**REVIEW PAPER**

# Natural Bioactive Compounds and Traditional Chinese Medicine in Colorectal Cancer: A Comprehensive Review

Sanjay Samanth Manthena[1]*Santosh Kumar Ranajit[2], Kilari Eswar Kumar[3], Satya Obbalareddy[4]

*[1*]Department of Pharmacy Practice, AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, India*

*[2]Department of Pharmacology, School of Pharmacy and Life Sciences, Centurion University of Technology and Management, Bolangir, Odisha, India*

*[3]Department of Pharmacology, AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, India.*

*[4]Department of Health System Management Studies, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India*

**ABSTRACT**

Colorectal cancer (CRC) is a leading cause of cancer-related illness and death around the world. This situation calls for new treatment strategies that go beyond traditional chemotherapy and targeted therapies. Research shows that plant-based compounds and traditional Chinese medicine (TCM) can be effective in managing CRC. Phytochemicals like curcumin, berberine, resveratrol, and fangchinoline have anti-tumor effects through various pathways. They can induce cell death, regulate cell recycling, activate ferroptosis, change metabolism, affect gut bacteria, and suppress epithelial-mesenchymal transition (EMT). Additionally, TCM formulas such as Qingjie Fuzheng Decoction, Yiqi Huayu Jiedu Decoction, and Astragalus-Curcuma combinations also show significant promise. They work by targeting immune responses, the interactions between gut bacteria and the immune system, and important signaling pathways like PI3K/AKT/mTOR and Notch to inhibit tumor growth, liver spread, and cancer stemness. Together, these findings highlight the potential of plant-based treatments and TCM as valuable options for preventing and treating CRC. Future clinical trials and deeper understanding will be important for incorporating these natural methods into modern cancer care.

**Keywords** Colorectal cancer, Phytochemicals, Traditional Chinese Medicine, Apoptosis, Gut microbiota, Epithelial-mesenchymal transition (EMT)

**How to cite this article:** Manthena SS, Ranajit SK, Kumar KE, Obbalareddy S. Natural Bioactive Compounds and Traditional Chinese Medicine in Colorectal Cancer: A Comprehensive Review. Int J Drug Deliv Technol. 2026;16(10s): 610-624; DOI: 10.25258/ijddt.16.10s.74

**Source of support:** Nil.

**Conflict of interest:** Nil.

## INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies of the gastrointestinal tract and ranks as the second leading cause of cancer-related deaths globally [1]. Recent epidemiological evidence highlights that unhealthy eating patterns along with a sedentary lifestyle marked by minimal physical activity are major contributors to the rising annual incidence of CRC, thereby posing a severe threat to public health [2]. In contrast, developed nations have witnessed a reduction in CRC cases, largely due to widespread screening programs and continuous improvements in diagnostic technologies. The prognosis of CRC varies with disease stage: while patients diagnosed at stage I have a 5-year survival rate of nearly 90%, this falls to 72% in locally advanced cases and drops drastically to about 14% in metastatic disease [3].

Current clinical management strategies for CRC include surgery, radiotherapy, targeted biologics, and immunotherapy, each with notable limitations. For instance, endoscopic procedures are largely confined to early, non-metastatic lesions, and radiation therapy often leads to complications such as gastrointestinal disturbances and bone marrow suppression. Similarly, only a limited subset of patients benefits from targeted therapies, and these treatments may also cause unintended side effects [4,5].

Metabolic reprogramming is a key feature of CRC, as tumor cells compete for nutrients to grow and survive in a constantly changing environment. Oncogenes, tumor suppressor genes, and epigenetic changes all play a role in this adaptive metabolic shift. Metabolic reprogramming is a major area of interest in understanding the pathophysiology of CRC, as sporadic benign adenomas develop to malignant CRC due to changes in glucose, lipid, and amino acid metabolism [6]. Epigenetic remodelling and metabolic reprogramming are bidirectional regulatory pathways found in numerous malignancies, including CRC. Metabolic signalling and abnormal metabolite accumulation can lead to epigenetic changes, affecting gene expression and enzyme activity. Epigenetic changes and tumor metabolism play a key role in the development of

**Author for Correspondence:* Sanjay Samanth Manthena

CRC. The metabolome-epigenome connection is crucial for regulating cellular states and tumor heterogeneity. Colorectal cancer (CRC) develops through a complex, stepwise process involving genetic mutations, epigenetic modifications, and interactions within the tumour microenvironment [7]. The transformation of normal colonic epithelium into malignancy primarily occurs via three well-recognized molecular routes: chromosomal instability (CIN), microsatellite instability (MSI), and the CpG island methylator phenotype (CIMP). CIN, the predominant pathway, is marked by aneuploidy and alterations in key genes such as APC, KRAS, and TP53. MSI arises from deficiencies in DNA mismatch repair mechanisms and is commonly linked to BRAF mutations in sporadic cases. CIMP, on the other hand, is characterized by extensive promoter hypermethylation that silences tumour suppressor genes [8,9]. Phytomedicines have recently received increased interest as possible agents against CRC, either as standalone therapy or in combination with other treatments. According to research findings, phytomedicines work through a variety of mechanisms, including immune response modulation (via CD4+/CD8+ T cells, dendritic cells, Th17 cells, and regulatory T cells), gut microbiota regulation, targeting colorectal cancer stem cells, influencing macrophage polarization, altering glycolysis and ferroptosis pathways, affecting extracellular vesicle signalling, and protecting mitochondrial function [10] . They also control inflammation, oxidative stress, and autophagy. The purpose of this review is to address phytomedicines' therapeutic potential and underlying mechanisms in CRC, with a focus on promising prospects for future drug development [11].

