Acupuncture and Herbal Medicine

The interactions between gut microbiota and Chinese herbal medicine in colorectal cancer

Xinxin Hou[1], Xinyi Li[1,2], Wanqing Chen[2], Weikang Zhu[2], Haidong Guo[1,*], Ling Zhao[1,*]

[1]School of Integrative Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China; [2]Department of Oncology, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai, China

Abstract

Chinese herbal medicine (CHM), with a range of pharmacological and molecular targets, has unique advantages in the comprehensive treatment of colorectal cancer (CRC); however, its clinical application remains limited owing to undetermined anti-CRC mechanisms. Recent studies have shown that gut microbes mediate the intestinal barrier, metabolism, and immunity, which, in turn, affect CRC initiation, progression, and CHM therapy. Here, we summarize the mechanisms and clinical applications of the gut microbiota involved in CRC, together with the latest studies of CHM in CRC therapy and its anti-tumor molecular basis from the gut microbiota perspective. This review highlights the gut microbiota as a "bridge" to clarify the scientific of CHM in treating CRC. More efforts should be focused on how the gut microbiome interacts with CHM to elucidate the mechanism of action of CHM and provide a more applicable basis for CHM- and microbiota-related therapies for the treatment of CRC.

Keywords: Chinese herbal medicine, Colorectal cancer, Gut microbiota, Mucosal immunity, Tumor microenvironment

Graphical abstract: https://links.lww.com/AHM/A169.

Introduction

The morbidity and mortality rates of colorectal cancer (CRC) in China continue to increase despite an overall declining trend worldwide. In 2020, newly diagnosed CRC cases in China accounted for 28.8% of new global cases and CRC-related deaths accounted for 30.6% of global CRC-related deaths[1–2]. In approximately 20% of the patients, the initial diagnosis is metastatic CRC, whereas up to 50% of the patients with localized disease eventually develop metastases[3]. Metastatic stage IV CRC has a poor prognosis because of its poor response to current standard therapies, indicating that more effective and individualized strategies are required[4].

Chinese herbal medicine (CHM) has been used at all stages as an effective alternative therapy for the treatment of CRC. Clinical studies have confirmed the unique advantages of CHM in the comprehensive treatment of CRC; it enhances the efficacy of chemotherapy/radiotherapy and targeted therapy, prevents postoperative recurrence and metastasis, and reduces chemotherapy/radiotherapy-induced adverse effects[5]. However, the underlying mechanisms of action of CHM in the prevention and treatment of CRC have not yet been elucidated.

Recent studies have highlighted that a unique aspect of CRC is its intimate association with the gut microbiota, not only focusing on the role of the gut microbiota in contributing to colorectal tumorigenesis and development but also on modifying the chemotherapy and immunotherapy responses of patients with CRC[6–7]. The role of CHM in shaping the gut ecosystem has long been established, and numerous studies have reported that single Chinese herbs, formulas, and herbal compounds can inhibit CRC development by regulating the gut microbiota[8–9]. Therefore, clarifying how the gut microbes interact with medicinal herbs is beneficial for uncovering the mechanisms of CHM action. Increasing clinical and preclinical evidence supports that the microbiota is key to innovate or optimize current therapies for CRC; however, such issues are still far from being addressed due to the existing microbiota-targeted limitations. With the modulatory role of CHM on the gut microbiota, potential strategies that use CHM to target pathogenic bacteria may provide novel adjuvant therapy, and thus, facilitate precise clinical management.

Herein, we aimed to review the role of gut microbiota dysbiosis in the pathogenesis and treatment of CRC and update the microbiota-involved research progress of CHM in CRC therapy, thus illustrating the scientific

Xinxin Hou and Xinyi Li contributed equally to this work.

**Corresponding author. Haidong Guo, E-mail: hdguo@shutcm.edu.cn and Ling Zhao, E-mail: lzhao@shutcm.edu.cn.*

Received 18 September 2024 / Accepted 25 March 2025

How to cite this article: *Hou XX, Li XY, Chen WQ, Zhu WK, Guo HD, Zhao L. The interactions between gut microbiota and Chinese herbal medicine in colorectal cancer. Acupunct Herb Med 2025;5(2):147–159. DOI: 10.1097/HM9.0000000000000153*

Copyright © 2025 Tianjin University of Traditional Chinese Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

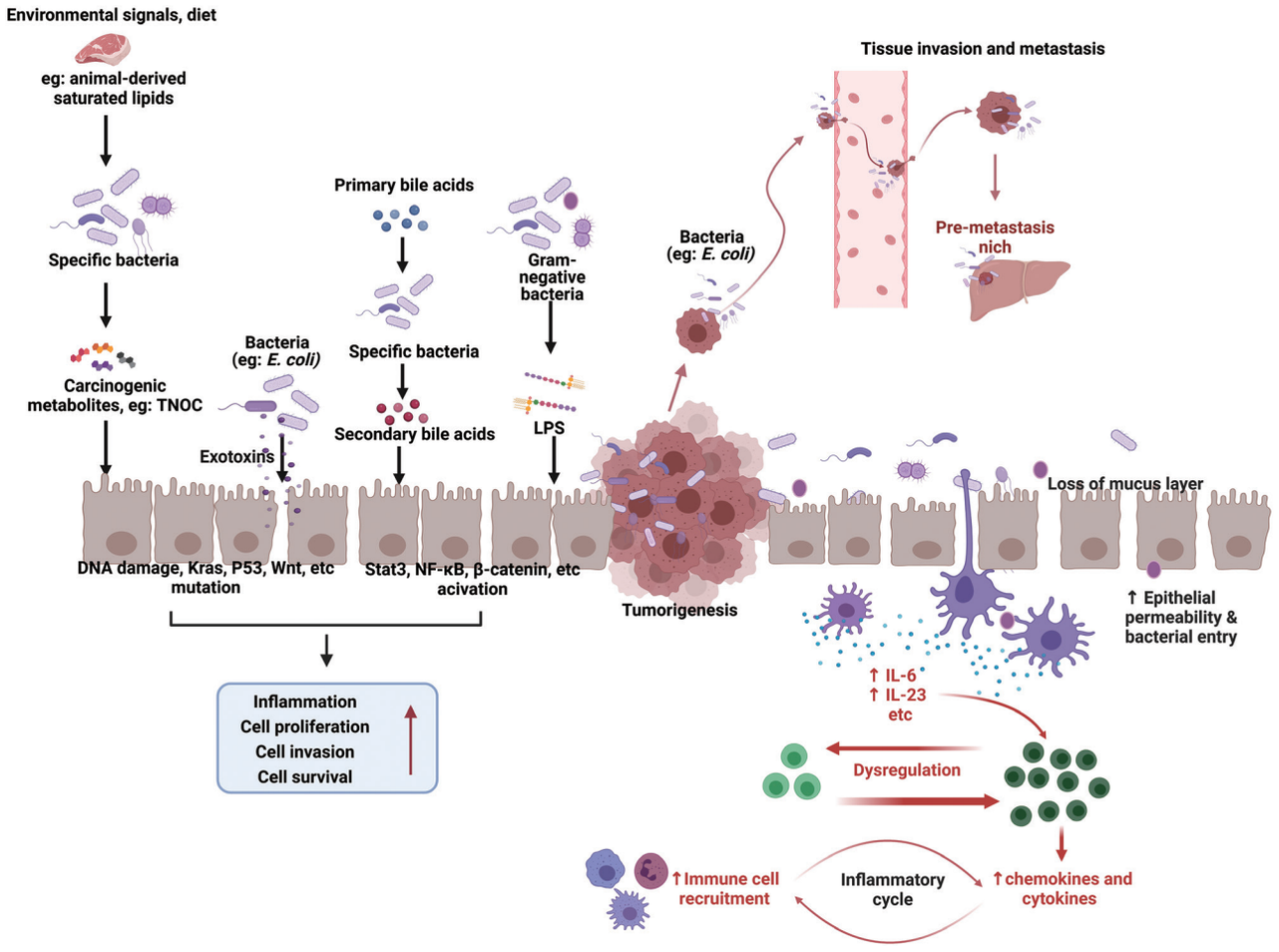


Figure 1. Microbiota-mediated mechanisms in CRC initiation and progression. Gut pathogens perform pro-carcinogenic actions *via* the following direct or indirect mechanisms: 1) generation of pro-carcinogenic metabolites; 2) secretion of genotoxins; 3) promotion of tumor inflammatory microenvironment formation, thus activating pro-carcinogenic pathways; 4) disruption of intestinal epithelial integrity and induction of mucosal immune dysregulation; and 5) dysregulation of gut microbiota homeostasis, which further forms a (pre-) metastatic niche. CRC: Colorectal cancer; *E. coli*: *Escherichia coli*; IL: Interleukin; LPS: Lipopolysaccharide; TNOC: Total N-nitroso compounds.

role of CHM in CRC therapy from a gut microbiota perspective.

Mechanistic role of gut microbiota in CRC initiation and development

The initiation and development of CRC are complex processes driven by both genetic and environmental factors, and approximately 60% of CRC cases are affected by environmental factors[10]. The gastrointestinal tract contains the largest number of microbes in the body that can be easily affected by diet, exercise, or medication[11]. Microbes may play tumor-promoting or tumor-suppressive roles, depending on the specific tissue milieu. It is widely recognized that gut pathogens *Fusobacterium nucleatum*, *Escherichia coli*, and *Bacteroides fragilis* can accelerate tumor initiation and progression[12–14]. Nevertheless, probiotic symbiotes in the gut can repair the intestinal barrier, suppress inflammation, and enhance host immune responses, thus protecting against tumor progression[15–17]. To date, the regulation of gut microbial changes during CRC progression and the precise mechanisms involved in CRC development have not been completely elucidated. It remains unclear whether changes in the intestinal microbiome contribute to the development of sporadic CRC or whether gut dysbiosis may also occur following CRC formation, as clearly observed in animal CRC carcinogenesis models[18]. Thus, there is a bidirectional interaction between the gut microbiota and CRC. Nevertheless, whether pre- or post-CRC, gut dysbiosis results in disrupted intestinal physiology and function and explains the pathological outcomes of CRC. In this section, we discuss the pro-tumoral mechanisms of gut microbes in CRC. Accumulating data have highlighted that altered gut microbiota facilitates CRC through several mechanisms, including genotoxin overproduction, inflammation, intestinal barrier disruption, and aberrant immunomodulation. Here, we have updated the microbiota-associated mechanisms of CRC carcinogenesis and progression (Figure 1).

