

# Gut microbiota-metabolism axis in digestive tumors: Emerging targets for novel therapies (Review)

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Received November 16, 2025; Accepted January 20, 2026

DOI: 10.3892/etm.2026.13108

**Abstract.** Digestive tumors, including malignancies associated with the gastrointestinal tract, represent a notable global health burden. Advances in microbiome research have highlighted that the gut microbiota-metabolism axis and its associated metabolic derivatives are key modulators of tumorigenesis, immune evasion and treatment responses. The present review aimed to comprehensively discuss how key microbial metabolites, such as polyamines, short-chain fatty acids, bile acids and other compounds reshape the tumor microenvironment, modulate cellular signaling and affect immune responses. By integrating insights from microbiology, immunology, oncology and metabolic changes in digestive tumors, evidence suggests that the microbiota contributes to cancer progression through mechanisms involving epigenetic regulation, metabolic reprogramming, genotoxicity and production of inflammatory mediators. Beneficial bacteria, such as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, exhibit antitumor activity, whereas pathogenic species, such as *Helicobacter pylori* and *Fusobacterium nucleatum*, are associated with oncogenic properties. Based on a literature search, microbiota-targeted therapy seems to be promising for the management of pathological

conditions, especially digestive diseases. Further investigations into the pharmaceutical application of microbiota through prebiotics, probiotics and metabolite-targeted interventions, along with multi-omics integration and microbiome-host interactome validation, would be promising for improving personalized medicine and precision oncology.

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## 1. Introduction

Digestive tumors are a series of malignancies affecting the gastrointestinal tract and associated tissues, including the esophagus, stomach, liver, pancreas, colon, rectum and biliary ducts (1). These malignancies, especially colorectal, gastric and hepatocellular cancers (HCC), account for a substantial proportion of cancer-related mortality worldwide. According to the Global Cancer Statistics, ~4.7 million new cases and >3.2 million reported mortalities were associated with digestive tumors in 2022. Among them, the most frequent types of digestive malignancies were colorectal cancer (CRC), which accounted for 1.9 million new cases with >900,000 mortalities annually, and gastric cancer, which accounted for ~1.1 million new cases and >800,000 mortalities annually (2). Gastric cancer is more frequent in Eastern Asian countries, such as Japan, South Korea and China (3). Genetic predisposition, environmental risk factors, infections, metabolic changes and microbial factors are markedly involved in the pathogenesis of these malignancies (1). Over the years, researchers have

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*Abbreviations:* AFB-1, aflatoxin-B1; *A. muciniphila*, *Akkermansia muciniphila*; CagA, cytotoxin-associated gene A; CRC, colorectal cancer; DCA, deoxycholic acid; *F. nucleatum*, *Fusobacterium nucleatum*; *F. prausnitzii*, *Faecalibacterium prausnitzii*; GPR, G-protein coupled receptors; *H. pylori*, *Helicobacter pylori*; HCC, hepatocellular carcinoma; HDAC, histone deacetylase; IAA, indole-3-acetic acid; IPA, indole-3-propionic acid; LCA, lithocholic acid; LPS, lipopolysaccharides; NF- $\kappa$ B, nuclear factor  $\kappa$ B; SCFA, short-chain fatty acids; TME, tumor microenvironment; TLR-4, Toll-like receptor 4

*Key words:* gut microbiota, digestive tumor, microbial dysbiosis, tumor microenvironment

focused on gut-microbial interactions, particularly regarding how dysbiosis influences host metabolic alterations and participates in tissue microenvironment changes, tumor development, progression and response to treatment (4-7). Within this framework, manipulation of the gut microbial metabolism axis represents a promising avenue for developing innovative therapeutic strategies for cancer management.

The human gastrointestinal tract harbors a complex and diverse microbial ecosystem composed of bacteria, archaea, fungi and viruses, known as the gut microbiota (8). This ecosystem has emerged as a fundamental regulator of human physiology in health and disease, particularly affecting metabolism, immunity and tissue homeostasis (9). It serves as a repository for numerous microorganisms that encode a complex pool of enzymes and facilitate the digestion of complex dietary components of the gut. In addition, gut microbiota can orchestrate the host metabolic functions, including fermentation of the dietary fibers, modulation of protein and amino acid metabolism, vitamin synthesis and bile acid transformation (10).

Disruption of the equilibrium between the host and microbiota, known as dysbiosis, is characterized by a decreased proportion of beneficial commensals and overrepresentation of pathogenic or proinflammatory species (6,7). This imbalance has been associated with a range of pathological consequences, including metabolic dysregulation, chronic inflammatory diseases, digestive tumors and even neurodegenerative complications (7). The gut microbiota-host metabolism axis produces various bioactive metabolites, such as amino acid derivatives, short-chain fatty acids (SCFAs), secondary bile acids and other microbial products. These compounds serve notable roles in immune cell activation, inflammation, cellular signaling and epigenetic modification (8,11). These microbial metabolites can potentially influence the tumor microenvironment (TME) by activating or suppressing tumor immune cells, checkpoint inhibitors and contributing to tumor immune escape, therapeutic response or resistance (12-14).

Due to the rapid expansion of research in this field, a comprehensive focus on how the gut microbiota-host interplay affects metabolic changes and their therapeutic implications for digestive tumors is essential. Through a multidisciplinary search approach, the present review aimed to integrate current knowledge, summarizing evidence on compositional changes in the gut microbiota across various digestive malignancies and providing detailed mechanistic insights into microbiota-based applications in oncology and targeted therapeutic strategies. The challenges in translating microbiome research into clinical practice are also addressed and emerging microbial-targeted interventions are discussed, focusing on the prospects of microbiome-based personalized medicine.

## 2. Search strategy, inclusion and exclusion criteria

The present narrative review was performed based on targeted literature searches spanning January 2000 to September 2025 across major online medical academic databases, including MEDLINE/PubMed ([https://www.nlm.nih.gov/medline/medline\\_home.html](https://www.nlm.nih.gov/medline/medline_home.html); <https://pubmed.ncbi.nlm.nih.gov/>), Scopus (<https://www.scopus.com/>), and Web of Science (<https://www.webofscience.com/>), supplemented with

manual screening of references from the included studies. The primary search syntax was combined using the Boolean operators (AND, OR and NOT), and included the following terms as keywords: ‘Gut microbiota’, ‘microbiome’, ‘digestive tumors’, ‘gastrointestinal cancer’, ‘hepatocellular carcinoma’, ‘pancreatic cancer’, ‘colorectal cancer’, ‘microbial metabolites’, ‘short-chain fatty acids’, ‘bile acids’, ‘polyamines’ and ‘tumor microenvironment’.