## 2. DRUGS FOR COLO RECTAL CANCER

### 2.1 Plant Extracts and Phytochemicals in CRC Therapy:

Lentinan (LNT) is a water-soluble polysaccharide extracted from Lentinus edodes (Berk.) sing., known for its potent immune-enhancing properties. Mao et al. found that LNT could promote the maturation of DCs and polarize tumor-associated macrophages to the anti-tumorigenic M1 phenotype (CD11b+CD80+) in the CT26 CRC tumor model. Huang and colleagues also found that LNT suppressed [12,13].

Th17 cells, a subset of CD4+ T cells that produce interleukin-17, are considered protumorigenic immune cells in CRC. Curcumae longae Rhizoma, the root of Curcuma longa L., has been utilized as a dietary supplement for thousands of years. It is also used to treat metabolic problems and cancer. Curcumae Longae Rhizoma primarily consists of curcuminoids, with curcumin being the active element. Wan et al. discovered that a surfactant-formulated curcumin suppressed SW480 cell proliferation by boosting cyclin B1-induced apoptosis and causing cell cycle arrest. It reduced Th17 cell development, reducing intestinal inflammation [14].

Periploca sepium periplosides, derived from the dried root of Periploca sepium Bunge (P. sepium), are used to treat rheumatoid arthritis, dyspepsia, and stomach-aches. Lin et al. found that Periploca sepium periplosides improved gut microbiota structure and suppressed colitis and CAC by inhibiting pathogenic Th17 cells in DSS-induced acute colitis and DSS + AOM-induced CAC models (C57BL/6) [15].

Ginseng fruit (Panax ginseng C.A. Meyer), including both berries and seeds, is known for its immune-boosting benefits. Wang et colleagues. discovered that ginseng berry concentrates strongly suppressed Th17 cell development, modulating the Th17/Treg balance in adaptive immunity. Future study will explore this mechanism using CRC animal models. Plant-derived chemical substances, such as dihydroartemisinin, have been proven to suppress CRC by targeting Th17 cells [16,17].

Rubiginosin B is derived from Rhododendron brachypodum. Geng et al. discovered that rubiginosin B inhibited TGFβ-induced CD4+Foxp3+ Treg cell development, improving the immune system's ability to detect and eliminate tumor cells by modulating the calcineurin-NFAT pathway in CT26 and MC38 xenograft tumor models [18].

Cyasterone is derived from Ajuga decumbens Thunb (Labiatae) or Cyathula officinalis. CRC with mutations in the BRAFV600E gene is highly malignant and has a poor prognosis. Cyasterone treatment in a BRAFV600E-mutant mouse model of CRC increased gut microbiota variety and beneficial bacteria abundance, including Prevotellaceae, Muribaculaceae, and Ruminococcaceae. The study found that cyasterone affects the quantity of beneficial bacteria, although its effectiveness in BRAFV600E-mutant CRC was not explored. The relevance of these probiotics remains unknown [19].

Berberine, a chemical produced from Coptis chinensis, may inhibit CRC via decreasing the Hedgehog pathway and influencing gut microbiota in mice. 5-fluorouracil has been found to decrease the α-diversity of the microbial community in CRC mice. Berberine reduces intestinal flora variety in mice with CRC, according to various research.

Research indicates that berberine does not affect the variety of the intestinal microbiota in animals with CRC. Some research suggests that berberine can improve the diversity of the gut microbiota in animals with CRC [20-30].

Vitexin (apigenin-8-C-glucoside), found in plants such as Crataegus pinnatifida and Vigna radiata, inhibits colitis-associated colorectal cancer (CAC) in AOM/DSS-induced mice by regulating macrophage polarization. It induces M1 polarization in tumor tissues to increase anti-tumor inflammation, while suppressing M1 activity in nearby normal tissues to prevent carcinogenesis. Tang et al. discovered that vitexin targets the vitamin D receptor (VDR) and modulates macrophage polarization via the VDR/PBLD pathway, inhibiting the progression from chronic colitis to CRC. Similarly, Jiedu Xiaozheng Yin, a multi-herb combination, slows CRC growth by boosting M1 and suppressing M2 polarization via the TLR4 pathway [31-34].

Dictamnine, a derivative of Dictamnus dasycarpus Turcz., inhibits CRC growth in DLD-1 xenograft mice by

triggering ferroptosis and decreasing M2 macrophage polarization via MAPK pathway modulation. Similarly, hydroxy genkwanin, macelignan, Jianpi Jiedu decoction, emodin, curcumin, 23-hydroxybetulinic acid, and cucurbitacin B inhibit M2 polarization, leading to their anti-proliferative and anti-metastatic actions on CRC [35-42].

Rhus chinensis Mill., a traditional medicinal herb used in China, India, and Japan, has powerful anticancer properties. Wang et al. found that its triterpenoids (TER) block glycolysis in SW620 and HCT116 CRC cells by decreasing glucose uptake, lactate generation, and downregulating genes such GLUT1, LDHA, and PKM2 [95]. TER suppresses glutaminolysis [96] while increasing glycolytic gene expression in $CD8^+$ T cells, boosting immunological recognition and decreasing CRC tumor development [43-45].

Atractylenolide I, isolated from Atractylodis Macrocephalae Rhizoma, has significant anti-CRC action. Wang et al. demonstrated that it affects the Warburg effect and stemness by inhibiting the AKT/mTOR pathway, resulting in death and decreased invasion in COLO205, HCT116 cells, and HCT116 xenograft models [46]. Similarly, Ma et al. found that atractylenolide I induce apoptosis and inhibits glycolysis in HCT116 and SW480 cells via the JAK2/STAT3 pathway, supporting its therapeutic potential [47].

