fecal samples. Several studies confirmed the link between *S. bovis/gallolyticus* and CRC	*S. bovis* leads to pro-inflammatory mediators and release of prostaglandin E2 (PGE2)	26
Clostridium septicum	High virulence of *C. septicum* is associated with CRC	The release of the pro-inflammatory cytokine TNF-α, leads to a pro-inflammatory environment propitious for cancer development by the MAPK signaling pathway	27
Helicobacter pylori	*H. pylori* have increased risk for CRC development	*H. pylori* as a direct effect on CRC. *Helicobacter pylori* infects the epithelium by causing systemic pro-inflammatory, hormonal, or metabolic changes and TNF-α	28
Pks^+ *Escherichia coli*	*E. coli* was detected in individuals with CRC	*E. coli* could influence CRC through colibactin leading to a DNA mutation	29
Pasteurella multocida	Not applicable	Rho GTPases activate and determine cell signaling and proliferation	30
Citrobacter rodentium	Not applicable	Target host mitochondria and disrupt the epithelial barrier and rearrange the cytoskeleton	31
Parvimonas micra	This species was highly enriched in stool samples from CRC patients	The Ras/ERK/c-Fos pathway activation promotes colorectal cancer progression	32
Solobacterium moorei	*S. moorei* was enriched in stool samples from CRC patients	*S. moorei* advances of the adenomatous polyps by causing inflammation and disrupting the intestinal layer	33
Peptostreptococcus stomatis/anaerobius	Significantly high in stool samples from patients with CRC	*P. stomatis/anaerobius* promotes CRC by regulating immune cells and association with toll-like receptors (TLR-2 and TLR-4) on epithelial cells to accelerate ROS formation	34
Gemella morbillorum	This bacteria was found in stool samples associated with CRC patient	The study has reported that this bacterium regulates IL-12 production; therefore, *G. morbillorum* immunoregulates CRC	35
Faecalibacterium	*Faecalibacterium* was found in human CRC samples	*Faecalibacterium* is an important butyrate-producing bacterium which is found in human intestines	36
A. finegoldii	This bacterium was enriched in CRC	These bacteria regulated pathways ranging from oxidative stress to autophagy and fatty acid metabolism which increases intestinal tumorigenesis	37

Table 1 Continued

Bacterial species	Human CRC study	Mechanisms	Ref.
Coriobacteriaceae	CRC-enriched bacteria in tissue biopsies	The CPT1A-ERK axis promotes colorectal tumorigenesis through the growth of *Coriobacteriaceae* in high-fat foods	38
Atopobium parvulum	CRC-enriched bacteria in tissue biopsies	Inflammation of the gut mucosa is caused by *Atopobium parvulum*, which produces hydrogen sulfide (H2S). It also may support *Klebsiella/Enterobacter* species migration from the oral mucosa to the gut mucosa	39
Prevotella intermedia	CRC-enriched bacteria in tissue biopsies	Not applicable	
Actinomyces odontolyticus	CRC-enriched bacteria in tissue biopsies	Membrane vesicles (MVs) can be secreted by it to cause colorectal dysplasia. DNA damage and subsequent cellular transformation are caused by these vesicles, which cause mitochondrial dysfunction and ROS production in the colonic epithelium	40
BFT-producing Bacteroides fragilis	CRC-enriched bacteria in tissue biopsies	*Bacteroides fragilis* infection causes chronic intestinal inflammation, and tissue injury, and has a crucial role in the progression of colorectal cancer	41
Campylobacter gracilis	CRC-enriched bacteria in tissue biopsies	The commensal bacteria in the epithelium are being transported by *C. concisus*, which produces a cytokine that increases translocation and proinflammatory cytokines and chemokines released by intestinal epithelial cells recruit immune cells to the site of infection and contribute to inflammatory response development CRC	42
Selenomonas sputigena	CRC-enriched bacteria in tissue biopsies	By infiltrating B cells into the gut, the microbiota may activate the mucosal immune response, attracting macrophages to exert an immunoreactive effect. B cell infiltration will impact on tumor progression and prognosis in CRC	43
Staphylococcaceae	CRC-enriched bacteria in stool samples	*Staphylococcaceae* could be related to the induction of extracellular inflammatory compounds that damage colonic epithelial cell DNA	20
Parvimonas micra	CRC-enriched bacteria in stool samples	After infection by this bacteria, the Ras/ERK/c-Fos signaling pathway could be activated	32
Solobacterium moorei	CRC-enriched bacteria in stool samples	*S. moorei* induces the proliferation of CRC cells and promotes inflammation	33
Clostridium symbisum	CRC-enriched bacteria in stool samples	*Clostridium symbiosum* is involved in the production of butyric acid which influences CRC in human development	44
Shigella spp.	CRC-enriched bacteria in stool samples	The mechanisms of CRC are still undergoing	
Campylobacter rectus	CRC-enriched bacteria in stool samples	The mechanisms of CRC are still undergoing	
Alistipes spp	CRC-enriched bacteria in stool samples	The mechanisms of CRC are still undergoing	
Prophyromondaceae	CRC-enriched bacteria in stool samples	The mechanisms of CRC are still undergoing	
Prevotella nigrescens	CRC-enriched bacteria in stool samples	After infection by this bacteria, the Ras/ERK/c-Fos signaling pathway could be activated	
Coriobacteriaceae	CRC-enriched bacteria in stool samples	Interleukin-6 activates STAT3 signaling and its pro-inflammatory effects contribute to immunosuppression, angiogenesis, increased tumor cell proliferation, and metastasis	45
Akkermansia muciniphila	CRC-enriched bacteria in stool samples	Induction of M1-like macrophage response *via* the NLRP3/TLR2 pathway suppresses colonic tumorigenesis	46
Treponema spp.	CRC-enriched bacteria in stool samples	The mechanisms of CRC are still undergoing research	

