REVIEW

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The impact of fermented foods and microbiota modulation on colorectal cancer

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ABSTRACT

Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality worldwide. Chemotherapy, immunotherapy, and surgical interventions are the available CRC treatment options. Nevertheless, they have limited effects on overall survival while causing serious side effects. Therefore, alternative interventions that complement the available treatment options are required. Fermented foods contain bioactive components that exhibit antioxidant and anti-inflammatory effects. They are also effective in modulating the microbiota and regulating the immune system, with living/non-living microorganisms and metabolites such as short-chain fatty acids produced by these microorganisms. This review article outlines the potential of using fermented foods in CRC.

Introduction

Colorectal cancer (CRC) begins as a benign adenomatous intestinal polyp in the colon epithelium. It can progress to high-grade dysplasia, invasive adenocarcinoma and eventually to advanced adenoma with metastasis to distant organs such as the liver (1). It is the third most prevalent cancer worldwide, accounting for approximately 10% of all cancers. By 2020, Europe had the highest CRC incidence, followed by Australia and New Zealand, and the highest mortality rates were in Eastern Europe (2). CRC mainly affects people aged 50 years and older (2) and the average age for CRC diagnosis in a population-based study including seven European nations was 71.1 years (3). The burden of CRC is estimated to reach 3.2 million additional cases annually by the year 2040, reflecting a

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63% increase, along with 1,6 million deaths each year, marking a 73% rise (2).

Modifiable lifestyle factors, including physical activity, diet, smoking, and alcohol consumption, can affect both CRC incidence and survival. The report of the World Cancer Research Fund and the American Institute for Cancer Research concluded that consumption of fruits, vegetables, nuts/seeds, calcium, milk, yogurt, β-carotene, vitamin E, vitamin C, and dietary fiber is protective effects against the risk of CRC, while the consumption of alcohol and processed and red meat significantly increases the CRC risk (4).

Fermented foods include kefir, boza, yogurt, vinegar, bread, sausage, soy sauce, beer, wine, kombucha, and pickles (5). The main goal of the fermentation of foods, which dates back to the time before Christ, is to preserve food by increasing its longevity without spoilage. So far, fermented foods have proven to have favorable effects on atherosclerosis, metabolic syndrome, inflammatory bowel diseases, colon cancer, depression, anxiety, and neurodegenerative diseases (6).

There is a need for less-toxic therapies in cancer treatment. Fermented foods show anticancer properties through modulation of the host immune response and reduction of oxidative damage (7). This review aims to explore the impact of fermented foods on CRC based on current literature and to assess the effectiveness of incorporating them into the diet to prevent and manage CRC.

1. Colorectal cancer

Colorectal carcinogenesis is a multifactorial neoplastic disease involving genetic and environmental factors. The pathophysiological mechanisms of colorectal carcinogenesis include aberrant cell proliferation, differentiation, resistance to apoptosis, invasion of adjacent structures by colorectal tumor cells, and distant metastasis (8).

Different mutations affect disease progression and survival in CRC. Mutations in the DNA mismatch repair system are usually associated with alterations in oncogenes and tumor suppressor genes such as Kirsten rat sarcoma viral oncogene homolog (KRAS), alpha isoform of the p110 catalytic subunit of the phosphatidylinositol 3-kinase, adenomatous polyposis coli (APC), and tumor protein p53 (TP53) (1). The Wingless-related integration site (WNT) signaling pathway, a major mediator of stem cell activation, is the most commonly dysregulated oncogenic pathway in CRC, with the most frequently mutated gene in sporadic CRC being APC, a crucial component of this system (9). Most patients with colorectal adenomas have early APC gene mutations and activating mutations of the KRAS oncogene and later inactivating mutations of the tumor suppressor genes TP53 and mothers against decapentaplegic homolog 4 cause the condition to proceed to carcinoma (8). In addition, the proinflammatory state triggered by the transcription factor nuclear factor kappa-B (NF-κB) is among the most significant pathways in CRC progression. Most risk factors linked to CRC, such as grilled meat, saturated fatty acids, fried meals, stress, and pollutants, have been found to activate this transcription factor (10).