Saponin monomer 13 (DT-13), isolated from Liriopes Radix, has significant anti-inflammatory and anti-tumor properties [98-101]. In CRC, DT-13 inhibits GLUT1-mediated glycolysis in HCT-15 and HT-29 cells, as well as in HCT-15 orthotopic xenograft models, and lowers spontaneous adenomas in APC^min mice by regulating the AMPK/mTOR system. Interestingly, a lower dose (1.25 mg/kg) had stronger antitumor activity than a higher dose (2.5 mg/kg), presumably due to variations in absorption, metabolism, or target selectivity. Further research on its pharmacokinetics, pharmacodynamics, and toxicity is required. Other botanical drugs, such as diosgenin, epigallocatechin-3-gallate, kaempferol, curcumol, naringin, cannabidiol, and Quxie capsule, also slow CRC growth by controlling glycolysis [48-58].

Ferroptosis, an iron-dependent form of cell death characterized by lipid peroxide accumulation, ROS rise, mitochondrial shrinkage, and membrane rupture, has emerged as a viable CRC treatment option, albeit clinical trials are still in their early phases. Ginsenoside Rh3 (GRh3), a microbial metabolite of ginsenoside Rg5, produces ferroptosis by inhibiting SLC7A11 and activating the Stat3/p53/NRF2 pathway, as well as inducing gasdermin D-dependent pyroptosis in HT29 and HCT116 cells in xenograft models. Importantly, GRh3 exhibits no substantial toxicity in hepatic, renal, or normal colorectal cells. Similarly, Lu et al. demonstrated that solanine, the main alkaloid of Solanum nigrum L., causes ferroptotic death in HCT116 and SW480 cells via the ALOX12B/ADCY4 axis [59-64].

Curcumin, the primary bioactive compound of Curcumae longae Rhizoma, induces ferroptosis via a variety of mechanisms, including JNK pathway regulation, inhibition of GPX4 and ferroptosis suppressor protein-1 (in combination with andrographis), PI3K/AKT/mTOR pathway suppression, and modulation of the p53-SLC7A11-glutathione/GPX4 axis. It improves the anticancer activity of chemotherapeutics like 5-fluorouracil and natural medicines like andrographolide while posing minimal toxicity to healthy tissues. However, limited solubility and quick metabolism limit its therapeutic value. To address this, new delivery methods, including as nanocarriers and plant-derived extracellular vesicles, are being developed to improve curcumin's solubility, stability, and targeted distribution, thereby optimizing its therapeutic potential [65-68].

Tai et al. discovered that pennogenin 3-O-beta-chacotrioside and polyphyllin VI from Paris polyphylla can inhibit the release of extracellular vesicles from Fusobacterium nucleatum, a bacterium found in CRC lesions and associated with CRC proliferation and metastasis. This inhibits the invasion of Caco-2 and HT-29 cells [69].

Coptisine, an isoquinoline alkaloid isolated from Coptis chinensis Franch., has demonstrated significant antitumor activity. Han and colleagues found that coptisine significantly reduced cell survival and migration in HCT-116 cells by compromising mitochondrial function, as revealed by a decrease in mitochondrial membrane potential (MMP) and increased reactive oxygen species (ROS) levels. Based on their findings, they postulated that coptisine promotes apoptosis in HCT-116 cells via activating mitochondrial-dependent apoptotic pathways. Furthermore, an examination of the visceral index and survival rates in animals treated with coptisine found no evidence of drug-related toxicity. Overall, our findings indicate that coptisine is a low-toxicity chemical with intriguing anticancer properties [70].

Tanshinone IIA, a natural substance isolated from Salvia miltiorrhiza Bunge, has been shown to have physiological effects on hepatic steatosis, insulin resistance, cardiovascular diseases, and malignancies. Excessive mitochondrial fission affects physiological function, resulting in decreased MMP, increased ROS levels, and mitochondria-mediated apoptosis. Tanshinone IIA inhibits SW837 cell growth and migration via activating the JNK-Mff pathway, which regulates mitochondrial fission. Huo et al. found that Tanshinone IIA triggers IL2-mediated apoptosis in SW480 cells by activating INF2-mediated mitochondrial fission and stimulating the Mst1-Hippo signalling pathway [71-75].

Recent findings indicate that the combination of piperine with celecoxib (CXB) exerts a synergistic effect in colorectal cancer (CRC) therapy. This combination was shown to enhance mitochondrial-mediated apoptosis through elevated ROS generation, caspase activation, and upregulation of apoptotic proteins. Importantly, piperine with CXB markedly reduced the population of CD133+/CD44+ cancer stem cells (CSCs) and downregulated stemness-associated proteins, highlighting its potential role in targeting CSC-driven tumor progression. In vivo studies using the CT26 xenograft

BALB/c mouse model further supported these results, where the combination treatment significantly suppressed tumor growth compared to either agent alone. Mechanistically, piperine was found to synergize with CXB by inhibiting the Wnt/β-catenin signalling pathway and inducing mitochondrial-dependent apoptosis in HT-29 cells. Multiple independent studies consistently confirm the role of piperine in regulating mitochondrial-mediated apoptosis, thereby reinforcing its promise as a potential adjuvant in CRC management [76-80].

Kanglaite injection is an extract of Coix lacryma-jobi (adlay) seed. Wang et colleagues. found that Kanglaite improved the sensitivity of CRC cells to Taxol by inhibiting NF-κB and increasing connexin 43 in a mouse model with subcutaneous tumors. Shi et al. proposed that Kanglaite inhibits EMT via inhibiting NF-κB in CRC cells in a mouse model of subcutaneous tumors using CT26 cells [81,82].