The included studies were English-written original research articles, review articles and meta-analyses in the field of the study. Studies were excluded if they addressed non-digestive malignancies or lacked substantial information on microbiota-metabolism related mechanisms. Due to the narrative design of the present review, formal systematic review procedures (such as protocol registration or risk-of-bias scoring) were not applied. Instead, emphasis was placed on mechanistic and clinically relevant studies to provide an integrative prospective.

## 3. Gut microbiota in digestive tumors: Current understanding

Distinct microbial signatures have been observed in various digestive tumors, and are often associated with disease stage, progression and treatment outcomes (15-17). These patterns suggest that the gut microbiota is not only effective in digestive biology but also in pathogenic status, serving as a driver, modulator and notable therapeutic target for personalized medicine (15,18). The following section details the specific composition of microbiota and their alterations in dysbiosis observed across major digestive malignancies.

## 4. Composition and dysbiosis of the gut microbiota in digestive tumors

Understanding the alterations in microbial composition across different digestive tumors can provide insights into cancer etiology and offer novel biomarkers and therapeutic targets (Fig. 1). Common features of dysbiosis in digestive tumors, such as pancreatic, liver, gastric and CRCs, substantially contribute to tumorigenesis through mechanisms such as genotoxicity, metabolic reprogramming, chronic inflammation and immune evasion (19,20).

**CRC.** The gut bacterial composition of colon tissue in healthy individuals is dominated by Firmicutes and Bacteroidetes, with a lower proportion of Proteobacteria, *Fusobacteria* and *Acinetobacter* (21,22). Dysbiosis in CRC is marked by the abundance of pathogenic species in the colon tissue, including *Bacteroides fragilis*, *Fusobacterium nucleatum* (*F. nucleatum*) and some strains of *Escherichia coli*. (*E. coli*), such as phylogroups B2 and A (23-26). These bacteria contribute to tumorigenesis by inducing chronic inflammation, promoting DNA damage and suppressing the antitumor immune responses in cancerous tissues. Additionally, the overrepresentation of species, such as *Peptostreptococcus* and *Parvimonas*, is frequently reported in the advanced stages of CRC (18,27,28). Furthermore, depletion of beneficial commensals, such as *Faecalibacterium prausnitzii* (*F. prausnitzii*), Lachnospiraceae and *Akkermansia muciniphila* (*A. muciniphila*), serving as the

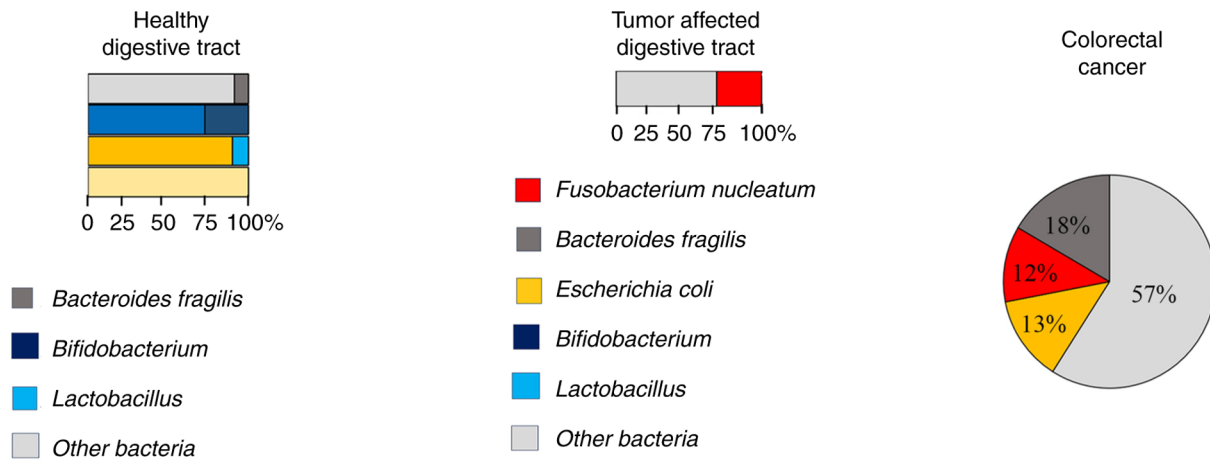


Figure 1. Comparative image of microbial composition shift across cancer specific and healthy individuals is depicted, where the key elements and their approximate frequencies are represented as pie and bar charts relatively associated with bacterial composition.

key regulators of intestinal barrier function, was associated with decreased production of anti-inflammatory SCFAs (26,29,30). Decreased production of SCFAs, such as butyrate, impedes the inhibitory effects of histone deacetylase (HDAC), thereby improving survival and increasing the proliferation of CRC cells through the Warburg effect (31-33). In addition, carcinogenic metabolites, such as secondary bile acids, N-nitroso compounds and hydrogen sulfide, induce genotoxic stress (caused by production of colibactin by pathogenic strains of *E. coli* that results in DNA double-strand breakage and somatic mutations) and epithelial transformation (34-37).

**Gastric cancer.** Compared with the intestine, the gastric microbiota has less diversity, owing to the acidic environment of the gastric tissue (38). Nevertheless, distinct microbial shifts have been reported in terms of gastric complications. *Helicobacter pylori* (*H. pylori*) induces chronic gastritis, epithelial damage and carcinogenesis in the gastric tissues (4,39). The bacterial load of *H. pylori* is markedly increased in >70% of patients with gastric adenocarcinoma (40). Beyond *H. pylori*, the other changes in the gastric microbiota, including increased *Lactobacillus reuteri* (25) and *Streptococcus*, have been identified in gastric atrophy and intestinal metaplasia (41).

In gastric cancer, *H. pylori* induces oncogenic signaling pathways through its virulence factors, including cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A gene. CagA activates nuclear factor κB (NF-κB) and STAT3, resulting in the overexpression of IL-8/cyclooxygenase-2 and gastric epithelial apoptosis (35,42,43). *H. pylori* also increases the production of reactive oxygen species, causes mutations in the tumor protein p53 gene and chromosomal instability (44). By contrast, decreased proportions of beneficial bacteria such as *Lactobacillus gasseri* and *Bifidobacterium* have been observed in patients with gastric cancer (45,46). *Lactobacillus gasseri* is needed for lactic acid production, gastric mucosa protection and maintenance of gastric acidity. Gastric bacteria dysbiosis results in overgrowth of opportunistic bacteria such as *Streptococcus*, which contributes to alteration in arginine metabolism and increased mucosal inflammation, activation of oncogenic signaling pathways, and increase in

the production of N-nitroso compounds in the gastric tissue, thereby promoting DNA damage and mutagenesis in gastric epithelial cells (4,47,48).