millions of microbiomes that influence the efficacy and side effects of metabolizing drugs. The intestinal microbiota has an essential role in maintaining metabolic health and digestion and has been identified to interact with > 60 drugs, a number that is anticipated to increase[58]. The complexity of microbiomes presents vast potential for developing personalized and precise medical treatments. Advances in understanding microbiome interactions with CRC are expected to transform healthcare, leading to innovations in drugs, diagnostic tools, management strategies, and rehabilitation programs. Increased investment in microbiome research and development is crucial for realizing these benefits. Although microbiome therapy faces challenges, including antibiotic resistance, biologists predict the emergence of microbiome-based drugs and therapies in the near future that could benefit both industrial sectors and populations in affluent nations. The growing concern of antibiotic resistance extends beyond pathogens to microbiomes in humans, animals, and the environment. Modulating gut microbiota through targeted dietary changes may offer a promising therapeutic avenue. Addressing antimicrobial resistance and existing knowledge gaps requires a multifaceted approach involving widespread community education, collaboration across industries and nations, active participation of governmental and non-governmental organizations (NGOs), civil society coalitions, and proactive recognition and engagement by individuals and families. Managing CRC through microbiome-based approaches presents significant challenges for individual patients. Effective treatment requires the development of economical, efficient, and accurate drug delivery systems supported by robust government policies. Advances in microbiome-CRC research are redefining the understanding of health and disease, offering promising avenues for innovative therapies. NGS technology provides alternative strategies to discover new target drugs by identifying genetic, epigenetic, immune, and tumor microbiome markers. This approach facilitates the identification of clinically beneficial microbes or biomarkers that can enhance early screening and diagnosis of CRC[59]. Additionally, precise management of CRC can be achieved by understanding microbially derived metabolic pathways, which influence nutrition, medication, infection, obesity, alcohol consumption, and cigarette smoking habits. These insights could lead to more personalized and effective CRC prevention and treatment strategies.

This review focuses on advancing the understanding of the relationship between gut microbiomes and CRC. Various factors contributing to CRC are examined along with strategies that influence treatment effectiveness and the challenges faced in this domain. The potential role of the gut microbiota in guiding precision nutrition for the rehabilitation of CRC survivors is also explored. Additionally, the review emphasizes leveraging advanced technologies for the precise management of CRC. The overarching goal is to highlight the pressing global challenges and concerns surrounding CRC treatment and to underscore the importance of innovative approaches in addressing these issues.

Role of the gut microbiome in CRC tumorigenesis

The gut microbiome has a complex and dynamic role in CRC development, contributing through mechanisms, such as inflammation, genotoxin production, microbial dysbiosis, and the promotion of carcinogenic metabolites. Some gut bacteria initiate chronic inflammation, a well-established risk factor for CRC. *E. coli* and *B. fragilis* produce toxins that induce inflammation, causing DNA damage, tumorigenesis, and immune evasion by activating pathways, such as the NF-κB pathway, which drive the production of pro-inflammatory cytokines that facilitate CRC progression[60]. Notably, *B. fragilis* has been linked to human colon inflammation and early CRC formation. *B. fragilis* activates STAT3 in colonic epithelial cells, inducing a pro-carcinogenic Th17 inflammatory response and promoting IL-17 secretion, underscoring the role of *B. fragilis*-induced inflammation in colon carcinogenesis[61]. Similarly, other bacterial toxins, such as *Helicobacter pylori* CagA toxin, *E. coli* colibactin, and *Citrobacter rodentium* MAP toxin, trigger chronic inflammation in colonic epithelial cells. These toxins facilitate bacterial infiltration through pathways involving toll-like receptors and NOD-like receptors[62]. Furthermore, the *Clostridium* bacterial group activates mitogen-activated protein kinase (MAPK) signaling, deregulating cellular processes and promoting release of the pro-inflammatory cytokine, TNF, in epithelial cells, which creates an environment conducive to CRC progression[63]. *F. nucleatum* is a notable contributor to CRC through its virulence factor (FadA), which modulates the E-cadherin signaling pathway. This modulation activates transcription factors, such as T-cell factor (TCF), β-catenin, NF-κB, c-Myc, and cyclin D1, which promotes CRC progression[64]. Similarly, *Streptococcus bovis*/*gallolyticus* has been implicated in CRC by activating IL-1β, COX-2, and IL-8 pathways, indicating its role in inflammation-induced CRC[65].

Pathogenic strains of *E. coli*, including enteropathogenic (EPEC), enteroinvasive (EIEC), enteroaggregative (EAEC), enterotoxigenic (ETEC), and diffusely adherent (DAEC), are associated with various diseases and are recognized as CRC risk factors[66]. Inflammation induced by pks-harboring *E. coli* is closely linked to CRC because pks-mediated DNA damage in mammalian cells significantly contributes to tumorigenesis[67].

Diagnosis and challenges in early detection of CRC

Several bacterial species have been linked to CRC development with evidence suggesting that the genetic structure of an individual mirrors the status of the gut microbiome, a factor potentially pivotal for early CRC diagnosis[68]. However, current biomarkers, such as biomarkers of microsatellite instability (MSI), often fall short due to practical limitations, including issues with screening protocols, reporting, interpretation, molecular test applicability, and sample requirements[69]. Effective screening technology must be carefully chosen while considering the risks and benefits. Colonoscopy, though widely regarded as the gold standard for CRC detection, is an invasive procedure involving the insertion of a flexible tube into the colon under sedation or anesthesia. This procedure has higher risks for elderly or frail patients, including complications like bleeding, perforation, infection, and procedural drawbacks (time requirement and high cost)[70]. Developing non-invasive, efficient, and accessible diagnostic methods are essential for improving CRC detection and management outcomes. Flexible sigmoidoscopy, while useful, only assesses the lower part of the colon, potentially missing cancers or polyps in the upper colon[71]. Double-contrast barium enema (DCBE) may overlook flat lesions or small polyps that could precede cancer. CT colonography, although effective, raises concerns about repeated radiation exposure, particularly for younger patients or patients requiring frequent screenings, in addition to being costly. Guaiac-based fecal occult blood tests (gFOBTs) often yield false-positive results due to non-cancerous bleeding causes and have lower sensitivity for detecting polyps or early-stage cancer compared to other screening methods. Similarly, the fecal immunochemical test (FIT) detects blood but cannot identify precancerous polyps, potentially missing early-stage disease if bleeding has not occurred, and still necessitates follow-up colonoscopy, introducing additional steps for patients. These methods face challenges, including limitations in the accuracy of detection, procedural risks, low patient compliance, and rare instances of mortality[72]. Developing a more effective, non-invasive CRC detection approach remains a significant challenge. Recent studies, such as the studies conducted by Shah et al.[73], have emphasized the potential of microbial markers in CRC diagnosis. Specific gut bacteria have shown promise in aiding CRC detection and combining microbial markers from fecal samples may lead to sensitive, non-invasive clinical diagnostic tests. Advanced analysis of the human fecal microbiome using techniques like 16S rRNA sequencing and capillary electrophoresis time-of-flight mass spectrometry has been reported for early CRC detection. Evidence suggests that microbiota-based diagnostic tests may offer greater sensitivity in detecting polyps compared to tests for fecal hemoglobin[74]. These findings highlight the potential of microbiome-focused approaches in overcoming existing diagnostic challenges. Feng et al.[75] identified bacterial species as biomarkers for early CRC detection and screening, demonstrating the potential of fecal microbial markers for CRC screening. Specific microbiota species, including *F. nucleatum*, *B. fragilis*, *Gemella morbillorum*, *Peptostreptococcus stomatis*, *E. coli*, *Porphyromonas asaccharolytica*, *Parvimonas micra*, *A. parvulum*, and *Actinomyces odontolyticus*, have been associated with CRC detection, although further advances in accuracy and simplicity of analysis are needed[68]. Additionally, metagenomic research into the virome, fungal microbiome, and mycobiome in CRC has revealed significant potential for these microbial biomarkers in CRC diagnosis and screening[76]. Studies have highlighted the potential of fecal sample-based diagnostic tests targeting specific microbial species through metagenomic markers[18,19]. Non-invasive analyses of the fecal microbiome and multi-omics approaches are particularly promising for enhancing early CRC screening and diagnosis, potentially enabling improved outcomes through timely interventions. These findings suggest that microbiome-based markers, supported by metagenomic and proteomic sequencing technologies, are likely to become standardized tools for CRC detection in the future.