Evodiamine is an anti-tumor substance derived from Tetradium ruticarpum (A. Juss.) T. G. Hartley [182]. Sui et al. discovered that evodiamine inhibits ABCG2-mediated drug resistance by reducing NF-κB in HCT-116/L-OHP cells and a colorectal multidrug-resistant cancer xenograft model in nude mice. Zhao et al. discovered that evodiamine inhibited migration and induced apoptosis in HCT-116 cells by inhibiting the JAK2/STAT3 pathway that triggers NF-κB. Numerous studies indicate evodiamine's ability to regulate inflammation and prevent CRC. Scutellarin, a flavonoid from Scutellaria altissima L., suppresses the Hedgehog pathway and NF-κB-mediated inflammation in mice with AOM/DSS-induced CRC. Xu and colleagues found that scutellarin inhibited the Wnt/β-catenin signalling pathway, lowering blood TNF-α and IL-6 levels in mice, increasing Bax expression, and decreasing Bcl-2 levels in CAC tissues. These data indicate that scutellarin may reduce inflammation through several routes, potentially treating CAC [83-88].

Jujube (Ziziphus jujuba Mill.), a fruit from the Rhamnaceae family, has been used for decades to treat CRC. Ruan et al. discovered that bioactive triterpenes in jujube can prevent CRC by blocking the PI3K/AKT/NF-κB pathway. This investigation revealed several triterpenes that helped with future development attempts [89].

Pristimerin, a triterpenoid, originates from the Celastraceae and Hippocrateaceae families. Yousef et al. discovered that pristimerin inhibited CRC growth by blocking the NF-κB pathway in HCT-116 cells and a BALB/c nude mice model with HCT-116 xenografts. Kim and coworkers found that pristimerin reduces inflammation and cellular proliferation caused by AOM/DSS in colonic tissue. Pristimin increased apoptosis and influenced the AKT/FOXO3a signalling pathway [90-92].

Puerarin, an isoflavone found in Pueraria lobata (Willd.) Ohwi, has been shown to have strong anti-CRC activity. Puerarin's clinical efficacy is restricted by its low solubility and bioavailability. Deng et al. used emulsification/internal gelation to create colon-specific microspheres loaded with puerarin. These microspheres reduced carcinogenesis and metastasis in CRC by decreasing inflammation. More research is needed to confirm the mechanism by which puerarin regulates inflammation and treats CRC [93-97].

Cryptotanshinone, a natural substance produced from Salvia miltiorrhiza Bunge, has been demonstrated to strongly inhibit the proliferation and growth of CRC. Cryptotanshinone inhibits Stat3, a recognized NF-κB activator, leading to death in CRC cells (Li et al., 1999). Zhang et al. discovered that cryptotanshinone inhibited inflammation and angiogenesis in CT26 cells and a CT26 xenograft model using BALB/c mice, preventing CRC proliferation and metastasis. These data indicate that cryptotanshinone's influence on the inflammatory response is critical for treating CRC [98-101].

Zerumbone, a sesquiterpene produced from edible ginger (Zingiber zerumbet Smith), has been proven to reduce CRC through several pathways such as oxidative stress, gut microbiota, and inflammation. Memari et al. discovered that zerumbone increased ROS levels in HT-29 cells, leading to increased apoptosis and inhibited metastasis. Sithara et al. found that zerumbone causes apoptosis in SW480 cells by increasing ROS levels and lowering antioxidant levels [102-109].

Dihydroartemisinin (DHA), a derivative of Artemisia caruifolia Buch. -Ham. ex Roxb. and a widely used antimalarial drug, has demonstrated promising anticancer properties in colorectal cancer (CRC). Yu et al. reported that DHA enhanced the antitumour efficacy of oxaliplatin by modulating the PRDX2–ROS signalling pathway in HCT116 and RKO cells, as well as in HCT116 xenografts in nude mice. Similarly, Yao et al. observed that DHA sensitized 5-fluorouracil-resistant HCT116 TP53−/− cells by inducing ROS-mediated apoptosis. Despite these encouraging findings, further investigations across diverse cell lines and animal models are required to fully elucidate the mechanisms by which DHA regulates oxidative stress in CRC [110,111].

In parallel, dihydromyricetin (DHM), a flavonoid isolated from the leaves of Vitis heyneana Roem. et Schult., has also attracted attention for its anticancer potential. Wang et al. demonstrated that DHM reversed multidrug resistance mediated by MRP2 through inhibition of the NF-κB–Nrf2 signalling pathway in HCT116 and HCT8 cells, and in a BALB/c xenograft model with NF-κB/p65-overexpressing HCT116/OXA cells. Furthermore, Zhang et al. suggested that semaphorin 4D plays a pivotal role in mediating the antioxidant and anti-inflammatory effects of DHM in colon cancer, thereby underscoring its multifaceted therapeutic potential [112-115].

Rhus coriaria (sumac), a member of the Anacardiaceae family, has recently been recognized for its potential role in colorectal cancer (CRC) therapy. Ali Eid et al. demonstrated that extracts of Rhus coriaria exerted notable anti-CRC activity by promoting proteolysis and inducing both autophagic and apoptotic cell death, as shown in HT-29 and Caco-2 cell models. Given that resistance to 5-fluorouracil (5-FU) remains a major limitation in CRC treatment, further studies by the same group revealed that Rhus coriaria inhibited viability, colony formation, and tumour growth in both HCT-116 wild-type and 5-FU-resistant (HCT-116-

5FU-R) cells through the induction of autophagy-mediated cell death. Collectively, these findings highlight Rhus coriaria as a promising natural source for the development of novel therapeutic strategies, particularly in overcoming chemoresistance in CRC [116-121].

