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Harmony unveiled: Intricate the interplay of dietary factor, gut microbiota, and colorectal cancer—A narrative review

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Abstract

Diet plays a critical role in shaping the gut microbiome, which in turn regulates molecular activities in the colonic mucosa. The state and composition of the gut microbiome are key factors in the development of colorectal cancer. An altered gut microbiome, linked to weakened immune responses and the production of carcinogenic substances, is a significant contributor to colorectal cancer pathogenesis. Dietary changes that involve low-fiber and phytomolecule intake, coupled with higher consumption of red meat, can raise the risk of colorectal cancer. Salutary filaments, which reach the colon undigested, are metabolized by the gut microbiome, producing short-chain fatty acids. Short-chain fatty acids possess beneficial anti-inflammatory and antiproliferative properties that promote colon health. A well-balanced microbiome, supported by beneficial fibers and phytochemicals, can regulate the activation of proto-oncogenes and oncogenic pathways, thereby reducing cell proliferation. Recent research suggests that an overabundance of specific microbes, such as *Fusobacterium nucleatum*, may contribute to adverse changes in the colonic mucosa. Positive lifestyle adjustments have been demonstrated to effectively inhibit the growth of harmful opportunistic organisms. Synbiotics, which combine probiotics and prebiotics, can protect the intestinal mucosa by enhancing immune responses and decreasing the production of harmful metabolites, oxidative stress, and cell proliferation. This narrative review provides a concise understanding of evolving evidence regarding how diet influences the gut microbiome, leading to the restoration of the colonic epithelium. It underscores the importance of a healthy, plant-based diet and associated supplements in preventing colorectal cancer by enhancing gut microbiome health.

Keywords

Colorectal cancer, gut microbiome, dietary factors, microbial diversity, short-chain fatty acids

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Introduction

One of the most common forms of cancer and the third most cause of death globally is colorectal cancer (CRC).[1] Several epidemiological studies have shown that dietary fiber intake and a western diet are associated with the prevalence of CRC, underscoring the significance of the diet-cancer relationship.[1–4] In this regard, the gut environment which includes the microbiome has gained attention and shown to be a significant risk factor for CRC.[5] The collective genes and genome of all microorganisms living in the gastrointestinal tract (GIT) is referred to as the gut microbiome.[6] The human GIT is home to over 100 trillion microbes, most of which are found in the colon.[7] Metagenomic research has revealed that 1952 uncultured bacterial species exist in the human gut, many of which have not yet been assigned a class, adding to the substantial diversity of the microbial ecosystem.[8] The relationship between the host and microbe can be pathogenic or symbiotic, and the microbial ecosystem

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is greatly influenced by a number of external factors, including diet, medication, and lifestyle.[9]

The effects of symbiotic relationships between microbes and hosts on physiological processes and general health are numerous. The advantageous commensals perform a number of roles, including supplying vital micronutrients, controlling the immune system, altering enterocyte function, affecting metabolism, and halting the colonization of harmful microbes. Because the microbes in the gut ecosystem metabolize and flourish on the foods that humans eat, the human diet and its composition have a significant impact on the ecosystem. Short-chain fatty acids (SCFAs) are produced through the metabolism of dietary fibers, certain plant-based proteins, and microbiota accessible carbohydrates. SCFAs preserve microbial diversity, mucosal integrity, and anti-inflammatory qualities.[10,11] Cancer is one of the many diseases linked to imbalances in the ratios of harmful toxins to essential nutrients. The main microbiome-induced mechanisms linked to cancer pathogenesis are altered microbial diversity, weakened immune response, and release of genotoxic or carcinogenic substances.[12–15]

The aim of this review is to provide new information regarding the dietary factors linked to the emergence of CRC. It examines the potential role of the gut microbiome, specifically focusing on how it influences the tumorigenesis processes linked to CRC. Additionally, we go over CRC treatment strategies involving the manipulation of the gut microbiota. Furthermore, we investigated how a nutritious diet can prevent CRC by reestablishing the colonic epithelium's ability to function.

