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A Review of the Role of Enterotoxigenic *Bacteroides fragilis* in the Development of Colorectal Cancer

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ABSTRACT

Enterotoxigenic *Bacteroides fragilis* (ETBF) plays a significant role in the development and progression of colorectal cancer (CRC) through the production of *Bacteroides fragilis* toxin (BFT). This toxin activates Wnt, NF-κB, and STAT3 signaling pathways, leading to chronic inflammation, DNA damage, and abnormal cellular proliferation. ETBF in the gut microbiota can increase the risk of CRC by enhancing immune cell infiltration, triggering inflammatory responses, and disrupting cell cycle regulation. ETBF detection is performed using molecular methods such as polymerase chain reaction (PCR) and immunomagnetic separation-PCR (IMS-PCR), which offer high accuracy in identifying this bacterium. Immunomagnetic separation enhances the sensitivity and precision of detection. In addition to precise diagnostic methods, preventive strategies play a crucial role in reducing the risk of CRC. A healthy diet, including increased fiber intake, reduced consumption of processed meats and saturated fats, along with maintaining a healthy weight and regular physical activity, are among the effective factors in preventing this disease. Furthermore, stress reduction and avoidance of alcohol and tobacco can positively impact lowering the risk of CRC. A deeper understanding of the role of ETBF in CRC and its effects on molecular pathways can contribute to the development of novel preventive approaches. Investigating the composition of the gut microbiota and implementing preventive strategies based on lifestyle modifications not only aids in identifying at-risk individuals but also plays a significant role in reducing the prevalence and progression of this disease.

Keywords: Colorectal Cancer; *Bacteroides Fragilis*; *Bacteroides Fragilis* Toxin

INTRODUCTION:

Colorectal cancer (CRC) is the leading cause of cancer-related deaths in the gastrointestinal tract, the second leading cause of cancer-related mortality, and the third most common cancer globally in both men and women (1). Geographic diversity is associated with variations in the incidence and mortality rates of this cancer. Asia (52.3%) has the highest incidence of CRC, followed by Europe (26.9%), North America (9.3%), Latin America and the Caribbean (7%), and Africa (3.4%) (2). Individual characteristics such as age and lifestyle are linked to CRC (3). Environmental and genetic factors also play a significant role in this disease, with alcohol consumption, red and processed meat intake, smoking, obesity, and physical inactivity being examples of environmental risk factors (4). A causal relationship has been established between certain bacterial and viral infections and cancer development (5). Microorganisms, bacterial metabolites, and toxins contribute to the initiation, progression, and spread of CRC, with bacterial toxins increasing cancer risk through DNA damage (6, 7). Certain strains of *Bacteroides fragilis* (*B. fragilis*), *Escherichia coli* (*E. coli*), *Enterococcus faecalis* (*E. faecalis*), and *Streptococcus gallolyticus* (*S. gallolyticus*) are among the microbial species associated with CRC (8). Enterotoxigenic *Bacteroides fragilis* (ETBF) is the most common carcinogenic bacterium and a key factor in CRC development. Additionally, studies indicate that biofilm formation by *B. fragilis* is strongly associated with CRC (9). The *B. fragilis* toxin (BFT) is responsible for the pathogenicity of ETBF. It binds to a specific receptor on the colonic epithelium, activating Wnt and NF-κB signaling pathways, leading to increased cellular proliferation, the release of pro-inflammatory mediators by the epithelium, and DNA damage (10). Today, numerous therapeutic strategies exist to modulate the gut microbiota, including probiotic and prebiotic strains as approaches to alter the gut microbiome in CRC treatment (11). This study aims to investigate the role of ETBF in the initiation and progression of CRC. It also evaluates the impact of BFT on cellular signaling pathways, its association with chronic inflammation, and DNA damage. Furthermore, the influence of environmental, microbial, and genetic factors on increasing CRC risk, as well as the importance of gut microbiota modulation in preventing this disease, are discussed.