Origanum majorana, an herbaceous plant native to southern Europe and the Mediterranean region, has shown promising anticancer potential in colorectal cancer (CRC). Ali Eid and colleagues reported that ethanolic extracts of O. majorana exhibited strong anti-proliferative effects in HT-29 and Caco-2 cells by inducing autophagy and apoptosis. In addition, the essential oil of O. majorana was found to activate p38 MAPK-mediated signalling, leading to autophagy, apoptosis, and caspase-dependent cleavage of P70S6K, ultimately suppressing cell viability and colony formation in HT-29 cells. These findings highlight O. majorana as a potential natural agent for CRC therapy through simultaneous modulation of multiple cell death pathways [122-124].

Dehydroevodiamine, a quinazoline alkaloid isolated from Tetradium ruticarpum (A. Juss.) T. G. Hartley has demonstrated notable anticancer effects in colorectal cancer (CRC). Seung-Heon Hong and colleagues reported that dehydroevodiamine reduced the viability of HCT116, CT26, SW480, and LoVo cells through the induction of caspase-dependent apoptosis and autophagy. Moreover, in an in vivo CT26 mouse model, dehydroevodiamine effectively suppressed lung metastasis by modulating epithelial–mesenchymal transition (EMT). These findings suggest that dehydroevodiamine exerts both anti-proliferative and anti-metastatic activities, underscoring its therapeutic potential in CRC treatment [125,126].

Fangchinoline, an isoquinoline alkaloid derived from Stephania tetrandra S. Moore (Menispermaceae), has been shown to exert anticancer effects in colorectal cancer (CRC). Feng et al. demonstrated that fangchinoline induced apoptosis in HT-29 and HCT116 cells, as well as in an HT-29 xenograft model, through the activation of the AMPK/mTOR/ULK1 signalling axis, thereby promoting autophagy-mediated cell death. These findings highlight fangchinoline as a promising candidate for CRC therapy by targeting metabolic and autophagic pathways [127].

Wogonin, a flavonoid isolated from Scutellaria baicalensis, has demonstrated anticancer potential in colorectal cancer (CRC). Studies have shown that wogonin suppresses the proliferation of SW620 and RKO cells and inhibits epithelial–mesenchymal transition (EMT) by downregulating AKT expression. Its antitumour efficacy has also been confirmed in SW620 and HCT-29 xenograft models in BALB/c nude mice; however, the precise contribution of EMT inhibition to its overall mechanism remains to be fully clarified [128].

Gentisic acid, a phenolic acid and a minor metabolite of salicylic acid, has also been explored for its anti-metastatic role in CRC. In an experimental lung metastasis model, where MC38 cells were intravenously injected into mice, Feng et al. demonstrated that gentisic acid significantly reduced metastatic burden by modulating GPR81-mediated DEPDC5 degradation. These findings suggest that both wogonin and gentisic acid may serve as promising natural agents with complementary mechanisms in CRC therapy, targeting proliferation, EMT, and metastatic progression [129,130].

Echinacoside, a naturally occurring polyphenolic compound, has been shown to inhibit colorectal cancer (CRC) liver metastasis by enhancing the abundance of butyrate-producing gut microbiota. This modulation of the gut microenvironment subsequently suppressed the PI3K/AKT signalling pathway and epithelial–mesenchymal transition (EMT) in a mouse model of liver metastasis induced by intrasplenic injection. Similarly, macelignan, a lignan isolated from Myristica fragrans, demonstrated anti-metastatic effects by preventing macrophage M2 polarization via ROS-mediated inhibition of the PI3K/AKT pathway in a nude mouse model of CRC liver metastases. Another natural compound, brusatol, a quassinoid extracted from Bruceae fructus, was reported to suppress both proliferation and lung metastasis of HCT116, HT29, and SW480 cells. In BALB/c nude mice bearing HCT116 and HT29 xenografts, brusatol exerted its therapeutic effects by activating ARRDC4 and regulating the PI3K/YAP1/TAZ signalling pathway [131-133].

Ji et al. discovered that resveratrol inhibited lung metastases of LoVo cells in a mouse tail vein injection model and liver metastases in a mouse orthotopic transplantation tumor model. Resveratrol prevented cell invasion by reducing EMT via the TGF-β1/Smads pathway, regulating Snail/E-cadherin expression [134].

### 2.2 Traditional Chinese Medicine (TCM) Formulations in CRC Therapy:

Qizhen decoction, a traditional Chinese medicinal mixture, has been effective in treating CRC [29]. In a mouse model of AOM/DSS-induced CRC, QZD paired with a PD-1 inhibitor (InVivoMab) stimulated DC maturation, resulting in IL-12 release and activation of the JAK2/STAT4 pathway. This increased the quantity of Akkermansia, leading to effector T-cell activation.

TXYF is a traditional Chinese formula for treating digestive ailments. TXYF inhibits the hypothalamic-pituitary-adrenal axis and promotes DC maturation, reducing tumor growth in CRC mice under chronic restraint stress. The reaction was characterized by a rise in CD4+ T cells, CD4+/CD8+ T cells, and Th1 cells.

Yi-Yi-Fu-Zi-Bai-Jiang-San (YYFZBJS) is a popular herbal remedy for gastrointestinal illnesses in China. A study on C57BL/6J ApcMin/+ mice found that YYFZBJS efficiently regulates gut flora, specifically Bacteroides fragilis and Lachnospiraceae. Additionally, administering feces from YYFZBJS-treated human volunteers to both conventional and germ-free mice significantly reduced intestinal tumor growth.

Research suggests that the underlying mechanisms involve gut microbiota regulation, suppression of CD4+CD25+Foxp3+ Tregs, and reduced intestinal inflammation (41). Zhang et al. found that YYFZBJS inhibits tumor growth by increasing CD4+CD25+ Tregs.