1.1. Gut microbiota in colorectal cancer

The gut microbiome plays critical roles in the digestion of nutrients, regulation of host immunity, gut hormone production, neurotransmission, toxin removal, and drug metabolism (11). *Firmicutes*, *Proteobacteria*, *Bacteroidetes*, and *Actinobacteria* are the most common bacterial phyla in the human gut, while *Bacteroides*, *Bifidobacterium*, *Clostridium*, *Ruminococcus*, *Peptostreptococcus*, *Faecalibacterium*, *Eubacterium,* and *Peptococcus* are the most prevalent species (12). The microbial community in a healthy gut is diverse, stable, resistant, and resilient. On the other hand, an unhealthy gut microbiota has low abundance, lacks diversity, and shows signs of commensalism (13). Disturbed equilibrium of bacteria within the gut can result in heightened inflammation and the emergence of multiple ailments, encompassing ailments affecting the gastrointestinal tract, metabolism, immune system, and brain (12).

The microbiota might activate CRC via oxidative stress, genotoxicity, virulence factors, and epigenetic alterations (8). The “driver-passenger” model proposes that the microbiota contains two types of bacteria: bacterial drivers (pathogens) that initiate carcinogenesis and passengers (pathobionts), which, though less abundant in the intestinal tract, provide advantages due to their prevalence in the tumor microenvironment (TME). As the tumor environment changes, pathobionts become more numerous than the drivers and can infiltrate the disrupted colonic tissue (14).

Multiple studies have found that certain types of bacteria are more common in patients with CRC than in healthy individuals. In a systematic review, *Fusobacterium*-enterotoxigenic *Bacteroides fragilis* (ETBF), *Salmonella, Clostridium,* and *Peptostreptococcus* have been linked to CRC development (15). In another systematic review, patients with adenoma showed increased frequencies of *Fusobacteria*, *Proteobacteria*, and *Bacteroidetes* phyla in their mucosa-associated microbiota and fecal luminal microbiome (16). *Prevotella copri, Bacteroides vulgatus,* and *Ruminococcus torques* were detected at a higher frequency in the CRC group compared to the control group in a meta-analysis of data from France, China, and the USA (17). These bacteria may activate various signaling pathways leading to the transformation of normal intestinal epithelium into malignant cells and may influence carcinogenesis by inducing the expression of inflammatory cytokines (15).

Fusobacterium nucleatum

Fusobacterium nucleatum (F. nucleatum), frequently detected in CRC tissues and feces, may take part in the occurrence and progression of the disease by promoting the proliferation and metabolism of cancer cells, causing a proinflammatory tumor environment, inhibiting anticancer immune responses, causing genetic and epigenetic lesions, and promoting metastasis and chemoresistance (18). It was also associated with reduced survival (19). In a recent study, Zepeda-Rivera et al. (20) identified *F. nucleatum* subspecies animalis C2 as a subspecies enriched in the microbiome of CRC patients. The also found that, in mice treated with this subspecies, the number of intestinal adenomas was higher. A study that analyzed 100 paired tumors and normal tissues showed higher *F. nucleatum* colonization in cancerous tissue than in normal tissue. The authors also observed positive correlations between the amount of *F. nucleatum* and the expression of tumor necrosis factor (TNF)-a and interleukin (IL)-6 genes (21).

There is ongoing debate about whether *F. nucleatum* has a causal relationship with CRC. It was suggested to have a triggering effect on precancerous lesions such as hyperplastic polyps and adenomas, potentially leading to CRC (21,22) and promoting an oncogenic and inflammatory response through its virulence factor-*Fusobacterium nucleatum* adhesin A**,** which interacts with E-cadherin and activates the B-catenin pathway. Based on the available evidence, some researchers argue that *F. nucleatum* is more likely to be a cause of rather than a consequence of CRC (22).