Producing carcinogenic metabolites

The interplay between diet and the gut microbiota has long been studied. Dietary components fermented by the gut microbiota not only fuel bacterial metabolism, but also regulate molecular events in the colonic mucosa. However, when this ecological balance is disturbed, the metabolites produced by the gut microbes may have genotoxic and pro-carcinogenic effects[19]. Certain

bacteria, including *E. coli*, *Enterobacteriaceae*, and *Clostridium*, can produce metabolites such as amines, ammonia, hydrogen sulfide, indoles, and phenols, all of which are associated with CRC[20]. Excessive intake of red or processed meat produces carcinogens, such as N-nitroso compounds and hydrogen sulfide, through the metabolism of specific bacteria[21]. A high-fat diet significantly increases the risk of CRC, which is closely linked to abnormal bile acid (BA) metabolism caused by disturbances in the gut ecosystem[22]. Studies have shown that deoxycholic acid (DCA) can induce oxidative DNA damage *in vitro* and promote intestinal tumor formation *in vivo*[23]. Another example is trimethylamine, produced by gut microbes, which is N-oxidized in the liver by flavin-containing monooxygenase to trimethylamine N-oxide and contributes to several genetic pathways associated with colon cancer[24].

Generating genotoxins

Emerging studies have reported that the gut microbiota is involved in the pathogenesis and development of CRC by producing genotoxins, such as colibactin-producing polyketide synthase (pks) + *E. coli*[25–26], enterotoxigenic *Bacteroides fragilis* (ETBF)[27], and *Enterococcus faecalis*[28]. Potential *E. coli* strains generate cytolethal-distending toxins and colicin, both of which can engender inter-strand crosslinks and induce double-stranded DNA breaks in intestinal epithelial cells, further aggravating CRC in animal studies[25,29]. In susceptible azoxymethane (AOM)-treated *Il10*$^{-/-}$ mice, pks + *E. coli* monocolonization promotes invasive adenocarcinoma by inducing DNA damage[30]. Recently, additional genotoxins have been identified; for example, *Campylobacter jejuni* induces DNA damage in *Apc*$^{min/+}$ mice *via* the genotoxic action of *cdtB*[31]. Cao et al.[32] identified a distinctive family of DNA damage–inducing genotoxins (termed indolimines) produced by *Morganella morganii* that exacerbated the tumor burden in gnotobiotic mice. Using the Cancer Microbiome database, researchers found that *M. morganii* is enriched in colon and rectal adenocarcinomas, suggesting that genotoxic indolimines from *M. morganii* may play a role in intestinal tumorigenesis in humans[32]. Overall, these studies have extended the spectrum of microbiota-derived genotoxins involved in the development of CRC.

Altering tumor cell function and phenotype

Gut pathogens are also directly involved in tumor cell survival and invasion. *F. nucleatum* and its stimulated cytokines/chemokines [eg, interleukin (IL)-8, IL-21, and CXCL1] have been shown to promote CRC cell proliferation and invasion[33–36]. *F. nucleatum*–infected tumor cells release exosomes that facilitate the migration of non-infected cells and promote tumor metastasis[37]. *Peptostreptococcus anaerobius* was reported to directly interact with tumor cells *via* α_2/β_1 integrin through its surface protein putative cell wall binding repeat 2 and activate cellular PI3K/Akt pathway activation, leading to increased cell proliferation[38]. Adhesin FadA from *F. nucleatum* activates the E-cadherin/β-catenin pathway, inducing epithelial-mesenchymal transition in CRC cells[39–41]. Another pathogen, ETBF, was found to enhance CRC cell stemness by enhancing the expression of the core stemness transcription factor Nanog homeobox *via* upregulation of JmjC-domain-containing histone demethylase 2B expression in a Toll-like receptor (TLR)4-dependent manner[42]. The above evidence illustrates the promotive role of pathogens in tumor cell proliferation, invasion, and/or migration.

Eliciting tumor-promotive inflammation

Inflammation is a well-known hallmark of cancer and has an unanticipated paradoxical effect of enhancing tumorigenesis and progression[43]. It is well established that microbe-associated molecular patterns and TLRs play important roles in initializing inflammation and promoting carcinogenesis[44]. TLR4 is the main mediator of responses to the gram-negative bacterial cell wall component, lipopolysaccharide (LPS). TLR4 activation appears to promote the development of colitis-associated cancer by mechanisms including enhanced cyclooxygenase 2 (COX-2) expression and increased epidermal growth factor receptor signaling[44], and enhanced IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-11, CCL3, S100A8, and S100A9 expression in gut tumors, resulting in a loss of homeostasis that drives a pro-neoplastic inflammatory environment[45].

F. nucleatum as a driver of intestinal inflammation and carcinogenesis has been found to activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway through TLR4 and promote the production of proinflammatory cytokines (IL-8, IL-6, IL-17, and COX-2)[36,46]. Additionally, *F. nucleatum* activates the autophagy pathway and induces CRC chemoresistance through TLR4 and MyD88 innate immune signaling[47]. Moreover, *F. nucleatum* activates the inflammation-associated regulator, caspase activation, and recruitment domain 3 and promotes intestinal cancer metastasis[48]. *B. fragilis* targets the colonic epithelium STAT3/IL-17 signaling to induce a multi-step inflammatory cascade that activates the NF-κB pathway to promote intestinal carcinogenesis in *Apc*$^{Min/+}$ mice[49]. Inflammasomes are another key factor in inflammation-related CRC that mainly contributes to the occurrence of CRC by regulating inflammatory cytokines[50]. Hu et al.[51] observed aberrant inflammasome-induced microbiota in mice lacking the nucleotide-binding and oligomerization domain (NOD)-like receptor family pyrin domain containing 6 inflammasome feature, exacerbating inflammation-induced CRC.

Inducing intestinal barrier dysfunction and immune dysregulation

The intestinal epithelium, mucus, and immunological and microbial components form a physical barrier crucial for preserving gut homeostasis and the crosstalk between bacteria and immune cells[52]. Clinical evidence has demonstrated an altered microbial composition and a dysfunctional gut barrier manifested by epithelial hyperpermeability and high enrichment of mucosa-associated bacteria in patients with inflammatory bowel disease and patients with CRC[53–56]. Strain-specific

bacterial internalization and intracellular survival (such as *Escherichia*, *Staphylococcus*, and *Bacteroides*) may act as initial triggers that evoke damage to the intestinal barrier, leading to the infiltration of commensal bacteria, which in turn activates immune cells and induces tumor-promoting inflammation[57].

B. fragilis and *F. nucleatum* can induce mucosal permeability, rapidly, and prolonged activation of STAT3 signaling in colonic immune and epithelial cells, leading to a Th17 immune response in the colonic mucosa[49,58–59]. Furthermore, the complex relationship between dysbiosis and immune regulation may facilitate an immunosuppressive milieu that eventually maintains tumor cell survival and immune escape in CRC[7]. For example, in $Apc^{Min/+}$ mice, *F. nucleatum* increases tumor multiplicity and selectively recruits immunosuppressive tumor-infiltrating myeloid cells, which can promote tumor progression[60]. The Fap2 protein of *F. nucleatum* can directly interact with the immune inhibitory receptor T cell immunoglobulin and ITIM domain, leading to the inhibition of NK cell cytotoxicity[61]. *P. anaerobius* can also expand tumor-infiltrating immune cell populations such as myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages, and tumor-associated neutrophils, which are associated with chronic inflammation and tumor progression[38]. Microbial dysbiosis also contributes to colon tumor susceptibility and reduces anti-tumor immunity by stimulating $CD8^+$ T cells to promote chronic inflammation and early T cell exhaustion[62]. Thus, the gut microbiota can regulate CRC onset and development through immunomodulation, but the "immuno-oncology-microbiome axis" warrants further study.

Promoting pre-metastatic niche formation

Microbiota inevitably participate in the development of CRC metastasis, as evidenced by the presence of microbiota in metastatic liver or lung organs in patients with CRC, although the underlying mechanisms are not fully understood. Recent studies have highlighted that bacteria can modify the microenvironment and local immune profile at a metastatic site, forming a (pre-) metastatic niche that favors distant metastases[63–64]. *F. nucleatum* facilitates liver metastasis of CRC through mechanisms including reprogramming of the tumor microenvironment by inducing M2 macrophage polarization[65], modulating hepatic immune response featuring an accumulation of MDSCs and Tregs, and a reduction of NK and Th17 cells in the liver[66]. In another study, Bertocchi et al.[67] found that *E. coli* disrupts the gut vascular barrier, inducing bacterial dissemination to the liver, thus initiating the recruitment of immunosuppressive cells and boosting the formation of a pre-metastatic niche. These results highlight the potential of early microbiota-targeted therapy in preventing the metastatic spread of CRC.

Advances of intestinal microbiome in clinical applications

Early diagnosis and prognosis prediction

Since a specific microbial signature in CRC has been reported in the past decade, its important role in clinical translational applications has emerged as a new area of microbiome research. Nejman et al.[68] detected distinct intratumoral microbiomes among more than 30 cancer types, proposing their applicability to blood-based diagnostics and providing imaging evidence of the intratumoral spatial distribution and intracellular localization of these microbes in seven cancer types, including colon cancer. Wu et al.[69] compared fecal microbiota profiles among healthy subjects, and patients with colorectal adenoma and adenocarcinoma to screen and validate adenoma-specific markers across multiple populations, which would benefit the early diagnosis and treatment of CRC. Liang et al. searched for the diagnostic utility of bacterial marker candidates and found that a combination of four bacterial markers (increased *F. nucleatum*, *Roseburia intestinalis*, one undefined species, and decreased *Bacteroides clarus*) had good diagnostic value (sensitivity, 92.8%; specificity, 81.5%) for CRC in combination with fecal immunochemical assays[70]. Another study developed an oral and fecal microbiota-based classifier that could improve the diagnostic sensitivity of individuals with CRC and adenomas compared to healthy controls[71]. To explore the prognostic value of dysbiosis and CRC, Wei et al.[72] used 16S rRNA gene sequencing to determine differences in microbiota among tumor tissues with different prognoses and found that high abundances of *F. nucleatum* and *B. fragilis* were independent indicators of poor patient survival, whereas *Faecalibacterium prausnitzii* was more abundant in the survival group. A large cohort study by Mima et al.[73] also demonstrated that the amount of *F. nucleatum* in CRC tissues was associated with shorter survival and may potentially serve as a prognostic biomarker. These studies suggest that intestinal flora, in combination with other non-invasive techniques, could be a beneficial tool for the early diagnosis and prognosis of CRC.