Targeting HIF-1α induces immunosuppression in MC-38 cells and AOM/DSS-induced CRC animals.

Quxie pill, a natural medication, has been utilized to treat advanced CRC for many years. Chen et colleagues. discovered that the Quxie capsule reduced colorectal carcinogenesis in CRC mice and HCT26 and HCT116 cells by increasing Th17/Treg ratios and reducing Foxp3 expression, a key modulator of Treg activity. Quxie pill may cause gastrointestinal discomfort or diarrhoea due to its herbal components, including Crotonis fructus, which stimulates bowel function [43]. The bad effects of Quxie capsules are typically modest and tolerable, and many CRC patients are ready to continue treatment.

Huangqin decoction has been used to treat gastrointestinal complaints in China for many years. Zhu et al. found that Huangqin decoction reduced colitis and tumor volume, increased apoptosis, and inhibited the PI3K/AKT pathway in AOM/DSS-induced CRC mice, SW480, and HT-29 cells. This resulted in more Clostridium and higher feces butyric acid levels. Ji and colleagues found that Huangqin decoction increased the abundance of Lachnospiraceae, Firmicutes, Fusobacteria, and Clostridium while decreasing the abundance of Eggerthellales in a deoxycholic acid-induced CRC mouse model.

Xiaoyaosan has been used to treat depression in China for centuries. In a CRC xenograft mice model with depression, Xiaoyaosan reduced tumor growth and increased survival by controlling the amount of Bacteroides, Lactobacillus, Desulfovibrio, and Rikenellaceae.

Shao et al. found that Xiao-Chai-Hu-Tang, a well-known TCM prescription, suppressed tumor growth in CRC patients and a subcutaneous tumor model in C57BL/6J (MC38 cells) under depression. This was achieved by modulating the gut microbiota-mediated TLR4/MyD88/NF-κB axis.

This finding may provide hope for CRC patients suffering from depression. San-Wu-Huang-Qin decoction, a well-known TCM prescription, inhibited tumor growth and strengthened the mucosal barrier in CRC mice via modulating gut microbiota, including Escherichia-Shigella, a lipopolysaccharide (LPS)-producing bacterium.

Cheng et al. discovered that Xianlian Jiedu decoction, a popular TCM medicine, can decrease tumor growth in CRC mice. The Xianlian Jiedu decoction improved gut microbiota balance and boosted short-chain fatty acids, sphingolipids, and glycerophospholipids by reducing Turicibacter and Clostridium abundance.

Nanfang Hospital in China has been using the modified Shenlingbaizhu decoction (MSD), a traditional Chinese medicine formula, for cancer treatment for several years. Dai demonstrated that MSD effectively reduced tumors and CD133+ CSCs in CRC mouse tumor tissues. MSD decreased CRC cell pluripotency by reducing TGF-β/Smad-induced epithelial-mesenchymal transition (EMT).

Pien Tze Huang (PZH), a traditional Chinese medicine formula, has shown potential in targeting colorectal cancer (CRC) stem-like cells. It reduces the side population fraction and sphere-forming capacity of HT-29 cells [70]. Peng et al. reported that PZH suppresses CSC properties in SW480 cells via inhibition of the Notch1 pathway [71]. Cao et al. further demonstrated that PZH enhances T-cell-mediated cytotoxicity by downregulating CSC markers in HCT15, HCT116, SW480, and patient-derived CRC organoids [72]. Additionally, phenethyl isothiocyanate from cruciferous vegetables inhibits CRC growth in HCT116 cells and xenograft models by modulating inflammation-linked tumor microenvironments.

Exosomes are small, membrane-bound vesicles that originate from the fusion of multivesicular bodies with the plasma membrane and are subsequently released by cells. These vesicles carry nucleic acids, proteins, lipids, and other biomolecules, acting as carriers of intercellular communication. They interact with recipient cells through specific surface receptors, enabling the transfer of their molecular cargo. Growing evidence highlights the pivotal role of exosomal microRNAs in mediating communication between tumour cells and the surrounding tumour microenvironment. Regulating the levels of exosomes with bioactive components has emerged as a potential therapeutic strategy for colorectal cancer (CRC). JianPi JieDu Recipe (JPJDR), a traditional Chinese medicine formulation, has been widely applied in the management of gastrointestinal malignancies. Research by Ji et al. demonstrated that JPJDR inhibited CRC cell proliferation and migration by influencing ITGBL1-enriched extracellular vesicle–mediated activation of the TNFAIP3-NF-κB pathway, thereby suppressing fibroblast activation. Similarly, the herbal medicine Paris polyphylla has been reported to exert multiple pharmacological activities, such as antifungal, antidiabetic, anti-inflammatory, antioxidant, and immunomodulatory effects, along with promising activity against digestive tract cancers.

Yiqi Huayu Jiedu Decoction, a traditional Chinese medicine (TCM) formulation, has been reported to suppress liver metastasis in colorectal cancer (CRC). In a CRC liver metastasis mouse model, established by intrasplenic injection of CT26-GFP cells, this decoction was shown to enhance the activity of natural killer (NK) cells, thereby reducing metastatic progression. These findings suggest that Yiqi Huayu Jiedu Decoction may exert its therapeutic effects through modulation of the host immune response, highlighting its potential as an immunoregulatory strategy against CRC metastasis.

Astragalus mongholicus Bunge combined with Curcuma aromatica Salisb. (AC), a traditional Chinese medicine (TCM) formulation, has been widely utilized in colorectal cancer (CRC) management. Tang et al. demonstrated that AC effectively suppressed CRC liver metastasis by regulating epithelial–mesenchymal transition (EMT) through modulation of the CXCL8/CXCR2 and PI3K/AKT/mTOR signalling pathways. These findings suggest that the AC combination exerts its therapeutic effects by simultaneously targeting metastatic signalling and EMT, highlighting its potential as a complementary strategy in CRC treatment.