Relationship between CRC and gut microbiome

As global dietary patterns shift toward a more Westernized style, there is a projected steady rise in the incidence of CRC, with an estimated 2.2 million new cases anticipated by 2030.[16] Research indicates that around 90% of CRC cases occur sporadically, with the remaining cases attributed to genetic factors or exposure to specific environmental influences.[17,18] Lifestyle choices, including physical inactivity, smoking history, adherence to a Western diet, low fiber intake, alcohol consumption, and obesity, play pivotal roles in CRC development.[19–22] Lifestyle factors such as smoking, alcohol consumption, diet, and obesity significantly influence cancer risk and the microbial/immune system. Smoking and alcohol impair immune function and alter the microbiome, leading to increased cancer susceptibility. A diet rich in fruits and vegetables supports a healthy immune system and microbiome, reducing cancer risk, while high consumption of red/processed meats, sugar, and high-fat foods promotes obesity and related cancers. Obesity itself contributes to chronic inflammation, immune dysfunction, and microbial imbalances, further elevating cancer risk.[23–26] Notably, these lifestyle factors often trigger alterations in the gut microbiota.[27–29] Numerous studies have demonstrated that changes in the gut microbiome contribute to susceptibility to CRC or impact tumor progression, triggering inflammation, DNA damage, or the production of metabolites by microorganisms.[30,31]

Numerous investigations have suggested a strong correlation between the gut microbiome and host physiology in CRC development. Utilizing high-throughput microbiome sequencing, researchers have examined microbial communities in both tumor-affected and healthy colon tissues, thereby enhancing our comprehension of the differences in the gut microbiome between CRC patients and those without the disease. Studies have revealed a decrease in the diversity and abundance of the gut microbiome in individuals with CRC. Analysis of the gut microbiome in CRC patients has highlighted significant alterations in specific microbial groups, potentially influencing mucosal immune responses in CRC patients compared to healthy individuals. Notably, certain operational taxonomic units linked to genera such as *Enterococcus*, *Escherichia*/*Shigella*, *Klebsiella*, *Streptococcus*, and *Peptostreptococcus* were found to be more prevalent in CRC patients' gut microbiota, while others, including *Roseburia* and other butyrate-producing bacteria from the Lachnospiraceae family, were less abundant. Additionally, dysbiosis, characterized by microbial imbalance, was observed in the gut microbiome of CRC patients. Dysbiosis, coupled with heightened intestinal permeability, may incite colonic inflammation, potentially exacerbating or accelerating CRC. Notably, *Fusobacterium nucleatum* presence was significantly elevated in human CRC compared to healthy counterparts. Moreover, discrepancies in microbiome composition were noted between early-stage CRC patients (advanced adenoma) and those with advanced-stage CRC (established CRC).[32–36] These studies underscore a closely intertwined relationship between CRC and the gut microbiome, although further research is essential for a comprehensive understanding of the gut microbiome's impact on CRC.

Effect of diet on gut microbiome and CRC development

Dietary components such as fibers, fats, and proteins play a vital role in fueling bacterial metabolisms in the gut. This not only aids in digestion but also results in the synthesis of byproducts that hold significant functional importance for the host. For example, bacteria residing in the colon play a crucial role in synthesizing essential co-factors like B vitamins, which are vital for host energy metabolism and gene expression regulation. Additionally, these microorganisms can biotransform plant-derived polyphenols with beneficial properties, such as antioxidant, anticancer, and anti-inflammatory effects. This transformation by the gut microbiota enhances the absorption of these compounds by the host, amplifying their potential health benefits. It underscores the importance of maintaining a healthy balance of gut bacteria for overall well-being.[37–39] However, an imbalance in this equilibrium can lead to the generation of toxic metabolites

by gut microbes, causing cytotoxic and genotoxic effects. Additionally, diets rich in prebiotics and probiotics have the potential to enhance the microbiome's richness by fostering microbial diversity and supporting existing microbiota.[40,41] In the contemporary era of increased processed food consumption, gut biodiversity and chemical composition are substantially impacted, leading to chronic colonic inflammation and an elevated risk of CRC.[2,30,42–44]

