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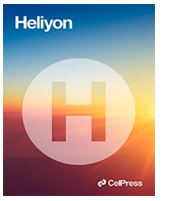

Review article

Gut microbiota and their derivatives in the progression of colorectal cancer: Mechanisms of action, genome and epigenome contributions

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ABSTRACT

Gut microbiota interacts with host epithelial cells and regulates many physiological functions such as genetics, epigenetics, metabolism of nutrients, and immune functions. Dietary factors may also be involved in the etiology of colorectal cancer (CRC), especially when an unhealthy diet is consumed with excess calorie intake and bad practices like smoking or consuming a great deal of alcohol. Bacteria including *Fusobacterium nucleatum, Enterotoxigenic Bacteroides fragilis* (ETBF), and *Escherichia coli* (*E. coli*) actively participate in the carcinogenesis of CRC. Gastrointestinal tract with chronic inflammation and immunocompromised patients are at high risk for CRC progression. Further, the gut microbiota is also involved in Geno-toxicity by producing toxins like colibactin and cytolethal distending toxin (CDT) which cause damage to double-stranded DNA. Specific microRNAs can act as either tumor suppressors or oncogenes depending on the cellular environment in which they are expressed. The current review mainly highlights the role of gut microbiota in CRC, the mechanisms of several factors in carcinogenesis, and the role of particular microbes in colorectal neoplasia.

1. Introduction

Colorectal cancer (CRC) is considered to be the third most frequently reported malignant tumor and is considered the second major source of death, with almost 1.8 million new patients and 881,000 reported mortalities throughout the world in 2018 [1]. According to some recent reports, the number of CRC cases among adults over 50 years of age slightly decreased, compared to the cases reported in ages <50 years. Developed countries have minimized the incidence of CRC by timely adopting its treatment plan after its initial screening through colonoscopy, however, a high number of cases and deaths is still reported in developing countries [2].

CRC may progress from the long-term interactions of the host with different environmental factors [3]. Such factors are famous for

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the development of various cancer types either by tumor generation, epigenetic modifications, and DNA damage within the host epithelial cells [4–6]. The human alimentary tract also harbors almost 10^{14} microorganisms, referred to as gut microbiota that includes different viruses, bacteria, and fungi where they live as commensalism (Bray). Most of the bacteria resident in the intestine belong to phyla: *Cyanobacteria, Firmicutes, Proteobacteria, Actinobacteria, Bacteroidetes*, *Fusobacteria,* and *Verrucomicrobia* [7]. The distribution of these bacteria in the intestine is the same where they maintain their homeostasis but their number is significantly varied in diseased people. Some recent pieces of evidence have explored the role of many bacteria, such as *Streptococcus bovis, Fusobacterium nucleatum, Bacteroides fragilis, Clostridium septicum,* and *Helicobacter pylori* in the development of CRC [8]. These bacterial species are found in high amounts in CRC patients and also can be a source of DNA damage and inflammation in intestinal cells [9]. Undeviating exposure of these microbes to host epithelial cells and disturbance in the microbiome or its homeostasis leads to the development of many disorders like CRC, inflammatory bowel disease, and irritable bowel syndrome [10,11]. Bacteria secrete toxic metabolites, including secondary bile salts through utilizing primary bile salts, hydrogen sulfide, trimethylamine-N-oxide (TMAO) from choline, indoxyl-sulfate from tryptophan, and many others which endorse acute and chronic inflammation that can progress into cancer [12,13]. Keeping in mind the deep interaction between gut microbiota and carcinogenesis of CRC, the current review mainly focuses on epigenetic modifications and its microbial footprints, mechanistic aspects of CRC, genetics, and dietary interventions involved in CRC.

2. Microbes involved in CRC

The human gut microbiome comprises a diversity of microorganisms i.e. viruses, protozoa, bacteria, and fungi. Their carcinogenic properties may depend on the different virulence factors, composition of bacterial communities (polymicrobial synergy) their metabolic activities, destruction of the host mucosal barrier, long-lasting inflammation, and a combination of all these aspects. In a previous study, a significant difference was observed in mucosal and fecal microbiota among healthy and CRC-affected individuals [14]. There was less bacterial diversity in the patients suffering from CRC as shown in Fig. 1. However, the number of *Bacteroides, Firmicutes*, and *lactic acid* declined but there was a marked increase in *Porphyromonas* and *Fusobacterium*. Moreover, increased count of *F. nucleatum*, *E. coli,* and *E. faecalis* initiate Wnt mitogenic signaling. This signaling increases DNA damage, disrupts the DNA repair mechanism, and by rendering adhesion molecules (e-cadherins) increases the permeability of the mucosal membrane, all of the mechanisms play an important role in CRC carcinogenesis [15,16]. Various studies proved that a sufficient number of beneficial bacteria like *lactobacillus*, can reduce the risk of tumor growth. However, *Bacteroides* and related bacterial communities increase the tumor burden. Indeed, the equilibrium between *Firmicutes* and *Bacteroidetes* seems to be important in the prevalence of CRC [17,18]. The European Molecular Biology Laboratory (EMBL) performed a metagenomics sequencing study on 156 subjects suffering from CRC revealing the relative abundance of twenty-two bacterial species like *Fusobacterium* and *Porphyromonas*. Generally, fecal occult blood test (FOBT) is normally used for screening and detection of tumor progression. In early and late-stage cancers, the accuracy in the detection of metagenomic CRC can be significantly different. Later on, various studies validated this concept [19].