1.2. Relationship between colorectal cancer, gut microbiota, and immunity

Key players in determining the immunological response include the gut microbiota, innate immune system, macrophages and dendritic cells, acquired immune system, T and B lymphocytes, and gut-associated lymphoid tissue. The gut microbiota plays a role in combating harmful pathogens by activating T cells, producing antibodies, and releasing antimicrobial substances like short-chain fatty acids (SCFA) (23). Additionally, it aids in the maturation of immune cells, facilitating the immune response and playing a crucial part in establishing and maintaining the host's immune system (24).

The gut microbiota can also impact antitumor immunity in several ways. Microbial elements or pathogen-associated molecular patterns can boost the activity of antigen-presenting cells through pattern recognition receptors like toll-like receptors (TLRs), elevate cytokine production by immune cells, and indirectly affect immune responses through metabolites generated by microorganisms (25). For example, when TLR4 is overexpressed, it may promote tumor development by increasing the expression of inflammatory cytokines. However, when TLR4 signaling activates TNF-related apoptosis-inducing ligand, a strong inducer of tumor cell death, cytokine expression with anticancer effects increases (26).

Oxidative cellular damage and chronic inflammation may be key players in CRC development (10). While the bacteria such as *F. nucleatum*, *Candida albicans*, ETBF, and *Pks+ E. coli* can inhibit antitumor immunity, others such as *A. Muciniphila*, *Lactobacillus plantarum, Ruminococcus gnavus*, and *Blautia producta* can promote antitumor immunity (24). Pathogens with pro-tumorigenic effects can induce tumor formation by activating intracellular oncogenic growth through hyperactivation of the WNT-β-catenin pathway, triggering the release of inflammation-promoting cytokines such as bacterial metabolites, IL-17 and TNF (27). A study conducted with tumor, peritumor, and intact tissue samples from different parts of the colon of Mexican CRC patients reported significantly lower IL-23 levels in tumor samples and a nonsignificant increase in IL-17 and IL-10, suggesting that the IL-23/IL-17 pathway contributes to the onset and progression of CRC (22).

Gut microbiota influences cancer immunotherapy, particularly immune checkpoint inhibitors (ICIs), by shaping antitumor immune responses (28). *Alistipes shahii*, *B. Fragilis*, *Faecalibacterium* spp., and *Eubacterium limosum* enhance the response to immunotherapy (29). Enhanced comprehension of the synergy mechanisms between ICI treatment and the intestinal microbiome and the accurate identification of immunostimulatory and immunosuppressive strains or pathways hold promise for individualized medicine strategies (28).

2. Fermented foods

The International Scientific Association for Probiotics and Prebiotics defined fermented foods as "foods made through desired microbial growth and enzymatic conversions of food components" (30). Fermented foods are categorized based on live microorganism content. While some fermented foods contain live microorganisms (e.g., kefir, sour cream, most cheeses, yogurt, miso, natto, boza), others do not (e.g., pasteurized fermented vegetables, vinegar, bread, soy sauce, sausage, some kombucha, distilled spirits, most beer and wine, and roasted chocolate beans). They can be categorized into types (e.g., cereals, dairy products, meat products, legumes, beverages, fish products, fruit, and vegetable products) and diverse commercial products (e.g., fermented animal protein, fermented vegetable protein), as well (5).

Fermented foods are produced through a process known as fermentation, which involves the activity of bacteria, yeasts, and mycelial fungi. These microorganisms' presence, suitable substrate, and environmental conditions, including temperature,

pH, and moisture content, are essential for food fermentation (31). Traditional food fermentation relies on the natural microbiome in the food or from previously fermented products, whereas commercial food production systems utilize starter cultures to ensure consistent product quality (32).

Current fermentation processes include lactic acid bacteria (LAB), alcoholic fermentation, alkaline fermentation and mixed fermentation (33). Throughout the fermentation process, the concentration of numerous crucial vitamins such as B2, B9, B12, and K, SCFAs, conjugated linoleic acid (CLA), γ-aminobutyric acid, bioactive peptides, and phenolic compounds increases (6). Fermentation is a natural strategy that enhances the appearance, taste, and odor of food with protein, vitamins, and essential amino acids while potentially reducing tannins and phytic acids that limit nutrient availability by reducing the nutritive value of foods (34).

