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Gut microbiota: An emerging therapeutic approach of herbal medicine for prevention of colorectal cancer

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The gut dysbiosis has emerged as a prominent player in the pathogenesis and development of colorectal cancer (CRC), which in turn intensifies dysregulated gut microbiota composition and inflammation. Since most drugs are given orally, this dysbiosis directly and indirectly impinges the absorption and metabolism of drugs in the gastrointestinal tract, and subsequently affects the clinical outcome of patients with CRC. Herbal medicine, including the natural bioactive products, have been used traditionally for centuries and can be considered as novel medicinal sources for anticancer drug discovery. Due to their various structures and pharmacological effects, natural products have been found to improve microbiota composition, repair intestinal barrier and reduce inflammation in human and animal models of CRC. This review summarizes the chemo-preventive effects of extracts and/or compounds derived from natural herbs as the promising antineoplastic agents against CRC, and will provide innovative strategies to counteract dysregulated microbiota and improve the lives of CRC patients.

KEYWORDS

intestinal homeostasis, natural products, chronic inflammation, probiotic, immunoenhancement, tumor microenvironment

Abbreviations: AMPK, adenosine 5'-monophosphate-activated protein kinase; APC, adenomatous polyposis coli; AOM, azoxymethane; CAC, colitis associated cancer; COX2, cyclo-oxygenase-2; CRC, colorectal cancer; DSS, dextran sodium sulfate; FOXO3, forkhead box O3; IL-17, interleukin 17; MAPK, mitogen-activated protein kinase; NF- κ B, nuclear factor kappa-B; PI3K, phosphoinositide 3-kinase; TGF- β 1, transforming growth factor- β 1; ROS, reactive oxygen species; SCFAs, short chain fatty acids; STAT3, signal transducer and activator of transcription 3.

1 Introduction

The incidence of colorectal cancer (CRC) has boosted greatly in the last decades and has become the third leading cause of cancer death, which now accounts for approximately 10% of cancer-related mortality in the world (Bray et al., 2018). The high incidence of CRC has been attributed to the increasingly aging population, unfavorable dietary habits, low physical exercise and excessive obesity (Lund et al., 2011). With the in-depth application of high-throughput sequencing technologies, such as 16S rRNA, metagenomics and metatranscriptomics, in human gut microbiota, emerging evidence has implicated the microbiota in the pathogenesis and prognosis of CRC (Watanabe et al., 2020). Some bacterial species including *Fusobacterium* spp., *Enterococcus* spp., *Escherichia coli*, and *Bacteroides* spp. are most commonly associated with the onset and progression of CRC (Lennard et al., 2016). Changes in microbiota composition (dysbiosis) impair the gut barrier function of epithelial tight junctions and the mucus layer. Consequently, it increases the exposure of the epithelium to bacteria and their toxic metabolites, which may have carcinogenic potential to interfere with cell cycle regulation or directly damage DNA. Bacterial translocation also induces chronic inflammation and triggers a cascade of suppressive immune responses associated with the production of procarcinogens or chemicals such as reactive oxygen species (ROS), bacterial genotoxins (colibactin), and hydrogen sulfide (H₂S) (Gagnière et al., 2016). In turn, the excessive oxidative stress aggravates colitis and neoplastic processes. Thus, targeting and improving gut microbial dysbiosis could be plausible therapeutic strategies for the prevention and treatment of CRC.