Colorectal cancer

CRC encompasses both colon cancer (CC) and rectal cancer (RC), which are considered as a single tumor entity. The progression of CRC involves cellular changes from normal tissue to precancerous lesions known as adenomatous intermediates, which ultimately develop into invasive adenocarcinoma (12). Multiple factors contribute to the development of CRC. A family history of the disease significantly increases the risk of developing CRC (13). Two common hereditary syndromes associated with an increased susceptibility to CRC are Hereditary Nonpolyposis Colorectal Cancer (HNPCC), also known as Lynch Syndrome (LS), and Familial Adenomatous Polyposis (FAP) (14). Colon polyps, which are precancerous neoplastic lesions, are defined as abnormal tissue growths originating from the mucosal layer of the large intestine. Histologically, they are classified into two main categories: non-neoplastic polyps (hamartomas, hyperplastic, and inflammatory) and neoplastic polyps (adenomatous). Adenomatous polyps are of particular importance due to their potential to become malignant (15). It is estimated that approximately 95% of CRC cases arise from adenomatous polyps (16). Among environmental factors, high-energy diets, consumption of red or processed meat, high-glycemic index foods (such as carbohydrates, fried foods, and sugary beverages), excessive salt (NaCl) intake, and low daily water consumption are associated with an increased risk of CRC. Conversely, the consumption of white meat, plant-based oils, fish rich in omega-3 fatty acids, fiber, and diets abundant in vitamins E, D, C, B6, folic acid, selenium, and magnesium are considered protective against CRC (17). Recently, the gut microbiome has garnered increased attention as a factor in CRC. This community of symbiotic microorganisms residing in the gastrointestinal tract has been linked to conditions such as obesity and inflammatory bowel disease (18). Under normal conditions, the colonic microbiome coexists symbiotically with the host. Disruption of this balance can lead to inflammation and DNA mutations, ultimately increasing the risk of CRC (19). Patients with CRC exhibit less bacterial diversity in their fecal and intestinal mucosal samples compared to healthy individuals. Additionally, significant changes in specific bacterial groups may impact mucosal immune responses (20). Microbial species associated with CRC include specific bacteria such as *E. coli*, *E. faecalis*, *S. gallolyticus*, *Fusobacterium nucleatum* (*F. nucleatum*),

Helicobacter pylori (*H. pylori*), and *B. fragilis,* among others (8, 21) (Table 1). These microbes possess distinct pathogenic and carcinogenic properties. For example, toxins secreted by *E. coli*, known as Cytolethal Distending Toxins (CDTs), induce excessive proliferation of intestinal epithelial cells and the formation of adenomas, which invade the submucosal tissues and ultimately lead to cancerous changes. *E. faecalis* contributes to DNA damage through the production of free radicals (22). *S. gallolyticus* is an opportunistic pathogen that can cause sepsis and endocarditis in elderly individuals, and a link between infections with this bacterium and colonic neoplasia has been identified (23). *F. nucleatum* is closely associated with CRC. This bacterium adheres to intestinal cells through factors such as Flavin Adenine Dinucleotide A (FadA) and Fibroblast Activation Protein 2 (Fap2), suppresses the immune system, and accelerates cancer progression by creating a pro-inflammatory microenvironment. Additionally, it promotes CRC progression and recurrence through Toll-like receptor signaling and alterations in microRNAs (24). *H. pylori*-associated gastritis has been weakly linked to an increased risk of colorectal adenomas and CRC (25). *B. fragilis* also plays a role in CRC development through the production of the BFT toxin, and certain strains of *B. fragilis* are associated with secretory diarrhea in humans (6). Further research into CRC and global advancements is crucial for informing future strategies to control the disease burden through population-based preventive measures (13).