Adjuvant therapy

Emerging evidence suggests that microbes can influence the therapeutic efficacy of anti-tumor drugs. For example, the gut microbiota has been shown to affect host responses to chemotherapy by influencing drug efficacy, promoting chemoresistance, and mediating chemotherapeutic toxicity and side effects. Different strategies of gut microbiota modulation, including probiotics, prebiotics, postbiotics, antibiotics, and fecal microbiota transplantation (FMT) can synergistically treat CRC by restoring microbial dysbiosis and maintaining intestinal microbial balance[74]. Although this evidence comes mainly from preclinical studies, some clinical translational trials employing microbiota modulation approaches have been initiated and are now under recruitment. Notably, the combined use of gut microbiota-modulated strategies in patients with CRC in clinical trials has been shown to alleviate treatment-induced side effects (NCT01410955[75], NCT01839721[76], NCT02313519[77], and NCT03782428[78]). To date, there have been no reports of microbiota-based modulations regarding beneficial clinical efficacy outcomes such as progression-free survival (PFS) and overall survival (OS). Some studies are still recruiting, which are assessing the

survival of patients (NCT05279677, NCT04729322, NCT05570942, and NCT04682665); these are expected to aid in finding more precise and effective intervention for CRC treatment. Meanwhile, new techniques based on genetically modified bacteria have emerged. Chung et al.[79] genetically modified the lactic acid bacterium *Pediococcus pentosaceus* engineered to deliver anti-cancer drugs, and found that this strain was effective in suppressing colorectal carcinogenesis. Conversely, pathogenic bacteria, such as *F. nucleatum*, are associated with chemoresistance to 5-fluorouracil (5-FU) in CRC[80]. The intratumor bacterium *Mycoplasma hyorhinis* was also found to induce gemcitabine resistance in a CRC mouse model, whereas a gemcitabine-antibiotic ciprofloxacin combination therapy abrogated resistance and potentiated treatment efficacy[81].

The gut microbiome can also influence the response to immunotherapy in CRC. In the MC38 colon cancer model, the anti-tumor effect of CTLA-4 blockade was dependent on distinct *Bacteroides* species. Specific T-cell responses against *Bacteroides thetaiotaomicron* and *B. fragilis* were correlated with the efficacy of CTLA-4 blockade[82]. In microsatellite stability (MSS)-type CRC tumor-bearing mouse models, *Prevotella_sp._CAG:485* and *Akkermansia*, were shown to maintain the normal immunotherapy response to PD-1 antibody[83]. Mager et al.[84] found that intestinal *Bifidobacterium pseudolongum* may be associated with an enhanced immunotherapy response by producing the metabolite inosine, which is dependent on the T cell expression of the adenosine A_{2A} receptor. Isolation of a consortium of 11 bacterial strains from healthy human donor feces also enhanced the therapeutic efficacy of immunotherapy in CRC tumor models by inducing interferon-γ-producing $CD8^+$ T cells in the intestine which required $CD103^+$ dendritic cells and major histocompatibility complex class Ia molecules[85]. As one of the most common products of the gut microbiota, Song et al.[86] found that LPS was enriched in CRC tissues *in situ* and was associated with poor responses to anti-PD-L1 therapy. Using an engineered LPS trap system to block LPS inside the tumor significantly relieved the immunosuppressive microenvironment and boosted anti-PD-L1 mAb therapy against CRC tumor[86]. Collectively, these studies highlight the importance and promising prospects of microbial-based adjuvant therapies for CRC.

Application of CHM in comprehensive treatment of CRC

As an integral part of the comprehensive treatment of CRC, combining Western medicine with CHM in a collaboratively positive manner could be effective in treating tumors, as revealed by increased clinical effectiveness, enhanced immunity, improved quality of life, and prolonged survival time in patients with CRC[87–88]. Xu et al.[89] conducted a prospective cohort study in eight medical centers in China and found that a longer duration of CHM use was associated with improved disease-free survival and OS among postoperative stage II and III CRC survivors. Another study investigating the efficacy of integrated Chinese and Western medicine (IM) compared to Western medicine alone in the treatment of metastatic CRC found that IM prolonged the survival of patients with metastatic CRC (ChiCTR-IOR-17010497)[90]. Liu et al.[91] performed a randomized, controlled, and double-blind trial and showed that Huangci Granule (*Ligustrum lucidum*, 15 g; *Cistanche deserticola*, 12 g; snakeberry, 15 g; edible tulip, 15 g; *Salvia miltiorrhiza* Bge, 15 g; and Fruit of Fiverleaf Akebia, 9 g) combined with chemotherapy and cetuximab or bevacizumab can prolong the PFS of metastatic CRC, improve the quality of life, reduce adverse reactions, and have good safety (ChiCTR-IOR-16008843). Moreover, patients with metastatic CRC after failure of conventional second or above lines treatment can benefit from the treatment of Jianpi Bushen Jiedu Decoction (*Radix pseudostellariae*, 30 g; *Atractylodis macrocephalae Rhizoma*, 10 g; *Poria cocos*, 10 g; *Radix glycyrrhizae*, 6 g; *Ligustrum lucidum* Ait, 10 g; *Eclipta prostrata* L., 10 g; *Gastrodia elata* Blume, 10 g; *Uncaria rhynchophylla* (Miq.) Jacks, 10 g; *Hedyotis diffusa* Willd, 15 g; and *Rhizoma Smilacis glabrae*, 15 g) combined with low-dose apatinib and S-1 (ChiCTR1900022673)[92]. To go further, well-designed large-scale randomized controlled clinical trials will favor the development of evidence-based guidelines for using CHM in CRC treatment.

The basic principle of traditional Chinese medicine (TCM) in treating CRC is based on syndrome differentiation and specific treatment. By analyzing the prescription patterns of Chinese herb medicine, Lin et al.[93] found that *Atractylodes macrocephala* (Baizhu) and *Poria* (Fuling) were the most commonly prescribed single herbs identified through analysis of medical records, with the function of nourishing *qi* and eliminating dampness. With the in-depth exploration of the biological basis of TCM syndrome, gut microbiota has attracted more attention to study its connection between differential TCM syndrome classification. Wang et al.[87] investigated the distribution of gut microbiota between two CRC syndromes called Deficiency of vital *qi* and excess of pathogenic toxins and found that the compositions of the microbiota in two syndromes were significantly different. This study suggests that the gut microbiota may present a new approach for TCM syndrome differentiation, classification, and treatment system.

Microbiota-related anti-tumoral mechanisms of CHM

Due to the complex component, CHM has a range of pharmacological and molecular targets which are associated with its anti-cancer mechanisms. Numerous studies reported the effects of CHM against CRC are mediated by regulating gut microbiota (Table 1). FMT experiments in germ-free mice have clearly demonstrated the protective role of CHM-manipulated gut microbiota in preventing CRC tumorigenesis[94]. Multiple mechanisms, including the inhibition of inflammation, regulation of intestinal immune homeostasis, and strengthening of the intestinal barrier (Figure 2), have been reported to be associated with the intricate interactions between CHM and the gut microbiota. Thus, an in-depth study of the precise mechanisms underlying the multiple targets of CHM will provide fundamental evidence for its use in CRC treatment.