Advanced strategies for treating CRC *via* gut microbiome modulation

The application of microbial drugs for CRC treatment marks a notable advance in therapeutic approaches. Understanding the production of bioactive molecules by microbes and

interactions with the host or biological pathways is essential. Researchers are innovating drug delivery methods, but critical questions remain about the effects of different methodologies on stability[77], accuracy, efficacy, safety, cost-effectiveness[78], dosage, and toxicity reduction in human disease treatments. Various microbiome-based drug delivery strategies for CRC treatment are being investigated, leveraging the commensal gut microbiota. Progressive strategies focus on utilizing the gut microbiome for eradicating or preventing CRC. Advanced clinical interventions target the commensal gut microbiota through approaches, such as phage therapy, antibiotic therapy, immunotherapy, chemotherapy, fecal microbiota transplant (FMT), and gut bacteria engineering. These strategies aim to refine treatment outcomes and enhance the efficacy of CRC therapies. Researchers are actively exploring these innovative treatment modalities to optimize CRC therapy and achieve superior clinical results (**Figure 2**).

Bacteriophages (BPs) as modulators of gut bacteria in CRC (phage therapy)

BP therapy offers a promising approach for targeting and eliminating harmful bacteria associated with CRC, while preserving beneficial microbiota. With greater than one century of history, BPs or bacterial viruses combat pathogenic infections by targeting specific bacterial strains, binding to receptors, injecting DNA, and replicating within the bacterial cells, ultimately lysing the host bacteria[79]. Despite the potential of phage therapy, the use of BPs in CRC treatment faces several challenges. The high specificity necessitates precise identification and isolation of the appropriate phages to target CRC-associated bacteria, a process that can be labor-intensive and time-consuming. Additionally, the application of BPs in medicine is relatively new and not yet widely accepted. Innovative approaches, such as a phage-guided hybrid nanosystem, have been developed to exploit the anti-tumor effects of BPs. Phages interact with *F. nucleatum* and dextran nanoparticles (DNPs) in this system to form irinotecan (IRT)-loaded DNPs (IDNPs), which bind to phages pre-accumulated in CRC tumors using a bio-orthogonal chemistry strategy. The DNPs enhance bacterial butyrate production, which has demonstrated anti-tumoral effects. Additionally, BPs have been explored as drug carriers for anticancer agents, with studies showing effectiveness in suppressing CRC tumor growth in mouse models[80]. Gogokhia et al.[81] further validated BPs for treating colon cancer and demonstrated a direct link between phage activity and immune responses. BP production is economical and safe with practical applications already approved by the US FDA in 2006 for use as antibacterial additives in ready-to-eat meat and poultry products. These advances underscore the potential of BP therapy in CRC treatment, despite the need for continued research and validation to overcome existing limitations.

Antibiotic-induced modulation of gut microbiome in CRC (antibiotic therapy)

The administration of antibiotics to target harmful bacteria associated with CRC offers potential therapeutic benefits but also presents notable challenges. Antibiotics can reduce toxic compounds in the gut microbiome and help prevent CRC by eradicating bacterial infections or suppressing undesirable microbiota components[82]. Specific bacteria, such as *B. intestinihominis* and *E. hirae*, contribute to anti-tumor immune responses during antibiotic therapy by modulating interactions among pTh17 cells, gamma T cells, immune cells, and signaling molecules in the intestine. Additionally, *Lactobacillus acidophilus* enhances CD8+ T cell function through interactions with other microbiome members, inhibiting tumor growth and supporting anti-tumor effects. Evidence also suggests that gut microbiota depletion through antibiotic treatment suppresses inflammation, obesity, and CRC[83]. For example, Bullman et al.[84] reported that *Fusobacterium* strains present in primary and metastatic tumors are significantly reduced following antibiotic treatment, leading to decreased cancer cell proliferation and CRC growth. However, prolonged antibiotic use can disrupt gut microbial networks and promote the emergence of antibiotic-resistant bacteria, such as *Enterobacteriaceae* and *Staphylococcus epidermidis*[85]. Despite these findings, antibiotics face substantial limitations in CRC treatment. CRC is driven by complex genetic and molecular alterations that antibiotics cannot address and clinical trials have shown that antibiotics are generally ineffective for direct cancer treatment. Additionally, the use of antibiotics in CRC patients may cause adverse effects, including microbiota disruption, higher infection risks, and potential drug interactions. Ethical and regulatory concerns further complicate application in CRC therapy. Thus, while antibiotics may have a role in modulating gut microbiota to complement CRC treatment, use requires careful consideration to balance benefits against risks.