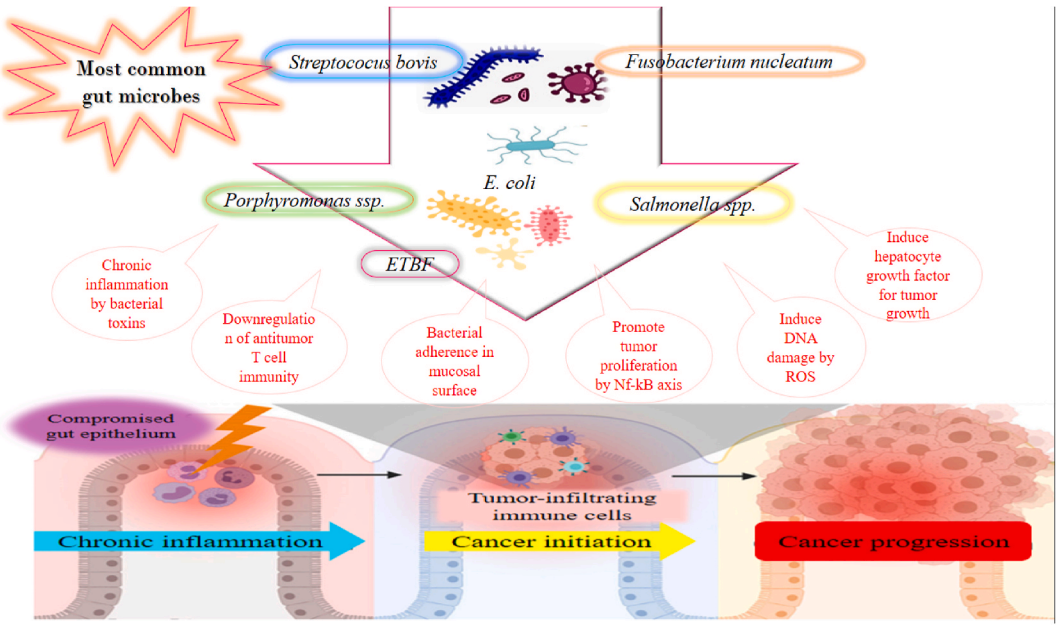

Fig. 1. Involvement of common microbes in CRC.

2.1. *Fusobacterium nucleatum*

There has been extensive research reported on the correlation between colorectal cancer and *F. nucleatum*. Recent studies provide emphasis on the mechanism of this potential pathogen. A study suggests that colorectal cancer cell proliferation is initiated by the FadA attachment to E-cadherin which is expressed in colorectal cancer cells involving DLD1, HCT116, HT29, and SW480 [20]. As compared to *streptococcus*, the *Fusobacterium nucleatum* in the APCmin/+ rat model resulted in more colonic tumors [21]. Moreover, *F. nucleatum* does not propagate colitis and colitis-associated carcinogenesis. However, for the initiation and propagation of CRC, it provides the pro-inflammatory micro-environment by recruiting the immune cells. Further, *F. nucleatum* shows an invasive ability by isolation from the inflamed tissue and induces a more intense expression of MUC2 and tumor necrosis factor-alpha both in *in-vitro* and *in-vivo* studies [22]. A recent study reported that *F. nucleatum* disrupts the NK cell function by attaching to TIGIT which is an inhibitory receptor by its protein known as Fap2 [23]. However, studies also suggest that not all strains of *F. nucleatum* show the same pathogenicity. Besides, based on recent studies, isolated *F. nucleatum* from inflamed parts possess more invasive ability than the general tissues either from the healthy subjects or IBD patients [22,24].

2.2. *Bacteroides fragilis*

One of the known carcinogenic bacteria of CRC is *Enterotoxigenic Bacteroides Fragilis* (ETBF), which is encoded as *B. Fragilis* (a gut pathogen), and responsible for inducing diarrhea [25]. Many clinical studies showed the +ve correlation between colorectal cancer and *B. Fragilis*. Previous studies mainly focused on the capacity of this bacterium to remodel the epithelial cytoskeleton and F-actin structure through E-cadherin targeting [7]. In several rat-based studies, ETBF has been shown to trigger colon tumors and colitis [26–28]. ETBF has the potential to trigger or activate the transcription-3 (Stat3) pathway with the characterization of T helper type 17 response [29]. Moreover, it can also activate cell proliferation and trigger c-Myc expression in vitro studies, as well as initiate DNA damage and upregulation of polyamine metabolism [16,30].

2.3. *Porphyromonas spp*

Porphyromonas is strictly anaerobic bacteria, which is abundantly present in a variety of biological niches including the oral cavity, gastrointestinal tract, and other mucous membrane-assisted areas in the body. Mostly, *Porphyromonas* spp penetrates in epithelium through the damaged epithelial layer colonizes and invades neighbor cells. *Porphyromonas* disrupts the apoptosis in the cells by inhibition of cytochrome C, which was released from mitochondria by down-regulation of caspase 3 activity. Besides, anti-apoptosis genes, which encode Bcl-2 and survivin, changes in the level and phosphorylation status of cyclins, and p53 and PI3K control the cell cycle. Furthermore, it has been observed an increase in nitric oxide synthetase and TNFα expression. Further, the accumulation of *porphyromonas* leads to an inflammatory environment which increases tumor formation [31,32].

2.4. *E. coli*

One of the common microbes in gut pathogenesis is *E. coli*, which is an anaerobic commensal bacterium that shows gram-negative properties. Many studies correlated a high risk of colorectal cancer with *E. coli*, but the exact mechanism of action is still unknown. Some clinical studies show the colonization of cyclomodulin-producing *E. coli* in many cancerous samples [33,34]. Many studies examine isolates of colon cancer cells and found that they initiate interleukin-8 expression and display attachment and invasive potential to specific cell lines [34,35]. Further, the pks island contains *E. coli* with the colibactin gene which triggers DNA damage, gene mutation, and chromosomal aberrations [36]. The higher gene mutation can be due to the depletion of the DNA mismatch repair system associated with the effector protein of *E. coli* [37]. The colibactin gene directly attaches to the DNA strand with Spyro bicyclic structure, which specifies the significance of *E. coli* in the context of carcinogenesis. Further, the pks-positive *E. coli* was first extracted from the inflammatory disease [38,39]. This research leads to the fact that there is a strong association between inflammatory diseases and CRC. In addition, earlier research suggested that enteropathogenic *E. coli* facilitates the growth of cancer cells by inducing macrophage inhibitory cytokine 1, activating the transformation of growth factor-activated kinase 1, activating RhoA GTPase following pathogen infection, and maintaining COX-2 expression [40,41]. Further, it has also been observed, that when *E. coli* is 3 co-cultured with Caco-2 cells, the genes, associated with the oxidative stress were articulated, showing a defending reaction that can be due to microenvironment alteration in the system [42]. Besides, many other microorganisms which can contribute to carcinogenesis involve *H. pylori*, *S. bovis,* and *clostridium species*[15]. However, changes in gut microbiota can also initiate cytokine imbalance. From the TH-17 cell, the IL-17 group is closely linked to CRC. In the early stages, IL-17A, IL17F, and IL-22 are found to promote tumor formation associated with CRC. In several rat studies, IL-17C is identified to be needed in the development of CRC in gene knockdown. The remaining mechanism affects epithelial cells by triggering BCL-xL and BCL-2 expression [43]. Further findings demonstrate the progression of CRC through the activation of the EGFR-MAPK pathway [44]. In colon fermentation high level of alcohol is transformed into acetaldehyde, but this can be prevented by the use of antibiotics [45]. The research proved that the microbial community by targeting the metabolites can upsurge the CRC progression. However, SCFA is lower in number in CRC individuals, but if the concentration is higher, it lowers the load of intracellular O_2, promotes epithelial metabolism, and protects the tight barrier function.