Table 1

Effects and mechanisms of CHM on gut microbiota in treating CRC

CHM	Gut microbial alterations	Associated mechanisms	Diseases/ animal models	Ref
Formulas				
PZH	Increased abundance of probiotics *Pseudobutyrivibrio xylanivorans* and *Eubacterium limosum*; depleted pathogenic bacteria *Aeromonas veronii*, *Campylobacter jejuni*, *Collinsella aerofaciens*, and *Peptoniphilus harei*.	Restoring gut barrier function; suppressing oncogenic and proinflammatory pathways.	AOM/DSS and *Apc*$^{min/+}$ mice	[94]
GQD	Increased abundance of *Bacteroides*, *Akkermansia,* and *Prevotella*; decreased abundance of *Megamonas* and *Veillonella*.	Enhancing anti-tumor immunity; reducing inflammation; protecting intestinal barrier function.	CRC patients	[95]
XYS	Increased abundances of *Bacteroidetes* and *Proteobacteria*; reduced abundance of *Firmicutes*.	Protected the intestinal barrier; corrected gut dysbiosis.	CRS with CRC xenografted mice	[96]
XCHT	Increased abundances of, *Anaerostipes* and *unclassified*; reduced abundances of *Alistips, Blautia, Corprobacillus, Corynebacterim, Eubacterium, Escherishia-Shigella, Megamonas, Parabacteroides,* and unclassified *Ruminococcaceae*.	Anti-depression; modulating gut dysbiosis; suppressing the TLR4/MyD88/ NF-κB signaling pathway.	CRC patients and CRS with CRC xenografted mice	[97]
SND	Increased beneficial bacteria *Lactobacillus*, *Bacillus coagulans*, *Akkermansia muciniphila,* and *Bifidobacterium*; reduced pathogenic bacteria *Bacteroides fragilis* and *Sulphate-reducing bacteria*.	Regulating intestinal immunity, protecting the colonic mucosal barrier.	AOM/DSS mice	[98]
YYFZBJS	Increased probiotic genera *Bifidobacterium* and *Prevotellaceae*; reduced *Lactobacillus* and *Dubosiella*.	Modulating the function of regulatory T cells.	*Apc*$^{min/+}$ mice	[99]
XLP	Enrichment of beneficial bacteria, particularly *Akkermansia*, *Parabacteroides*, and *UBA1819*; lower levels of *Muribaculaceae* and *Lactobacillus*.	Reducing fecal DCA; suppressing activation of TLR4/MyD88 pathway; ameliorating inflammation; maintaining mucosal barrier integrity; restoring metabolic dysfunction	AOM/DSS mice exposed to HFD	[100]
Monomers				
Apple polysaccharides	Increased level of *Lactobacillus* and decreased level of *Fusobacterium*; decreased abundance of *Firmicutes* and increased abundance of *Bacteroides*.	Increasing the intestinal microbiota diversity; reducing the infiltration of colonic immune cells and alleviating colonic inflammation; inhibiting the activation of classical Wnt pathway in colon tissues.	AOM/DSS mice	[101]
Triterpenoid saponins	Deduced the sulfate-reducing bacteria; boosted the beneficial microbes	Improving the intestinal epithelial barrier; reversing the host's inflammatory phenotype; alleviating intestinal inflammatory gut environment.	*Apc*$^{min/+}$ mice	[102]
Berberine	Suppressed pathogenic species, such as *f_ Erysipelotrichaceae*, *Alistipes*; elevated some SCFA-producing bacteria, including *Alloprevotella*, *Flavonifractor*, and *Oscillibacter*.	Changing composition of gut microbiota; increasing SCFAs metabolism.	AOM/DSS mice	[103]
Echinacosides	Attenuated pro-carcinogenic or proinflammatory bacteria *Bilophila*, *Alloprevotella*, *Prevotellaceae_UCG-001*, *Parabacteroides*, and *Escherichia-Shigella*; recovered SCFA-producing bacteria *Faecalibacterium*, *Parasutterella*, *Bifidobacterium*, *Blautia*, *Parvibacter*, *Lactobacillus*, *Dubosiella*, *Akkermansia*, and *Coriobacteriaceae_UCG-002*.	Facilitating butyrate-producing gut bacteria; downregulating PI3K/AKT signaling and EMT.	Intrasplenic injection-induced liver metastatic CRC mice	[104]
Alisol B 23-acetate	Reduced expansion of pathogenic bacteria, such as *Klebsiella*, *Citrobacter*, and *Akkermansia*; increased growth of bacteria including *Bacteroides*, *Lactobacillus*, and *Alloprevotella*.	Attenuating the production of inflammation-related cytokines; droving the gut microbiota in CAC mice toward normal; suppressing inflammatory signaling pathway; maintaining intestinal integrity and functionality.	AOM/DSS mice	[105]

(Continued)

Table 1
(Continued)

CHM	Gut microbial alterations	Associated mechanisms	Diseases/ animal models	Ref
Resveratrol	Increased *Ruminococcus*, *Akkermansia*, *Dehalobacterium*, *Anerostipes*, *Anaeroplasma*, *Blautia*, and *Clostridium*; decreased *Oscillospira* and *Desulfovibrio*.	Preventing early onset of inflammation; increasing anti-inflammatory T cell response; suppressing inflammatory T cell response.	AOM/DSS mice	[106]
Kaempferol	Colonized by SCFA and lactic acid-producing bacteria; lower abundances of potential pathogens such as *Anaerostipes*, *Desulfovibrio*, *Helicobacter*, *Lachnospira*, *Marvinbryantia*, *Oscillibacter*, *Roseburia*, and *Ruminococcus*	Modulating the BA signaling and gut microbiota homeostasis; restoring the damaged intestinal barrier.	*Apc*$^{min/+}$ mice	[107]

AOM: Azoxymethane; BA: Bile acid; CAC: Colitis-associated cancer; CDCA: Chenodesoxycholic acid; CHM: Chinese herbal medicine; CRC: Colorectal cancer; CRS: Chronic restraint stress; DCA: Deoxycholic acid; DSS: Dextran sodium sulfate; EMT: Epithelial-mesenchymal transition; GQD: Gegen Qinlian Decoction; HFD: High-fat diet; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; PZH: Pien Tze Huang; SCFA: Short-chain fatty acid; SND: Sini Decoction; XCHT: Xiaochaihu decotion; XLP: Xianglian pill; XYS: Xiaoyao power; YYFZBJS: Yiyi Fuzi Baijiang san.

Regulating gut microbiota structure and metabolic function

Chinese herbal compounds, single medicinal materials, and monomer components can directly affect the composition of the gut microbiota, thus adjusting the balance of flora to treat CRC[9]. Based on AOM/dextran sodium sulfate (DSS)–induced CRC, researchers found that apple polysaccharides can increase intestinal flora diversity and inhibit colorectal carcinogenesis[101]. In a *Apc*$^{Min/+}$ mouse model, triterpenoid saponins promoted the growth of beneficial bacteria such as *Bifidobacteria*, *Lactobacilli*, *Bacteroides acidifaciens*, and *Xylanomycetes*, while inhibiting the growth of cancer-promoting bacteria (*Aeromonas* and *Helicobacter pylori*)[102]. In particular, in CRC patients with psychiatric disorders, CHM for treating depression also exerts anti-cancer effects by modulating gut dysbiosis. Xiaoyao powder (*Angelica sinensis*, 10 g, *Paeonia lactiflora*, 10 g; *Bupleuri Radix*, 10 g; *Atractylodis Macrocephalae Rhizoma*, 10 g; *Glycyrrhizae Radix*, 6 g; *Poria* 10 g; *Zingiberis Rhizoma Recens*, 8 g; and *Menthae Haplocalycis Herba*, 6 g), a CHM prescription for treating depression, was shown to suppress tumor growth by regulating the abundance of *Bacteroides*, *Lactobacillus*, *Desulfovibrio*, and *Rikenellaceae* in CRC xenografted mice handled with chronic restraint stress (CRS)[96]. Xiaochaihu decoction (*Radix bupleuri*, 30 g; *Radix scutellariae* 9 g; *Radix glycyrrhizae*, 9 g; *Radix codonopsis*, 9 g; *Rhizoma pinelliae*, 9 g; *Rhizoma zingiberis recens*, 9 g; and *Fructus jujubae*, 10 g) exhibited both tumor-suppressive and anti-depressive effect in patients with CRS-associated CRC (ChiCTR1900027373) and mice, which was mediated by the gut microbiota (reduced abundances of *Parabacteroides*, *Blautia*, and *Ruminococcaceae*), and the underlying mechanism involves in downregulation of TLR4/MyD88/NF-κB signaling[97]. In addition to altering the structure of the gut flora, CHM mediates the metabolism of the gut microbiota. Chen et al.[103] found that berberine significantly upregulated the abundance of short-chain fatty acid (SCFA)-acid-producing bacteria and significantly reduced the occurrence of intestinal tumors in mice. Echinacoside, a dominant phenylethanoid glycoside identified in huangci granules, also benefited the SCFA-producing microbiota with a high butyrate-producing capability to inhibit CRC liver metastasis[104]. The Xianglian pill (*Coptis chinensis Franch*, *Euodia rutaecarpa Benth*, and *Aucklandia lappa Decne*) was shown to effectively inhibit high-fat diet-associated colorectal tumorigenesis by remodeling the gut microbiota and restoring metabolic BA dysfunction with reduced DCA levels[100], as DCA has been associated with CRC growth[108]. Kaempferol attenuated the tumor burden in *Apc*$^{Min/+}$ mice by modulating BA signaling and gut microbiota homeostasis by increasing the abundance of beneficial bacteria (SCFA and lactic acid–producing bacteria) and decreasing the abundance of pathogenic bacteria[107]. To date, most of the current studies are limited to the observation of changes in intestinal flora before and after drug administration; the causal relationship verification and the specific molecular mechanism still need more in-depth studies.

Protecting intestinal mucosal barrier

CHM, which improves intestinal barrier integrity, has been widely investigated and can affect the intestinal flora. Sini decoction (SND; *Aconitum carmichaelii Debx*, 103 g; *Glycyrrhiza uralensis Fisch*, 385 g; and *Zingiber officinale Roscoe*, 512 g), a classic CHM prescription, upregulates the expression of occludin in the colonic mucosal layer, indicating that SND can restrain CRC development by protecting the intestinal barrier[98]. Indole compounds (derived from herbal extracts or biosynthesized from intestinal microbiota) have been shown to act as ligands for the aryl hydrocarbon receptor, which could induce antimicrobial peptide and tight junction molecule production, suggesting a role for indole compounds in the mucosal healing process[109]. Alisol B 23-acetate, a natural tetracyclic triterpenoid found in *Alismatis rhizome*, ameliorates AOM/DSS-induced inflammation by modulating the composition of the gut microbiota and upregulating the expression of mucin-2 and tight junction proteins to improve the intestinal barrier[105]. Flower buds, such as *Sophorae japonica* and *Lonicerae Japonicae* also significantly upregulate the expression of extracellular tight junction protein complexes in the gut epithelial barrier, which is associated with changes in the gut microbiome[110].