B. fragilis and Enterotoxin

Although most *B. fragilis* strains are commensal and non-pathogenic, enterotoxigenic strains (ETBF) can produce a toxin called BFT or Fragilysin, which plays a role in the pathogenesis of inflammatory bowel diseases. *B. fragilis* is one of the dominant members of the normal gut flora in humans, residing symbiotically in the gut microbiota. The normal flora is beneficial to the host as it maintains intestinal health and homeostasis. However, when bacteria such as ETBF undergo dysbiosis in the gut, they exert harmful effects on the host. An imbalance in the microbiota leads to bacterial infection, which can progress to chronic inflammation. One of the key environmental risk factors contributing to CRC is chronic intestinal inflammation (31-33). The BFT enterotoxin is a zinc-dependent metalloprotease with a molecular weight of 20 kDa, encoded by the bft gene located on a pathogenicity island. This toxin binds to specific receptors on intestinal epithelial cells and degrades E-cadherin a key molecule in intercellular junctions disrupting the gut epithelial barrier function, increasing mucosal permeability, and activating inflammatory pathways such as NF-κB. Epidemiological studies have shown an association between ETBF strains and multiple diseases, including acute diarrhea, colitis, and inflammatory bowel disease (IBD). Furthermore, emerging evidence suggests a potential role of this toxin in CRC through the induction of chronic inflammation and DNA damage. Recent molecular studies indicate that BFT promotes a pro-inflammatory environment by inducing the secretion of cytokines such as Interleukin (IL)-8 and

Table 1. Bacteria associated with CRC

Bacteria	Effectant	Mechanism of Carcinogenesis	References
E. coli	Genotoxin	Genotoxin production in colon cancer	(26)
E. faecalis	Superoxide	DNA breaks due to extracellular superoxide production	(27)
H. pylori	VacA	Producer of VacA (a multifunctional toxin) that targets mitochondria	(28)
S. gallolyticus	SGG	*S. gallolyticus* activates the Wnt/β-catenin signaling pathway in CRC	(29)
F.nucleatum	FadA, Fap2	Stimulates nuclear factor-kb and the Wnt signaling pathway	(30)
B.fragilis	BFT	Induces Th17/IL-17 inflammatory response, induces E-cadherin degradation, and produces *B. fragilis* toxin	(11)

Tumor necrosis factor (TNF)-α, thereby facilitating the progression of gastrointestinal pathologies (34, 35).

B. fragilis in the colon microbiome

Since 1897, the genus Bacteroides has been recognized as a potential causative agent of various infections. These bacteria are naturally present in the microbiomes of the gastrointestinal tract, upper respiratory system, and urogenital system(36). Bacteroides species are the primary source of gastrointestinal infections, and it was reported in 1956 that the majority (56%) of these infections occur following intestinal surgery. They are also identified as the most common pathogens in gynecological and obstetric disorders (37). Bacteroides strains are Gram-negative, obligate anaerobic bacteria that constitute approximately 25% of the anaerobic bacteria in the human gut microbiota (38). One of the most significant species within this genus, known as a primary agent of endogenous purulent infections in clinical samples, is *B. fragilis*. This species is naturally found in the colonic flora of humans and some animals (26). At least six species are included in the *B. fragilis* group: *B. fragilis*, *B. ovatus*, *B. distasonis*, *B. vulgatus*, *B. thetaiotaomicron*, and *B. uniformis* (27). *B. fragilis* is encapsulated, non-piliated, and non-motile. It is a Gram-negative bacillus measuring 1.5 to 6 micrometers in length. Isolates of this bacterium are bile-resistant and can proliferate even in the presence of 20% bile. Species-specific variations in catalase and indole activity can aid in species-level identification(28). Although *B. fragilis* is a gut commensal with a tendency to colonize the mucosal membrane, it constitutes only a small portion (approximately 0.5%–1%) of the fecal microbiota (10). The pathogenicity of *B. fragilis* is facilitated by several virulence factors, one of which is capsule formation. In addition to the capsule, other notable virulence characteristics include the synthesis of immunoglobulin proteases, superoxide dismutase, catalase, coagulative and spreading factors (such as collagenase, fibrinolysin, and hyaluronidase), and adhesion factors(29). There are two strains of *B. fragilis*: ETBF and non-toxigenic *B. fragilis*(NTBF) (31). ETBF secretes BFT, a zinc-dependent metalloproteinase that induces inflammation in preclinical models of CRC. BFT increases intestinal permeability and, before the pathogen translocation process, activates the Wnt signaling pathway and stimulates the release of β-catenin to activate the expression of genes such as MYC. Additionally, BFT-mediated cleavage of E-cadherin initiates carcinogenic responses (39). These characteristics enable *B. fragilis* to bypass the body's immune barriers and cause serious infections. Furthermore, exposure to the toxin produced by this bacterium increases the risk of developing CRC. Investigating the prevalence of this bacterium in CRC-related samples is of particular importance, as it may help us halt the progression of cancer and provide more accurate predictions of its occurrence (40)