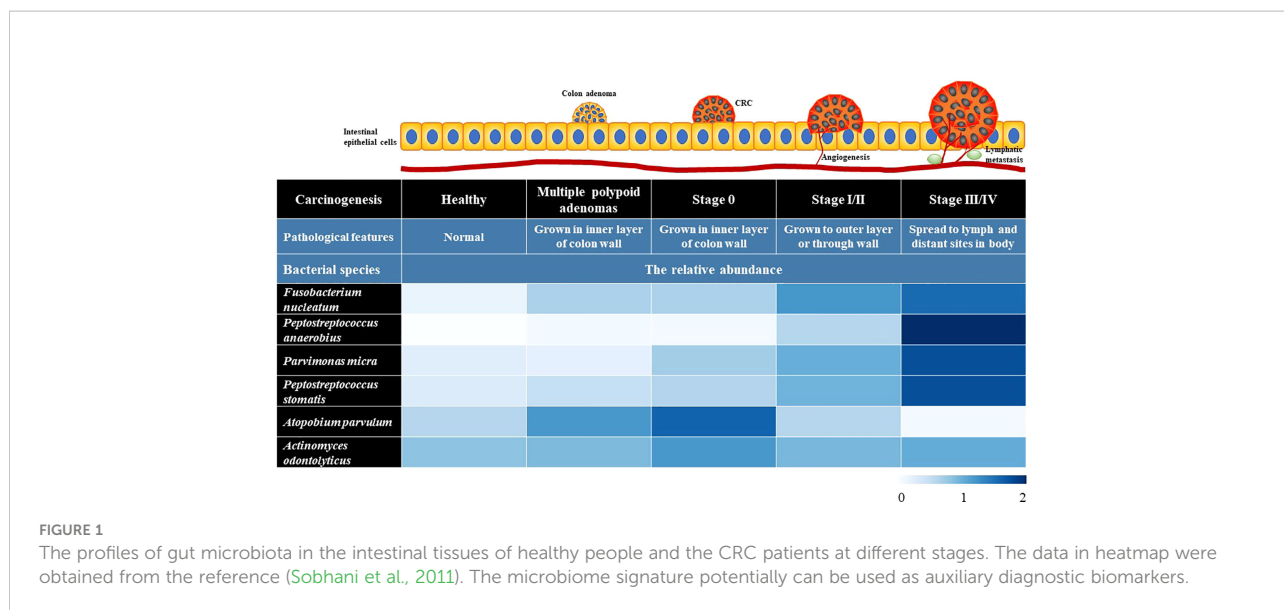
Herbal medicines have been used to prevent and treat diseases for thousands of years which are being developed into decoction and liquid extract for clinical application. When herbal medicines enter the digestive system, they will inevitably come into contact with gut microbes, which could limit excessive inflammatory response and maintain intestinal homeostasis (Chen et al., 2017). Some prodrugs derived from herbal medicines are produced under the metabolism of gut microbes, and subsequently display their antitumor effects to reduce tumor mass and prevent tumorigenesis through several mechanism (Meng et al., 2013; Chen et al., 2016). In addition, bioactive ingredients in herbal medicines may stimulate microorganisms to secrete certain endogenous substances which can enhance barrier stabilization and immune surveillance (Vivarelli et al., 2019). Despite these advances, the underlying molecular mechanism of herbal medicines and their bioactive compounds on microbe-mediated CRC remains extremely deficient. In this review, we highlight the importance of herbal medicine intervention on the intestinal microbiota as an instrument for dysbacteriosis, and consequently, for the prevention of colorectal cancer, suggesting anti-inflammatory, antioxidant and anticarcinogenic properties.

2 Gut microbiota and CRC: Potential disease mechanism

The gut microbiota constitutes a natural defensive barrier to infection. Growing evidence has demonstrated the role of gut microbes in promoting inflammatory responses, creating a suitable microenvironment for the development of skewed interactions between the gut microbiota and cancer initiation (Perillo et al., 2020). Thus, the gut microbiota has been proposed as a novel therapeutic target in light of recent promising data in which it seems to modulate the response to cancer immunotherapy. Moreover, the microbiota involves in numerous protective, structural and metabolic roles in the intestinal epithelium to maintain gut homeostasis. The human intestinal mucosal surface area is more than 200 m². There are about 10³ different microorganisms, which are 10-fold more than the total number of human cells (Sekirov et al., 2010). More than 3×10⁷ genes in the gut microbiota are considered as the second genome of humans, and approximately 10% of the metabolite cycles occur in the human intestinal microecological environment (Gill et al., 2006; Wu et al., 2013). CRC is frequently associated with dramatic alterations in the microbial composition of the tumor and adjacent mucosa (Figure 1). Clinical trials proved that the abundance of *Fusobacterium nucleatum* started at stage 0 and increased as the CRC progressed, while *Atopobium parvulum* and *Actinomyces odontolyticus* were significantly increased in patients with multiple polypoid adenomas and/or stage 0 but no longer increased in more advanced stages, *Peptostreptococcus anaerobius*, *Peptostreptococcus stomatis*, and *Parvimonas micra* increased at stage I–IV (Sobhani et al., 2011). In addition, the number of beneficial bacteria such as *Bifidobacterium*, *Helicobacter oxysporum*, and *Haemophilus* was reduced from the polyps to CRC stage 0 (Mizutani et al., 2020). Although the causal relationship between gut dysbiosis and CRC remains unclear, gut dysbiosis exacerbates the development of colorectal cancer mainly *via* intestinal inflammation, immunotolerance, and oxidative stress (Figure 2).