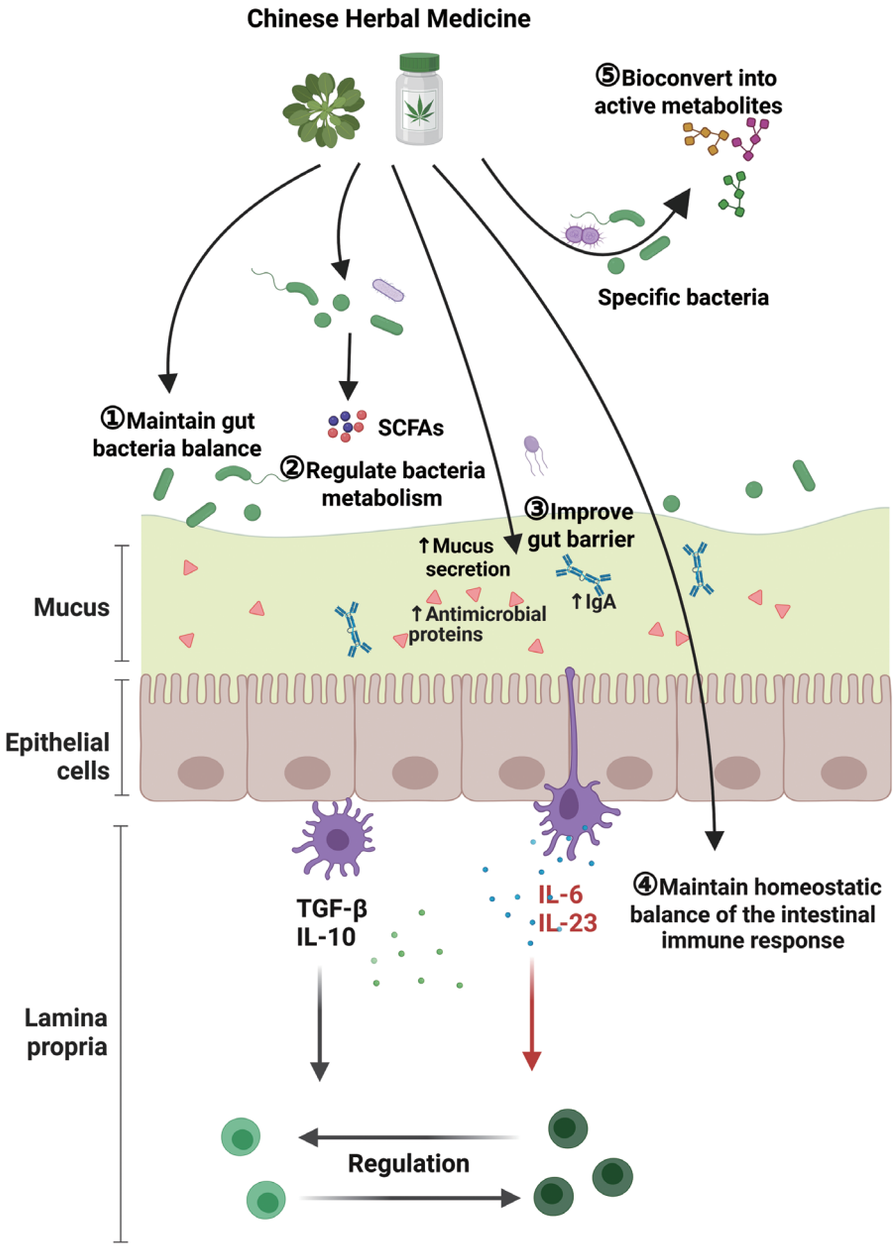


Figure 2. Gut microbiota-based anti-CRC mechanisms of CHM. The anti-CRC mechanisms of CHM from gut microbiota mainly include the following: 1) inhibition of pathogens or promotion of probiotics to restore gut microbiota homeostasis; 2) upregulation of anti-carcinogenic metabolites such as SCFAs; 3) promotion of intestinal mucus layer formation and intestinal barrier repair; 4) modulation of intestinal immune homeostasis; and 5) bioconversion into new active pharmaceutical ingredients that exert stronger anti-cancer effects. CHM: Chinese herbal medicine; CRC: Colorectal cancer; IL: Interleukin; SCFA: Short-chain fatty acid; TGF: Transforming growth factor.

Modulating intestinal immune homeostasis

In the AOM/DSS model, resveratrol treatment attenuated CRC development by causing an increase in anti-inflammatory Tregs and a decrease in proinflammatory Th1 and Th17 cells, which are associated with an altered gut microbiome and SCFA production[106]. Baicalin also maintains the Th17/Treg balance in the colon tissue and regulates oxidative stress and inflammation-induced apoptosis by affecting the intestinal flora and BA metabolism[111]. Furthermore, treatment with baicalin alleviates the tumor immunosuppressive milieu by decreasing PD-L1 expression, reducing MDSCs populations, and inducing $CD4^+$ and $CD8^+$ T cells in tumor models, thus improving antitumor immunity[112]. In addition to its protective role in the intestinal barrier, SND upregulates $CD8^+$ T lymphocytes in the colonic mucosal layer, inhibits $CD4^+$ T cells in intestinal cancer tissues, and significantly reduces intestinal pathogenic bacteria (*B. fragilis* and sulfate-reducing bacteria)[98]. Yiyi Fuzi Baijiang san (*Coix seed*, 10 g; *Radix Aconiti Lateralis*, 2 g; and *Patrinia villosa*, 5 g) treatment blocked tumor initiation and progression in $Apc^{Min/+}$ mice by regulating their natural gut flora, including *B. fragilis* and *Lachnospiraceae*. In turn, the reshaped gut microbiota reduces immunosuppressive Tregs in the intestinal lymphatic and mesenteric lymph nodes[99]. Despite these research endeavors, the deep and complex relationships among CHM, microbiota, and immune regulation in CRC are still obscure and remain important research areas in the future.

Biotransforming into bioactive compound by gut microbiota

The interaction between gut microbes and CHM is complex and bidirectional; gut microbiome composition and function can be influenced by CHM, and vice versa, gut microbiota can also directly interfere with the absorption and metabolism of TCM and affect its pharmacological activities[9]. Specific metabolic enzymes produced by the intestinal flora can transform the structure of a drug and alter its bioavailability, bioactivity, or toxicity[113], thereby producing new active pharmaceutical ingredients that exert stronger anti-cancer effects. Ferulic acid, a hydroxycinnamic acid abundant in TCM, can be biotransformed to 4-vinylguaiacol (2-methoxy-4-vinylphenol) by the intestinal microflora; 4-vinylguaiacol exhibits significantly enhanced anti-tumor activity in chemotherapy-resistant colon cancer cells[114]. Baicalin, the main constituent of the Chinese herb *Scutellaria baicalensi*, is bioconverted into baicalein by the intestinal microbiota. In the *Apc*$^{Min/+}$ mouse model, intestinal bacteria can rapidly convert baicalin into baicalein, which has stronger bioactive effects than baicalin, significantly inhibits intestinal inflammation, and induces apoptosis in tumor cells[115]. As the main ingredient of ginseng species, Ginsenoside Rb1 can be biotransformed into compound K (CK) by the gut microbiota, and the latter exerts stronger potential for cancer chemoprevention and anti-inflammatory effects[116]. Panax notoginseng saponins (PNS) can also be biotransformed to ginsenoside CK by the gut microbiota, and studies have shown that PNS inhibits the progression of CRC owing to its regulation of the microbiome balance and the microbial bioconverted product ginsenoside CK[117]. Therefore, the biotransformation of CHM into bioactive compounds by the gut microbiota may offer new avenues for the treatment of CRC.

CHM–microbiota interactions in combined anti-CRC therapy

The combined use of CHM and Western therapy (such as chemotherapy and immunotherapy) in treating CRC has been established to reduce the adverse effects and enhance the efficacy of Western therapy. However, the mechanism of how combined use of CHM boosts the effectiveness of Western therapy remains undetermined. Here, we provide such evidence from the interaction between CHM and gut microbiota.

Enhancing chemotherapeutic efficacy

Combining CHM and conventional chemotherapy in CRC treatment shows to significantly enhance chemotherapeutic efficacy. Co-administration of resveratrol was shown to enhance the efficacy of 5-FU, and moreover, overcome drug resistance *via* various mechanisms, including regulation of cell cycle distribution, oxidant, apoptosis, anti-inflammatory effects[118–120]. Accumulating studies report that resveratrol has a positive effect on gut barrier integrity, microbial composition, and its metabolites[121], indicating gut microbiota might be a potential mechanism for the enhanced chemotherapeutic efficacy by resveratrol. Gegen Qinlian decoction (GQD, *Radix Puerariae*, 20 g; *Scutellariae Radix*, 12 g; *Coptidis*, *Rhizoma*, 12 g; and *liquorice*, 8 g) also shows to reverse chemoresistance of oxaliplatin in CRC as evidenced with reduced volume of tumor xenografts in nude mice, and adjusted intestinal flora with decreased Firmicutes/Bacteroidetes ratio[122]. Lang et al.[123] constructed a capecitabine-loaded nanoparticle using the prebiotic xylan-stearic acid conjugate (SCXN) for CRC treatment in CT26 tumor-bearing mouse model, and showed that SCXN enhances the anti-tumor effect of capecitabine, facilitates probiotics proliferation and SCFAs production. These data suggest that prebiotics-based nanoparticle delivery may be a promising CRC treatment by combining gut microbiota modulation and chemotherapy.

Enhancing immunotherapeutic efficacy

Immune checkpoint inhibitors (ICIs) have offered promising approaches for tumor treatment. Researchers indicate that CHM can work synergistically with ICIs to boost drug sensitization. The combination of GQD and anti-PD-1 antibodies effectively inhibited the growth of CT26 transplanted tumors, significantly enriched intestinal probiotics, increased the proportion of $CD8^+$ T cells in peripheral blood and tumor tissues, demonstrating the potential of CHM application to enhance tumor immunotherapy through the modulation of intestinal flora[95]. Since gut microbiota can influence ICIs therapeutic efficiency, GQD may boost the anti-tumor efficacy of PD-1 by modification gut microbiome. Changweiqing decoction (CWQ, *Astragalus mongholicus*, 30 g; *Codonopsis pilosula*, 15 g; *Atractylodes*, 15 g; *Polyporus umbellatus*, 24 g; *Coix seed*, 30 g; *Fructus akebiae*, 24 g; *Sargentgloryvine*, 30 g; *Wild grapevine*, 30 g) can enhance the anti-tumor effect of PD-1 inhibitor therapy by regulating the immune microenvironment and gut microbiota. CWQ increased the abundance of *Akkermansia*, which was found to be positively correlated with the proportion of infiltrated $CD8^+PD\text{-}1^+$, $CD8^+$, and $CD3^+$ T cells, thus, CWQ may modulate the TME by modifying the gut microbiota and consequently enhance the anti-tumor effect of PD-1 inhibitor therapy[124].

Reducing side effects

Despite having been widely used in clinics, chemotherapy may cause severe toxicity such as myelosuppression, nausea, vomiting, diarrhea, and peripheral neuropathy[125]. CHM has been shown to alleviate chemotherapeutic toxicity. Carboxymethylated pachyman (CMP) in combination with 5-FU could reverse intestinal shortening and alleviate 5-FU–induced colon injury. CMP counteracted the intestinal microflora disorders produced by 5-FU with an increased proportion of *Bacteroidetes*, *Lactobacilli*, butyric acid– and acetic acid–producing bacteria, and restoring the intestinal flora diversity[126]. Berberine and dehydrodiisoeugenol (DDIE) showed to mitigate irinotecan-induced intestinal mucositis by improving mucosal barrier function, decreasing both bacterial β-glucuronidase (GUS) activity and GUS-producing bacteria, without impairing the anti-CRC efficacy of irinotecan[127–128]. Therefore, by controlling

gut microbiota, CHM can reduce the side effects, paving a way for developing CHM-based strategies to reduce drug toxicity.