The Role of *B. fragilis* in Pathogenesis and Cancer

One of the primary factors in the pathogenicity and pathogenesis of *B. fragilis* is the production of a capsule. In addition to the capsule, these anaerobic bacteria possess other important virulence factors, including superoxide dismutase and catalase, immunoglobulin proteases, coagulation-promoting factors, spreading factors (such as collagenase, fibrinolysin, and hyaluronidase), and adhesion factors. Other factors that enhance the pathogenicity of this aerobic bacterium include hemoglobin or blood present in the infected area, reduced oxidation-reduction potential, and damage to the mucosal membrane (29, 41). The normal gut microbiota produces and releases toxins that can bind to specific cell surface receptors and influence intracellular signaling. For example, ETBF bacteria can asymptomatically colonize humans or secrete the BFT toxin, which can cause inflammatory diarrhea in humans (38, 42). ETBF has been observed in fecal samples from some CRC patients. *B. fragilis* degrades the E-cadherin protein, activates nuclear beta-catenin signaling, and increases c-Myc expression and cell proliferation(43). The BFT is a zinc-dependent metalloproteinase that participates in multiple signaling pathways in colonic epithelial cells, including NF-κB, Wnt, and mitogen-activated protein kinase (MAPK). By doing so, it stimulates the synthesis of inflammatory mediators that contribute to cancer development (44). Colonization by BFT+ *B. fragilis* can lead to the accumulation of regulatory T cells (Tregs) and ultimately promote IL-17-mediated pro-carcinogenic inflammatory responses (45). BFT can also induce bacterial dysbiosis locally by stimulating the growth of other pro-carcinogenic bacteria, disrupting the host immune system and gut barrier, and promoting mucin degradation(46). Administration of BFT toxin to human colonic epithelial cells (HT29/C1) increases cell volume and induces time- and concentration-dependent redistribution of actin microfilaments (F-actin) without causing cell damage. This promotes early tumor growth

by inducing the differentiation of myeloid cells into myeloid-derived suppressor cells (26, 44).