3. Microbial-metabolites and CRC

Carcinogenesis of CRC is a very complex mechanism, as it is influenced by various etiological lines of flow including environmental, microbial metabolites, and genetic factors. The gut microbiota produces and secrete a huge amount of microbial metabolites or toxic bioactive compounds, which cause the diseases. These bioactive compounds are derived from endogenous biomolecules, produced by gut microbiota and host, besides anaerobic fermentation of non-digestible dietary components, which ultimately pushed in the large intestine [46]. Some common metabolites produced by the gut microbiome are; low molecular weight volatile molecules, small peptides, biogenic amines, lipids, secondary bile products, simple sugars, terpenoids, glycolipids, oligosaccharides, organic acids, and glycolipids [47], which can control the inflammatory response of the host [48]. Scientific studies has revealed that these microbial metabolites affect the host's immunity and trigger the production of genotoxic virulence factors [20,21,49,50]. These microbial metabolites can translocate mucosal membranes more easily and modulate cancer lenience and progression as illustrated in Fig. 2. High levels of secondary bile acid derivatives through microbiota, specifically deoxycholic acid, have been associated with the progression of CRC [51]. Moreover, carcinogenesis is triggered through the depletion of probiotic metabolites, like acetate, butyrate, and propionate.

Current review mainly focuses to highlight the gut microbiota-related components responsible for CRC carcinogenesis, potential translation, and modulation to clinical studies. Further, different bacterial species, their metabolites responsible for the progression of CRC, and possible mechanism is given in Table 1.

4. Short-chain fatty acids

Short-chain fatty acids (SCFAs) are generally considered/categorized as immune-modulatory components and recognized as important metabolites in gut physiology including immunity modulation and sustaining mucosal homeostasis of the intestine. Indigestible carbohydrates are found in major concentrations for microbial fermentation in the colon and SCFAs are the noticeable end products of gut fermentation, including butyric, propionic, and acetic acid. However, their concentration mainly dependent on the gut microbial composition, the metabolic flux of SCFAs from host and microbiota, intestinal transit time, and fiber content in the diet (as a prebiotics source) [46,70]. These microbial metabolites are considered as primary source of energy for gut diversity and IECs. Besides serving as a substrate for energy generation, SCFAs also perform a variety of regulatory roles and have effects on host immunity and physiology.

SCFAs have anti-inflammatory effects and provide nutrients and vitality for energy expenditure to its host by attachment with G protein-coupled receptors 43 (GPR43) [71] that appear in immunity cells including macrophages [72]. Further, SCFAs also help in maintaining homeostasis between intestinal immunity and inflammation [73]. Among the various SCFA, butyrate significantly antagonizes inflammation in the colon, and *Clostridia*, *Firmicutes*, *Ruminococcaceae,* and *Eubacterium* are the main producers [74]. Moreover, butyrate exhibits an anti-inflammatory response through the inhibition of NF-kB [75], which serves as a transcription factor for maintaining innate immunity and inflammation. Similarly, it inhibits the signaling mechanism of interferon-gamma (IFN-g) to prevent ongoing inflammation [76], in the colon by controlling peroxisome proliferator-activated receptor-g (PPARg) [75]. In many clinical trials, a decrease in butyrate-generating bacterial species and a similar decline in fecal butyrate have been associated with

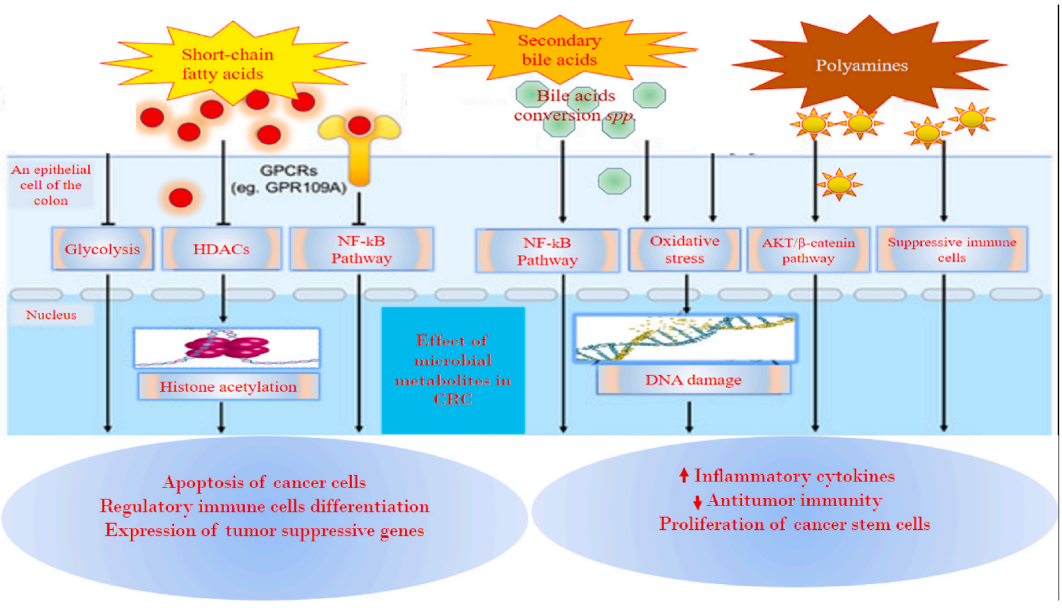

Fig. 2. Most common microbial metabolites in CRC.

Table 1
Bacterial metabolite and their mechanism of action.