2.1. Fermented foods and microbiota modulation

Fermented foods may interact with the gut microbiota via its microbiome or substances existing within its matrix by delivering nutrients that encourage or inhibit components of the gut microbiota or establishing members of the food microbiome as gut residents and/or engaging with the resident gut microbiota (32). Microorganisms within fermented foods (yogurt, kefir, cheese, and kimchi) are known to survive gastrointestinal transit and are alive when consumed (30). However, some fermented foods undergo further processing, such as pasteurization, baking, or filtering that kills the live microorganisms. The quality and quantity of these methods differ according to the production methods, storage conditions, and durability (34).

2.2. Fermented foods in colorectal cancer

The consumption of fermented milk and its derivatives in CRC has interested researchers because it forms a part of everyday diets. There is evidence that fermented dairy products can lower the risk of CRC. A meta-analysis comprising 61 studies revealed that fermented dairy products significantly reduce the risk of bladder cancer, CRC, and esophageal cancer (35). A meta-analysis that evaluated the relationship between fermented dairy products and CRC reported an inverse correlation between cheese consumption and CRC incidence. Yogurt consumption was also associated with a lower risk of CRC, attributed to the probiotic content of yogurt (36). The combination of two large-scale case-control studies [the Johns Hopkins Biofilm Study and the Tennessee Colorectal Polyp Study (TCPS)] indicated that daily and occasional yogurt consumption in the TCPS was associated with a reduced chance of hyperplastic polyps (37).

LAB genera frequently found in fermented milk and its products include *Lactobacillus, Lactococcus, Enterococcus, Pediococcus*, and *Streptococcus* and are considered “generally recognized as safe (38). The microorganisms involved in fermentation enhance health by partially breaking down lactose, proteins, and lipids in milk, producing peptides, free fatty acids, and CLA, and improving digestibility (39). Hence, incorporating fermented dairy products into consumption habits may be an effective and low-cost strategy for preventing CRC (36). A clinical study on the impact of a 10-week intervention with 100 grams of fermented kimchi daily on the gut microbiota in 32 volunteers with normal colon, simple adenoma, and advanced colon adenoma found that the intervention resulted in significant changes in the diversity of the fecal microbiome. The same study also showed increased fecal *Cyanobacteria, Acinobacteria, Clostridiumsensu, Gastronaeophillales,* Turicibacter content in patients with advanced colon adenoma following intervention, whereas fecal *Enterococcua Roseburia, Bifidobacterium* spp., *Coryobacteriaceau*, and *Akkermansia* content reduced significantly in patients with advanced colon adenoma (40). The beneficial effects of fermented foods in human studies (35,36,37) and preclinical studies (41,42) include the induction of apoptosis, inhibition of cancer cell proliferation, suppression of carcinogenic signaling pathways like WNT-B catenin, and prevention of tumor progression by reducing proinflammatory cytokine production. Combining chemotherapy with fermented food intake alleviates histological changes such as colonic shortening and spleen enlargement (43). Preclinical studies have proven the adjuvant effects of fermented foods by reducing the side effects of chemotherapy (43,50). The effects of fermented foods on CRC are summarized in Table 1 (animal models) and Table 2 (cell models).

Conclusion

Alternative treatments with fewer side effects are necessary for CRC treatment. Bioactive compounds with antioxidant properties and SCFAs, which play a central role in regulating the intestinal microbiota, increase with fermentation. Fermented foods may be beneficial in preventing and treating CRC by modulating the intestinal microbiota and immunity through the metabolites produced by the bacteria they contain. Fermented foods are considered safe and effective in microbiota modulation. Adding fermented foods to the diet is advantageous due to their low cost and easy applicability. However, since the data on fermented foods other than dairy products have been obtained using preclinical models, future research is needed to evaluate the effectiveness and safety of fermented foods in CRC treatment.