Eating processed meat has been associated with a higher chance of developing CRC. The chemicals used in processing red meat can combine to form carcinogenic N-nitroso compounds. Besides poor dietary habits, factors like obesity, heme iron consumption, and changes in the gut microbiota contribute to cancer-related changes in the colon lining. Notably, consuming emulsifiers like carboxymethylcellulose and polysorbate 80 has been linked to changes in the gut microbiome, potentially increasing the risk of intestinal inflammation and the formation of adenomas. The intake of emulsifiers can alter the abundance of specific groups of microbes, potentially affecting how the immune system in the colon responds in individuals with CRC compared to those without the disease.[45–48] Moreover, the imbalance observed in the gut microbiome of individuals with CRC disturbs the microbial equilibrium, triggering inflammation in the colon and facilitating the advancement of CRC. Notably, there is a significant increase in *F. nucleatum* levels in human CRC patients compared to those who are healthy, indicating its potential involvement in CRC development.[49,50]

While evidence suggests a close relationship between red and processed meat consumption, gut microbiota alterations, and CRC, epidemiological support is limited. Red meat, rich in Neu5Gc, can trigger chronic inflammation, potentially contributing to cancers. Nonetheless, the relationship between red meat and CRC is not strong, and certain food combinations can change how the colonic microbiome influences this. For example, consuming red meat alongside high amylose-resistant starch can change how the gut processes food, possibly reducing the risk of CRC. Include alterations in the production of SCFAs in the gut. SCFAs, such as butyrate, acetate, and propionate, are produced by the fermentation of dietary fiber by gut bacteria. These SCFAs have been associated with several beneficial effects, including promoting colon health, reducing inflammation, and potentially inhibiting the growth of cancerous cells in the colon. Additionally, this dietary combination may also influence the composition and activity of the gut microbiota, leading to a favorable gut environment that is less conducive to CRC development.[51–53]

Empirical Dietary inflammatory pattern (EDIP) scoring system assesses the inflammatory potential of foods, assessed by, influences *F. nucleatum* abundance in CRC patients. Higher EDIP scores, indicating inflammatory effects, are associated with CRC positivity for *F. nucleatum*, Consumption of anti-inflammatory foods like whole grains is associated with a reduced likelihood of developing *F. nucleatum*-positive CRC.[54–57] Fermented foods like yogurt contribute to colonic mucosal protection and stabilizing microbial diversity, potentially reducing CRC.[58,59]

Antioxidant consumption is crucial for the survival of certain gut bacterial strains. Supplementation of antioxidants enhances the survival of anaerobic microbes, leading to the synthesis of protective SCFAs like butyrate that have a positive impact on CRC. Additionally, legume consumption by CRC survivors increases the production of beneficial metabolites, potentially detoxifying carcinogens and reducing oxidative stress. This has been linked to heightened production of beneficial metabolites, including piperidine, N-methylpipecolate, vanillate, and 2-aminoadipate. These metabolites are generated through the metabolism of indigestible substrates present in navy beans by gut microbes, resulting in a total of 237 beneficial metabolites. Notably, individuals who consume navy beans exhibit a 5.25-fold increase in ophthalmic acid levels, which play a pivotal role in glutathione metabolism. Ophthalmic acid is crucial for detoxifying xenobiotics such as carcinogens and reducing oxidative stress, thereby conferring protective effects against cancer. This underscores the significance of dietary choices in modulating gut microbiota metabolism and subsequently influencing overall health outcomes.[60–63]

Alcohol consumption alters the gut microbiota and accelerates CRC carcinogenesis. The microbiota in alcoholics exhibits a decrease in beneficial organisms and an increase in harmful ones, potentially contributing to genotoxic insults on the colonic mucosa. Restricting alcohol consumption could be a preventive measure against such genotoxic effects on the colon.[64–66]

In summary, the combination of specific foods in one's diet plays a crucial role in mitigating toxicity on the colonic epithelium, consequently reducing the risk of CRC development. Dietary constituents significantly influence chronic inflammation by modulating the immune response, and various foods have been related with either increased or decreased risk of CRC.