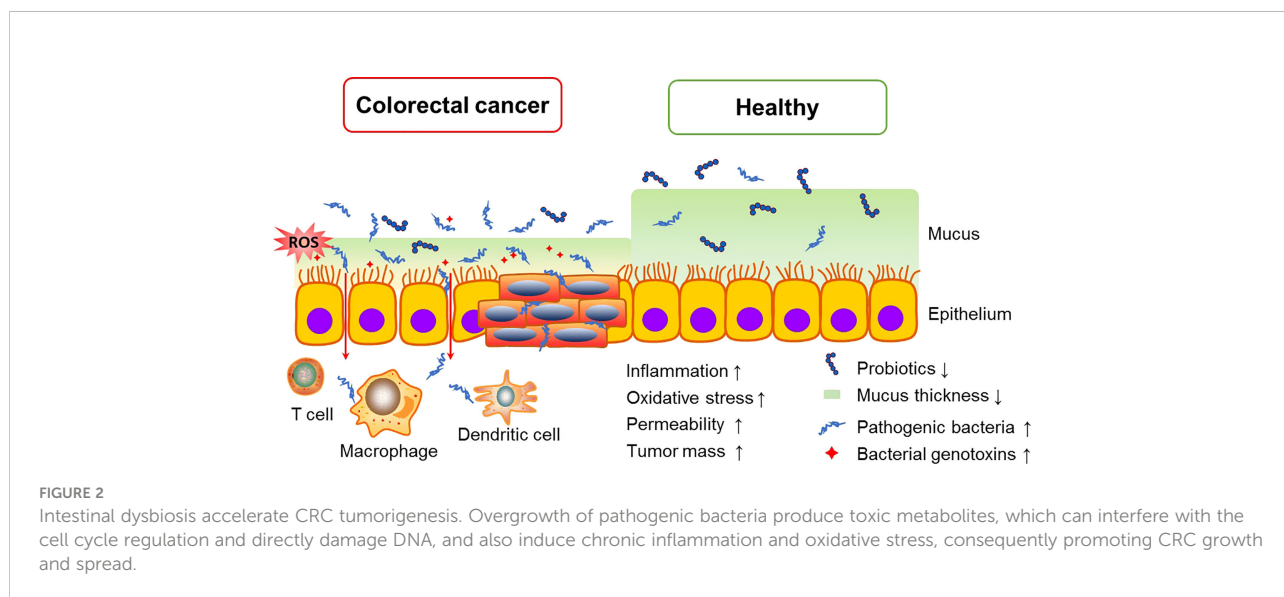
2.1 Inhibition of intestinal inflammation

Inflammations caused by gut microbes are the main mechanisms to induce tumorigenesis (Konstantinov et al., 2013). The disorder of gut microbiota induces the hyperpermeability of the intestinal wall, and then helps the pathogenic bacteria and its endotoxin to break out into the bloodstream, resulting in chronic inflammatory response and immuno-suppression (Avril and DePaolo, 2021). Chronic inflammation reshapes the tumor microenvironment, and promote tumorigenesis and even metastasis *via* activating



numerous exogenous and endogenous signaling pathways (Yu and Fang, 2015). Pathogen recognition receptors (PPRs) are a series of innate immune receptors mainly including toll-like receptors (TLRs) and Nod-like receptors (NLRs). Once the intestinal epithelial barrier is breached, PPRs rapidly sense nucleic acids and antigen components from bacteria and subsequently induce the secretion of type I interferon and antimicrobial peptides to defense against intestinal pathogens. However, inappropriately vigorous innate immune responses can also activate cell survival signaling mainly via NF-κB, STAT3 and MAPK pathways, which elevate the transcription of pro-inflammatory cytokines. Then secondary enteric inflammatory challenges prolong systemic inflammation and expedite proliferation and metastasis of tumor cells (Fukata

and Abreu, 2009). Indeed, the patients with inflammatory bowel disease (IBD) presented an increased risk of developing CRC (Feagins et al., 2009; Rogler, 2014). In those patients, the number of probiotics such as *Lactobacillus* and *Bifidobacteria* is reduced, while *Parvimonas micra*, *Phascolarctobacterium*, *Streptococcus bovis* and *S. gallolyticus* are increased (Uronis et al., 2009; Richard et al., 2018). Oral administration of antibiotics, probiotic preparation or antioxidants significantly decrease the number of mucosal nodules and suppress colon tumorigenesis in the azoxymethane (AOM) and dextran sulfate sodium (DSS)-induced CRC mouse model (Hattori et al., 2019; Luo et al., 2019), suggesting that altering mucosa-associated bacterial microbiota and chronic inflammation in the IBD patients may be beneficial for CRC prevention.