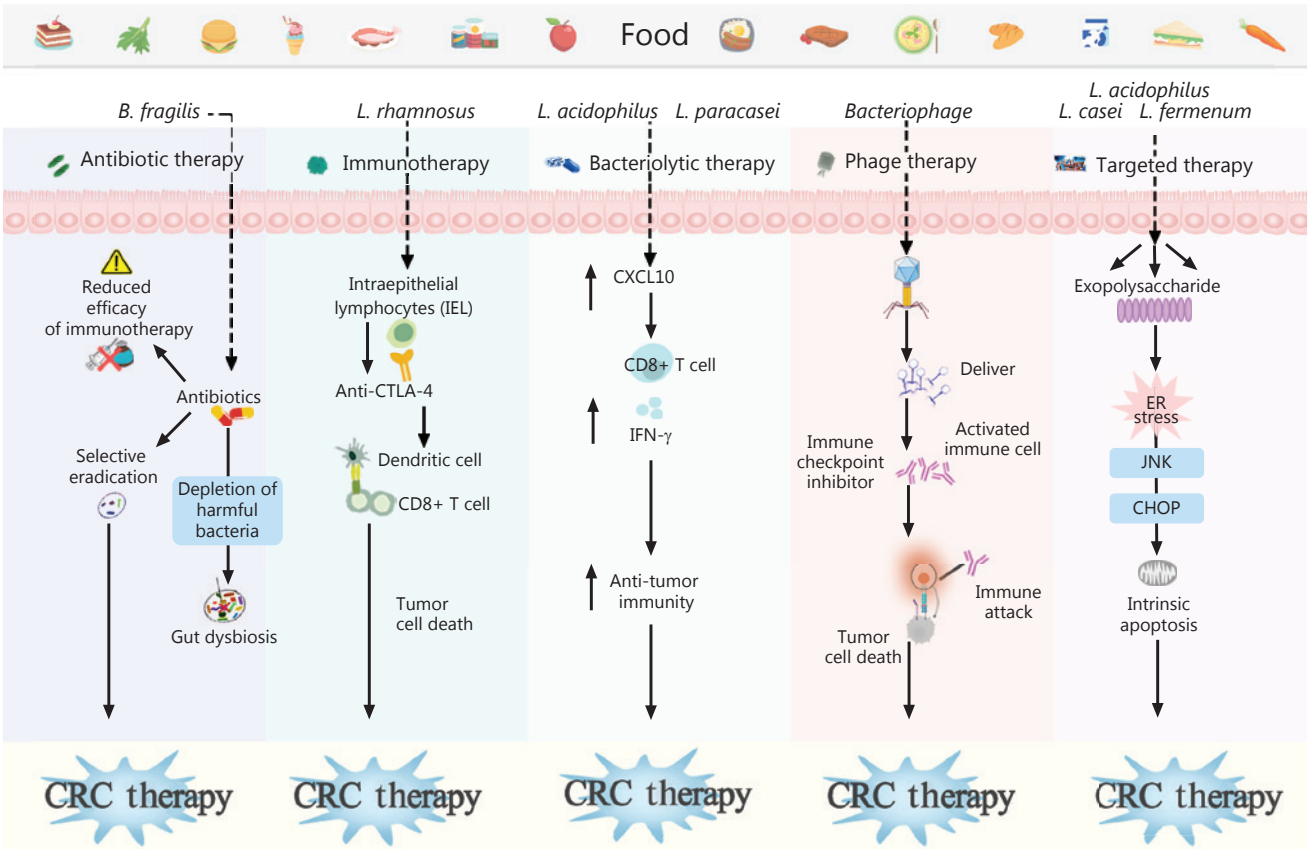


Figure 2 The underlying mechanisms by which modulation of the gut microbiota influences various strategies for colorectal cancer treatment. The following microbiota are involved in different therapeutic approaches for colorectal cancer. **Antibiotic therapy:** Selective antimicrobial strategies are essential for effective cancer treatment to minimize side effects. Combining selective antibiotics with approaches that modulate *Bacteroides fragilis* strains could offer an effective way to personalize colorectal cancer therapies. **Immunotherapy:** *Lactobacillus rhamnosus* interacts with intraepithelial lymphocytes (IELs) to enhance the activity of anti-CTLA-4, which in turn activates dendritic cells. These dendritic cells promote the generation of CD8+ T cells, leading to tumor cell death. This mechanism could offer an effective strategy for colorectal cancer therapy. **Bacteriolytic therapy:** Using *L. acidophilus*, *L. paracasei* strains helps stimulate the immune system to produce CXCL10 and IFN-γ, leading to enhanced anti-tumor immunity. This approach could be a promising strategy for improving colorectal cancer treatment outcomes. **Bacteriophage therapy:** Bacteriophages can deliver immune checkpoint inhibitors, which activate immune cells. These activated immune cells then initiate an immune response against the tumor, ultimately leading to destruction of colorectal cancer cells. This mechanism could provide an effective strategy for colorectal cancer therapy. **Targeted therapy:** The use of exopolysaccharides (EPS) from *Lactobacillus* strains in targeted therapy works by triggering ER stress in colorectal cancer cells, which leads to selective apoptosis *via* the JNK-CHOP pathway. This mechanism could provide a highly effective and precise strategy for treating colorectal cancer.

Immunotherapy and gut microbiota modulation in CRC

Exploiting the immune-modulating properties of the gut microbiome represents a promising approach to enhancing natural antitumor immune responses, particularly in conjunction with immune checkpoint inhibitors (ICIs). Numerous studies have emphasized the critical influence of microbiota composition on the effectiveness of immunotherapy in cancer patients, especially ICIs. Gut microbiota has been shown to significantly impact immunotherapy outcomes in patients with CRC[86]. Specific microbial taxa, such as *Burkholderiales*, *B. thetaiotaomicron*, and *B. fragilis*, have been identified as contributors to improved efficacy of cytotoxic T lymphocyte-associated antigen 4 (anti-CTLA-4) therapy for tumor treatment. *B. thetaiotaomicron* and *B. fragilis* are prevalent components of intestinal flora and are closely associated with immune system functionality. Furthermore, *B. breve*, *Ruminococcaceae*, *B. adolescentis*,

and *E. faecium* have been implicated in the anti-tumor effects of programmed cell death protein 1 (anti-PD-1) immunotherapy, which reactivates T-cell-mediated antitumor responses by inhibiting the interaction between PD-1 and its ligand (PD-L1).

Synthetic biology approaches for gut bacteria modulation in CRC

Synthetic biology provides innovative tools for creating advanced drug delivery systems aimed at the gut microbiome in CRC therapy. These approaches offer potential solutions to key challenges in CRC treatment, including toxicity, stability, and efficiency. Research has indicated that specific bacterial genera, such as *Clostridium* and *Salmonella*, possess tumor-inhibiting properties and have demonstrated promising outcomes in animal studies[87]. For example, Ho et al.[88] engineered commensal microbes capable of preventing carcinogenesis and promoting CRC regression when combined with a cruciferous vegetable diet. Despite these advances, the use of synthetic biology in CRC therapy remains in the nascent stages and associated technologies are still under development. Current methodologies may encounter difficulties in accurately modeling or manipulating the intricate biological processes that underlie CRC. Moreover, synthetic biology techniques, such as gene editing and transfer, may present biosafety risks. Ethical and legal considerations, including concerns over genetic privacy and discrimination, require thorough evaluation as this field progresses.