The impact of dietary measure on CRC

Dietary fibers derived from diet rich in plant foods undergo minimal digestion by human intestinal enzymes, reaching the colon in an unchanged state. Enzymes that metabolize and ferment soluble dietary fibers into beneficial metabolites like SCFAs possessed by colonic bacteria, which play a crucial role in reducing inflammation in the colonic mucosa, consequently lowering the risk of CRC.[67,68] Butyrate, a prominent SCFA, inhibits histone deacetylases (HDAC) enzymes, promoting the expression of genes that arrest the cell cycle.[69] Furthermore, butyrate functions as a fuel source for healthy enterocytes, whereas CRC cells, which proliferate rapidly, prioritize glycolysis over utilizing butyrate for their energy requirements.[70] Co-cultivating specific bacterial strains in animal models has been shown to enhance butyrate production, offering SCFA-mediated protection against CRC. For instance, when

Faecalibacterium prausnitzii ATCC 27768 strain is co-cultured with *Bifidobacterium catenulatum* KCTC 3221 and supplemented with fructooligosaccharides in anaerobic conditions, there is a significant increase in butyrate production, suggesting potential protective effects.[70] This co-culture's supernatant, when exposed to colon cancer cells and macrophages, exhibited anti-inflammatory effects in vitro, and when administered in a dextran sodium sulfate (DSS)-induced colitis mice model, it increased SCFA levels and decreased gene expression of pro-inflammatory cytokines.[71] Butyrate was observed to enhance the abundance of tight junction protein complexes in an Apcmin/+ mice model, underscoring its potential in lowering CRC risk. Phytochemicals obtained from dietary sources, like polyphenols and flavonoids, also play a role in safeguarding the colonic mucosa.[72,73] Most polyphenols ingested through plant-based diets reach the colon unaltered and are metabolized by intestinal bacteria into more active substances that decrease oxidative stress, inflammation, and tumorigenesis.[74] Polyphenols also interact with the gut microbiota, promoting the growth of beneficial strains like Lactobacillus and Bifidobacterium, which inhibit inflammation, alleviate colitis, and reduce CRC risk.[75] Examples include epigallocatechin-3-O-gallate and theaflavins from tea extracts, which exhibit anti-inflammatory effects on *F. nucleatum*-induced inflammatory bowel disorders, consequently lowering CRC risk.[76] Berries, rich in polyphenols, act as prebiotics, enhancing microbial richness and decreasing CRC growth. Mango pulp, containing gallotannins and gallic acid, demonstrates anti-inflammatory effects on the intestinal mucosa, reducing pro-inflammatory cytokines and increasing the abundance of beneficial bacteria like Lactobacillus.[77] Date palms, another source of polyphenols and fibers, may not significantly alter gut microbiota but decrease genotoxicity and fecal ammonia levels, contributing to a decreased risk of CRC.[78,79] Green tea extracts rich in polyphenols enhance the Firmicutes to Bacteroidetes ratio and the presence of SCFA-producing gut microbes. Polyphenols, therefore, play a crucial role in reshaping the gut microbiome and potentially decreasing CRC risk. Curcumin, a polyphenol from the Curcuma longa plant, significantly decreases inflammation, oxidative stress, and alterations in the gut microbiome.[80,81] The breakdown of curcumin by gut bacteria yields beneficial metabolites that offer protection against CRC, as indicated by enhanced taxonomic profiles of gut microbiota observed in IL-10-deficient CRC mice models fed a diet rich in curcumin. This enhancement was linked to a decrease in both tumor size and visible macroscopic lesions. Additionally, a combination of essential turmeric oil-curcumin and tocotrienol-rich fraction of vitamin E isomers demonstrated antiproliferative effects on colon cells in vitro studies and suppressed the growth of mice xenografts formed of colon cells in vivo studies. The intervention increased the abundance of anti-inflammatory bacterial genus and decreased harmful microbes, supporting curcumin's potential role in reducing CRC risk.[82–85] Flavonoids, which are another set of beneficial polyphenols found abundantly in fruits and vegetables, are transformed by gut microbiota into active compounds with anti-inflammatory, antioxidant, and anticancer properties.[86] For example, neohesperidin, a flavonoid plentiful in citrus fruits, demonstrates cancer-killing effects in models of CRC in mice, altering the composition of gut microbiota and reducing the formation of tumors in the colon.[87] Likewise, anthocyanins found in black raspberries, which are a type of flavonoid, reduce tumor formation in mice with colitis-associated CRC by prompting epigenetic alterations. These flavonoids, commonly present in plant-centered diets, enhance the diversity of gut microbes and inhibit the growth of CRC.[88]