**Pancreatic cancer.** Contrary to traditional beliefs, the pancreas is not a completely sterile organ (49). Previous studies have demonstrated that pancreatic ductal adenocarcinoma is influenced by microbial translocation from the oval cavity or gut, indicating a notable link between dysbiosis and pancreatic tumors (50-52). Genomic studies have demonstrated the presence of Proteobacteria, *Acinetobacter* and Enterobacteriaceae within the pancreatic tumor environment, where they may contribute to immune responses modulation and chemoresistance (20,53-55). In addition, the decreased abundance of beneficial bacteria, particularly *Bacteroides* and *Clostridium* in the gut reduces the production of SCFAs which may support cancer progression by disturbing mucosal defense and providing an inflammatory microbial environment (20). Periodontal pathogens, such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*, have also been identified as risk factors for pancreatic cancer, possibly through the oral-gut axis, systemic inflammation and immune modulation (50). Pancreatic dysbiosis may contribute to the regulation of bile acid metabolism, tumorigenic microenvironment development and tumor progression (20).

**HCC.** The development of HCC is notably associated with chronic liver diseases, such as viral hepatitis and non-alcoholic steatohepatitis (1); both conditions are affected by disturbances in the gut microbiota-liver axis. Dysbiosis in HCC is characterized by increased abundance of pathogenic bacteria (*Enterococcus faecalis*, *Clostridium scindens* and *Escherichia* species) and depletion of beneficial bacteria (*Lactobacillus* and *Bifidobacterium adolescentis*), thus reducing the production of SCFAs and impairing epithelial repair and anti-inflammatory signaling (19). Pathogenic bacteria in HCC produce endotoxins, such as lipopolysaccharides (LPS) and other microbial products, that infiltrate the gut, activate hepatic Kupffer cells and promote chronic inflammation and fibrosis in the liver. For instance, *Clostridium scindens* exerts bile acid toxicity by converting primary bile acids to deoxycholic

acid and activating hepatic stellate cells through farnesoid X receptor (FXR)/G protein-coupled bile acid receptor (TGR5) signaling (56,57).

**Esophageal cancer.** The esophageal microbiota is markedly influenced by diet, reflux and oral hygiene. Dysbiotic alterations in esophageal adenocarcinoma include an increase in the abundance of *Veillonella*, *Campylobacter* and Proteobacteria (1). These bacteria can produce proinflammatory molecules and LPS in the esophageal tissue (24). Continuous exposure of esophageal cells to LPS results in the activation of NF- $\kappa$ B and STAT3 signaling pathways and increasing the production of TNF- $\alpha$  and IL-6, which pro-tumorigenesis events, supporting cell survival, proliferation, migration and invasion associated with malignant phenotypes (58,59).

### 5. Key microbial metabolites in digestive tumors

The gut microbiota produces various metabolites that directly or indirectly influence the immune response, inflammation, signaling pathways and cellular microenvironment in digestive tumors. These bioactive compounds serve as signaling mediators, epigenetic modifiers, inflammatory modulators and TME modifiers. The major microbial metabolites of the gut microbiota in patients with digestive tumors are presented in Table I and discussed in the present section.

**SCFAs.** Beneficial commensals, such as *F. prausnitzii* and Lachnospiraceae, are gut microbiota that produce SCFAs (acetate, butyrate and propionate) through bacterial fermentation of dietary fibers in the colon tissue (31,60). Butyrate serves a bifunctional role in digestive tumors, acting as an epigenetic regulator (inhibition of HDAC) and modulating cell cycle checkpoints, NF- $\kappa$ B and Wnt/ $\beta$ -catenin pathways, which are context-dependent (33,61). This means that in healthy colonocytes, butyrate helps improve differentiation, increases apoptosis and promotes anti-inflammatory signaling primarily by inhibiting HDAC and binding to G-protein-coupled receptors (such as free fatty acid receptor 2/3 and hydroxycarboxylic acid receptor 2) (62-64). However, in advanced colorectal tumors, particularly under hypoxia which results in increased glycolytic effects (Warburg phenotype), the uptake and oxidation of butyrate are altered as its intracellular accumulation suppresses HDAC and arrests cellular growth and differentiation. In addition, butyrate interacts with immune and stromal components within the TME, thereby promoting the differentiation of T lymphocytes and enhancing the epithelial barrier integrity (32). Acetate and propionate affect lipid metabolism and glucose homeostasis in CRC cell lines and exhibit anti-inflammatory properties by activating G-protein-coupled receptors (GPR41 and GPR43) that regulate cytokine production and immune cell function (64-66). In addition, propionate inhibits the activation of the NLR family pyrin domain containing 3 inflammasome and exerts protective effects by reducing colitis-associated CRC (67).

**Bile acids.** Within the gut, bile acids originate from two distinct sources as follows: Primary bile acids are naturally synthesized in the liver and secreted in conjugated form to the intestine, whereas secondary bile acids, such as deoxycholic acid (DCA)

and lithocholic acid (LCA) are produced through transformation by gut microbiota, such as *Clostridium* species (37). DCA and LCA subsequently contribute to tumor biology and metabolic reprogramming by activating cell-surface receptors (such as FXR and TGR5) in epithelial, immune and hepatic cells, inducing pro-inflammatory cytokines, as well as oxidative and nitrosative stress, thereby modulating DNA damage through the activation of NADPH oxidase. In addition, they can activate oncogenic signaling pathways by affecting the expression of gene involved in the Wnt/ $\beta$ -catenin, NF- $\kappa$ B and EGFR/MAPK pathways (36). Although LCA can induce apoptosis in some types of cancer (such as nephroblastoma, acute myeloid leukemia, and breast cancer), it exhibits inflammatory properties and induces epithelial injury under dysbiotic conditions (68-72). Furthermore, LCA promotes metastasis in gastric cancer cells by activating TGR5, modulating the EGFR/MAPK signaling pathway and inducing cell migration (11,37,61,73,74).