Table 1. Effects of fermented foods on colorectal cancer or adenomas in animal models

Study	Models and groups used	Type of fermented food	Fermentation method	Dose	Time	Mechanism of action
Han et al. (41), 2020	AOM/DSS colitis cancer mouse models (fermented kimchi-non-fermented kimchi) (6 groups*10 pieces)	Fermented kimchi	Obtained by fermentation that involves the production of *lactobacilli*, such as *L. plantarum*.	1.7 g/kg/day ve 5.0 g/kg/day	11 weeks	- Decreasing TNF-α, iNOS, Cox-2, γ-IFN and IL-6 (mRNA levels) - Suppression of NF-κB, particularly NF-κB p65 - Increasing caspase-3 and PARP cleavage or decreasing Bcl-2 expression - Proliferation-related β-catenin nuclear translocation and inhibition of c-Jun
Lim et al. (42), 2023	AOM/DSS colitis cancer mouse models -Normal group; water only (n=8) -Control group; AOM/DSS (n=8) -Positive control group; AOM/DSS group treated with AOM/DSS and 5-aminosalicylic acid -AOM/DSS group treated with fermented soy	Fermented soybeans (Cheonggukjang)	Produced using the traditional method of Kangjin-gun (Jeollanam-do, Republic of Korea)	100 mg/kg/day	-	-Alleviated pathological symptoms such as colonic shortening and increased spleen weight -Modulation of proinflammatory and anti-inflammatory cytokine levels by suppressing NF-κB and inflammatory mediator signaling pathways (decrease in TNF-α, IFN-γ, IL-1β and IL-6 levels and increase in IL-4 and IL-10 levels in soya group compared to the control group) -Phospho-p65 inhibited NF-κB, iNOS, and Cox-2 expression -By regulating mucin-related and tight junction proteins (increased MUC-2, occludin, and ZO-1 levels) improved intestinal integrity -Suppressed tumor growth by regulating apoptosis and proliferation
Chang et al. (43), 2019	CT26 orthotopic colon cancer mouse model (n=30)	NTU 101 Fermented skim milk	*Lactobacillus paracasei* subsp. *Paracasei* NTU 101	1.0 g/kg	5 weeks	NTU 101FM+chemotherapy combined treatment compared to chemotherapy alone; -Improved anorexia -Significantly suppressed tumor growth and metastasis by regulating VEGF, MM-9, and TIMP-1 levels -Controlled proinflammatory cytokines and oxidative stress in tumor, intestine, and serum (increased SOD activity) -Suppressed increases in spleen weight and factors associated with chemotherapy-induced inflammation
Kumar et al. (44), 2022	AOM/DSS male mouse germ-free model -Rice bran group (n=20) -Fermented rice bran group (n=20) -Control group (n=20)	Fermented rice bran	*Bifidobacterium longum*	-	15 weeks	-The incidence of high-grade dysplasia was found to be relatively higher in the fermented group -A significant increase in both the number and size of goblet cells was found in both rice bran groups compared to the control -CD-44 expression decreased in both rice bran groups -Occludins and claudins (tight junction proteins) and zonula occludin increased in both rice bran groups -Cox-2 and NF-κB/p65 decreased in both rice bran groups -Fermentation of rice bran plays an important role in intestinal microbiota metabolism

L. plantarum: Lactobacillus plantarum, AOM/DSS: Azoxymethane-induced/dextran sulfate sodium, NTU 101FM: NTU 101-fermented skim milk, NTU 101: Lactobacillus paracasei subsp. paracasei NTU 101, VEGF: Vascular endothelial growth factor, MM-9: Matrix metallopeptidase-9, TIMP-1: Tissue inhibitor of matrix metalloproteinase-1, SOD: Superoxidase dismutase, NO: Nitric oxide, iNOS: Inducible nitric oxide synthase, IL: Interleukin, TNF-α: Tumor necrosis factor alpha, NFκB: Nuclear factor kappa B, SOD: Superoxide dismutase, Cox-2: Cyclooxygenase-2, MUC-2: Mucin-2, CD-44: Cluster of differentiation-44, IFN: Interferon