Olive oil, a prominent element of the Mediterranean diet, containing abundant monounsaturated fatty acids, squalene, phytosterols, and phenols, exhibits favorable effects on mucosal cells in comparison to other oils. Consumption of extra virgin olive oil (EVOO) has been linked to reduced levels of harmful microbes and disruptions in gut microbiota, along with inflammatory alterations, highlighting its potential in preventing CRC. N-3 polyunsaturated fatty acids (PUFA), when combined with fermentable dietary fibers, play a protective role in pathways associated with programmed cell death and epigenetic irregularities observed in CRC. However, careful selection of dietary lipids, particularly EVOO and n-3 PUFA, is essential for optimizing a healthy colonic mucosa, as the benefits of n-3 PUFA may only be significant when sourced from marine origins and consumed alongside dietary fibers. Overall, a combination of dietary fibers and various diet-derived components such as phytochemicals, essential fatty acids, as well as prebiotics, probiotics, and postbiotics collectively forms a multifaceted protective strategy against CRC.[89–91]

Generally, in vitro studies highlight that the diet can influence the gut microbiome by regulating molecular events in the colonic mucosa through controlled experiments with cultured cells. In vivo studies further show that these dietary effects translate into significant changes in gut health in animal models. Human studies have confirmed these findings, demonstrating that dietary habits significantly impact the gut microbiome and CRC risk in human populations.

Impact of the gut microbiome on CRC formation

While much remains unknown about the development of CRC, the onset of CRC is often associated with chronic inflammation, with around 20% of colon malignancies thought to be preceded by prolonged inflammation. Throughout the process of carcinogenesis, cancer cells release inflammatory proteins known as cytokines and chemokines. These molecules attract immature myeloid cells and pro-inflammatory helper T cells, fostering a microenvironment conducive to tumor growth. This environment is marked by the production of growth factors and angiogenic factors, the activation of enzymes involved in tissue remodeling, and the suppression of the body's antitumor T-cell responses.[92,93]

The role of the gut microbiome in the development of CRC was initially acknowledged in the early 1970s. Studies involving germ-free mice exposed to the carcinogen 1,2-dimethylhydrazine showed a notable decrease in CRC occurrence. Further investigations utilizing different CRC models consistently highlighted the substantial impact of intestinal microbes, whether present or absent, on the formation of colon cancer. Advanced techniques such as high-throughput microbiome sequencing have pinpointed specific microorganisms within the intestines that exert influence over the development of CRC.[94–97]

Streptococcus bovis has been identified as a CRC risk factor, with its proinflammatory proteins playing a role in colon carcinogenesis.[98] *F. nucleatum* is associated with CRC tumor formation and early carcinogenesis, producing a protein, Fusobacterium adhesin A (FadA), that activates the oncogenic b-catenin signaling pathway. *Enterococcus faecalis* increases CRC risk by inducing DNA damage to intestinal epithelial cells.[99–103]