2.2 Regulation of bacterial enzymes and metabolites

Gut microbiota is also involved in the production of various enzymes and metabolites. During gastrointestinal tumorigenesis, the physiological capacities of several bacteria are changed, resulting in the odd levels of bacterial enzymes and their metabolites. Bacterial enzymes including β -glucuronidase, nitroso-reductase, nitrate reductase, β -glucosidase, azo-reductase and 7α -dehydrooxygenase from gut microbiota disorders can induce the alteration of intestinal metabolites (such as secondary bile acids and H_2S), thereby producing various carcinogens and promoting the occurrence of colorectal cancer (Azcárate-Peril et al., 2011). Primary bile acids excreted into the gut are converted into secondary bile acids which can increase reactive oxygen species through microbial derived-metabolism, such as hydrolase, leading to DNA damage and genomic instability, and finally induce the growth of tumors (Saracut et al., 2015). Clostridium converts primary bile acid into deoxycholic acid, increasing free radicals and ROS to induce chronic inflammation and colorectal cancer. H_2S is a metabolite produced by sulfate-reducing bacteria in the gut tract which can cause DNA damage, free radical release, colonic mucosal inflammation and hyperplasia, suppress cytochrome oxidase and DNA methylation, and ultimately contribute to tumor initiation (Wang et al., 2021).

2.3 Reduction of oxidative stress

ROS is also blamed as being a driving force behind CRC initiation. *Enterococcus faecalis* releases extracellular superoxide, and after transformed by hydrogen peroxide, these free radicals as powerful mutagens can cause DNA breakage, and local genomic instability in CRC patients with colorectal cancer (Kabwe et al., 2021; Rivas-Domínguez et al., 2021). Similarly, *Helicobacter pylori* promotes the development of gastrointestinal inflammation and carcinogenesis via elevating ROS and reactive nitrogen species (RNS) to upregulate oncogenic pathways such as HIF-1 α , NF- κ B and PI3K/AKT (Liu et al., 2019; Lu et al., 2020). Therefore, targeting those pathogenic bacteria or counteract their deleterious effects (reducing ROS generation) have been considered as potential strategies for preventing CRC.

3 Herbal medicine, gut microbiota and colorectal cancer

Herbal medicines including herbal formulas, extracts, and compounds have been studied for many years in the treatment of gut-related diseases via regulating gut micro-ecosystem. It can apparently alter the composition and metabolism of gut microbiota, and dramatically affect the number and function of intestinal epithelial cells to achieve the rebalancing of gut microecology (Figure 3) (Li et al., 2021).

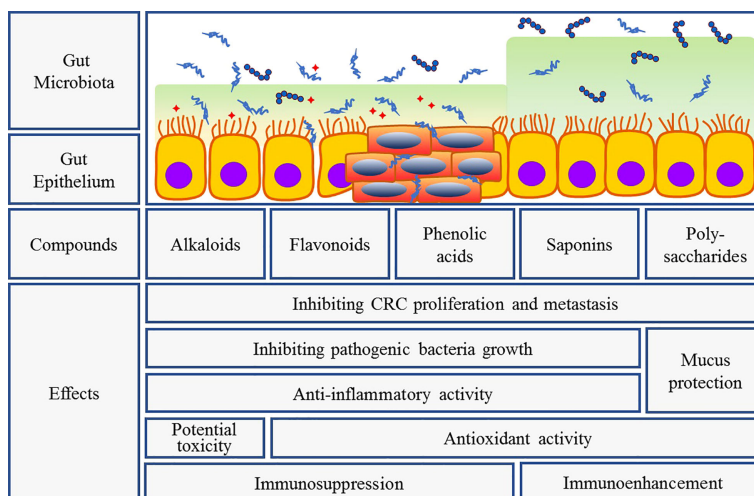


FIGURE 3 Intervention of herbal bioactive components on gut bacteria and CRC. Interaction between herbal medicine and gut microbiota can fight tumor growth and prevent tumorigenesis through several mechanisms: (1) inhibiting pathogenic bacteria overgrowth and promoting probiotics growth; (2) anti-inflammatory and antioxidant activities as well as intestinal mucosal protection and immune regulation; (3) direct anti-tumor activity. But different components exert their respective features.