Bacteria	Metabolites	Possible mechanism	Bacterial concentration	Ref.
Faecalibaculum rodentium Holdemanella biformis	SCFAs	Inhibiting calcineurin/NFATc3 activation	Decreased	[52]
Bifidobacterium Streptococcus thermophilus	Bile acids hydrolase β-galactosidase	Hippo signal	Decreased	[53–55]
Butyricicoccus pullicaecorum Clostridium butyricum	Butyrate	SCFAs metabolism	Decreased	[56,57]
Lacto bacillus	lactic acid, Bile acid hydrolase	Wnt/b-catenin, Bile acid metabolism	Decreased	[53,58]
Peptostreptococcus anaerobius	TLR2 and TLR4	PI3K-Akt–NF–kB signaling	Increased	[59,60]
Streptococcus gallolyticus	Gallocin	Wnt/b-catenin	Increased	[61]
Enterococcus faecalis	ROS	Wnt/b-catenin, Formation of bacterial biofilms, DNA damage	Increased	[61–63]
Enterotoxigenic Bacteroides fragilis	BFT	IL-17R, NF-kB, Wnt/b-catenin, Stat3 signaling	Increased	[64]
Escherichia coli	Colibactin	DNA damage	Increased	[65–68]
Fusobacterium nucleatum	Adhesin Fap2/SCFAs, FadA, Formyl methionyl	Wnt/b-catenin signaling	Increased	[69]
Porphyromonas spp	Down-regulation of caspase 3 activity	Apoptosis disruption	–	[31,32]

colon carcinogenesis, highlighting that SCFAs may have anti-carcinogenic activity [77]. Butyrate counters the progression of CRC by regulating the translation of different genes involved in tumor suppression, especially preventing the function of HDACs. It also affects some other alternate reactions, such as tumor cell metabolic reprogramming and stimulation of GPCR signaling mechanisms, that may lead to apoptosis of tumor cells and anti-inflammatory reactions [78]. Butyrate reduces the possibilities of CRC progression through some modifications in tumor metabolism besides epigenetic reforms. It is concluded from recent catharsis that SCFAs are considered to have a preventive effect on CRC. however, further research is still required to deeply inquire into possible interactions among the gut microbiota and colon epithelium during carcinogenesis.

5. Long-chain fatty acids

Long-chain fatty acids (LCFAs) are considered essential components and earned from the edible foodstuff because the mammalian body cannot synthesize and metabolize them to construct mediators of various bioactive lipids which are involved in the regulation of inflammation by the reduction of inflammatory cytokines [79]. Commensal bacterial species like *Enterococcus faecalis*, *Bacillus thetaiotaomicron*, and *Lactobacillus plantarum* are responsible for various conjugated linoleic acids, oxygenated fatty acids, and hydroxy fatty acids production [80]. Furthermore, LCFAs especially found in vegetable oils include margaric, palmitic, arachidic, stearic, and behemic acids ranging from 16 to 22 carbon, among them stearate and palmitate have an important role in CRC carcinogenesis. It has been reported in different studies that LCFAs exhibit anti-neoplastic activity but further research is also required to understand the relationship between CRC and LCFAs [81].

6. Tryptophan

The amino acid digestion by the intestinal microbiota produces a large number of different bioactive metabolites, Tryptophan (essential amino acid) is more prominent among them, converted into indole through the action of tryptophanase (bacterial enzyme) [82]. Tryptophan is generally found in routine-based protein diets and is most common in fish, egg, cheese, and meat. Rothhammer et al. [83], reported the role of dietary tryptophan in the inflammatory process. After the utilization of such foodstuff, intestinal microbiota like *Lactobacillus, and Clostridium sporogenes* transform tryptophan into a variety of indole derivatives including indole-3-acetic acid, indoxyl-3-sulfate, indole-3-aldehyde and indole-3-propionic acid which serves as ligands for most common aryl hydrocarbon receptor (AHR), which on activation increases the production of IL-22 which involve in protection against CRC-induced inflammation. Similarly, different indole derivative's bioactive compounds reduce the damaging LPS-mediated hepatic inflammation by modifying the NLRP3 pathway [84]. In the investigational autoimmune encephalomyelitis on a model of manifold sclerosis, the indole metabolites reduced the inflammation of central nervous system by diminishing the astrocyte's pathogenic activity [85]. Moreover, metabolites of tryptophan apart from suppressing inflammation also maintain the abdominal wall lining, coupled with intestinal probiotics, slowing the progression of CRC. It is reported in different research that the metabolism of tryptophan plays a key role in the recession of CRC carcinogenesis [86,87].

7. Taurine

Taurine is a non-proteinogenic amino sulfonic acid whose concentration generally fluctuates through the bacterial de-conjugation, and production of a higher level of taurine inside the lumen [88], which promotes the signaling pathway of the NLRP6 inflammasome,

thus decreasing the inflammatory bowel disease [89]. Taurine also serves as a protective compound against CRC and diabetes. In different cohorts, metabolomic studies highlighted the association between the dysfunction of bile acid and CRC. Multi-omics research reported that patients with a high risk of CRC had increased fecal levels of cancer-promoting Deoxycholic acid (DCA) and high concentrations of 7-dehydroxylating bacteria [90]. Yachida et al. [91], reported in their study that different bile acids such as DCA were raised in patients having various intra-mucosal carcinomas and polypoid adenomas. In CRC-affected cells, mitochondrial oxidative stress induced by DCA will initiate NF-Kβ signaling, promoting tumor progression and inhibiting apoptosis [92].

In contrast to DCA, Ursodeoxycholic acid (UDCA) and tauroursodeoxycholic acid (TUDCA) are associated with the inhibition of colon tumor progression. UDCA blocks the cell cycle in tumor cells that appear in the colon and reduces the growth of colon cancer cells through the regulation of reactive oxygen species (ROS) production inside the cell [93].

8. Polyamines

Polyamines are well-known for their involvement in the initiation of inflammatory bowel diseases like colitis [89,94,95]. Spermidine (polyamine metabolite), produced by gut microbiota, host, or from the diet, acts in the NLRP6 inflammasome pathway, thus affecting microbial composition. It is produced by amino acid decarboxylation that suppresses NLRP6 inflammasome association and reduces the concentration of IL-18 in the colon. Any abnormality in polyamine synthesis could be a cause of CRC development. Polyamines-induced oxidative stress in cells may progress into DNA damage that causes CRC in a mouse model [96]. Polyamines are also responsible for carcinogenic signaling, which subsequently increase spermine and spermidine levels, and similarly, expression of catenin both are involved in tumor metastasis and cell proliferation [97].