Conclusions and perspectives

With emerging omics technologies such as metagenomics and metabolomics, the role and mechanism of intestinal flora in the development of CRC and in the diagnostic/therapeutic clinical application of CRC have been revealed. As an important method for comprehensive treatment of CRC, CHM has been proven to exert anti-tumor effects by acting on the intestinal flora. However, most studies on the regulation of intestinal flora in the prevention and treatment of CRC by CHM remain phenomenal, and limitations, such as large heterogeneity, low comparability, and poor reproducibility among different studies, still exist. To this end, we propose relevant research recommendations in the following aspects: 1) based on epidemiological research, multi-omics techniques should be combined to systematically describe the characteristics of the intestinal flora in diverse types of TCM syndromes, thus benefiting the exploration of the biological basis of TCM syndromes in CRC and facilitating precision treatment with CHM; 2) regarding CHM clinical trials, large samples and multicenter, prospective clinical trials are needed to clarify the association between specific flora and the efficacy of CHM, thus promoting evidence-based clinical use of CHM in CRC therapy; and 3) research on the underlying mechanisms of intestinal flora-mediated anti-tumor effects should be directed at the level of a single strain using engineered bacteria, germ-free, and gene-modified animals. In addition, the pivotal targets of tumor-promoting or tumor-suppressive processes should be elucidated. Comprehensive research on how the gut microbiome interacts with CHM will facilitate interventions using CHM and microbiota-modulated strategies for CRC treatment to achieve greater clinical efficacy.

Conflict of interest statement

The authors declare no conflict of interest.

Funding

This work were supported by the National Natural Science Foundation of China (82104955, 82205223), the Shanghai Rising-Star Program (22QA1408700, 21YF1444500), and the China Postdoctoral Science Foundation (2022M712154).

Author contributions

Xinxin Hou, Haidong Guo, and Ling Zhao conceived and designed the study. Xinxin Hou and Xinyi Li wrote the paper. Wanqing Chen and Weikang Zhu screened the literature and gave feedback on drafts of the paper. Haidong Guo and Ling Zhao reviewed the manuscript. All authors approved the final version.

Ethical approval of studies and informed consent

Not applicable.

Acknowledgments

None.

Data availability

All data generated or analyzed during this study are included in this published article.

References

[1] Li N, Lu B, Luo C, et al. Incidence, mortality, survival, risk factor and screening of colorectal cancer: a comparison among China, Europe, and Northern America. *Cancer Lett* 2021;522:255–268.
[2] Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 Countries. *CA Cancer J Clin* 2021;71(3):209–249.
[3] Ciardiello F, Ciardiello D, Martini G, et al. Clinical management of metastatic colorectal cancer in the era of precision medicine. *CA Cancer J Clin* 2022;72(4):372–401.
[4] Biller LH, Schrag D. Diagnosis and treatment of metastatic colorectal cancer: a review. *JAMA* 2021;325(7):669–685.
[5] Sun Q, He M, Zhang M, et al. Traditional Chinese medicine and colorectal cancer: implications for drug discovery. *Front Pharmacol* 2021;12:685002.
[6] Wong CC, Yu J. Gut microbiota in colorectal cancer development and therapy. *Nat Rev Clin Oncol* 2023;20(7):429–452.
[7] Hou X, Zheng Z, Wei J, et al. Effects of gut microbiota on immune responses and immunotherapy in colorectal cancer. *Front Immunol* 2022;13:1030745.
[8] Zhong LL, Chen HY, Cho WC, et al. The efficacy of Chinese herbal medicine as an adjunctive therapy for colorectal cancer: a systematic review and meta-analysis. *Complement Ther Med* 2012;20(4):240–252.
[9] Zhao H, He M, Zhang M, et al. Colorectal cancer, gut microbiota and traditional Chinese medicine: a systematic review. *Am J Chin Med* 2021;49(4):805–828.
[10] Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000;343(2):78–85.
[11] Appunni S, Rubens M, Ramamoorthy V, et al. Emerging evidence on the effects of dietary factors on the gut microbiome in colorectal cancer. *Front Nutr* 2021;8:718389.
[12] Slade DJ. New Roles for fusobacterium nucleatum in cancer: target the bacteria, host, or both? *Trends Cancer* 2021;7(3):185–187.
[13] Pleguezuelos-Manzano C, Puschhof J, Rosendahl Huber A, et al. Mutational signature in colorectal cancer caused by genotoxic pks(+) E. coli. *Nature* 2020;580(7802):269–273.
[14] Cao Y, Wang Z, Yan Y, et al. Enterotoxigenic bacteroides fragilis promotes intestinal inflammation and malignancy by inhibiting exosome-packaged miR-149-3p. *Gastroenterology* 2021;161(5):1552–1566.e12.
[15] Ma X, Zhou Z, Zhang X, et al. Sodium butyrate modulates gut microbiota and immune response in colorectal cancer liver metastatic mice. *Cell Biol Toxicol* 2020;36(5):509–515.
[16] Mi H, Dong Y, Zhang B, et al. Bifidobacterium infantis ameliorates chemotherapy-induced intestinal mucositis via regulating T cell immunity in colorectal cancer rats. *Cell Physiol Biochem* 2017;42(6):2330–2341.
[17] Shi L, Sheng J, Chen G, et al. Combining IL-2-based immunotherapy with commensal probiotics produces enhanced antitumor immune response and tumor clearance. *J ImmunoTher Cancer* 2020;8(2):e000973.
[18] Lu Y, Cui A, Zhang X. Commensal microbiota-derived metabolite agmatine triggers inflammation to promote colorectal tumorigenesis. *Gut Microbes* 2024;16(1):2348441.
[19] Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell* 2006;124(4):837–848.
[20] Dzutsev A, Badger JH, Perez-Chanona E, et al. Microbes and cancer. *Annu Rev Immunol* 2017;35:199–228.
[21] Loke YL, Chew MT, Ngeow YF, et al. Colon carcinogenesis: the interplay between diet and gut microbiota. *Front Cell Infect Microbiol* 2020;10:603086.