3.1 Regulation of gut microbiota and metabolites by herbal medicine

Herbal medicines are rich in chemical constituents which contains not only bioactive ingredients such as glycosides, flavonoids, alkaloids, quinones and steroids, but also nutrients such as protein and vitamins, leading to the variety of their pharmacodynamic effects. The mechanism of herbal medicine in improving gut microbiota imbalance includes two aspects: inhibiting pathogenic bacterial overgrowth and promoting probiotics growth. At present, CRC-associated probiotics are mainly divided into three categories: *Lactobacillus*, *Bifidobacterium*, and Gram-positive cocci. On the one hand, probiotics indirectly inhibit the growth and invasion of pathogenic bacteria through strengthening the barrier function of intestinal epithelial cells and producing beneficial metabolites (Kaur et al., 2021). On the other hand, probiotics have physiologically positive effects on the host (animals or human) through regulating the immune function of the host mucosa and system, or improving the balance of gut nutrition and microbiota composition. What's more, probiotics also play a role in inhibiting allergies, controlling serum cholesterol level, and regulating immune function such as metabolic transformation and metabolic detoxification for preventing the gastrointestinal carcinogenesis (Paveljšek et al., 2021).

Many herbal medicines, such as *Ganoderma Lucidum*, American Ginseng, Red Ginseng, *Gynostemma Pentaphyllum*, and Curcumin, significantly inhibit the growth of pathogenic bacteria such as *Clostridium*, *Escherichia*, *Staphylococcus*, *Verrucomicrobia* but increase the number of probiotic *Bifidobacteria* and *lactobacilli*, resulting in the increased diversity of the gut microbiota in DSS-induced CRC mouse model (Guo et al., 2015; McFadden et al., 2015; Yu et al., 2015; Chen et al., 2016; Wang et al., 2016; Gong et al., 2019; Lv et al., 2019; Jiang et al., 2020; Shen et al., 2020; Sui et al., 2020; Sun et al., 2020; Zhang et al., 2020; Hao et al., 2021; Wang et al., 2021; Zhang et al., 2021; Zhu et al., 2021). These anti-CRC profiles of herbal medicine on gut microbiota are summarized as shown in Table 1.

3.2 Anti-inflammatory and intestinal mucosal immunity of herbal bioactive ingredients

It has been known that chronic intestinal inflammation is closely related to gut microenvironment, and gut inflammation mostly leads to colorectal cancer (Konstantinov et al., 2013; Avril and DePaolo, 2021). Under physiological conditions, both gut bacteria and viruses can't transmit through the mucosa. However, when inflammatory and neoplastic intestinal disorders exist, the permeability of intestinal barrier will

increase, causing higher translocation of bacteria and viruses into the bloodstream. The active ingredients of herbal medicines can alleviate the stimulating effect of gut microbiota on tumors by improving the tumor microenvironment, such as inflammation and immunosuppression, thus inhibiting the development of tumors and even the metastasis and recurrence after operation.

Coptidis Rhizoma (also called as Huanglian), is derived from the rhizome of *Coptis chinensis* Franch., *Coptis deltoidea* C.F. Cheng et Hisao or *Coptis teeta* Wall. Berberine is a main active alkaloid isolated and identified from this herb. Evidences support the folkloric medicinal properties of *Coptidis Rhizoma*, in particular berberine, as a promising anticancer candidate in CRC via inducing AMPK activation and autophagic cell death (Huang et al., 2017; La et al., 2017). Berberine mitigates intestinal inflammation and oxidant stress through blocking the IL-6/STAT3, Nrf2 and PPAR pathways on colitis-associated tumorigenesis in mice (Li et al., 2017; Zhu et al., 2019). Moreover, it can not only significantly increase the abundance of *Brucella*, *Bacteroides*, *Clostridium butyricum* and *Helicobacter* in gut tract, but also protects intestinal epithelial cells against CRC-induced intestinal barrier dysfunction (Zhu et al., 2019).

Genistein is the predominant isoflavone found in Leguminous plants (such as *Sophora japonica* L. and *Glycine max*) and acts as the strong tyrosine kinase inhibitor, topoisomerase inhibitor and PPAR γ agonist. It exerts phytoestrogenic, antioxidant and anti-inflammatory effects on gut microenvironment via regulating COX-2-related signaling pathway in CRC mice (He et al., 2016; Song et al., 2018). Crocin, a natural carotenoid from saffron (*Croci stigma*) and gardenia (*Gardeniae fructus*), can inhibit the expression of pro-inflammatory cytokines and inducible inflammatory enzymes in AOM/DSS-induced colorectal inflammation model, and significantly reduce inflammation and mucosal ulcer (Kawabata et al., 2012). The flavanol-rich foods as well as red wine polyphenolics inhibited ROS generation and NF- κ B activation in colon cells by inducing miR-126 and miR-146a (Noratto et al., 2011; Angel-Morales et al., 2012).