**Amino acid-derived metabolites.** The gut microbiota can metabolize amino acids into different compounds, such as polyamines, hydrogen sulfide (H<sub>2</sub>S), kynurenine, indole-3-propionic acid (IPA) and indole-3-acetic acid (IAA), which influence tumor biology (75). Kynurenine, produced by *Lactobacillus*, serves as a biomarker of poor prognosis in digestive tumors (76); it suppresses the activation of T-lymphocytes, facilitates immune evasion and mediates tryptophan catabolism in the gut (77). Tryptophan can be metabolized in the gut by both kynurenine-dependent pathways and the gut microbiota-host metabolism axis. IPA, a byproduct of tryptophan catabolism, can impair T-cytotoxic immune function, improve epithelial barrier function and modulate the immune response in pancreatic cancer (78,79). In a CRC model, IPA demonstrated anti-inflammatory effects and inhibited tumor growth (80). *Bifidobacterium* produces IAA, which binding to and activating aryl hydrocarbon receptors on immune cell surface, therefore, contributes to downregulating the expression of interleukin-22 binding protein (IL-22BP), This results in decreasing the intercellular IL-22, a potent oncogenic cytokine, levels that indicates its protective effects in HCC (81-83).

Polyamines (putrescine, spermine and spermidine) are the other amino acid-derived metabolites, which can be produced by *Bacteroides* species and are derived from ornithine and arginine metabolism (84,85). Aberrant production of polyamines promote tumor proliferation, angiogenesis and metastasis (85). In gastric cancer, elevated polyamine levels are associated with angiogenesis through increased production of hypoxia inducible factor 1- $\alpha$  and VEGF (86). Increased polyamine levels have also been associated with the proliferation of CRC cell lines (87). Sulfate-reducing bacteria, such as *Desulfovibrio* and *Bilophila*, metabolize dietary cysteine and produce H<sub>2</sub>S, which has dual functions under different conditions. At low, physiological concentrations, H<sub>2</sub>S exerts a protective role by supporting mucosal barrier integrity, redox homeostasis and mitigating excessive inflammation in the gut (88,89), thereby contributing to epithelial defense and immune balance. In addition, H<sub>2</sub>S serves as a signaling molecule that supports intestinal homeostasis, prevents chronic injury development and preserves epithelial cell survival and repair. By contrast, increasing the abundance of sulfidogenic bacteria during

Table I. Major microbiota shift across digestive tumors.

Taxon	Primary tumor sites	Functional category	Principal mechanisms	Microbiota effect on tumor biology	(Refs.)
<i>Fusobacterium nucleatum</i>	Colorectal, gastric, esophagus	Pathogenic bacteria	Induce inflammation, promotes M2-macrophage polarization	Interfere with chemotherapeutic agents, such as 5-FU	(59,133,134)
<i>Bacteroides fragilis</i>	Colorectal, hepatocellular	Pathogenic bacteria	Produce enterotoxins, disrupts E-cadherin, activates Wnt/ $\beta$ -catenin signaling and promotes inflammation	Promote epithelial mesenchymal transition, increase genomic instability, promote tumor progression	(135-137)
<i>Escherichia coli</i> (colibactin-positive species)	Colorectal, hepatocellular	Pathogenic bacteria	Produce colibactin, promote double stranded DNA breakage and induce KRAS mutations	Causes genotoxicity injuries, incorporates in tumor initiation and progression	(105,106,138)
<i>Helicobacter pylori</i>	Gastric cancer	Pathogenic bacteria	Produce CagA and VacA factors, activates NF- $\kappa$ B and STAT3 signaling and promotes ROS-mediated DNA damage	Induce gastritis, gastric atrophy, metaplasia and gastric adenocarcinoma	(40,44)
<i>Streptococcus</i>	Gastric, esophagus	Pathogenic bacteria	Increase lactate production, activates VEGF/MMP9 signaling and promotes pro-inflammatory signaling	Induces angiogenesis in tumor microenvironment, enhance tumor invasion and metastasis	(39,48,59)
<i>Faecalibacterium prausnitzii</i>	Colorectal, hepatocellular	Beneficial commensal	Produces butyrate and other SCFAs, inhibits histone deacetylases and maintains epithelial barrier integrity	Tumor suppressive milieu, reduces inflammation, improves epithelial integrity	(24,139)
<i>Akkermansia</i>	Colorectal, metabolic diseases	Beneficial commensal	Maintaining mucosal integrity	Exert anti-inflammation and improves response to checkpoint inhibitors.	(23,27,123)
Lachnospiraceae	Colorectal, hepatocellular	Beneficial commensal	Produces butyrate and other SCFAs, inhibits histone deacetylases and maintains epithelial barrier integrity	Tumor suppressive milieu, reduces inflammation and improves epithelial integrity	(140,141)

Table I. Continued.

Taxon	Primary tumor sites	Functional category	Principal mechanisms	Microbiota effect on tumor biology	(Refs.)
<i>Bifidobacterium</i>	Gastric, colorectal	Beneficial commensal	Produces SCFA and indole derivatives, promotes dendritic cell maturation	Improves antitumor immunity, reduces colitis and associated tumorigenesis	(30,46)

SCFA, short chain fatty acid; CagA, cytotoxin-associated gene A; VacA, vacuolating cytotoxin A gene; NF-κB, nuclear factor κB; ROS, reactive oxygen species.

dysbiosis results in locally increased levels of H<sub>2</sub>S; therefore, a disequilibrium between H<sub>2</sub>S levels and detoxification pathways occurs in colonocytes and shifts its effects toward promoting tumor development (90,91). However, in dysbiosis and at high concentrations, H<sub>2</sub>S modulates DNA hypermethylation (inhibits DNA methyltransferase), silences the secreted frizzled related protein 2 tumor suppressor gene and activates NF-κB signaling (92).

*Other microbial metabolites.* The gut microbiota can produce other metabolites, including phenolic compounds (such as flavonoids), lactate and ammonia, which are functional in reshaping the TME and immune responses (93). LPS is a structural component of the outer membrane of gram-negative bacteria (45); LPS is a potent bacterial endotoxin that activates the innate immune system via Toll-like receptor 4 (TLR4) signaling, resulting in chronic inflammation by activating NF-κB signaling and increasing the production of tumor-promoting cytokines, such as IL-6 and IL-8, in gastric and pancreatic cancers (94). Increased LPS levels have also been identified in hepatocellular and gastric cancers (94).

## 6. Metabolic interaction between gut microbiota and digestive tumors

Beyond specific metabolites, the gut microbiota is involved in numerous metabolic interactions that contribute to the pathogenesis of digestive tumors. The gut microbiota is a key regulator of host physiology, particularly in digestive tumor biology, immune responses, cellular signaling and TME remodeling (7,26,79). A comprehensive list of microbial alterations in digestive tumors and their corresponding mechanisms is presented in Table II.