Enzyme-based modulation of gut microbiome in CRC

Enzymes have a crucial role in modulating cancer progression with particular significance in CRC. Elevated levels of DNA methyltransferase (DNMT) are commonly observed in CRC, contributing to gene silencing through DNA methylation, a process associated with tumor suppression[89]. The topoisomerase inhibitor, SN-38, is widely used for CRC treatment[90]. A targeted therapeutic approach involves inhibiting bacterial enzymes, such as β-glucuronidases produced by *E. coli*, *B. fragilis*, and *C. perfringens*, which can convert anti-cancer agents into toxic byproducts. Inhibition of β-glucuronidases prevents the transformation of inactive irinotecan metabolites (SN-38G) into harmful derivatives. Additionally, a 2019 study by the Chatterjee group[91] identified β-1,4-galactosyltransferase-V (β-1,4-GalT-V) as a potential therapeutic target for CRC. Similarly, research by Makar et al.[92] highlighted the role of angiotensin-converting enzyme in reducing CRC risk. Despite the critical functions of enzymes as biocatalysts, several challenges hinder application in CRC therapy[92]. The complex tumor microenvironment, characterized by hypoxia and acidosis, can adversely impact enzyme activity and stability. Furthermore, identifying enzymes with significant therapeutic potential from a broad spectrum of candidates remains a substantial obstacle.

Bacteriolytic therapy for gut microbiome modulation in CRC

Utilizing bacterial species that directly lyse cancer cells or release tumor-targeting toxins offers promising avenues for cancer eradication. These strategies, while innovative, involve distinct challenges and opportunities that are the focus of ongoing research aimed at enhancing clinical effectiveness. *B. fragilis* has been shown to influence the maturation and function of dendritic cells (DCs) through its metabolites or cell wall components, thereby regulating T-cell activation and differentiation to strengthen anti-tumor immunity. Furthermore, *B. fragilis* modulates the immune cell microenvironment by impacting the production and secretion of cytokines, such as IL-2, IL-6, and IL-22. These cytokines play critical roles in regulating immune cell differentiation and function, thereby contributing to the promotion of robust anti-tumor immune responses.

Target therapy for gut bacteria modulation in CRC

Targeted therapy for CRC aims to selectively attack cancer cells while minimizing damage to healthy tissues, thereby enhancing treatment effectiveness and reducing adverse effects. In cases involving *BRAF* mutations, which are linked to more aggressive forms of CRC, targeted agents, such as encorafenib, are utilized. These agents are often combined with other drugs to disrupt signaling pathways that facilitate cancer cell growth and survival[93]. Additionally, *B. thetaiotaomicron* has been shown to inhibit CRC tumorigenesis by producing SCFAs, a key mechanism for maintaining intestinal health and contributing to suppression of cancer development.

Chemotherapy-induced modulation of gut microbiome in CRC

Chemotherapy strategies for CRC involving the gut microbiota represent an innovative and rapidly evolving area of

research. The gut microbiota plays a significant role in CRC development and progression, influencing responses to chemotherapy by interacting with both the immune system and chemotherapeutic agents in complex ways, which can affect treatment efficacy and toxicity. The composition of the gut microbiota in CRC patients significantly impacts the response to chemotherapy because chemotherapeutic agents interact with the host immune system and microbiota in complex ways, potentially affecting both treatment outcomes and side effects.

First, identifying specific bacterial species that influence the chemotherapy response and developing methods to manipulate the bacterial species for optimal treatment outcomes remains a challenge. In cancer patients receiving chemotherapy, careful consideration is necessary when administering antibiotics due to the potential to disrupt the microbiome and affect treatment efficacy. Additionally, there is increasing interest in the potential for personalized microbiome-based therapies to improve chemotherapy outcomes and minimize associated toxicity[94]. Recent studies have shown that antibiotic treatment can disrupt microbial mechanisms and diminish the effectiveness of chemotherapeutic drugs, while also highlighting the intricate relationship between the intestinal microbiota and the host immune system. For example, 5-fluorouracil (5-FU), a commonly used chemotherapy agent for CRC, has reduced efficacy in patients with elevated levels of *F. nucleatum*, which promotes chemoresistance by impeding cancer cell apoptosis. Conversely, beneficial bacteria, such as *B. fragilis*, can potentiate the immune-mediated effects of 5-FU, resulting in an enhanced anti-cancer response[95]. Additionally, Iida et al.[96] reported that the microbiota can increase the therapeutic efficacy of chemotherapy through myeloid cell-derived activity within tumors. Microbes have the potential to function as biomarkers for predicting therapeutic responses, thereby optimizing the outcomes of clinical cancer immunotherapy, which is a rapidly advancing field of study. This concept proposes that microbes could act as natural antimicrobial agents, eliminating harmful bacteria through a "one nail drives out another" mechanism. However, the individuality of each individual's microbiome presents a significant challenge, highlighting the necessity of personalized microbiome-based interventions for effectively targeting CRC. Furthermore, while some beneficial microbes suppress tumor growth, other microbes may contribute to carcinogenesis under dysbiotic conditions, emphasizing the importance of carefully selecting microbial strains to prevent an increased risk of cancer[97].

Other potential gut microbiome drugs for CRC management

Probiotic modulation of the gut microbiome in CRC

The concept of probiotics, introduced by Russian Nobel Laureate Elie Metchnikoff in the early 20th century[98], refers to live microorganisms that confer health benefits when consumed in sufficient quantities. Probiotics, such as *Bifidobacterium* and *Lactobacillus* species, have demonstrated anti-cancer properties by enhancing immune function and are considered cost-effective therapeutic options[99]. These strains may counteract CRC by facilitating bacterial colonization, which can contribute to CRC prevention. However, the interaction between many probiotic strains and the existing gut microbiota often limits efficacy. Factors, such as strain specificity, dosage, duration, and individual variability, further influence efficacy, resulting in inconsistent outcomes among users. The absence of standardized guidelines for probiotic products complicates comparisons of safety and effectiveness. Ethical considerations, including informed consent and off-label usage, also pose challenges in the application of probiotics for CRC treatment.[100] Probiotic-host interactions occur through diverse mechanisms, including competitive inhibition of pathogenic microbes, enhancement of mucosal barrier integrity, and modulation of immune responses *via* DC interactions. Despite the promising roles of probiotics in modulating gut health and potentially influencing CRC outcomes, clinical evidence supporting the efficacy in CRC prevention or treatment remains limited.

Prebiotics as modulators of the gut microbiome in CRC

First introduced in 1995[101], prebiotics are defined as substances that selectively promote the growth of beneficial bacteria in the host, thereby providing health benefits. Typically, prebiotics are low-molecular-weight carbohydrates that are efficiently metabolized by gut bacteria and other microorganisms involved in breaking down high-molecular-weight oligosaccharides or short-chain polysaccharides[102]. Hu et al.[103] reported the protective effects of prebiotics against CRC in a rat model. Similarly, experiments using mouse models have shown that ginsenosides (Rb3 and Rd) derived from

Gynostemma pentaphyllum can improve the gut microenvironment and potentially prevent CRC. However, understanding the intricate ecology of the gut microbiota and the mechanisms by which prebiotics exert effects in CRC remains a significant challenge. While some prebiotics, such as lactulose and resistant starch, have been associated with reduced CRC risk, the findings across studies lack consistency. The mechanisms underlying the influence of prebiotics on CRC are not fully elucidated, which limits confidence in the efficacy for prevention and management. Furthermore, there is a scarcity of long-term studies on the impact of prebiotics on CRC, leaving the prolonged effects uncertain. Concerns also remain about the potential adverse effects of high or prolonged intake of prebiotics. Standardization and quality control issues further complicate the global application of prebiotic products with regulatory policies differing widely across countries[104]. These challenges underscore the need for more robust research to clarify the role of prebiotics in CRC prevention and establish standardized guidelines for prebiotic use.