Enterotoxigenic Bacteroides fragilis (ETBF) accelerates tumor growth by upregulating signal transducer and activator of transcription 3 (STAT3) and stimulating the Th17 immune response during the development of colon tumors. *Peptostreptococcus anaerobius* fosters a proinflammatory environment and facilitates tumor formation in the intestine by heightening levels of reactive oxygen species (ROS) and promoting cholesterol synthesis.[15,104–106]

Salmonella and *Campylobacter jejuni* have been linked to chronic infections that increase the risk of gastrointestinal diseases, including CRC. Sulfate-reducing bacteria can stimulate CRC progression by producing hydrogen sulfide (H_2S), inducing DNA damage and disrupting the gut barrier.[73,107–110]

Current research endeavors are focused on unraveling the connections between additional intestinal microorganisms and the development of CRC, highlighting the intricate interplay between the gut microbiome and CRC formation.

Gut microbiome's impact on CRC progression

The gut microbiome doesn't just impact the onset of colon cancer; it also plays a role in its progression.[111,112] Research indicates that various bacteria play a role in the development and progression of tumors. In CRC patients, *F. nucleatum* is linked to a poorer prognosis, as it facilitates the development of colonic tumors by suppressing the adaptive immune response mediated by anti-tumor T cells.[113–115] ETBF contributes to the advancement of cancer by triggering the recruitment and multiplication of $CD4^+CCR6^+IL17A^+$ Th17 cells through the IL-17 signaling pathway. *P. anaerobius* fosters the development of CRC by activating the oncogenic PI3K-Akt signaling pathway, which boosts the proliferation of tumor cells.[116–118]

Escherichia coli is closely related to CRC growth, with pathogenic strains correlating with inflammation, ROS production, and tumor infiltration. Colibactin, a genotoxin produced by certain *E. coli* strains, significantly impacts tumor growth.[119–124]

Certain intestinal strains, such as *F. prausnitzii*, *Lactobacillus rhamnosus* GG, and *Bifidobacterium lactis* Bb12, induce protective effects against CRC by downregulating proinflammatory pathways, preventing abnormal epithelial proliferation, and improving the intestinal epithelial barrier. In CRC mouse models, probiotics such as *Lactobacilli* and *Bifidobacteria* impede tumor advancement and reduce tumor size by enhancing the production of SCFAs, promoting apoptosis, and inhibiting tumor cell proliferation.[125–129]

In conclusion, the gut microbiome plays a multifaceted role in both the formation and progression of CRC, with specific bacterial strains influencing various pathways and processes in the complex landscape of CRC development.

Gut microbiome on CRC treatment

The close association between the gut microbiome and CRC has prompted extensive research into its impact on CRC treatment. This area constitutes a vital component of cancer-microbiome research, with numerous studies exploring its integration with diverse treatment modalities for clinical application. Beyond traditional chemotherapy or radiotherapy, emerging insights reveal synergistic effects of the gut microbiome with immune checkpoint inhibitors (ICIs).[130,131]

Chemotherapy. The gut microbiota plays a crucial role in determining the effectiveness of traditional chemotherapy. Certain gut bacteria can modulate cytotoxicity by engaging in the metabolic pathways of anticancer medications. For example, antibiotics-treated mice show reduced efficacy of platinum-based chemotherapeutic drugs like oxaliplatin, leading to decreased cytokine secretion and ROS production, ultimately resulting in diminished tumor necrosis in a mouse model of colon tumor transplantation.[132] Similarly, gemcitabine's anticancer potency diminishes in the presence of certain gammaproteobacteria in the tumor, emphasizing the microbial influence on chemotherapy effectiveness.[133,134] Antibiotic administration in CRC mouse models also reduces the anticancer effect of 5-fluorouracil (5-FU) administration, indicating the microbiota's role in chemotherapy response.[135,136] *F. nucleatum*, previously associated with both the onset and advancement of tumors, influences treatment responses, as elevated levels of *F. nucleatum* are associated with less-favorable outcomes to 5-FU and oxaliplatin treatments in CRC patients.[49,137]