9. Genotoxins

Another mechanism of carcinogenesis associated with the gut microbiota is the production of toxic compounds that damage the DNA also known as genotoxicity. Bacteria produce two well-characterized toxins, colibactin and Cytolethal distending toxin (CDT) and the most common CDT-producing enteric microbes are *E. Faecalis, B. fragilis, Enterobacteriaceae* spp., *Escherichia* spp., and *Campylobacter*. They secrete CDT by deoxyribonuclease activity and damage the double-strand DNA that contributes to carcinogenesis [33,36,98]. Moreover, excessive reactive oxygen species (ROSs) production is also linked with DNA impairment and genomic instability [99,100]. Deactivation and binding of these toxins can have prophylactic and therapeutic effects in CRC patients. A study conducted on a rat model has shown that small inhibitors target colibactin secreted from Enterobacteriaceae and some *Escherichia coli* spp. can minimize the progression of CRC [101].

10. Metabolism of nutrients

In the gastrointestinal tract, metabolism is the most important part in which microorganisms and the host environment interact with each other. The nutrients derived from diet can be metabolized by microorganisms, involving undigested carbohydrates like fructo oligosaccharides and galacto oligosaccharides, along with bile acids from the host. This leads to the study of Doll and Peto [102], that diet is the major factor in cancer progression, and about 35 % of cancers are reported due to dietary alterations and poor life style. Recent study reported that 38.3 % cancers are due to low nutrient diet and consumption of dehulled cereals grains with less dietary fiber contents, processed meats and insufficient consumption of dairy products [103]. There is a strong evidence that CRC can be due to processed and red meat consumption [78,104]. Various toxic chemicals have been identified, involving pro-carcinogenic components like hydrogen sulfide and N-nitroso components which are produced as a result of microbial metabolism [105]. As per research in the rat model, the microbial community of the gut produced heme-induced epithelial hyper-proliferation by disrupting the mucous barrier function [106]. By metabolism of dietary compounds, an important class of metabolites is produced known as short-chain fatty acids (like butyrate and propionate). The short-chain fatty acids in the colon are produced by microbial fermentation which is carried out when non-digestible carbohydrates like fiber and resistant starch are consumed in the diet, as a function of anti-inflammation [107], butyrate inhibits the immune cells and deacetylases in colonocytes to control pro-inflammatory components like cytokines [108], and initiation of apoptotic bodies in the colorectal cancer cells [109]. Moreover, rat models of butyrate and propionates have been shown to have an anti-inflammatory effect by controlling T-cells [110,111]. It is also observed that the subjects consume diet with low SCFAs are prone to the risk of CRC, as observed in the United States [112], and in people with ulcerative colitis [113] or advanced colorectal adenoma [77]. However, by studying the tumor-lowering effect of these metabolites [114], the harmful effects of butyrate have been stated which can accelerate the aberrant proliferation of epithelial cells in vitro [115]. This can be due to its different effects on the different types of the host, the indigenous milieu of metabolism (e.g. Warburg effect), and the presence of other correlating metabolites [116]. Closely associated with gut microbiota and diet, bile acids show the major and important class of metabolites. These bile acids are steroid acids that are produced via the liver and transformed into other forms by bacterial systems in the intestines [117]. Furthermore, people who consume high-fat diet are at the greater risk of CRC [118]. In a study, based on exposure to high amounts of bile acid metabolites in rat's colon by diversion surgery, a greater content of colonic tumors was seen when exposed to the carcinogen azoxymethane [118,119]. Several studies supported the view that, bile acids can accelerate tumor production in the colon. Moreover, oxidative DNA damage can be initiated by deoxycholic acid [120] and enhance tumor formation [121]. Besides this, the gut microbial community produces various metabolites that are important for human physiology. Most importantly, these metabolites can be controlled individually or by the manipulation of microorganisms, enhancing the risk of CRC.

11. Diet

Diet is the most important factor which can affect the composition of gut microbiota [122,123]. People from different regions of the world by consuming different diets have a variable composition of gut microbiota, which is associated with a variable risk of colorectal cancer. In the diet of rural Africans with African Americans who consume different diets, a lower occurrence of *Bacteroides* rural Africans as compared to African Americans has been noticed. As rural Americans consume more diets based on low fiber and high fat and animal protein [112], there has been much concern over the implementation of dietary interventions in colorectal cancer development and its acceleration by the gut microbiota. Several researchers in their studies show that, by switching diets of Americans low fiber and high protein and fat diets alter the gut microbiome, and decrease the inflammation and cell propagation markers in colon tissue samples [124]. Besides this, altering the diets of rural Africans with African Americans resulted in an increased risk of mucosal cancer. Several studies have shown that dietary fiber is the major factor in determining the risk of CRC by affecting the microbial community its composition and diversity [125,126]. Fiber can be consumed in a prebiotic form and from fruits and vegetables. Prebiotics act as a substrate which when utilized by a microbiota imposes a health benefit to the host [127]. Dietary fiber including galacto-oligosaccharides and fructans can transform the microorganism composition which can increase the content of *Lactobacillus* and *Bifidobacterium* spp. These microorganisms by fermentation increase the fecal butyrate concentration in human subjects [128]. Furthermore, a xenobiotic rat study confirmed the tumor-reducing effect of dietary fiber in CRC in a butyrate and microbiome-dependent manner [129]. In several clinical studies, it has been proved that for patients with a history of CRC, fiber supplementation has a preventive effect on recurrent adenomas [130–132]. The variable properties of SCFAs at the cellular level could lead to a discrepancy in the findings [114]. Various studies support that red and processed meat can be the major cause of the increased risk of CRC [78,104]. A study based on an organized review of 13 comprehensive studies confirms that the incidence of CRC propagates linearly through the consumption of processed and red meat when 140 g is consumed in a day.

International Agency for Research on Cancer has identified processed meat as a possible class 1 carcinogen and red meat as a probable class 2A carcinogen [133] and advised to reduce the consumption of meat and meat-based products. Based on this recommendation, there has been observed a 20 % decrease in CRC risk by taking a vegetarian diet as compared to non-vegetarians [134]. Moreover, digestive tract physiology can be intensely affected by fat intake, involving the composition of the gut microbiota as observed from the rat models [135–137]. Hepatic secretion of bile acids can be triggered by the fat to ease the process of fat emulsification, which can further elevate the enterohepatic circulation of the bile acids involving deoxycholic acid. These deoxycholic acids accelerated the mucosal tumor formation in the intestine of the rat model [120,138]. However, the association between CRC and fat consumption has resulted in discordant findings [139,140]. Many studies have shown that the reduced consumption of fat does not describe the lower risk for colorectal neoplasia, either with or without high fiber content [141,142].