The carcinogenic mechanism of BFT in CRC

B. fragilis is divided into two types: NTBF and ETBF. The main difference between NTBF and ETBF is the presence of the BFT gene and the ability to produce biofilm. BFT is a zinc-dependent metalloprotease toxin, also known as fragilysin (10, 47). Colonization of the intestine by ETBF is significantly associated with CRC, as the rate of ETBF colonization is increased in approximately 90% of CRC patients, while this amount is approximately 50% in healthy individuals (48). An increased number of ETBFs are observed even in mucosal biopsy samples from patients with precancerous lesions (49). Regarding the role of the gut microbiome in disease development, some members of the microbiota are associated with CRC. For example, *B. fragilis* has been shown to cleave E-cadherin via BFT and activate Wnt, NF-κB, and STAT3 signaling pathways; produces pro-inflammatory cytokines, and increase the expression of oncogenes (50). ETBF causes the expression of cyclooxygenase (COX)-2, which produces PGE2 and causes inflammation and regulates cell division (51). BFT activates the STAT3/Th17 immune response and damages DNA in an oxidizing manner by producing ROS. Therefore, colonic epithelial cells that have been colonized with ETBF over time increase the risk of developing CRC (7, 52). ETB causes the infiltration of T helper 17 (Th17) cells, the development of colitis, and the promotion of colonic carcinogenesis (53). Th17 cells begin to produce large amounts of cytotoxins such as IL-17. The initial inflammatory stages of the lesions are influenced by IL-17, which is produced by pathogenic Th17 cells. Carcinogenesis is made possible by promoting the survival, proliferation, and metastasis of tumor cells (51). BFT plays a role in many signaling pathways of colonic epithelial cells, and when it disrupts or activates signaling pathways, it has negative effects on the body and can lead to colorectal tumorigenesis (54). Signaling in colonic epithelial cells occurs through the NF-κB and Wnt pathways (55). BFT can activate the NF-κB pathway in intestinal epithelial cells and cause the expression of cytokines, which leads to mucosal inflammation. This pathway causes cancer cells to survive and prevents cell death (apoptosis), which ultimately leads to tumor formation (56). When NF-κB is activated in intestinal epithelial cells for a long time, it stimulates the production of the enzyme nitric oxide synthase, which breaks down L-arginine and produces nitric oxide. This nitric oxide can damage the DNA of cells (51). The Wnt signaling pathway is essential for maintaining the structures of the intestinal epithelium but may negatively affect cells involved in carcinogenesis and CRC progression (57). BFT also initiates carcinogenic reactions by activating the Wnt signaling pathway and stimulating the release of β-catenin to activate the expression of genes such as MYC from E-cadherin cleavage(39). This process allows cancer cells to move to other areas of the body and metastasize. As a result, cancer cells can spread to other organs (58) (Figure 1).

Methods for Detection and Identification of *B. fragilis* in CRC

To identify the biological activity of the BFT protein, cell-based assays such as HT29/C1 are used, which can directly identify the activity of this protein in the stool supernatants of patients with diarrhea (59). In addition to patients with intestinal disorders, there is usually a similar reduction in the amount of Bacteroides, especially *B. fragilis*, in their stool. This decrease may indicate the presence of microbial disorders in the intestine, which may lead to problems such as intestinal dysbiosis and even precancerous colorectal lesions (60). One of the main challenges in diagnosing Enterotoxigenic *B. fragilis* infection from stool samples is the need to identify the BFT gene or examine its biological activity (61). In general, direct methods such as PCR (polymerase chain reaction) that use stool samples for diagnosis are more accurate and sensitive than culturing bacteria and then identifying the BFT gene or protein (62). A major problem in using stool culture is the time-consuming processing of samples, especially for anaerobic culture of *B. fragilis*, which can reduce the accuracy of the results (63). Moreover, in the stool culture method, identification of ETBF can be complicated due to the high diversity of *B. fragilis* strains, which include both NTBF and ETBF strains. For this reason, more accurate diagnosis via stool culture may be problematic. Some reports indicate that in diarrheal conditions, ETBF may replace non-toxic strains and become dominant compared to them (64). Using overnight anaerobic culture in a molecular and cellular environment, enzyme immunoassays (EIA) are also available to identify the BFT protein. These methods are faster than others, but available data indicate that the sensitivity of these assays in identifying the BFT protein