FCT, a synbiotic combination of probiotic *Lactobacillus gasseri* 505 (LG) and *Cudrania tricuspidata* leaf extract (CT), reduced the risk of colitis-associated colon cancer via regulating inflammation, carcinogenesis, and gut microbiota composition. Compared with CT and LG, FCT significantly down-regulated pro-inflammatory mediators (TNF- α , IFN- γ , IL-1 β , IL-6, iNOS and COX-2), and up-regulated anti-inflammatory cytokines (IL-4 and IL-10). In addition, FCT enhanced gut barrier function via up-regulating mucus layer markers (MUC-2 and TFF3) and tight junction (occludin and ZO-1), decreasing *Staphylococcus* and increasing *Lactobacillus*, *Bifidobacterium*, and *Akkermansia*, resulting in the increased production of short-chain fatty acids (SCFAs) (Oh et al., 2020).

Table 1 Regulation of herbal medicine on gut microbiota changes in CRC-related animal models.

Herbal name	Animal model	Gut Microbiota change	Anti-CRC mechanism	Reference(s)
Red Ginseng (Radix Et Rhizoma Ginseng)	Trinitro-Benzene-Sulfonic acid induced ulcerative colitis Wistar rats	Bifidobacteriu↑ Lactobacillu↑ E.coli↓	Promotes probiotic growth; inhibits pathogenic bacteria growth	(Zhu et al., 2021)
American Ginseng (Radix Panacis Quinquefolii)	AOM/DSS-induced colitis and colon carcinogenesis A/J mice	Firmicutes↑ Verrucomicrobia ↓	Inhibits inflammatory cytokines; inhibits pathogenic bacteria growth	(Wang et al., 2021)
Gynostemma Leaf (Gynostemmatis Pentaphylli Folium)	C57BL/6J-Apc ^{Min/+} mice	Sulfate-reducing bacteria↓	Inhibits pathogenic bacteria growth; modulates inflammatory intestinal microenvironment.	(Zhang et al., 2021)
Curcumin	AOM-induced colitis and colon cancer IL10 ^{-/-} mice	Lactobacillus↑ Coriobacterales↓	Promotes probiotic growth; inhibits pathogenic bacteria growth	(Hao et al., 2021)
Berberine	DMH-induced colon cancer mice	Fusobacterium nucleatum↓ Tenericutes↓ Verrucomicrobia↓	Inhibits pathogenic bacteria growth; increases the secretion of IL-21/22/31 and CD40L; up-regulates the expression of p-STAT3, p-STAT5 and p-ERK1/2.	(Zhang et al., 2020)
Yi-Yi-Fu-Zi-Bai-Jiang-San (YYFZBJS)	C57BL/6J-Apc ^{Min/+} mice	Bacteroides fragilis Lachnospiraceae	Reduces Intestinal lymphatic, and mesenteric lymph nodes, accumulated CD4 ⁺ CD25 ⁺ Foxp3 ⁺ Treg cells, along with reduction of the phosphorylation of β-catenin.	(Shen et al., 2020)
Wu Mei Wan (WMW)	AOM/DSS-induced CAC mouse	Bacteroidetes↓ Bacteroidales_s24-7_group↓ Firmicutes↑ Lachnospiraceae↑	Regulates the balance between “tumor-promoting bacteria” and “tumor-suppressing bacteria” and inactivated the NF-κB/IL-6/STAT3 pathway.	(Sun et al., 2020)
Gegen Qinlian decoction (GOD)	Patients with CRC	Megamonas↓ Veillonella↓ Bacteroides↑ Akkermansia↑ Prevotella↑	Promotes probiotic growth; inhibits pathogenic bacteria growth.	(La et al., 2017)
Neohesperidin (NHP)	Apc ^{Min/+} mouse	Bacteroidetes↓ Firmicutes↑ Proteobacteria↑	Promotes probiotic growth; inhibits pathogenic bacteria growth.	(Huang et al., 2017)
Evodiamine (EVO)	AOM/DSS-induced CAC mouse	Enterococcus faecalis↓ Escherichia col↓ Bifidobacterium↑ Campylobacter↑ Lactobacillus↑	Promotes probiotic growth; inhibits pathogenic bacteria growth; inhibits the IL6/STAT3/P65 signaling pathway.	(Li et al., 2017; Zhu et al., 2019)
Pai-Nong-San (PNS)	AOM/DSS-induced CAC mouse	Firmicutes↑ Bacteroidetes↓ Proteobacteria↑ Lactobacillus↑	Regulates the expression of CD4 ⁺ and CD8 ⁺ T cells; inhibits the production of HIF-α, IL-6, and TNF-α; promotes the expression of IL-4 and IFN-γ in colon tissues; improves gut microbiota; inhibits the Wnt signaling pathway.	(He et al., 2016)