Diet is a major contributor to reshaping the gut ecology and greatly influences the initiation and progression of the disease. Several pieces of research have shown that unhealthy eating and lifestyle, as well as malnutrition, account for 30–40 % of cancers [143]. Dietary components not only alter the gut microbiota but also change the homeostasis and immune responses of the gut. Moreover, a study confirmed the association between microbes that affected the tumor and low/high-fat consumption in mice [144].

12. Genomic and epigenomic modifications

In the pathogenesis of CRC, two factors are usually considered i.e. direct interaction of microbiota with CRC and specific gene mutations. The most studied genotoxin-producing bacteria (pks + *E. coli*) produce colibactin which further causes cell arrest, DNA damage, and chromosomal abnormalities. Converging lines of evidence suggest the action mechanism of colibactin, when interacting with cells, causes intra-strand cross-linking in DNA, and this cross-linking leads to ATR-dependent replication stress response [36,145,146]. ATR phosphorylates many replication proteins and considered as master regulator in DNA damage [147]. A study conducted by Dejea et al. [148], reported that ETBF and pks + *E. coli* synergistically take part in DNA damage and tumor formation in mouse models. In another study, entero-pathogenic *E-coli* (EPEC) was found to inhibit the DNA mismatch repair proteins in host cells, and this inhibition leads to an enhanced mutation frequency [37].

Chromosomal instability in host epithelial cells also contributes to the formation of tumors and is a part of all cancers [149–151]. In order to understand the role of bacteria in chromosomal instability, immune cells (macrophages) were used as an intermediary. A group of researchers cultured the macrophages and *E. faecalis* together and cultured cells were then exposed to CEC. Results of the study showed that aneuploidy and chromosomal translocation were increased which is an indication of chromosomal instability. Further, CECs were injected into mice lacking immune cells, and found that only CEC-injected mice developed tumoral masses. Gene expression of masses revealed that the expression of at least 3 driver genes was altered [152].

13. DNA methylation

In DNA methylation, the methyl group is attached to the 5th carbon of cytosine residue and further converted into 5-methyl cytosine by using S-adenosyl-methionine (SAM) as a methyl donor [153,154]. Folic acid, a vitamin B9, is one of the most essential components to complete the process of DNA methylation and its deficiency leads to DNA hypo-methylation which is also a common cause of CRC. Probiotics especially consisting of *Bifidobacterium* and *lactobacillus* bacteria confer various health benefits including the production of folic acid and vitamin B9. Previous studies showed that the administration of *Bifidobacterium* increased the amount of folate in feces [154–157]. Further, pathogenic microbes, such as *H. pylori* are responsible for gastritis and cause epigenetic modifications. Upon comparison between normal individuals and gastritis patients, it was found that DNA hyper-methylation is associated

with gastritis. Further studies supports the view that, *F. nucleatum* strongly contributes in the epigenetic changes and leads towards the progression of tumor [158–161].

Besides DNA methylation, histone modification can also be the leading cause of carcinogenesis [153,162]. SCFAs are bacterial metabolites produced as the result of the fermentation of carbohydrates and proteins in the colon [163,164]. Butyrate is a SCFA, involved in the regulation of genes as well as natural cell death and cell cycle regulation, and also induces hyper-acetylation by inhibiting histone deacetylase and altering the regulatory cell cycle gene expressions in intestinal cells [165,166]. It suppresses NF-kB by triggering the formation of ROSs in epithelial cells [167]. Moreover, *Bacteroides* stimulate inflammatory signaling and inhibit NF-kB by an inhibition factor (IKB) [168]. A study reported that *L. monocytogens* infection is associated with the deacetylation of histones [169].

14. Bio-markers and CRC

CRC is a complex disease having underlined abnormalities in genetics and epigenetic. Genitical factor majorly include APC, K-RAS & P-53 results in Heterogenic neoplastic mutations. However, epigenetical factors include abnormal DNA methylation, abnormal RNA transcription & translation, extra cellular vesicles. These all have their subtypes according to their particular genomic location. CpG Island methylator phenotypes. They tend to have very high frequency of Gene methylation results as high Intra-tumor heterogeneity (ITH). Census molecular subtype Invading multi-systems simultaneously. To study ITH intra tumor Heterogeneity currently standardized approach is whole Exome sequencing, which needs multiple tissue biopsies and have their limitations and cautions regarding multiple samples, sample safety and other like these. However, advanced technique like liquid biopsies which are more effective, lass invasive & provide abundant genetic materials collected from specimen including blood, saliva by passing the limitations of tissue biopsy.

Noncoding RNA including small nuclear RNAs (snRNAs) and long non-coding RNAs (lncRNAs), are transcribed by DNA but not translated into amino acids or proteins. snRNAs are the most studied RNAs such as miRNA. miRNAs are around 22 nucleotides long and encoded by approximately 1 % genome [170]. At the transcriptional level, miRNA regulates various gene expressions and thus actively participates in colon carcinoma. The dysregulation of miRNA gives a deep insight into understanding the microenvironment of tumors and CRC [171]. A report suggested that several miRNAs are linked with CRC (Let-7, miR-17-19 cluster, miR-21, miR-145, miR-221, and miR-143), while other studies supports the view that the expressions of (miR-17, miR-20, miR 25, miR-31, miR-92, miR-93, miR-133b, miR-135a, miR-183, miR-203, and miR-223) upregulated in CRC (miR-16, miR-26b, miR-192, miR-145, let-7a, miR-143, miR-215, and miR-191) are downregulated in CRC. However, some miRNAs are considered as diagnostic markers (miR-106a, miR-133a, miR-139, miR-143, miR-145, and miR-484–5p) while some are potential biomarkers (miR-125b, miR125a, miR-143 miR-30a-3p, and miR-145) [172–176]. Many studies reported that diet plays a vital role in the regulation of miRNA. For instance, butyrate may be regulated by the expression of Let-7, miR-25-106b, miR-17-92a, and miR-18-106a in CRC. Genetic and environmental factors may cause CRC, but microbiota is still a major contributor in the pathogenesis [166,177]. RNA biomarkers found in different stages of CRC are given in Table 2.

Lnc-RNA; Long strand non-coding RNA consist of more then 200 nucleotides in length but lack the capability of protein translation. These molecules tend to play important role in both physiological and pathological processes ongoing in a cell such as genetic expression, gene regulation, RNA interaction, RNA protein interaction, structural importance, physiologic signaling pathways, cellular differentiation, & cell development.

Census molecular subtype.