*Remodeling of the TME.* The gut microbiota contributes to TME remodeling within cancer cells by regulating cellular interactions and cytokine production to support cellular proliferation and survival (14). Butyrate acts as an epigenetic regulator in normal colonocytes, inhibits HDAC, induces transcriptional changes to induce apoptosis and supports epithelial barrier integrity in normal colonocytes; however, within the hypoxic TME of CRC, it serves as an energy source, promoting the survival and chemoresistance of tumor cells (33). Lactate is another metabolite produced within the TME, owing to the increased demand for energy sources or by the in-house

microbiota (75). By binding to glycoprotein receptors, such as GPR81, it serves as a metabolic substrate for signaling molecules and therefore promotes immunosuppression and angiogenesis in the TME (95). *Streptococcus* species acidify the gastric TME by producing lactate, resulting in VEGF/MMP9 activation and immune evasion (96,97). Immune evasion is a unique characteristic of the cancer cells within the TME; this phenomenon is facilitated by the activation of inflammatory pathways, such as NF-κB, Wnt/β-catenin signaling and STAT3, which are mediated by secondary bile acids and the production of reactive oxygen species (98). In HCC, the overgrowth of *Clostridium scindens* was observed under dysbiosis, which is potentially associated with increased conversion of primary bile acids to secondary ones such as DCA (36). As aforementioned, the increased levels of DCA within the TME is mechanistically associated with DNA damage and inflammation resulting in cancerous cell migration, invasion and extracellular matrix remodeling (99,100).

*Metabolic reprogramming and immune evasion of microbiota-host immune cells.* Microbial metabolites, such as SCFA, kynurenine and indole derivatives, influence cancer cell proliferation and tumor growth (8). In dysbiosis, changes in amino acid metabolism by the gut microbiota (such as *Lactobacillus*) alter the levels of amino acid catabolites such as indole-3-acetic acid and kynurenine, Tryptophan derived catabolites, which can activate aryl hydrocarbon receptors on immune cell surface, promote immunosuppressive phenotypes, reduce T-cytotoxic lymphocytes and mediate immune tolerance in pancreatic ductal adenocarcinoma (93,101-103). In addition, increased ammonia levels, originating from proteolytic bacteria, result in T cell exhaustion and impair antitumor activity. Microbial metabolites also provide nutrients and immune cell energy sources within the TME. The microbiota can also act as proinflammatory mediators. For instance, LPS from gram-negative bacteria (such as *Klebsiella*) induce epithelial mesenchymal transition in pancreatic cancer by activating TLR4 signaling, resulting in the activation of NF-κB and the release of proinflammatory cytokines such as TNF-α and IL-6 (104).

*Genotoxicity and epigenetic alteration.* In CRC, some *E. coli* strains (such as phylogroups B1 and B2) can produce colibactin, a genotoxin that induces chromosomal instability and breakage in double-stranded DNA and exerts somatic mutations in the

Table II. Key microbial-derived metabolites and their mechanisms in digestive tumors.

Metabolite	Source microbes	Mechanisms of action	Clinical implications	(Refs.)
SCFAs-butyrate, acetate, propionate	<i>Faecalibacterium prausnitzii</i> , Lachnospiraceae, <i>Roseburia</i>	Inhibit histone deacetylases, modulate NF-κB pathway, activate G-protein coupled receptors (FFAR2/3 and GPR109A); regulate T regulatory cells	Potential adjuvant therapy; dietary fiber and probiotic supplementation to boost SCFAs	(26,63,142)
Secondary bile acids (deoxycholic acid, lithocholic acid)	A wide range of gut microbiota	Gut microbiota enzymatically converts primary bile acids, induce oxidative stress, stimulate oncogenic Wnt/β-catenin and NF-κB pathways; DNA damage induction	Target bile acid receptors (FXR and TGR5); bile acid metabolism modulators; antioxidants	(11,34,74)
Kynurenine	<i>Lactobacillus</i> , other gut microbes	Suppresses cytotoxic T cell activation by modulating tryptophan metabolism; facilitates immune evasion	Target immune checkpoints (PD1/PD-L1); therapeutic tryptophan pathway modulation	(77,86)
Indole compounds (indole-3-propionic acid, indole-3-acetic acid)	<i>Bifidobacterium</i> , other gut commensals	Modulate epithelial barrier function; regulate immune signaling and inflammatory responses	Prognostic biomarkers; therapeutic metabolites supplementation; microbiome-targeted therapies	(75,81,100)
Polyamines (putrescine, spermine, spermidine)	<i>Bacteroides</i> species	Stimulate angiogenesis, tumor cell proliferation, and metastasis through modulation of gene expression and signaling pathways	Target polyamine biosynthesis or uptake pathways; potential chemotherapy adjuncts	(85)
Hydrogen sulfide (H2S)	<i>Desulfovibrio</i> , <i>Bilophila</i>	Dual role: supports mucosal integrity at physiological levels but induces DNA hypermethylation, inhibits DNA repair, and promotes inflammation at high concentrations	Potential biomarker for stromal activation; therapeutic target for modulating H2S levels	(88,90)
ROS	Multiple gut microbial species	Produce by multiple gut microbial species and metabolic reactions and induces DNA damage, lipid peroxidation, and oxidative stress; promotes inflammatory cytokine production	Antioxidant therapy adjunct; microbiome modulation to reduce ROS-producing bacteria	(60,84)
Trimethylamine N-oxide	Various species	Gut microbiota metabolizes dietary choline and carnitine, promotes inflammatory responses and immune cell activation; induces pyroptosis in tumor cells	Potential immunotherapeutic adjuvant; dietary modulation of precursors	(85,143)
Lipopolysaccharides	<i>Klebsiella</i> , <i>Escherichia coli</i>	Activates TLR4 signaling, promotes NF-κB-mediated proinflammatory cytokine production	Target TLR4 pathway; anti-inflammatory agents; microbiome-directed therapy	(63)

SCFA, short chain fatty acid; ROS, reactive oxygen species; TLR-4 Toll-like receptor 4; NF-κB, nuclear factor κB; FFAR2/3, free fatty acid receptor 2/3; GPR109A, hydroxycarboxylic acid receptor 2; FXR, farnesoid X receptor; TGR5, G protein-coupled bile acid receptor; PD1, programmed cell death protein 1, PD-L1, programmed death-ligand 1.