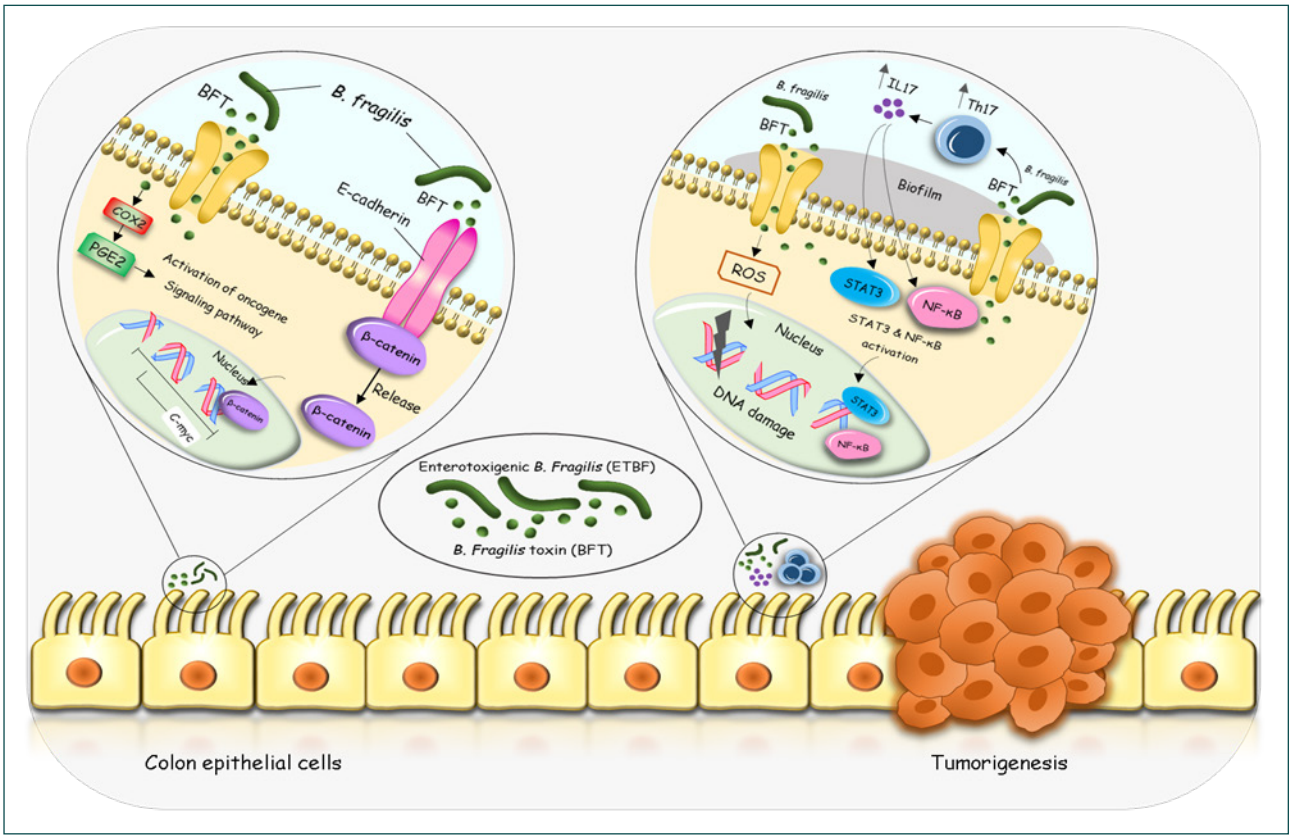

Figure 1: BFT stimulates β-catenin by cleaving E-cadherin, initiating carcinogenic reactions through the expression of the MYC gene. BFT induces the expression of cyclooxygenase (COX)-2, which produces PGE2, leading to inflammation and the regulation of cell division. BFT also activates Th17, resulting in the production of mucosal immune cells IL17, and initiates carcinogenesis through the activation of the NF-κB and STAT3 signaling pathways, as well as oxidative reactions that cause DNA damage.

in stool samples is limited and may be less accurate compared to other methods. Finally, a new combined method called IMS-PCR (immunomagnetic separation-polymerase chain reaction) exists for identifying ETBF. In this method, *B. fragilis* is first separated from the stool using immunomagnetism, and then ETBF is identified with the help of PCR. Due to its short time and high accuracy, this method may be a suitable solution for rapid diagnosis of this infection (61).