15. Census molecular subtype

The Census molecular subtype (CMS) of CRC provide framework for building molecular architecture of this heterogeneous disease.

1. Cms1; Immune system involvement as shown High microstallite instability. Lnc-RNA & HOTAIR is directly responsible for oncogenic activity.
2. Cms2; Canonical: chromosomal instability.
3. Cms3; Metabolic: metabolic dysregulation & K-Ras mutation
4. Cms4; Mesenchymal: Stromal invasion related to cell growth & migration.

Table 2
RNA biomarkers in different stages of CRC.

RNA (Biomarkers)	Regulation in CRC	Stage	Reference
mRNA (PACS1,TDP2,HPGD)	Up and down regulated expression	Prognosis	[178]
mRNA (CXCL3)	Up regulated	Prognosis, diagnosis	[179]
miRNA-1290	Up regulated	prognosis	[180]
miRNA-21	Up regulated	prognosis	[181]
miRNA-98	Up regulated	–	[182,183]
mRNA (SOX9)	Up regulated	diagnosis	[184]

The discussion above is still difficult to isolate these biomarkers solely because of lack of standards and technological limitations. Further research is required to explore more about the nature of biomarkers and their genomic activities.

16. Intestinal epithelia, gut microbiota, and CRC

Intestinal epithelia are considered a complex region having different phyla of microorganisms. The gut microbiota is mainly composed of bacterial diversity, archaea, fungi, and different species of protozoa. *Firmicutes, Bacteroidetes, Actinobacteria*, and *Proteobacteria* are the most prominent phyla found in the human intestine. An abrupt change in food or environmental conditions can switch the beneficial microflora into pathogenic by modifying the production of their metabolites, termed dysbiosis, which plays a critical role in the progression of colorectal cancer [185–187]. Dysbiosis in gut microflora has a greater chance of producing dysplasia, inflammation, and ultimately CRC [188,189]. Pathogenic symbiotic bacterial species also initiate localized inflammation in common tissues of the colon, where they stimulate the genotoxicity in epithelial cells of the intestine and strengthen the progression of CRC [190]. Many studies reveal the difference in microbiota associated with the mucosa in CRC sufferers and healthy subjects. Researchers also observed that tumorous tissues contain lesser microbial diversity as compared to normal tissues [191,192]. In the last few years, increasing evidence from different experiments has described the fundamental relationship between the dysbiosis of intestinal microbiota and CRC development. Further, dominating phyla of intestinal microbiota such as *enterotoxigenic Bacteroides fragilis, Fusobacterium nucleatum,* and *Pepto streptococcus anaerobius* play an important role in colorectal carcinogenesis through induction of tumor proliferation [193,194], enhancing inflammation [195], and triggering DNA damage [20] and provide protection to tumor from immune attack [194]. Emerging evidence has also proposed, that dysbiosis may participate in CRC development through the interaction of microbial metabolites and genotoxic virulence factors with the immune system of the host [20,21,49,50]. CRC patients exhibit significant variations in some bacterial groups and have a potential effect on the immune response of mucosa/submucosa in comparison to healthy individuals [196]. Particularly, CRC patients harbor higher levels of *Lactococus Fusobacterium nucleatum, Bacteroides fragilis, Enterococcaceae* or *Campylobacter, Enterococus faecalis, Peptostreptococus, Escherichia coli, Streptococcus gallolyticus,* and *Shigella* while low level of *Clostridium, Bifidobacterium, Faecalibacterium, Blautia* and *Roseburia* [197]. There are two common mechanisms to investigate the microbiota in cancerous tissue of the intestine. One is to determine the effect of such particular bacterial species in lab-based animal subjects and other especially healthy and CRC patients, to explore the difference in gut microflora among them [12].

Intestinal epithelial cells (IECs) construct a barrier that isolates the gut microflora from the internal tissue of the intestine and the main function of this barrier is to provide protection to the gut from an attack of symbiotic bacteria, ensure the ingestion of nutrients from the lumen and to sustain the homeostasis among the environment and gut. The intestinal layer is composed of the upper mass of glycoprotein mucus membrane and tight junctions among epithelial cells [198]. The other important roles of the intestinal membrane are also determined by gut microflora [199]. The concentration of lipopolysaccharides (LPSs) was significantly high in intestinal carcinogenesis tissue, indicating CRC chronic inflammation and metastasis. Inflammation causes the epithelial cells incapable of constructing an effective surface barrier against bacteria and all their metabolites. Hence, bacteria approach readily due to weak membrane barrier and consequently induce oncogenesis by stimulating inflammation [200].

17. Immunity involved in CRC

The digestive tract provides the stage for the exposure between the microbiota and immune cells. GI affected with chronic inflammation is considered to be the major source of the development of colorectal cancer. However, patients with gut inflammation are at high risk of CRC as compared to other populations [7]. Previous analysis has shown that patients suffering from ulcerative colitis have an 18.4 % while those patients affected with Crohn's disease have an 8.3 % risk of CRC development. However, the risk ratio can be varied depending on the population, hospital setting, and clinical practices [201–203]. The gut microbes have the potential to trigger inflammation in the digestive tract by suppressing the components of the immune system. Fecal contamination from subjects suffering from colorectal cancer and transferred to sterilized carcinogen-fed rats leads to enhanced inflammatory markers gene expression and tissue inflammation process. Gut microbiota initiates the chemotactic factors like CXCL9 and CXCL10 for the development of cytotoxic T lymphocytes, type 1 T helper cells (TH1), and CCL17 and CCL20 for IL-17-producing TH cells, which can apprentice T cells into tumors [204]. However, as far as single bacterial *spp.* is concerned, it has been observed that *F. nucleatum* can cause myeloid cell infiltration in tumors by activating the NF-kB pathway, producing an environment for the propagation of inflammation which is conducive for the progression of colorectal neoplasia in APC Min mice (model for CRC trials) [205].