Table 2. Effects of fermented foods in colorectal cancer cell models

Study	Model used	Type of fermented food	Fermentation method	Time	Dose	Mechanism of action
Al-Madboly et al. (45), 2023	HCT-116	Fermented juice of Kidachi aloe leaf	-	-	-	-Cell arrest in G1 phase; promotion of apoptosis -TNF-α decrease and IFN-γ increase; anti-inflammatory and/or immunomodulatory effect -Antimicrobial effect against opportunistic pathogens
Divisekera et al. (46), 2019	HCT-116 and HT-29 cells	LAB isolated from fermented millet flour	-	-	-	-Potential bactericidal activity against drug-sensitive pathogens (anti-bacterial activity)
Lizardo et al. (47), 2020	SW480	Fermented cherry silver fruit (Elaeagnus multiflora Thunb.)	*L. plantarum* KCTC 33131 and *L. casei* KCTC 13086	-	25 to 50 µg/mL	-Inhibited cell proliferation and reduced SW480 cell viability -Was able to suppress the proliferation of SW480 cells by inducing cell cycle arrest in S and G2/M phases by downregulating the expression of cyclin A, E, and B and cyclin-dependent kinases (CDKs) CDK1, CDK2, and CDC2 -Upregulated p53 expression -Tumor suppressive effect by inhibiting the chemotactic motility and invasiveness of SW480 cells, downregulating matrix MM-9, and PI3K/AKT/mTOR pathways, and upregulating TIMP-9 and E-cadherin
Jaiswal et al. (48), 2023	HT-29 and SW480	Fermented rice (Bhaati jaanr)	Traditional fermentation with a mixed starter culture called Marcha	-	50-100 µg	-Reduced the viability of both cancer cells -Suppressed LPS-induced inflammation through reduction of NO production and expression of the iNOS gene -Anti-proliferative, antioxidant and anti-inflammatory effects
Iga-Buitrón et al. (49), 2023	Caco-2, HT-29 and HT-116	Fermented broccoli	*Levilactobacillus brevis* (3M1) and *Lactococcus lactis* (3M8)		600 µg/mL	-Cellular antioxidant activity in Caco-2 cells -Anti-proliferative activity in HT-116 and HT-29 cells -Anti-inflammatory effect by reducing IL-8 production in HT-29 cells stimulated with TNF-α
Kim et al. (50), 2021	Drug-resistant human HT-29 cells	Kefir	*Lactobacillus kefiranofaciens, Lactobacillus kefiri, Streptococcus* spp., *Enterococcus* spp., Candida kefyr, Saccharomyces cerevisiae, Kluyveromyces marxianus	24 h	5% (h/h)	-Weakened multidrug resistance -Improved the anticancer effect of DOX chemotherapy -Intracellular ROS levels increased significantly up to 3.8 times in the 10% (v/v) kefir treatment group -HT-29 improves drug resistance of cells -Shows that it can modulate ERK1/2 and JNK signaling pathways -Increased nuclear translocation of NF-κB p65 was down-regulated by kefir treatments in a concentration-dependent manner

MM-9: Matrix metallopeptidase-9, HCT-116: Human colorectal carcinoma cells, HT-29: Human colon colorectal adenocarcinoma cells, SW480: Human colorectal adenocarcinoma cell line, NO: Nitric oxide, iNOS: Inducible nitric oxide synthase, Caco-2: Human epithelial colorectal adenocarcinoma cell line, DOX: Doxorubicin, LPS: Lipopolysaccharide, IL: Interleukin, TNF-α: Tumor necrosis factor alpha, NFκB: Nuclear factor kappa B, JNK: Jun N-terminal kinase, TIMP-9: Tissue inhibitor of matrix metalloproteinase-9, ROS: Reactive oxygen species, IFN: Interferon

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.S., T.K.C., Concept: D.S., T.K.C., Design: D.S., T.K.C., Data Collection or Processing: D.S., T.K.C., Analysis or Interpretation: D.S., T.K.C., Literature Search: D.S., T.K.C., Writing: D.S., T.K.C.

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