[22] Zhang X, Coker OO, Chu ES, et al. Dietary cholesterol drives fatty liver-associated liver cancer by modulating gut microbiota and metabolites. *Gut* 2021;70(4):761–774.
[23] Nguyen TT, Ung TT, Kim NH, et al. Role of bile acids in colon carcinogenesis. *World J Cases*. 2018;6(13):577–588.
[24] Xu R, Wang Q, Li L. A genome-wide systems analysis reveals strong link between colorectal cancer and trimethylamine N-oxide (TMAO), a gut microbial metabolite of dietary meat and fat. *BMC Genomics* 2015;16(Suppl 7):S4.
[25] Cuevas-Ramos G, Petit CR, Marcq I, et al. Escherichia coli induces DNA damage in vivo and triggers genomic instability in mammalian cells. *Proc Natl Acad Sci U S A* Jun 222010;107(25):11537–11542.
[26] Cougnoux A, Dalmasso G, Martinez R, et al. Bacterial genotoxin colibactin promotes colon tumour growth by inducing a senescence-associated secretory phenotype. *Gut* 2014;63(12): 1932–1942.
[27] Wang X, Huycke MM. Extracellular superoxide production by Enterococcus faecalis promotes chromosomal instability in mammalian cells. *Gastroenterology* 2007;132(2):551–561.
[28] Goodwin AC, Destefano Shields CE, Wu S, et al. Polyamine catabolism contributes to enterotoxigenic Bacteroides fragilis-induced colon tumorigenesis. *Proc Natl Acad Sci U S A* 2011;108(37):15354–15359.
[29] Buc E, Dubois D, Sauvanet P, et al. High prevalence of mucosa-associated E. coli producing cyclomodulin and genotoxin in colon cancer. *PLoS One* 2013;8(2):e56964.
[30] Arthur JC, Perez-Chanona E, Muhlbauer M, et al. Intestinal inflammation targets cancer-inducing activity of the microbiota. *Science* 2012;338(6103):120–123.
[31] He Z, Gharaibeh RZ, Newsome RC, et al. Campylobacter jejuni promotes colorectal tumorigenesis through the action of cytolethal distending toxin. *Gut* 2019;68(2):289–300.
[32] Cao Y, Oh J, Xue M, et al. Commensal microbiota from patients with inflammatory bowel disease produce genotoxic metabolites. *Science* 2022;378(6618):eabm3233.
[33] Salvucci M, Crawford N, Stott K, et al. Patients with mesenchymal tumours and high Fusobacteriales prevalence have worse prognosis in colorectal cancer (CRC). *Gut* 2022;71(8):1600–1612.
[34] Silva CJN, Eremina YO, Rodrigues S, et al. Detection of Fusobacterium spp in colorectal tissue samples using reverse transcription polymerase chain reaction with minor groove binder probes: an exploratory research. *Porto Biomed J* 2018;3(3):e22.
[35] Casasanta MA, Yoo CC, Udayasuryan B, et al. Fusobacterium nucleatum host-cell binding and invasion induces IL-8 and CXCL1 secretion that drives colorectal cancer cell migration. *Sci Signal* 2020;13(641):eaba9157.
[36] Yang Y, Weng W, Peng J, et al. Fusobacterium nucleatum increases proliferation of colorectal cancer cells and tumor development in mice by activating Toll-like receptor 4 signaling to Nuclear Factor-kappaB, and Up-regulating expression of MicroRNA-21. *Gastroenterology* 2017;152(4):851–866.e24.
[37] Guo S, Chen J, Chen F, et al. Exosomes derived from Fusobacterium nucleatum-infected colorectal cancer cells facilitate tumour metastasis by selectively carrying miR-1246/92b-3p/27a-3p and CXCL16. *Gut* 2021;70:1507–1519.
[38] Long X, Wong CC, Tong L, et al. Peptostreptococcus anaerobius promotes colorectal carcinogenesis and modulates tumour immunity. *Nat Microbiol* 2019;4(12):2319–2330.
[39] Guo P, Tian Z, Kong X, et al. FadA promotes DNA damage and progression of Fusobacterium nucleatum-induced colorectal cancer through up-regulation of chk2. *J Exp Clin Cancer Res* 2020;39(1):202.
[40] Rubinstein MR, Wang X, Liu W, et al. Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/beta-catenin signaling via its FadA adhesin. *Cell Host Microbe* 2013;14(2):195–206.
[41] Chen Y, Peng Y, Yu J, et al. Invasive Fusobacterium nucleatum activates beta-catenin signaling in colorectal cancer via a TLR4/P-PAK1 cascade. *Oncotarget* 2017;8(19):31802–31814.
[42] Liu QQ, Li CM, Fu LN, et al. Enterotoxigenic Bacteroides fragilis induces the stemness in colorectal cancer via upregulating histone demethylase JMJD2B. *Gut Microbes* 2020;12(1):1788900.
[43] Hanahan D. Hallmarks of cancer: new dimensions. *Cancer Discov* 2022;12(1):31–46.
[44] Fukata M, Chen A, Vamadevan AS, et al. Toll-like receptor-4 promotes the development of colitis-associated colorectal tumors. *Gastroenterology* 2007;133(6):1869–1881.
[45] Shi YJ, Zhao QQ, Liu XS, et al. Toll-like receptor 4 regulates spontaneous intestinal tumorigenesis by up-regulating IL-6 and GM-CSF. *J Cell Mol Med* 2020;24(1):385–397.
[46] Engevik MA, Danhof HA, Ruan W, et al. Fusobacterium nucleatum secretes outer membrane vesicles and promotes intestinal inflammation. *mBio* 2021;12(2):e02706-20.
[47] Yu T, Guo F, Yu Y, et al. Fusobacterium nucleatum promotes chemoresistance to colorectal cancer by modulating autophagy. *Cell* 2017;170(3):548–563.e16.
[48] Chen Y, Chen Y, Zhang J, et al. Fusobacterium nucleatum promotes metastasis in colorectal cancer by activating autophagy signaling via the upregulation of CARD3 expression. *Theranostics* 2020;10(1):323–339.
[49] Chung L, Thiele Orberg E, Geis AL, et al. Bacteroides fragilis toxin coordinates a pro-carcinogenic inflammatory cascade via targeting of colonic epithelial cells. *Cell Host Microbe* 2018;23(2):203–214 e5.
[50] Privitera G, Rana N, Scaldaferri F, et al. Novel insights into the interactions between the gut microbiome, inflammasomes, and gasdermins during colorectal cancer. *Front Cell Infect Microbiol* 2021;11:806680.
[51] Hu B, Elinav E, Huber S, et al. Microbiota-induced activation of epithelial IL-6 signaling links inflammasome-driven inflammation with transmissible cancer. *Proc Natl Acad Sci U S A* 2013;110(24):9862–9867.
[52] Usuda H, Okamoto T, Wada K. Leaky gut: effect of dietary fiber and fats on microbiome and intestinal barrier. *Int J Mol Sci* 2021;22(14):7613.
[53] Prorok-Hamon M, Friswell MK, Alswied A, et al. Colonic mucosa-associated diffusely adherent afaC+ Escherichia coli expressing lpfA and pks are increased in inflammatory bowel disease and colon cancer. *Gut* 2014;63(5):761–770.
[54] Martin HM, Campbell BJ, Hart CA, et al. Enhanced Escherichia coli adherence and invasion in Crohn's disease and colon cancer. *Gastroenterology* 2004;127(1):80–93.
[55] Liu X, Cheng Y, Shao L, et al. Alterations of the predominant fecal microbiota and disruption of the gut mucosal barrier in patients with early-stage colorectal cancer. *Biomed Res Int* 2020;2020:2948282.
[56] Yu Y, Cai Y, Yang B, et al. High-fat diet enhances the liver metastasis potential of colorectal cancer through microbiota dysbiosis. *Cancers (Basel)* 2022;14(11):2573.
[57] Yu LC. Microbiota dysbiosis and barrier dysfunction in inflammatory bowel disease and colorectal cancers: exploring a common ground hypothesis. *J Biomed Sci* 2018;25(1):79.
[58] Wu S, Rhee KJ, Albesiano E, et al. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. *Nat Med* 2009;15(9):1016–1022.
[59] Brennan CA, Clay SL, Lavoie SL, et al. Fusobacterium nucleatum drives a pro-inflammatory intestinal microenvironment through metabolite receptor-dependent modulation of IL-17 expression. *Gut Microbes* 2021;13(1):1987780.
[60] Kostic AD, Chun E, Robertson L, et al. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. *Cell Host Microbe* 2013;14(2): 207–215.
[61] Gur C, Ibrahim Y, Isaacson B, et al. Binding of the Fap2 protein of Fusobacterium nucleatum to human inhibitory receptor TIGIT protects tumors from immune cell attack. *Immunity* 2015;42(2):344–355.
[62] Yu AI, Zhao L, Eaton KA, et al. Gut microbiota modulate CD8 T Cell responses to influence colitis-associated tumorigenesis. *Cell Rep* 2020;31(1):107471.
[63] Seely KD, Morgan AD, Hagenstein LD, et al. Bacterial involvement in progression and metastasis of colorectal neoplasia. *Cancers (Basel)* 2022;14(4):1019.
[64] Zheng Z, Hou X, Bian Z, et al. Gut microbiota and colorectal cancer metastasis. *Cancer Lett* 2023;555:216039.
[65] Xu C, Fan L, Lin Y, et al. Fusobacterium nucleatum promotes colorectal cancer metastasis through miR-1322/CCL20 axis and M2 polarization. *Gut Microbes* 2021;13(1):1980347.
[66] Yin H, Miao Z, Wang L, et al. Fusobacterium nucleatum promotes liver metastasis in colorectal cancer by regulating the hepatic immune niche and altering gut microbiota. *Aging (Albany NY)*. 2022;14(4):1941–1958.
[67] Bertocchi A, Carloni S, Ravenda PS, et al. Gut vascular barrier impairment leads to intestinal bacteria dissemination and colorectal cancer metastasis to liver. *Cancer Cell* 2021;39(5):708–724. e11.