KRAS gene, resulting in mutagenesis (105-107). In dysbiosis, microbial compounds can also promote the accumulation of reactive oxygen and nitrogen species, thereby intensify oxidative DNA damage and promote lipid peroxidation (44). In

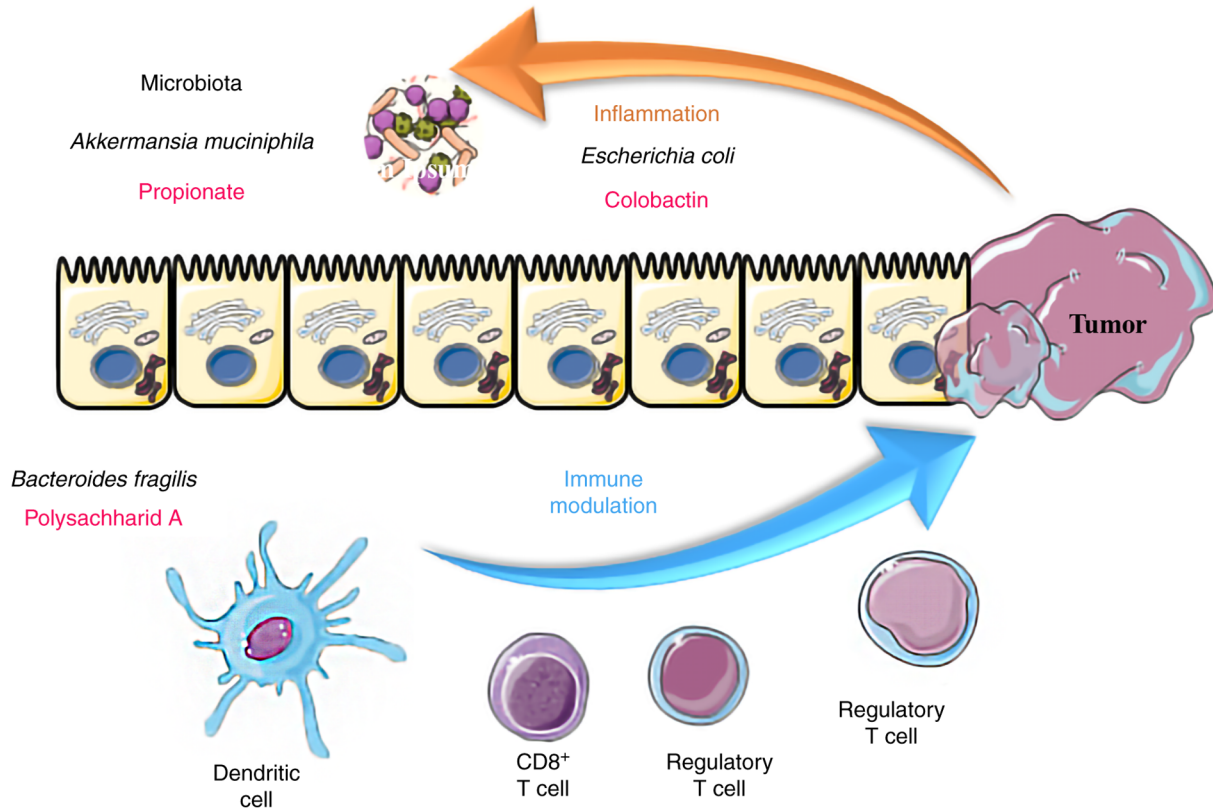


Figure 2. The interaction between the gut microbiota and the tumor microenvironment (TME) as a schematic diagram of bidirectional gut microbiota-TME interaction in digestive tumors is represented, where initiates from dysbiosis (diet, inflammation), and follows by producing microbial metabolites (propionate, colibactin), and circulatory repetition.

addition to directed DNA damage, microbial metabolites such as butyrate (HDAC inhibitor) can induce epigenetic alterations and affect cellular DNA condensation within the TME (33,79).

**Role of gut microbiota in metabolism of xenobiotic compounds.** Microbial biotransformation is a process by which the gut microbiota processes chemical compounds, including dietary substances and xenobiotics (108). Xenobiotics are chemical substances that do not originate intrinsically, such as medications, environmental pollutants, dietary compounds and other chemical substances. The gut microbiota serves a pivotal role in biotransformation and markedly affects the risk of cancer development in the digestive tissues. In dysbiosis, microbial biotransformation may activate carcinogenic compounds, induce DNA damage and affect host detoxification pathways (108).

The microbial metabolism of xenobiotic compounds typically involves two main phases (108). In the first phase, the oxidation, reduction and hydrolysis of xenobiotics are often mediated by analog compounds of cytochrome P450 (cytP450). For instance, aflatoxin B1 (AFB-1), a mycotoxin produced by *Aspergillus* species; AFB-1, is typically converted by cytP450 to a carcinogenic epoxide. Gut microbiota, such as *Lactobacillus*, produce enzymes that detoxify AFB-1. Under dysbiosis, overproduction of AFB-1 disrupts DNA structure and leads to HCC (109). The second phase of xenobiotic metabolism involves increasing the solubility and facilitating the excretion of xenobiotic compounds (110). This phase includes conjugation, sulfation and methylation reactions. For example, *Bacteroides* and *Clostridium* produce

enzymes similar to  $\beta$ -glucuronidase and azoreductase, which metabolize heterocyclic amines, such as polycyclic aromatic hydrocarbons (111). Heterocyclic amines potentially induce mutations in essential genes, such as adenomatous polyposis coli (APC) and KRAS, which are risk factors for CRC. Under dysbiosis, these transformation processes are probably disturbed, resulting in carcinogenesis (112,113).

In dysbiosis, the gut microbiota can reduce dietary nitrates to nitrites, and oral *Veillonella* and gastric *H. pylori* convert nitrites to nitrosamines, which are potent mutagens that contribute to gastric carcinoma (114,115). Environmental pollutants, such as heavy metals, can also be detoxified by some microbiota strains, such as *Lactobacillus* strains, which bind to and reduce the bioavailability and nephrotoxicity of cadmium and arsenic (116,117). Another notable role of the microbiota in the metabolism of xenobiotic compounds is detoxification and drug metabolism (117,118); for instance, *Eggerthella lenta* inactivates digoxin, a chemotherapeutic agent, and *Enterococcus* species can detoxify and mitigate the production of cisplatin-induced reactive oxygen species (119).