Yi Ai Fang, a TCM compound, affects the development of vasculogenic mimicry in CRC. Modulating HIF-1α and EMT in HCT-116 cells and a xenograft nude mice model.

These data indicate that Yi Ai Fang may have the ability to suppress tumor migration.

**2.3 Plant–Probiotic Synergy and Microbiota-Mediated Chemoprevention in Colorectal Cancer:**

Increasing data suggests that the alteration of the gut microbiota is pivotal in colorectal carcinogenesis. Probiotic microorganisms, notably species of Lactobacillus and Bifidobacterium, have been demonstrated to inhibit the activity of pro-carcinogenic bacterial enzymes such as β-glucuronidase, β-glucosidase, and nitro reductase, hence restricting carcinogen reactivation inside the colon [73,74]. Moreover, microbial metabolites, particularly short-chain fatty acids (SCFAs) like butyrate, modulate epithelial cell proliferation, trigger apoptosis, and inhibit pro-inflammatory signalling pathways such as NF-κB and Wnt/β-catenin, which play essential roles in colorectal tumor progression [75,76]. These results endorse microbiota-targeted approaches as a significant element of colorectal cancer chemoprevention.

Kefir, a multi-strain fermented dairy product comprising lactic acid bacteria and yeasts, has exhibited antioxidant, anti-inflammatory, and anti-tumor characteristics in experimental models. Research indicates that kefir supplementation diminishes oxidative stress, regulates immunological responses, and inhibits tumorigenesis in chemically caused cancer models [77,78]. Kefiran and other bioactive exopolysaccharides in it help its immunomodulatory and anti-proliferative activities even more [78]. Kefir offers a complex microbial consortium that can more effectively regulate intestinal homeostasis than single-strain probiotics.

Much research has looked at phytochemicals or probiotics separately in colorectal cancer models, but there isn't much in vivo evidence about how they work together. Bioactive components from plants, like flavonoids, anthocyanins, and triterpenoids, can help probiotics live longer and work better. Probiotics, on the other hand, can help phytochemicals become more available by changing them into different forms through enzymes [76,79]. Consequently, the amalgamation of plant extracts with probiotic matrices, such as kefir, constitutes a mechanistically sound approach to concurrently address oxidative stress, inflammation, microbial carcinogen activation, and carcinogenic signalling pathways. This integrative strategy enhances the biological feasibility of multi-target chemo preventive strategies in colorectal carcinogenesis [80].

**CONCLUSION**

Colorectal cancer (CRC) remains a major global health challenge, with high incidence, recurrence, and mortality rates despite advances in conventional therapeutic strategies. Increasing evidence demonstrates that plant-derived phytochemicals and Traditional Chinese Medicine (TCM) exert significant anti-cancer effects through diverse mechanisms, including the induction of apoptosis, modulation of autophagy, suppression of epithelial–mesenchymal transition (EMT), regulation of PI3K/AKT/mTOR and related signalling pathways, and reprogramming of the tumor microenvironment. Both single compounds and multi-herb formulations have shown promising efficacy in preclinical studies and, in some cases, clinical applications, highlighting their potential role as complementary or integrative approaches in CRC management. However, challenges such as poor bioavailability, lack of standardization, herb–drug interactions, and limited large-scale clinical validation remain barriers to translation into mainstream oncology. Addressing these gaps through advanced delivery systems, rigorous pharmacological evaluation, and well-designed clinical trials will be crucial for realizing the full therapeutic potential of herbal medicines. Ultimately, integrating evidence-based phytotherapy and TCM with modern oncological practices may offer a safer, more effective, and holistic strategy for the prevention and treatment of colorectal cancer.

**REFERENCE**


1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-63.
2. Patel SG, Karlitz JJ, Yen T, Lieu CH, Boland CR. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. Lancet Gastroenterol Hepatol. 2022;7(3):262-74.
3. Patel SG, Karlitz JJ, Yen T, Lieu CH, Boland CR. The rising tide of early-onset colorectal cancer: a comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. Lancet Gastroenterol Hepatol. 2022 Mar;7(3):262-74. doi:10.1016/S2468-1253(21)00426-X. Epub 2022 Jan 26. PMID: 35090605.
4. Wang Q, Shen X, Chen G, Du J. Drug resistance in colorectal cancer: from mechanism to clinic. Cancers (Basel). 2022;14(12):2928.
5. Abedizadeh R, Majidi F, Khorasani HR, Abedi H, Sabour D. Colorectal cancer: a comprehensive review of carcinogenesis, diagnosis, and novel strategies for classified treatments. Cancer Metastasis Rev. 2024;43(2):729-53.
6. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. Lancet. 2019;394(10207):1467-80.
7. La Vecchia S, Sebastián C. Metabolic pathways