Colorectal cancer patients commonly contain an enterotoxin bacterial strain known as *B. fragilis* [206], which can activate inflammatory cascade including signal transducer IL-17, which is a transcription 3 activator and NF-kB signaling in colon epithelial cells via its virulence factor (*B. fragilis* toxin) [29]. These series of pathways can initiate CXC chemokines in APC Min mice to recruit polymorphonuclear immature myeloid cells, by developing a pro-inflammatory milieu, especially in the distal colon [195]. An important marker for cancer-accelerating activities of other microbiota is inflammation, involving CRC-enriched genotoxic polyketide synthase (pks) + *E. coli* [207–209], *A. finegoldii* [210] and *E. faecalis* [211]. Pattern recognition receptors (PRRs) act as an interface in the microbial community and the immune system of the host. By identifying microbial antigens, PRRs by a downstream cascade of signaling molecules can activate the immune system of the gastrointestinal tract. Many of these PRRs have been linked in colitis-linked carcinogenesis in rat models, involving Toll-like receptors (TLRs) [212], receptors like nucleotide-binding oligomerization [213], the RIG-I-like receptors [214] and melanoma 2-like receptors [215]. Furthermore, the TLR4 signaling pathway can be triggered by the *F. nucleatum* to accelerate tumor development in the rat model [193,216]. However, another CRC-enriched strain called

Peptostreptococcus anaerobius can accelerate carcinogenesis in rat models by triggering TLR2 and TLR4 pathways [217].

18. Innate immunity

Natural killer (NK) cells perform a key role in the immunity of cancer. They not only protect tumor initiation but also control its progression and metastasis [218–220]. Generally, NK cells bear two types of receptors which include the activating Natural Killer Group 2D (NKG2D) receptor and killer inhibitory receptors (KIR). The receptor NKG2D can bind various overexpressed activating ligands on cancer cells while KIR identifies molecules of major histocompatibility (MHC) class I consequently, NK cells may also be activated through the reduced appearance of (MHC) class I on cancer cells. Both these mechanisms are involved in the activation of NK cells and encounter tumor cells. Additionally, NK cells may also possess a cytotoxic effect on tumor cells through mechanisms like secretion of cytokines, IFNγ, and antibody-dependent cell-mediated cytotoxicity (ADCC) [221,222].

In CRC patients, a good prognosis is associated with high intra-tumoral infiltration of NK cells, and a direct correlation was observed between better outcomes and NK cell infiltrates [218,223]. Specifically, NK cells might be involved in the defense against cancer-initiating cells (CICs) [224]. CICs have a crucial role in the recurrence of tumors because of slow growth patterns and resistance to radiation and anti-cancer drugs. Recent studies reported that CICs are highly sensitive to NK cells since they are overexpressed with activating ligands such as NKP44 and NKP30 while low-level expression of MHC class I proteins [225].

Natural killer T (NKT) cells possess the features of T cells and NK cells and identify glycolipid antigens such as α-galactosylceramide expressed by CD1d. On activation, these cells secrete large volumes of pro-inflammatory cytokines, and then effector molecules participate in cell death (TRAIL, perforin, Fas-L). Increased infiltration of NKT cells in CRC is linked with improved prognosis [226].

Human Gamma delta (γδ) T cells bear one γ chain and one δ chain and form a receptor for antigens. These receptors tend to identify a wide range of antigens generally in non-MHC-restricted like phosphorylated metabolites produced by tumor cells and heat shock proteins. (γδ) T cells have been explored as a powerful cytotoxic against cancer cells in CRC [227]. Tumor-infiltrated macrophages (TIM) have two main subtypes with various roles against tumors [228]. M1 TIM generally participates in innate immunity because of its ability to encounter altered cells and secrete pro-inflammatory cytokines like TNFα, IL-6, IL-12, and IL-23 consequently triggering an adaptive immune response by the over-expression of MHC proteins and related molecules. These macrophages also damage cancer cells attached to antibodies as they present a receptor for antibody constant fragments (ADCC).

19. Adaptive immunity

Adaptive immunity is mainly responsible for tumor protection, particularly αβ T cells [229–231]. The antigen-presenting cells (APCs) specifically dendritic cells (DCs), detain, damage, and express tumor fragments on CD4 T cells by MHC class II or on CD8 T cells via MHC class I [232–234]. Stimulation of T cells normally requires three signals [1]: identification of antigenic proteins expressed by the APCs [2]; stimulation of costimulatory proteins like CD40/CD40L, CD80/CD28, and [3] secretion of cytokines IFNγ, IL-1, IL-2, IL-6, and IL-12. Stimulated CD8 cells can identify and lyse tumor cells while CD4 T cells have the potential to modulate the antitumor immunity. Stimulated CD8 cells can identify and lyse tumor cells while CD4 T-cells have the potential to modulate antitumor immunity. These cells further differentiate into various subgroups of immune cells: The Th1 subset of CD8 cells secrete different cytokines such as IFNγ or IL-2 that enhance the antitumor response, on the other side, Th2 promotes the growth of cancer cells [235,236]. The subset Th17 produces a large volume of IL-17 but its role is still not clear in cancer response. Regulatory T cells (Tregs), a lineage of CD4 T cells, have the expression of proteins Foxp3 and CD25 to inhibit the response against tumor growth and present a diverse mechanism where the tumor cells may escape from the immune response.

20. Conclusion

CRC ranks third in incidence and second in mortality among all cancers according to census bureaus of different origins. In the past few years, much focus has been given to gut microbiota concerning CRC researchers. The gut contains a diversity of microorganisms that interact directly with the intestinal cells of the host, and affect the innate/adaptive immunity and metabolome in the GI tract. Many associated studies depicted the role of gut microbiota in CRC via several mechanisms. Although genetics, epigenetic factors, and other environmental factors are involved in the carcinogens of CRC, individual microorganisms play a vital role in CRC. Gut microflora can cause modifications in DNA, methylation patterns, and histone structures of the gut epithelial cells, which further lead to inflammation and cancer. Moreover, driver and passenger bacteria actively participate in the prognosis of CRC. It is worthy to deeply interrogate the exposure between gut microbiota and body cells to prevent this life-threatening disease. Gut modulation and implementation of research catharsis could be promising strategies to enhance treatment efficacy and reduce adverse aftereffects of CRC therapies, which can significantly lower the financial burden on the health and medical departments.

Future perspectives

CRC is considered as 3rd most diagnosed cancer among others, and its progression is due to multiple etiological factors. In the current review, we concluded that CRC is typically an amulgum of several abnormalities and multi factor involved disease, due to which various abnormalities ocuur both at genomic and epigenomic level. In order to understand the deep insights to cure from the CRC, more studies should be conducted to understand the biomarkers responsible for CRC progression, as limited data is available on epigenetic factors involed in CRC. Further, we should alter our dietary pattern and rely on minimal processed whole food compared to

Western diet and facilitate the colon with metabolite activity in tumor inhibition. With this we can also reduce the burden of the health departments which has been raised drastically to a great extent in the last decades.

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