(Continued)

Continued Herbal name	Animal model	Gut Microbiota change	Anti-CRC mechanism	Reference(s)
Xiaoyaosan (XYS)	CRC xenografts mice	Bacteroides Lactobacillus Desulfovibrio Rikenellaceae.	Promotes probiotic growth; inhibits pathogenic bacteria growth.	(Kawabata et al., 2012; Song et al., 2018)
Huangqin-tea (HQT)	Pseudo-germ-free rat model	Lachnospirillum↓ Altipes↑ Roseburia↑ Lactococcus↑ Bacteroides↓ Parasutterella ↓ Clostridiales↓.	Decreases IL-1β, IL-6, IL-10, and TNF-α expression; elevates IFN-γ production; Promotes probiotic growth; inhibits pathogenic bacteria growth.	(Noratto et al., 2011)
Qixie capsule	Patients with metastatic colorectal cancer	g_Bifidobacterium ↓ Collinsella ↓ Ruminiclostridium_9 ↓	Enhances CD4+ cells among mCRC patients; increase the abundance of gut anticancer bacteria Actinobacteria and butyrate-producing bacteria Lachnospiraceae.	(Angel-Morales et al., 2012)

AOM, azoxymethane; DSS, dextran sulfate sodium; DMH, 1,2-dimethylhydrazine; SCFAs, short-chain fatty acids; TCM, traditional Chinese medicine; APC, adenomatous polyposis coli; ↑, upregulate, ↓downregulate.

Most notably, clinical responses to immune checkpoint inhibitors are closely associated with the abnormal gut microbiome composition, especially the relative abundance of *Akkermansia muciniphila* (Routy et al., 2018). Although several herbal medicines had been demonstrated to prevent the CRC growth, reduce side effects of chemotherapy and enhance the efficacy of PD-1 inhibitors *via* modulating the gut microbiota composition and CD4+ T cell proportion in tumor beds (Lv et al., 2019; Zhang et al., 2021; Huang et al., 2022; Messaoudene et al., 2022), the key orchestrators responsible for the primary resistance to PD-1 blockers remain unclear.

3.3 Improving bioavailability of herbal medicine by gut microbiota

Gut microbiota modifies the chemical composition of herbal medicine through their own enzymatic system. Intestinal cells also influence the metabolism and absorption of herbal medicine through transporter proteins and metabolic enzymes. After underwent by gut microbiota biotransformation (including hydrolysis, oxidation and reduction reaction), the chemical composition, pharmacological activity and toxicity of the herbal medicines will be changed, and it will form new active metabolites. Therefore, the biotransformation induced by gut microbiota has a central impact on exerting the efficiency of herbal medicine (Shen et al., 2013).

3.3.1 Glycosides

Most glycosides, including saponins, flavonoids and anthraquinones, will be hydrolyzed by gut microbiota to remove glycosyl groups and form aglycones, which reduces polarity, increases lipo-solubility and facilitates absorption into the blood. Both licorice and ginseng contain saponins. Glycyrrhetic acid could be detected in normal rats after oral administration of glycyrrhizin, but not in sterile rats, indicating that gut microbiota could be converted into glycyrrhetic acid and then absorbed by organisms (Takeda et al., 1996). Gut microbiota can promote the absorption and metabolic transformation of ginsenoside Rb1 and ginsenoside Rd, which can promote the biosynthesis of RNA and protein, regulate body metabolism and enhance immune function (Kim et al., 2014). Compound K, the main metabolite of ginseng saponin, induces apoptosis of colorectal cancer cells by inhibiting histone deacetylase activity (Kang et al., 2013). Most flavonoids, such as baicalin and isoquercitrin, are α-glucosylated by gut microbiota, but those enzymatical modification enhances their intestinal absorption and pharmacological action (Wang et al., 2015; Lee et al., 2017; Terao, 2017). More notably, degraded by *Clostridium orbiscindens*, diet flavonoids were cracked and converted into desaminotyrosine, which can up-regulate the signal pathway of type I interferon and enhance the host antiviral immune response (Steed et al., 2017).