[68] Nejman D, Livyatan I, Fuks G, et al. The human tumor microbiome is composed of tumor type-specific intracellular bacteria. *Science* 2020;368(6494):973–980.
[69] Wu Y, Jiao N, Zhu R, et al. Identification of microbial markers across populations in early detection of colorectal cancer. *Nat Commun* 2021;12(1):3063.
[70] Liang Q, Chiu J, Chen Y, et al. Fecal Bacteria act as novel biomarkers for noninvasive diagnosis of colorectal cancer. *Clin Cancer Res* 2017;23(8):2061–2070.
[71] Flemer B, Warren RD, Barrett MP, et al. The oral microbiota in colorectal cancer is distinctive and predictive. *Gut* 2018;67(8):1454–1463.
[72] Wei Z, Cao S, Liu S, et al. Could gut microbiota serve as prognostic biomarker associated with colorectal cancer patients' survival? A pilot study on relevant mechanism. *Oncotarget*. 2016;7(29):46158–46172.
[73] Mima K, Nishihara R, Qian ZR, et al. Fusobacterium nucleatum in colorectal carcinoma tissue and patient prognosis. *Gut* 2016;65(12):1973–1980.
[74] Fong W, Li Q, Yu J. Gut microbiota modulation: a novel strategy for prevention and treatment of colorectal cancer. *Oncogene* 2020;39(26):4925–4943.
[75] Demers M, Dagnault A, Desjardins J. A randomized double-blind controlled trial: impact of probiotics on diarrhea in patients treated with pelvic radiation. *Clin Nutr* 2014;33(5):761–767.
[76] Liu ZH, Huang MJ, Zhang XW, et al. The effects of perioperative probiotic treatment on serum zonulin concentration and subsequent postoperative infectious complications after colorectal cancer surgery: a double-center and double-blind randomized clinical trial. *Am J Clin Nutr* 2013;97(1):117–126.
[77] Kotzampassi K, Stavrou G, Damoraki G, et al. A four-probiotics regimen reduces postoperative complications after colorectal surgery: a randomized, double-blind, placebo-controlled study. *World J Surg* 2015;39(11):2776–2783.
[78] Zaharuddin L, Mokhtar NM, Muhammad Nawawi KN, et al. A randomized double-blind placebo-controlled trial of probiotics in post-surgical colorectal cancer. *BMC Gastroenterol* 2019;19(1):131.
[79] Chung Y, Ryu Y, An BC, et al. A synthetic probiotic engineered for colorectal cancer therapy modulates gut microbiota. *Microbiome*. 2021;9(1):122.
[80] Zhang S, Yang Y, Weng W, et al. Fusobacterium nucleatum promotes chemoresistance to 5-fluorouracil by upregulation of BIRC3 expression in colorectal cancer. *J Exp Clin Cancer Res* 2019;38(1):14.
[81] Geller LT, Barzily-Rokni M, Danino T, et al. Potential role of intratumor bacteria in mediating tumor resistance to the chemotherapeutic drug gemcitabine. *Science* 2017;357(6356):1156–1160.
[82] Vetizou M, Pitt JM, Daillere R, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science* 2015;350(6264):1079–1084.
[83] Xu X, Lv J, Guo F, et al. Gut microbiome influences the efficacy of PD-1 antibody immunotherapy on MSS-type colorectal cancer via metabolic pathway. *Front Microbiol* 2020;11:814.
[84] Mager LF, Burkhard R, Pett N, et al. Microbiome-derived inosine modulates response to checkpoint inhibitor immunotherapy. *Science* 2020;369(6510):1481–1489.
[85] Tanoue T, Morita S, Plichta DR, et al. A defined commensal consortium elicits CD8 T cells and anti-cancer immunity. *Nature* 2019;565(7741):600–605.
[86] Song W, Tiruthani K, Wang Y, et al. Trapping of lipopolysaccharide to promote immunotherapy against colorectal cancer and attenuate liver metastasis. *Adv Mater* 2018;30(52):e1805007.
[87] Wang P, Ding S, Sun L, et al. Characteristics and differences of gut microbiota in patients with different traditional Chinese medicine syndromes of colorectal cancer and normal population. *J Cancer* 2020;11(24):7357–7367.
[88] Li W, Guo J, Wang Q, et al. The efficacy of Chinese herbal medicine as an adjunctive therapy for colorectal cancer: a protocol for systematic review of randomized controlled trials. *Medicine (Baltim)* 2020;99(51):e23216.
[89] Xu Y, Mao JJ, Sun L, et al. Association between use of traditional Chinese medicine herbal therapy and survival outcomes in patients with stage II and III colorectal cancer: a multicenter prospective cohort study. *J Natl Cancer Inst Monogr* 2017;2017(52):lgx015.
[90] Zhang T, He WT, Zi MJ, et al. Cohort study on prognosis of patients with metastatic colorectal cancer treated with integrated Chinese and Western medicine. *Chin J Integr Med* 2018;24(8):573–578.
[91] Liu N, Wu C, Jia R, et al. Traditional Chinese medicine combined with chemotherapy and cetuximab or bevacizumab for metastatic colorectal cancer: a randomized, double-blind, placebo-controlled clinical trial. *Front Pharmacol* 2020;11:478.
[92] Chen Y, Xu YY, Jiang HJ, et al. Patients with metastatic colorectal cancer after failure of second-line treatment may benefit from low-dose apatinib and S-1 combined with jianpi bushen jiedu decoction. *Chin J Integr Med* 2022;28(10):924–929.
[93] Lin YC, Huang WT, Ou SC, et al. Neural network analysis of Chinese herbal medicine prescriptions for patients with colorectal cancer. *Complement Ther Med* 2019;42:279–285.
[94] Gou H, Su H, Liu D, et al. Traditional medicine pien tze huang suppresses colorectal tumorigenesis through restoring gut microbiota and metabolites. *Gastroenterology* 2023;165(6):1404–1419.
[95] Lv J, Jia Y, Li J, et al. Gegen Qinlian decoction enhances the effect of PD-1 blockade in colorectal cancer with microsatellite stability by remodelling the gut microbiota and the tumour microenvironment. *Cell Death Dis* 2019;10(6):415.
[96] Zhang Z, Shao S, Zhang Y, et al. Xiaoyaosan slows cancer progression and ameliorates gut dysbiosis in mice with chronic restraint stress and colorectal cancer xenografts. *Biomed Pharmacother* 2020;132:110916.
[97] Shao S, Jia R, Zhao L, et al. Xiao-Chai-Hu-Tang ameliorates tumor growth in cancer comorbid depressive symptoms via modulating gut microbiota-mediated TLR4/MyD88/NF-kappaB signaling pathway. *Phytomedicine* 2021;88:153606.
[98] Wang Y, Zhang X, Li J, et al. Sini decoction ameliorates colorectal cancer and modulates the composition of gut microbiota in mice. *Front Pharmacol* 2021;12:609992.
[99] Sui H, Zhang L, Gu K, et al. YYFZBJS ameliorates colorectal cancer progression in Apc(Min/+) mice by remodeling gut microbiota and inhibiting regulatory T-cell generation. *Cell Commun Signal*. 2020;18(1):113.
[100] Ye C, Wu C, Li Y, et al. Traditional medicine Xianglian pill suppresses high-fat diet-related colorectal cancer via inactivating TLR4/MyD88 by remodeling gut microbiota composition and bile acid metabolism. *J Ethnopharmacol* 2024;333:118411.
[101] Li Y, Wang S, Sun Y, et al. Apple polysaccharide protects ICR mice against colitis associated colorectal cancer through the regulation of microbial dysbiosis. *Carbohydr Polym* 2020;230:115726.
[102] Chen L, Brar MS, Leung FC, et al. Triterpenoid herbal saponins enhance beneficial bacteria, decrease sulfate-reducing bacteria, modulate inflammatory intestinal microenvironment and exert cancer preventive effects in ApcMin/+ mice. *Oncotarget*. 2016;7(21):31226–31242.
[103] Chen H, Zhang F, Zhang J, et al. A holistic view of berberine inhibiting intestinal carcinogenesis in conventional mice based on microbiome-metabolomics analysis. *Front Immunol* 2020;11:588079.
[104] Wei J, Zheng Z, Hou X, et al. Echinacoside inhibits colorectal cancer metastasis via modulating the gut microbiota and suppressing the PI3K/AKT signaling pathway. *J Ethnopharmacol* 2023;318(Pt A):116866.
[105] Zhu HC, Jia XK, Fan Y, et al. Alisol B 23-acetate ameliorates azoxymethane/dextran sodium sulfate-induced male murine colitis-associated colorectal cancer via modulating the composition of gut microbiota and improving intestinal barrier. *Front Cell Infect Microbiol* 2021;11:640225.
[106] Alrafas HR, Busbee PB, Chitrala KN, et al. Alterations in the gut microbiome and suppression of histone deacetylases by resveratrol are associated with attenuation of colonic inflammation and protection against colorectal cancer. *J Clin Med* 2020;9(6):1796.
[107] Li X, Khan I, Huang G, et al. Kaempferol acts on bile acid signaling and gut microbiota to attenuate the tumor burden in ApcMin/+ mice. *Eur J Pharmacol* 2022;918:174773.
[108] Cong J, Liu P, Han Z, et al. Bile acids modified by the intestinal microbiota promote colorectal cancer growth by suppressing CD8(+) T cell effector functions. *Immunity* 2024;57(4):876–889.e11.
[109] Sugimoto S, Naganuma M, Kanai T. Indole compounds may be promising medicines for ulcerative colitis. *J Gastroenterol* 2016;51(9):853–861.
[110] Xia W, Khan I, Li XA, et al. Adaptogenic flower buds exert cancer preventive effects by enhancing the SCFA-producers, strengthening the epithelial tight junction complex and immune responses. *Pharmacol Res* 2020;159:104809.
[111] Hu Q, Zhang W, Wu Z, et al. Baicalin and the liver-gut system: pharmacological bases explaining its therapeutic effects. *Pharmacol Res* 2021;165:105444.

[112] Song L, Zhu S, Liu C, et al. Baicalin triggers apoptosis, inhibits migration, and enhances anti-tumor immunity in colorectal cancer via TLR4/NF-kappaB signaling pathway. *J Food Biochem* 2022;46(3):e13703.
[113] Weersma RK, Zhernakova A, Fu J. Interaction between drugs and the gut microbiome. *Gut* 2020;69(8):1510–1519.
[114] Luo Y, Wang CZ, Sawadogo R, et al. 4-vinylguaiacol, an active metabolite of ferulic acid by enteric microbiota and probiotics, possesses significant activities against drug-resistant human colorectal cancer cells. *ACS Omega* 2021;6(7):4551–4561.
[115] Wang CZ, Zhang CF, Luo Y, et al. Baicalein, an enteric microbial metabolite, suppresses gut inflammation and cancer progression in Apc(Min/+) mice. *Clin Transl Oncol* 2020;22(7):1013–1022.
[116] Yao H, Wan JY, Zeng J, et al. Effects of compound K, an enteric microbiome metabolite of ginseng, in the treatment of inflammation associated colon cancer. *Oncol Lett* 2018;15(6):8339–8348.
[117] Chen L, Chen MY, Shao L, et al. Panax notoginseng saponins prevent colitis-associated colorectal cancer development: the role of gut microbiota. *Chin J Nat Med* 2020;18(7):500–507.
[118] Moutabian H, Majdaeen M, Ghahramani-Asl R, et al. A systematic review of the therapeutic effects of resveratrol in combination with 5-fluorouracil during colorectal cancer treatment: with a special focus on the oxidant, apoptotic, and anti-inflammatory activities. *Cancer Cell Int* 2022;22(1):142.
[119] Bu F, Tu Y, Wan Z, et al. Herbal medicine and its impact on the gut microbiota in colorectal cancer. *Front Cell Infect Microbiol* 2023;13:1096008.
[120] Wu XY, Zhai J, Huan XK, et al. A systematic review of the therapeutic potential of resveratrol during colorectal cancer chemotherapy. *Mini Rev Med Chem* 2023;23(10):1137–1152.
[121] Prakash V, Bose C, Sunilkumar D, et al. Resveratrol as a promising nutraceutical: implications in gut microbiota modulation, inflammatory disorders, and colorectal cancer. *Int J Mol Sci* 2024;25(6):3370.
[122] Lin X, Xu L, Gu M, et al. Gegen Qinlian Decoction reverses oxaliplatin resistance in colorectal cancer by inhibiting YTHDF1-regulated m6A modification of GLS1. *Phytomedicine* 2024;133:155906.
[123] Lang T, Zhu R, Zhu X, et al. Combining gut microbiota modulation and chemotherapy by capecitabine-loaded prebiotic nanoparticle improves colorectal cancer therapy. *Nat Commun* 2023;14(1):4746.
[124] Wang T, Wu L, Wang S, et al. Chang Wei Qing Decoction enhances the anti-tumor effect of PD-1 inhibitor therapy by regulating the immune microenvironment and gut microbiota in colorectal cancer. *Chin J Nat Med* 2023;21(5):333–345.
[125] Yue B, Gao R, Wang Z, et al. Microbiota-host-irinotecan axis: a new insight toward irinotecan chemotherapy. *Front Cell Infect Microbiol* 2021;11:710945.
[126] Wang C, Yang S, Gao L, et al. Carboxymethyl pachyman (CMP) reduces intestinal mucositis and regulates the intestinal microflora in 5-fluorouracil-treated CT26 tumour-bearing mice. *Food Funct* 2018;9(5):2695–2704.
[127] Yue B, Gao R, Lv C, et al. Berberine improves irinotecan-induced intestinal mucositis without impairing the anti-colorectal cancer efficacy of irinotecan by Inhibiting Bacterial beta-glucuronidase. *Front Pharmacol* 2021;12:774560.
[128] Gao R, Yue B, Lv C, et al. Targeted inhibition of Gus-expressing Enterococcus faecalis to promote intestinal stem cell and epithelial renovation contributes to the relief of irinotecan chemotoxicity by dehydrodiisoeugenol. *Acta Pharm Sin B* 2024;14(12):5286–5304.