FMT for gut microbiome modulation in CRC

FMT, also referred to as stool transplant bacteriotherapy or human probiotic infusion, entails the transfer of gut bacteria from a healthy donor to a patient. This procedure is generally performed by administering a fecal sample *via* a nasogastric tube or through the biopsy channel during a colonoscopy[105]. FMT has been effectively demonstrated in human studies for the treatment of CRC with evidence supporting safety and non-toxicity[106]. Recent findings by Yu[49] from the Chinese University of Hong Kong have provided direct evidence associating intestinal microbes with CRC, suggesting that FMT might facilitate the development of targeted therapies for CRC. While FMT has shown promise in managing specific intestinal disorders, the direct efficacy in CRC treatment remains uncertain. The pathogenesis of CRC is multifaceted, involving interactions among genetic, environmental, and microbial factors that FMT alone may not comprehensively address. Moreover, age, gender, and the existing composition of gut microbiota could significantly impact the safety and therapeutic outcomes of FMT.

Modulation of the gut microbiome in CRC *via* traditional Chinese medicine (TCM)

The use of TCM in treating CRC offers a promising but underexplored avenue in the expanding field of microbiomes. Jiang et al.[107] identified tongue-coating microbiome biomarkers that could assist in the diagnosis of various diseases, including CRC. Research utilizing mouse models has demonstrated that TCM compounds, such as baicalin and curcumin, can suppress gut bacterial inflammation and promote cancer cell death, indicating potential anti-CRC properties. Additionally, PHY906, a TCM-based formulation, has been shown to mitigate the intestinal toxicity associated with IRT, a chemotherapy agent, while also exhibiting anti-tumor effects in CRC[108]. Despite these findings, elucidating the specific mechanisms by which TCM influences the gut microbiome to produce clinically significant outcomes in CRC treatment remains a considerable challenge.

Modulation of the gut microbiome in CRC *via* Ayurveda (traditional Indian medicine)

Ayurveda, the traditional Indian medical system with a > 5,000-year history, provides insights that align with the modern understanding of microbiome functioning, despite limited explicit documentation on microbial-related aspects. The principles of Ayurveda emphasize the influence of bodily systems, including microbial balance, on health and disease. *Withania somnifera* L. (ashwagandha) is an Ayurvedic medicinal plant recognized for its potential role in CRC treatment[93]. Curcumin, extracted from *Curcuma longa*, has a longstanding use in Ayurveda for managing chronic diseases, including cancer, and is increasingly incorporated into contemporary medicine for CRC management[109]. *Terminalia arjuna*, another plant-based remedy, has demonstrated biological activities with possible applications in CRC treatment[110]. Furthermore, the Triphala formulation, comprised of fruits from *Emblica officinalis* (Amalaki), *Terminalia bellerica* (Bibhitaki), and *Terminalia chebula* (Haritaki), exhibits anti-CRC properties, such as chemopreventive and antimicrobial effects, while also contributing to reductions in body fat, weight, and energy intake[111]. Collectively, these Ayurvedic remedies present promising therapeutic and rehabilitative potential for CRC treatment.

Challenges in drug efficiency and design for CRC treatment

The development of drugs for CRC treatment is a multifaceted process that involves significant complexity, expense, and time investment. These challenges stem from the biological

intricacies of the disease and the demanding nature of the drug development pipeline. Addressing the need to reduce costs and expedite the creation of anti-cancer therapies is increasingly critical for the medical industry. A multidisciplinary strategy integrating Environmental factors, Genomics factors, Artificial Intelligence (AI) factors, Microbial factors, Immunological factors, and Personalized factors has been proposed to streamline drug production and improve therapeutic outcomes. Each of these approaches contributes to overcoming specific hurdles in drug design by leveraging advanced technologies and tailored interventions. Despite these advances, ensuring drug efficacy, minimizing side effects, and addressing individual variability in treatment response are persistent challenges. These challenges are highlighted in various approaches to CRC therapies, as depicted in **Figure 3**.

Environmental factors

This approach investigates the potential of environmental interventions as therapeutic methods, focusing on elucidating mechanisms of action and evaluating effectiveness in minimizing damage to normal tissues. Emphasis is placed on rigorous efficacy assessments and monitoring for adverse reactions to ensure the safety and effectiveness of treatments. Achieving selective efficacy is paramount as selective efficacy reduces toxicity and enhances therapeutic outcomes. However, the heterogeneity of tumors, both within individual patients and across different patients, poses significant challenges in designing drugs that can selectively target cancerous cells while sparing healthy tissues[112]. Addressing these complexities necessitates meeting specific requirements, such as conducting exploratory studies in cases where the target remains unidentified, ensuring selective efficacy, and developing robust implementation strategies.

Genomics factors

The integration of genomics into CRC drug design encompasses multiple aspects, including target identification, drug screening, efficacy evaluation, patient-specific variability, off-target effects, toxicity, epigenetic modifications, and personalized treatment strategies, thereby providing substantial support for precision medicine in CRC[113]. Despite these advances, verifying drug efficacy and evaluating safety remain significant challenges. Emerging technologies, such as patient-derived xenograft (PDX) models, cell-free DNA, and circulating tumor cells (CTCs), present innovative methodologies and tools for CRC drug development and efficacy assessment, enhancing the precision of therapeutic strategies.

Microbial factors

The design and application of microbial-based therapies in cancer treatment require a comprehensive and multifaceted approach to ensure efficacy and safety. Critical factors include the optimal timing of administration, selection of appropriate bacterial species, challenges in delivery mechanisms, and addressing ethical concerns and public perceptions[114]. Foundational research, refinement of drug delivery systems, exploration of combination therapy strategies, and stringent regulation of clinical trials are essential components of this process, aiming to optimize therapeutic outcomes while mitigating risks.

Immunological factors

Immunotherapy holds significant promise for drug development in CRC, however, many challenges and limitations remain. Designing immunotherapy drugs for CRC treatment requires careful consideration of efficacy, target selection, side effect management, reduced toxicity effect, and the use of specific drugs[115]. Because our understanding of tumor biological characteristics deepens and technology continues to advance, immunotherapy drug design is expected to play an increasingly important role in CRC treatment.