3.3.2 Alkaloids

Alkaloids are a class of nitrogen-containing organic compounds, which have strong pharmacological activities in the central nervous system, cardiovascular system, immune function, anti-bacterial, anti-inflammatory and anti-cancer. As like as flavonoids, many alkaloids, such as berberine, aconitine and scopolamine, are usually characterized by small molecules, or by ether bonds and coordination bond which are prone to hydrolysis and dehydration under the action of gut microbiota. Under the action of gut bacteria, aconitine, a poisonous alkaloid mainly obtained from *Aconitum carmichaeli* *Debx* which shows chondroprotective activity can produce new monoester, diester and lipid alkaloids through deacetylation, demethylation, dehydroxylation and esterification, which greatly reduces the toxicity of aconitine and alleviates intestinal irritation (Tong et al., 2014). α -Chaconine, a potato glycoside alkaloid, induces apoptosis of HT-29 colon cancer cells by activating caspase-3 and inhibiting ERK 1/2 phosphorylation, and inhibits *Enterobacter aerogenes*, *Escherichia coli* and *Staphylococcus aureus* (Yang et al., 2006).

3.3.3 Phenylpropanoids

Phenylpropanoids generally have lactone structure, including phenylpropionic acid, coumarin and lignans. After the catalysis of gut microbiota, lactone structure can be broken or demethylated. The metabolic transformation of silymarin in *Eubacterium limosum* produced demethylsilybin A, demethylsilybin B, demethylisosilybin A and demethylisosilybin B which had stronger inhibitory effects on Alzheimer's amyloid protein- β 42 (Zhang et al., 2014). Proteasome degraded flaxseed lignans in human intestinal tract bacteria. Hydrolysis and deglycosylation removed two sugars to form isopine resin diol diester (SECO). Pine resin diol diester was produced by digestive *Streptococcus Petostreptococcus productus*, *Eubacterium limosum*, *Clodium methoxybenzo-vorans* and *Eggetalata tarda* under the action of digestive *peptococcus*, *Eubacterium limosum*, *Clodium methoxybenzo-vorans* and *Eggetalata tarda*. They were demethylated and dehydroxylated to form enterediol and enterolactone (Eeckhaut et al., 2008; Woting et al., 2010; Mabrok et al., 2012). A study of the metabolic mechanism of lignans in flaxseed, demonstrated that Ruminal Prevotella was the main microbial group for lignans metabolism (Schogor et al., 2014).

4 Conclusion and perspectives

Herbal medicines contain a variety of bioactive compounds and have unique advantages on maintenance of intestinal homeostasis and regulation of host immune. It precisely regulates the microbiota composition to indirectly prevent the CRC occurrence and development. On the other hand, the active ingredients in herbal medicine can directly inhibit the growth of colon cancer cells. Gut microorganisms produce many metabolic

enzymes during their growth and reproduction, such as hydrolase, lyase, transferase and redox enzymes, which improve the bioavailability of the effective components of herbal medicine by biotransformation. Many active ingredients of Chinese herbal medicines can be transformed by gut microorganisms to produce metabolites with strong pharmacological effects, which can be easily absorbed by the body and exert anticancer activity. Thus, herbal medicine has the promise of preventing or delaying CRC progression *via* maintenance of intestinal homeostasis.

However, it should be pointed out that, in terms of current research, there is no evidence that herbal medicine can cure tumors only by improving gut microbiota, or more by exerting direct effects on cancer cells. Secondly, it is difficult to determine the sequence of the effects of herbal medicine and gut microbiota, just like the problem of "eggs and chickens" which one appears first. Although some specific bacteria that cause a precancerous phenotype *in vivo* have been identified, whether gut dysbiosis is the culprit behind CRC rather than a result of inflammation is still in dispute. Thus, deep signal regulation pathways and key targets of gut microbiota as a potent herbal medicine intervention in colorectal cancer need to be further explored.

Author contributions

H-ZY, WX, and M-CW searched the articles and drafted the manuscript. J-QH and H-HZ checked the contents. H-ZY and C-HY revised the manuscript. C-HY was responsible for the project administration and funding acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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