Current Prevention and Treatment Strategies for *B. fragilis*-Associated CRC

Currently, proteins, DNA (detection of mutations and methylation markers), RNA (mainly microRNAs), volatile organic compounds, and changes in the composition of the gut microbiome are among the colorectal biomarkers that are being investigated (65). Vaccines can create anti-tumor immunity by employing cancer-related microbes and tumor neoantigens, preventing cancer (66). The gut microbiota plays an important role in various CRC treatments such as chemotherapy, immunotherapy, and laparoscopic radical surgery (67). Consuming a diet high in fiber reduces the risk of CRC (8). Complementary treatments based on probiotics and prebiotics are used by changing the composition of the microbiota and determining (Microsatellite Instability-MSI) and (Kirsten rat sarcoma virus-KRAS) mutations in tumor samples for diagnostic purposes and treatment management (3). Common anti-CRC chemotherapy drugs include cyclophosphamide, 5-fluorouracil (5-FU), and irinotecan (CPT-11) (67). Adjuvant chemotherapy, including 5-FU and oxaliplatin, is the recommended treatment option for advanced CRC cases that cannot be completely resolved with surgery (68). For the treatment of *B. fragilis* infections to have a desirable clinical outcome, effective antibiotics are known to be essential, and different doses of β-lactams, metronidazole, clindamycin, and newer fluoroquinolones are prescribed to treat *B. fragilis* infections in different countries and hospitals. Additionally, fecal enterotoxigenic *B. fragilis* is

associated with CRC, suggesting that its detection may be a potential marker for CRC diagnosis. *B. fragilis*-positive patients had better recurrence-free survival and overall survival compared with *B. fragilis*-negative patients. The presence of *B. fragilis* may predict outcome, especially recurrence-free survival, in patients with curatively resected stage II and III CRC. Research has also found that *B. fragilis* and *E. coli* in biofilms have a synergistic pro-carcinogenic involvement (69).

Conclusion

The present study indicates that the identification of ETBF is achieved through molecular methods such as PCR and IMS-PCR, which offer high accuracy in detecting enterotoxigenic strains. Beyond medical treatments, attention to lifestyle modifications can significantly impact the prevention and improved management of this condition. Furthermore, chemotherapy with drugs like 5-FU, widely used for treating this type of cancer, is only one of the available treatment modalities. Immunotherapy, which enhances the body's immune system to identify and eliminate cancer cells, is another treatment option. Additionally, the use of probiotics as a novel approach to modulate the gut microbiota and promote gut health in patients with CRC is being investigated. Molecular diagnostic techniques like PCR offer enhanced accuracy and speed for diagnosing infections. Molecular methods for antimicrobial resistance (AMR) diagnosis vary in complexity and require different laboratory capacities. Molecular techniques based on genomic and proteomic approaches are also used for diagnosis.

List of Abbreviations

ETBF: Enterotoxigenic *Bacteroides fragilis*
CRC: colorectal cancer
BFT: *Bacteroides fragilis* toxin
PCR: polymerase chain reaction
IMS-PCR: immunomagnetic separation-PCR
B. fragilis: *Bacteroides fragilis*
E. coli: *Escherichia coli*
E. faecalis: *Enterococcus faecalis*
S. gallolyticus: *Streptococcus gallolyticus*
CC: colon cancer
RC: rectal cancer
HNPCC: Hereditary Nonpolyposis Colorectal Cancer
LS: Lynch Syndrome
FAP: Familial Adenomatous Polyposis
F. nucleatum: *Fusobacterium nucleatum*
H. pylori: *Helicobacter pylori*
CDTs: Cytolethal Distending Toxins
FadA: Flavin Adenine Dinucleotide A
Fap2: Fibroblast Activation Protein 2
IBD: Inflammatory bowel disease
IL: Interleukin
TNF: Tumor necrosis factor
NTBF: non-toxigenic *B. fragilis*
MAPK: Mitogen-activated protein kinase
Tregs: Regulatory T cells
COX: cyclooxygenase
Th17: T helper 17
EIA: enzyme immunoassays
MSI: Microsatellite Instability
KRAS: Kirsten rat sarcoma virus
5-FU: 5-fluorouracil
AMR: antimicrobial resistance

Statement of contribution of the authors

Idea: A.J.S, M.P; Data Collection or Processing: A.J.S; Writing-Review & Editing: M.F.S, E.N.L, N.Y.A, M.S; Figure design: E.N.L; Supervision: A.J.S, M.P. All authors reviewed the results and approved the final version of the manuscript.

Ethics declarations

Ethical approval and consent to participate

None.

Consent for publication

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Conflicts of Interests

Authors declare that there is no conflict of interests.

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