Radiotherapy. Radiation therapy-induced dysbiosis can adversely impact other CRC treatment modalities. After radiation treatment, there is a decline in commensal bacteria and an increase in potentially tumor-promoting microbiota, leading to impaired gut barrier function and additional inflammatory responses. These changes highlight the potential consequences

of radiation therapy on the gut microbiome and its subsequent impact on CRC treatment outcomes.[138–140]

Immunotherapy. Certain intestinal microbes play a role in regulating the immune response and, consequently, tumor growth. Research has aimed to understand how intestinal microbes influence the efficacy of immunotherapeutic agents. Commensal gut microbiota have been shown to enhance the antitumor efficacy of ICIs like programmed death-ligand 1 (PD-L1) inhibitors. The gut microbiota composition influences the efficacy of ICIs, including CTLA-4 and PD-L1 inhibitors, with bacterial species such as *Bacteroides*, *Akkermansia*, *Faecalibacterium*, *Clostridiales*, and *Bifidobacterium* spp. being associated with improved antitumor effects.[141–145] The modulation of ICIs extends to direct interactions between host immune cells and specific bacteria, such as *Akkermansia muciniphila* and *Bacteroides* spp., demonstrating their role in enhancing the effectiveness of immunotherapeutic agents. The microbial metabolites, such as SCFAs like butyrate and propionate, have also been implicated in the antitumor effects observed in response to ICIs.[145–147]

Potential clinical utilizations of the gut microbiome

The potential roles of the gut microbiome in addressing CRC are diverse. It can serve as a screening, prognostic, and/or predictive biomarker, and it can also influence CRC prevention and the effectiveness of systemic treatments. As a screening marker, the gut microbiota acts as a detector for high-risk adenomas or CRC in asymptomatic individuals. Specific bacterial strains, like *F. nucleatum*, can act as screening markers, with their higher abundance in adenomas and CRC patients detectable in fecal samples. Other screening markers, such as metabolic and genotoxic by-products of certain strains, may aid in the early detection of CRC. As a prognostic and/or predictive biomarker, the gut microbiome has the potential to predict patients' clinical outcomes, treatment responses, and potential treatment-related adverse effects. Potential biomarkers may include microbial genes, metabolites, and microbiota-related serological markers detectable in blood, tumor tissue, feces, and samples from the oral cavity. Modulating the gut microbiome offers opportunities for preventing CRC in high-risk populations, improving responses to chemotherapy and immunotherapy, and reducing potential adverse effects. This modulation can be achieved through dietary interventions, prebiotics, probiotics, postbiotics, antibiotics, and fecal microbiota transplantation (FMT).[31,148–150]

Gut microbiota modulation

The makeup of the gut microbiome can be changed through dietary adjustments, which may involve consuming prebiotics such as dietary fiber, cutting back on fat consumption, following a plant-based diet, minimizing or eliminating red and processed meat intake, or boosting the intake of probiotics and postbiotics (microbial fermentation byproducts, like SCFAs). These dietary practices should be coupled with weight reduction and regular exercise. Probiotics, live microorganisms administered in adequate amounts, play a role in improving or restoring gut flora. In CRC, preclinical studies highlight certain bacteria like *Bifidobacterium* and *Lactobacillus* spp., exhibiting anticancer properties. These include inhibiting cell proliferation, inducing cancer cell apoptosis, modulating host immunity, deactivating carcinogenic toxins, and producing anticarcinogenic compounds like butyrate. Although widely used as a food supplement, the effectiveness of probiotics in preventing or treating diseases, including acute antibiotic-associated diarrhea and *Clostridium difficile*-associated diarrhea, remains inconclusive in both preclinical and clinical studies. Questions persist regarding the selection, ratio, activities, colonization, physiological effects, interactions with the intestinal microbiome, safety issues, and overall impact on the host. Prebiotics defined as nondigestible food ingredients that selectively stimulate the growth and/or activity of specific bacteria in the colon, can be combined with probiotics to induce beneficial changes in the fecal microbiota. For instance, inulin, in combination with *L. rhamnosus* GG and *B. lactis* Bb12 probiotics, increases beneficial *Lactobacillus* and *Bifidobacterium* strains while decreasing harmful Clostridium strains.[148–154]