**Gut microbiota modulates immune response and TME remodeling.** The intricate association between the gut microbiota and immune response in digestive tumors supports their pivotal role in regulating inflammatory signals, immune cell differentiation, cytokine production and immune checkpoint alterations within the TME of digestive tumors (Fig. 2). The gut microbiota can directly affect the local immunity of the TME within digestive tumors, such as gastric and CRC. Within

the gastrointestinal tract, a consistent interplay between the gut microbiota and mucosal immune system is evident. In dysbiosis, pathogenic bacteria such as *F. nucleatum* suppress local immunity, and in CRC, *F. nucleatum* inhibits tumor cell cytotoxicity by binding to the T cell immunoreceptor with Ig and ITIM domains receptor on natural killer cells and cytotoxic T lymphocytes (Fig. 3). Dysbiotic microbiota, such as *F. nucleatum* induce M2-polarization of tumor-associated macrophages and block the production of tumor-suppressor cytokines, such as IL-10 and TGF- $\beta$  (78,86).

Commensal bacteria are essential for maintaining epithelial integrity and equilibrium between pro- and anti-inflammatory signals. A balanced intestinal microbiota is essential for the host to support immune homeostasis by inducing the maturation of circulating immune cells, including dendritic cells, macrophages and different subtypes of T lymphocytes within secondary lymphoid organs (7,45). *Bifidobacterium* and *F. prausnitzii* produce SCFAs, tryptophan derivatives and secondary bile acids that can enter the bloodstream, interact with immune cells and promote anti-inflammatory responses and cytotoxicity of tumor-infiltrating lymphocytes (23,24,29). In addition, microbial translocation has been proposed as a risk factor for premetastatic niches, mainly because of the immune suppression and inflammation induced by microbial metabolites. Some *Escherichia* strains and *Proteus mirabilis* have been found to be incorporated into liver metastases from colorectal tumors. In dysbiosis, the translocation of gut microbiota, such as Enterobacteriaceae, results in locally elevated LPS levels and the activation of TLR4 in hepatic Kupffer cells. These events induce the activation of IL-6/STAT3 signaling and the progression of tumor cells in HCC (35,43).

## 7. Application of gut microbiota in therapeutic approaches

Mechanistic insights into the interactions of the gut microbiota-metabolism axis are beneficial for developing targeted therapeutic strategies, such as manipulating microbiome composition to induce favorable metabolic or immunological responses, which is possible through microbiota profiling. Integrating knowledge of microbiota profile on regulation of the host-metabolic pathways provides a roadmap to understand how microbiota-based intervention can be translated in personalized therapeutic approaches.

*Gut microbiota determines response to treatment.* Gut microbiota profiling is useful for predicting therapeutic outcomes, particularly in digestive tumors. Beyond its influence on tumor biology, microbial composition can also affect drug metabolism and determine the efficiency of checkpoint inhibitors and chemotherapeutic agents (7,118,120). Therefore, microbial diversity can be used as a determining factor for whether a patient is resistant or responsive to treatment. For instance, Heshiki *et al* (121) investigated the intestinal microbiota profile in patients with different cancers and identified a significant microbiota diversity in patients who were responded successfully to treatment than non-responder patients. Based on microbiota profile, the authors developed a machine learning model to predict treatment outcome indicating a positive correlation between *Bacteroides* and positive response to treatment, and validated the accuracy of model in a different cohort.

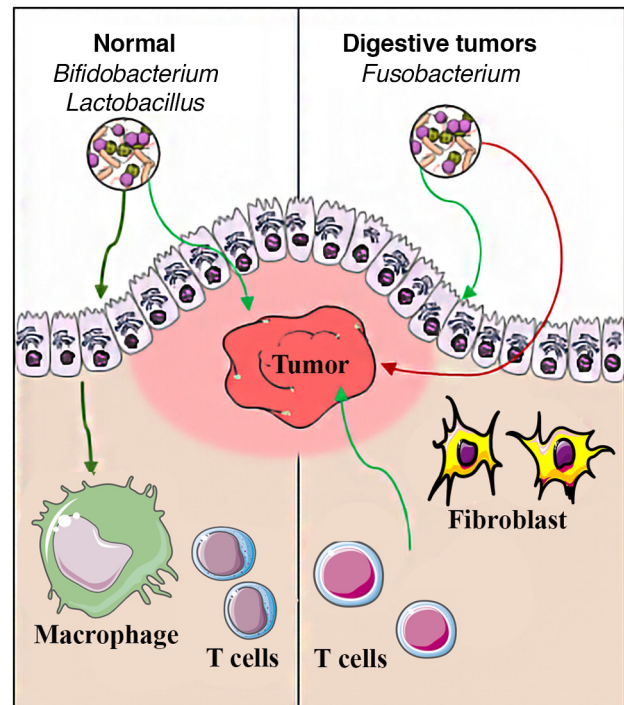


Figure 3. Tumor microenvironment and gut microbiota crosstalk in health and digestive tumors is depicted.

*Microbiota modulates response to immune checkpoint inhibitors.* The use of antibodies against immune checkpoint inhibitors, including anti-programmed cell death protein 1, anti-programmed death-ligand 1 and anti-cytotoxic T-lymphocyte associated protein 4, is an emerging therapy that affects T cell-mediated antitumor activity. Currently, gut microbiota composition has been introduced as a predictor of response to treatment with checkpoint inhibitors (12,122). Patients with a microbiota profile enriched in beneficial commensals, such as *A. muciniphila* and *Bifidobacterium*, usually respond favorably to treatment (123). These bacteria have the potential to increase antigen presentation, increase effector T-cells levels and promote dendritic cell maturation. Transferring beneficial microbiota to non-responders to immune checkpoint inhibitors is a promising hypothesis for restoring immunomodulatory and therapeutic outcomes in a personalized medicine approach.

*Microbiota interacts with chemotherapeutic agents.* Multiple studies on the influence of gut microbiota on treatment outcomes with chemotherapeutic agents have indicated that microbial enzymes can induce the activation or degradation of certain medications (124,125). For example, *Mycoplasma hyorhinis* produces cytidine deaminase, which inactivates gemcitabine in patients with pancreatic cancer. In addition, *Lactobacillus* species exert a synergistic effect on 5-FU cytotoxicity by producing thymidylate synthase inhibitors (126).

## 8. Challenges in clinical translation of microbiota-targeted therapies

Although the use of beneficial microbiota in the real world seems promising through the administration of probiotics,

prebiotics, fecal microbiota transplantation or medications targeting the gut microbiota, several challenges confine its clinical translation. First, inter-individual variability exists in the microbial composition; these variabilities, which arise from geography, genetics, age and lifestyle, can complicate patient stratification and prediction of the response to treatment (127). The possibility of confounding factors, such as the use of medications targeting proton pump inhibitors, antibiotics or dietary habits, are other challenging factors that limit the reproducibility of microbiota in different populations (128). For instance, antibiotics can eradicate beneficial taxa, such as *A. muciniphila* (129); another example is the variability in the use of dietary fibers, as they enhance the production of SCFAs. Therefore, it is necessary to control dietary intake when designing clinical trials (130). Beyond the inter-individual variabilities, the long-term safety of sustained microbiota-targeted interventions remains incompletely characterized; in addition, the standardization of sampling, sequencing and functional validation, along with its regulatory framework is essential for more robust, guideline-based clinical validation.