Artificial intelligence (AI) factors

AI has significant potential and value in CRC drug development. However, there are several challenges that need to be addressed, particularly with respect to big data management, data integrity assurance, data integration, drug ability, drug-target interactions, and providing treatment[116]. AI is expected to have an increasingly important role in precision medicine and drug development for CRC, providing more accurate and effective treatment plans that enhance the quality of life for patients.

Personalized factors

The application of personalized medicine in CRC drug development appears to be very promising. However, several key challenges remain to be addressed, including accurate target

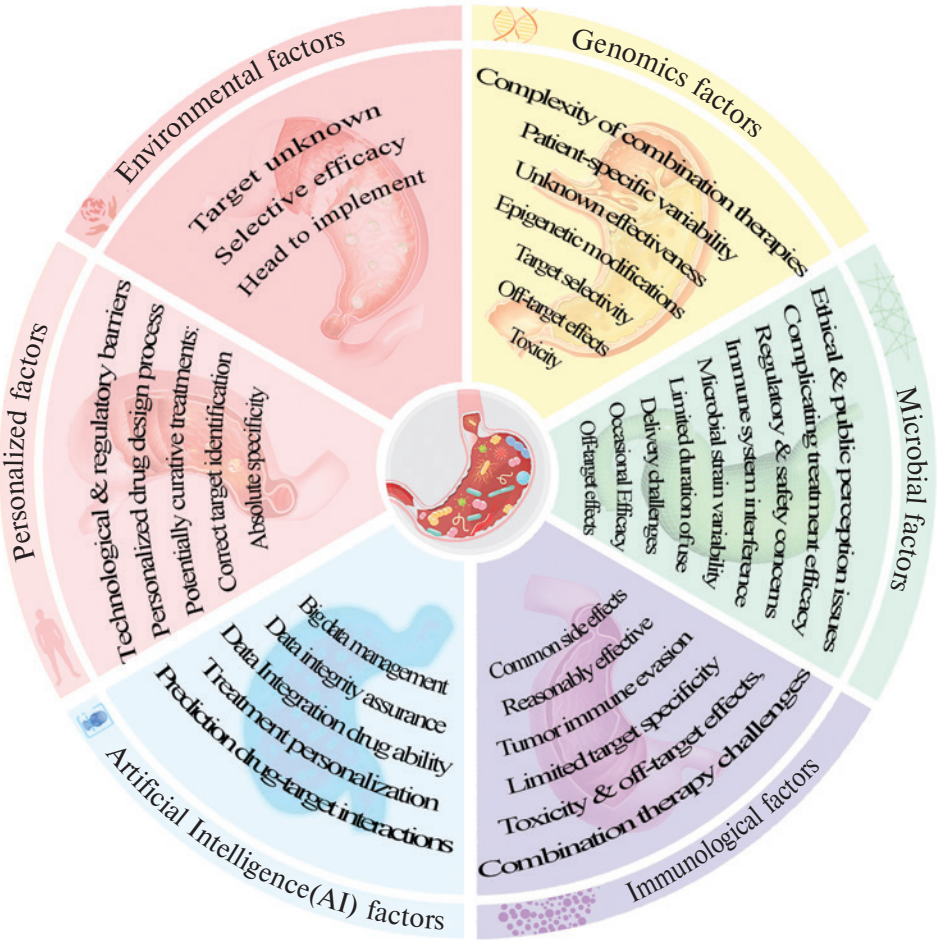


Figure 3 Major issues in drug design efficacy for colorectal cancer treatments emerge across various strategies, including environmental, genomic, microbial, immunological-based, artificial intelligence-driven, and personalized drug design. **Environmental factors**: Targets unknown: difficulty in identifying specific molecular targets related to the environment. Selective efficacy: achieving selective efficacy is challenging because environmental factors often affect a wide range of biological processes. Implementation: translating environmental interventions into practical and effective treatment strategies is still in early stages. **Genomics factors**: Complexity of combination therapies: combining genomic therapies with other treatments presents challenges due to drug interactions and patient variability. Patient-specific variability: genetic differences among patients lead to variable responses to treatment, complicating treatment outcomes. Unknown effectiveness: the efficacy of genomic-based treatments is often uncertain and not fully understood. Epigenetic modifications: the role of epigenetic changes in colorectal cancer complicates drug design, as these modifications can influence gene expression. Target selectivity: difficulty in identifying highly specific targets for therapeutic interventions. Off-target effects and toxicity: genomic drugs may affect non-target genes, leading to unintended side effects and toxicity. **Microbial factors**: Ethical and public perception issues: ethical concerns and public perception of using microbes in cancer treatment present additional challenges and may challenges complicating treatment efficacy. Regulatory and safety concerns: microbial-based therapies face significant regulatory hurdles and concerns regarding safety. Immune system interference: microbial agents may interfere with the immune system. Microbial strain variability: variability among microbial strains can affect the consistency and effectiveness of treatments. Limited duration of use: these therapies are typically effective only for short periods, limiting their long-term use. Delivery challenges: effective delivery of microbial therapies to target sites remains a major challenge. Occasional efficacy: microbial-based therapies show inconsistent efficacy across different patients and microbiome profiles. Off-target effects: microbial therapies often do not specifically target cancer cells, leading to potential off-target effects. **Immunological factors**: Combination therapy challenges: combining immune therapies with other treatments may not always be effective and can increase complexity in managing side effects and resistance. Toxicity and off-target effects: immune therapies can lead to toxicity by attacking healthy cells in addition to cancer cells. Limited target specificity: immune therapies may not selectively target cancer cells, leading to potential side effects. Tumor immune evasion: tumors can evade immune detection, reducing the effectiveness of immune therapies. Reasonably effective: immune-based therapies, such as checkpoint

inhibitors, are effective for certain patients. Common side effects: immune therapies often cause immune-related adverse effects, such as inflammation. **Artificial intelligence (AI) factors**: Big data management: AI-based drug design requires the management and analysis of large volumes of data, including genomic, clinical, and patient response data. Data integrity assurance: ensuring the accuracy and reliability of data used in AI models is essential for developing effective treatments. Data integration drug ability: integrating diverse data sources (e.g., genomics, clinical, and imaging) to guide treatment decisions is a complex task. Treatment personalization: AI can help personalize treatment plans by identifying the most effective therapies based on individual patient data. Prediction drug-target interactions: it is a pivotal task in AI-driven drug design, but challenges, such as data quality, model interpretability, and the complexity of biological systems, remain significant obstacles. **Personalize factors**: Technological and regulatory barriers: overcoming technological limitations and navigating complex regulatory frameworks are significant obstacles to the widespread implementation of personalized therapies. Personalized drug design process: the process of designing drugs tailored to individual genetic and molecular profiles requires advanced tools, continuous research, and a deep understanding of cancer biology. Potentially curative treatments: personalized treatments aim for curative outcomes, but developing therapies with such potential is still an ongoing challenge. Correct target identification: identifying the precise molecular targets specific to an individual patient's cancer is critical but challenging. Absolute specificity: achieving complete specificity to avoid damaging healthy cells is a key hurdle in personalized drug design.

identification, achieving absolute specificity, and developing potentially curative treatments[117]. Additionally, realizing these goals requires significant advancements in modern biotechnology, bioinformatics, genomics, proteomics, structural biology, computer-aided drug design, as well as continuous drug research and innovation.