Postbiotics, which include microbial fermentation components such as metabolites, SCFAs, microbial cell fractions, and functional proteins, enhance the potency of prebiotics. Oncomicrobiotics, a potential postbiotic, represents a mixture of bacteria or bacterial products that enhance the immune response.[155,156]

Selective antibiotics can be pivotal in preventing CRC by inhibiting cancer-associated bacteria, boosting beneficial microbes to improve cancer therapies, or acting as small molecule inhibitors to alleviate treatment side effects. Notably, targeting cancer-associated *F. nucleatum* with antibiotics like β-lactams, metronidazole, and clindamycin offers a specific treatment option, although combining these antibiotics with other methods to modulate the gut microbiome is crucial for optimal outcomes. FMT, which involves introducing healthy microbiota from a donor into a patient's intestine, represents a direct manipulation of the gut microbiome. FMT has shown remarkable success in treating *C. difficile* infection, with a cure rate exceeding 90%, and it is governed by stringent international guidelines. Its potential applications extend beyond intestinal diseases to include metabolic, neurological, cardiovascular, and rheumatological conditions. Innovative strategies for modulating the gut microbiome encompass bioengineering the gut microbiota, developing genetically engineered probiotics, and using bacteriocins or bacteriophages to modify the gut microbiota.[31,148,149,157–160]

Limitation of the study

The review compellingly demonstrates the significant influence of diet-modulated gut microbiota on CRC development and progression through diverse molecular mechanisms,

providing an illuminating exposé on this complex relationship. However, as a narrative review, it lacks the methodological rigor of a systematic review or meta-analysis. Additionally, the reliance on preclinical and observational human data makes it difficult to infer causality from the reported associations. Addressing these limitations in future research will enhance the understanding and applicability of the findings.

Conclusion

CRC is a global health concern, with lifestyle choices, particularly dietary habits, playing a pivotal role in its development. The gut microbiome, a complex ecosystem of microorganisms residing in the GIT, is closely linked to CRC, influencing various stages from initiation to progression. Several studies on animals and humans have shown that modifications to the gut microbiota can influence the emergence of precancerous lesions and the advancement of cancer. Research suggests that dysbiosis is more common in CRC patients than in healthy individuals, suggesting that CRC is particularly affected by these alterations. An increase in opportunistic pathogens, intestinal inflammation, and a decrease in butyrate-producing bacteria are the hallmarks of dysbiosis. According to epidemiological studies, dietary factors that have been linked to the development of CRC include low-fiber intake and a Western diet. The gut microbiota plays a part in this process. Dietary fiber is fermented by intestinal bacteria into SCFA, such as butyrate, which has been demonstrated in animal studies to influence the development and spread of cancer. Moreover, the gut microbiome may shed light on the association between antibiotic use and an increased risk of CRC. Our knowledge of this intricate system is still lacking, despite the fact that numerous published studies have demonstrated the importance of the gut microbiota in controlling CRC. In order to treat and prevent CRC, more research is required to clarify the underlying mechanisms and investigate methods for altering the gut microbiota. The goal of this review is to give a general overview of the mechanisms underlying the various gut microbiome strains implicated in each stage of carcinogenesis. This review paves the way for further research into the connection between the gut microbiome and CRC by identifying the microbiota species most likely linked to CRC.

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Author contributions

HTE: conceived the design, searching the literature, drafting the article; WBA, FSH, WT, EYT, YYS, TA, and HTE: searching literature, supervising and critical review of the article. All authors read and approved the final article for publication.

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