## 9. Discussion and future directions

In the present review, the intricate and multifaceted importance of the gut microbiota in digestive tumors was comprehensively explored. The microbiota-metabolism axis exerts substantial influence on digestive tumorigenesis through mainly regulating cellular processes such as metabolic reprogramming, epigenetic remodeling and immunomodulating within the TME. In particular, microbial dysbiosis and its related key metabolites, including polyamines, SCFA, secondary bile acids and indole derivatives, were found to be critical mediators of epithelial integrity and tumor immunity by promoting chronic inflammation, DNA damage, genotoxic injury and metabolic reprogramming.

In addition, the bridging of immunology, oncology, microbiology and pharmacology is a unique aspect, highlighting the bidirectional TME-microbial metabolites in the digestive system, which have often been overlooked in research. As previously discussed, microbial compounds and metabolites can be incorporated into the host metabolism-gut microbiome to regulate signaling pathways (such as Wnt/ $\beta$ -catenin, STAT3 and NF- $\kappa$ B pathways), epigenetics, inflammation and immune evasion of CRC cells. The present review discussed the influence of microbial metabolites, such as SCFA and bile acids, on immunomodulation, inflammation and regulation of cellular signaling. For instance, beneficial commensals such as *A. muciniphila* and *F. prausnitzii* were identified to have anti-inflammatory and antitumor properties owing to the production of SCFA and maintenance of epithelial barrier integrity. However, pathogenic bacteria such as *H. pylori*, *F. nucleatum*, and some strains of *E. coli* produce destructive metabolites and toxins that result in inflammation, impaired immune activity, DNA damage and oncogenesis.

Another unique aspect of the present review is the consideration of the gut microbiota as both a modulator and predictor in the counterpart aspects of health and pathogenesis. According to this concept, the microbiota is valid in research on precision oncology and personalized medicine. Future studies may

identify these findings not only as biomarkers for early diagnosis but also to elucidate the microbial metabolic pathways for future interventions to block tumor-promoting pathways.

In clinical practice, microbiota modulation can be achieved using antibiotics, probiotics, prebiotics, dietary approaches and fecal microbiota transplantation to restore a healthy microbiome that can enhance antitumor immunity or even remove inflammation. New emerging data have demonstrated the role of microbiota composition in influencing the efficacy of immune checkpoint inhibitors or chemotherapy, emphasizing the role of this axis in personalized treatment strategies.

Despite the unique aspects of the present review, it has some limitations that should be considered. Although it was attempted to explore the functional role of the microbiota in the digestive system, it was not possible to completely address the complexity of the host microbiota-metabolism axis across different conditions. Through increasing knowledge of the mechanistically influence of microbiome aiming for biomarker discovery and therapeutic targeting across digestive tumors, future research can utilize them as determinant biomarkers for risk stratification, predict the response to treatments or consider them as checkpoint inhibitors. Future research should explore the functional validation of microbiota-host interplay by designing observational studies utilizing dietary, probiotic or prebiotic interventions. Future studies should investigate gut microbiome alterations under different pathological and physiological conditions across different populations. By systematically increasing knowledge of microbiome-metabolite complexities in health and disease, they could be considered promising therapeutic candidates for routine clinical cancer treatments. Although some studies have investigated the short-term influence of gut microbiota in clinical trials (131,132); studies investigating the long-term effects of probiotic administration on digestive diseases could not be found. Future research should focus on the dynamic changes in the gut microbiota during cancer management of clinical interventions.

In addition, crosstalk studies on the integration of multi-omics data, combining emerging genomics, metabolomics and immune profiling as part of longitudinal cohorts, will enhance the understanding of causal relationships and identify potential predictive biomarkers. Future research should be designed to address several specific multi-omics aspects to develop personalized microbiota information for precision medicine. First, prospective cohort studies would be beneficial to integrate metagenomics and meta-transcriptomics profiling of the gut microbiota, which is associated with host multi-omics alterations across pathogenic conditions. Improving knowledge in this field (from premalignant lesions to advanced digestive tumors) will be applied in personalized medicine, both in biomarker discovery and personalized therapeutic strategies. Second, studies on multilayer datasets, combining microbiome composition and host interactions, will enhance knowledge of the mechanisms of pathogenesis, immune escape, pharmacokinetic aspects of anticancer agents and clarifying how microbiota taxa influence drug efficiency, dose optimization and treatment selection. Third, integrative studies on detailed dietary patterns with microbiome signatures and host-specific signaling pathways could be promising, bridging lifestyle modifications in high-risk populations.

Clinical trials in the field of microbiota modulation should be designed to assess the integrity of microbiome. Future studies should investigate the interaction of dietary components with gut microbiota dynamics and their influence on gut microbiota function to develop new nutritional strategies for the prevention of tumorigenesis or to improve treatment response. Future studies should elucidate and characterize how gut microbes alter the pharmacokinetics and pharmacodynamics of anticancer drugs to optimize dosing and limit their toxicity.

In conclusion, the gut microbiota-metabolism axis represents a disruptive paradigm in the field of digestive tumors, with potentially important implications for novel diagnostics and therapeutics. Highlighting the dual function of gut microbial metabolites in tumor progression and repression, the present review emphasizes the importance of microbiome analysis in personalized medicine. The integration of microbiology, oncology, immunology and systems biology will enable interdisciplinary discovery of actionable targets. Ultimately, these combinatorial strategies and personalized microbiome-based therapies can improve patient outcomes.

#### Acknowledgements

Not applicable.

#### Funding

No funding was received.

#### Availability of data and materials

Not applicable.

#### Authors' contributions

ZY as the first author was contributed to the study conceptualization and design, data acquisition and interpretation, and providing the primary draft of the manuscript. SW and XY were the co-authors who contributed to the study design, literature searching, data collection and interpretation, and assistance for writing the manuscript. The project administration was equally supported by SW and XY. BS as the correspondence was involved in all the study process including conceptualization and the study design, supervision, consensus and discussion and review and editing of the manuscript. All co-authors participated in writing and evaluating the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

#### Ethics approval and consent to participate

Not applicable.

#### Patient consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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