Summary and suggested directions for CRC treatment

Recent advances in microbiome research have significantly expanded our understanding of gut microbiota and the interplay with the immune system, offering new insights into preventing and managing CRC. However, the clinical application of these findings remains complex, as the influence of gut microbiota on CRC must be considered in the context of genetic, internal, and external factors and the limitations of current treatment efficacy. Personalized nutrition emerges as a key factor in shaping the gut microbiome. Dietary interventions can promote the growth of beneficial microorganisms, including dietary interventions that support CRC treatment.

In contrast, host genetics influence the intestinal microbiome and environmental factors also have a significant impact[118]. Numerous studies indicate that alterations in dietary macronutrients, including fat, fiber, protein, and carbohydrates, significantly influence gut microbiota composition, thereby impacting CRC development through diverse mechanisms[119]. Therefore, dietary modifications hold significant potential to improve recovery outcomes for CRC survivors.

The importance of data and information in guiding decision-making and communication regarding CRC treatment cannot be overstated. Emphasizing personalized nutrition informed by the interplay of microbiome, nutrition, and host metabolism is pivotal in a multidisciplinary approach to managing complex diseases. This strategy incorporates nutritional insights into clinical decision-making, thereby improving treatment outcomes.

The present review proposes that incorporating gut microbiome sequencing data into CRC patient management, particularly within the framework of personalized nutrition, represents a promising strategy for enhancing rehabilitation and achieving better outcomes. The application of AI to analyze individual dietary responses allows for the development of tailored dietary recommendations aimed at supporting recovery and potentially mitigating CRC progression (**Figure 4**).

Advances in research and clinical practice are progressively establishing precision nutrition as a cornerstone of clinical nutrition, highlighting the necessity of understanding the impact of nutrition on disease progression and its role in multifactorial inflammatory, metabolic, and neoplastic disorders. Furthermore, evidence indicates that diet-induced alterations in gut microbiota contribute to the increasing prevalence of CRC. Understanding the metabolism underlying interactions among diet, lifestyle, gut microbiota, and the host could provide effective strategies for CRC management in humans.

It is recommended that government bodies and NGOs initiate comprehensive health education awareness programs to address the current state of CRC treatments and emphasize effective management strategies using advanced technologies. Such initiatives should focus on enhancing the regulatory

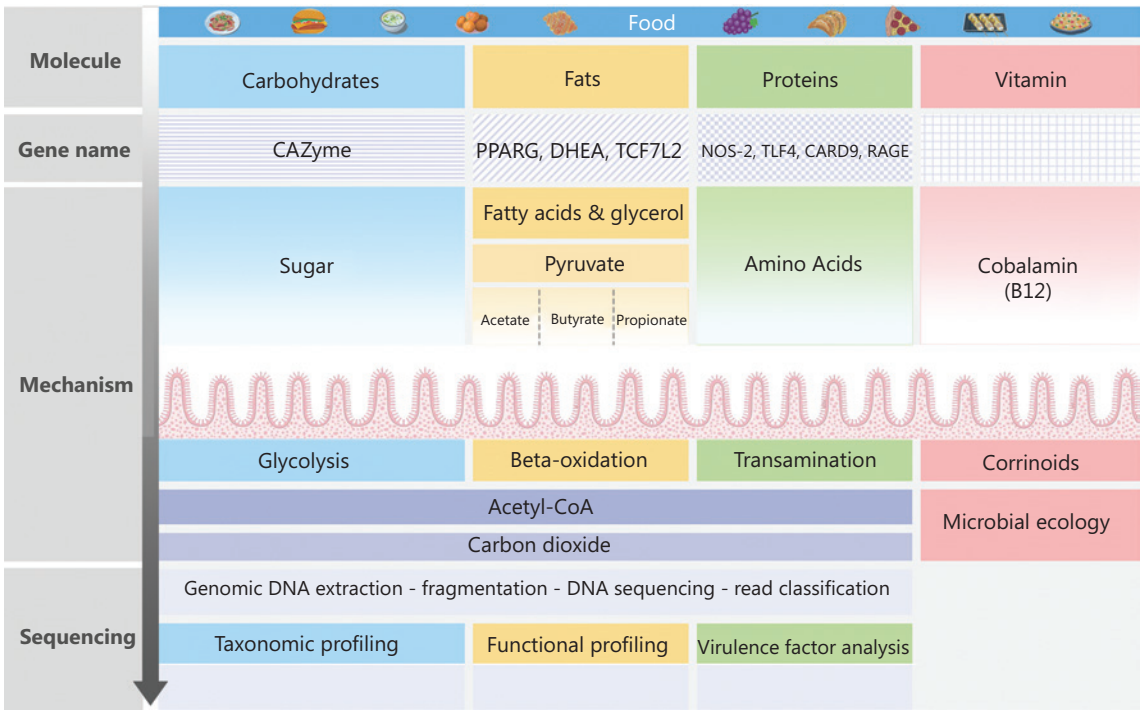


Figure 4 A systematic review flow diagram illustrating the sequencing methodology for acquiring and analyzing patient data to personalize treatment. **Food-related molecules**: The process begins with identifying food-related molecules, such as carbohydrates, fats, proteins, and vitamins, which influence the body's biological functions. **Gene identification**: Genes and proteins that play a role in key metabolic pathways are identified. These include genes and pathways like CAZyme, PPARG, DHEA, TCF7L2, Nos-2, TIF4, and CARD9 RAGE, which impact the body's response to these nutrients. **Sequencing**: Once the relevant food molecules, genes, and pathways are identified, sequencing is performed to capture the genetic data and understand the mechanisms at play based on the data analysis to uncover patterns and relationships between genetic factors and the patient's condition. Then, follow-up personalized treatment of colorectal cancer is arranged.

and policy framework and implementing population-based screening programs to assess the efficacy and cost-effectiveness of CRC screening[120]. Additionally, it is anticipated that advances in understanding the role of gut microbiota in CRC will contribute to significant progress in the areas of diagnosis, prevention, and treatment in the future.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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