regulating colorectal cancer initiation and progression. Semin Cell Dev Biol. 2020;98:63-70.
8. Okugawa Y, Grady WM, Goel A. Epigenetic alterations in colorectal cancer: emerging biomarkers. Gastroenterology. 2015;149(5):1204-25.e12.
9. Kanai Y, Hirohashi S. Alterations of DNA methylation associated with abnormalities of DNA methyltransferases in human cancers during transition from a precancerous to a malignant state. Carcinogenesis. 2007;28(12):2434-42.
10. Gil J, Ramírez-Torres A, Encarnación-Guevara S. Lysine acetylation and cancer: a proteomics perspective. J Proteomics. 2017;150:297-309.
11. Pino MS, Chung DC. The chromosomal instability pathway in colon cancer. Gastroenterology. 2010;138(6):2059-72.
12. Mao Q, Min J, Zeng R, et al. Self-assembled traditional Chinese nanomedicine modulating tumor immunosuppressive microenvironment for colorectal cancer immunotherapy. Theranostics. 2022;12(14):6088-105.
13. Deng S, Zhang G, Kuai J, et al. Lentinan inhibits tumor angiogenesis via interferon γ and in a T cell independent manner. J Exp Clin Cancer Res. 2018;37(1):260.
14. Wan C, Ma Q, Anderson S, et al. Effects of curcuminoids and surfactant-formulated curcumin on chemo-resistant colorectal cancer. Am J Chin Med. 2023;51(6):1577-94. doi:10.1142/S0192415X23500714.
15. Lin Z, Chen L, Cheng M, et al. Cortex Periplocae modulates the gut microbiota to restrict colitis and colitis-associated colorectal cancer via suppression of pathogenic Th17 cells. Biomed Pharmacother. 2022;153:113399.
16. Wang CZ, Wan C, Luo Y, et al. Ginseng berry concentrate prevents colon cancer via cell cycle, apoptosis regulation, and inflammation-linked Th17 cell differentiation. J Physiol Pharmacol. 2021;72(2):225-37.
17. Wang CZ, Wan C, Luo Y, et al. Effects of dihydroartemisinin, a metabolite of artemisinin, on colon cancer chemoprevention and adaptive immune regulation. Mol Biol Rep. 2022;49(4):2695-709.
18. Geng CA, Chen FY, Zheng JB, et al. Rubiginosin B selectively inhibits Treg cell differentiation and enhances anti-tumor immune responses by targeting calcineurin-NFAT signaling pathway. Phytomedicine. 2023;116:154898.
19. Xiong Y, Zheng X, Xie Y, Gong Y, Luo YI. Effect of cyasterone on intestinal flora in a (BRAF)V600E-mutant mouse model of colorectal cancer. Pharmazie. 2022;77(10):291-4.
20. Sun Q, Yang H, Liu M, et al. Berberine suppresses colorectal cancer by regulation of Hedgehog signaling pathway activity and gut microbiota. Phytomedicine. 2022;103:154227.
21. Wang H, Guan L, Li J, Lai M, Wen X. The effects of berberine on the gut microbiota in Apc (Min/+) mice fed with a high-fat diet. Molecules. 2018;23(9):2298.
22. Wang M, Ma Y, Yu G, et al. Integration of microbiome, metabolomics and transcriptome for in-depth understanding of berberine attenuates AOM/DSS-induced colitis-associated colorectal cancer. Biomed Pharmacother. 2024;179:117292.
23. Chen H, Ye C, Wu C, et al. Berberine inhibits high fat diet-associated colorectal cancer through modulation of the gut microbiota-mediated lysophosphatidylcholine. Int J Biol Sci. 2023;19(7):2097-113.
24. Chen H, Ye C, Cai B, et al. Berberine inhibits intestinal carcinogenesis by suppressing intestinal pro-inflammatory genes and oncogenic factors through modulating gut microbiota. BMC Cancer. 2022;22(1):566.
25. Yan S, Chang J, Hao X, et al. Berberine regulates short-chain fatty acid metabolism and alleviates the colitis-associated colorectal tumorigenesis through remodeling intestinal flora. Phytomedicine. 2022;102:154217.
26. Chen H, Zhang F, Zhang J, Zhang X, Guo Y, Yao Q. A holistic view of berberine inhibiting intestinal carcinogenesis in conventional mice based on microbiome-metabolomics analysis. Front Immunol. 2020;11:566.
27. Wang X, Peng A, Huang C. Suppression of colon cancer growth by berberine mediated by the intestinal microbiota and the suppression of DNA methyltransferases (DNMTs). Mol Cell Biochem. 2024;479(8):2131-41.
28. Wu C, Yang J, Ye C, et al. Berberine attenuates 5-fluorouracil-induced intestinal mucosal injury by modulating the gut microbiota without compromising its anti-tumor efficacy. Heliyon. 2024;10(14):e34528.
29. Deng J, Zhao L, Yuan X, et al. Pre-administration of berberine exerts chemopreventive effects in AOM/DSS-induced colitis-associated carcinogenesis mice via modulating inflammation and intestinal microbiota. Nutrients. 2022;14(4):726.

30. Yang W, Yang T, Huang B, Chen Z, Liu H, Huang C. Berberine improved the microbiota in lung tissue of colon cancer and reversed the bronchial epithelial cell changes caused by cancer cells. Heliyon. 2024;10(2):e24405.
31. He M, Min JW, Kong WL, He XH, Li JX, Peng BW. A review on the pharmacological effects of vitexin and isovitexin. Fitoterapia. 2016;115:74-85.
32. Chen Y, Wang B, Yuan X, et al. Vitexin prevents colitis-associated carcinogenesis in mice through regulating macrophage polarization. Phytomedicine. 2021;83:153489.
33. Chen Y, Liang J, Chen S, et al. Discovery of vitexin as a novel VDR agonist that mitigates the transition from chronic intestinal inflammation to colorectal cancer. Mol Cancer. 2024;23(1):196.
34. Liu H, Yan S, Yang R, et al. Jiedu Xiaozheng Yin inhibits the progression of colitis-associated colorectal cancer by stimulating macrophage polarization towards an M1 phenotype via the TLR4 pathway. Integr Cancer Ther. 2024;23:15347354241247061.
35. Zuo X, Lin H, Song Z, Yu B, Zhao C. Antitumor activity of dictamnine against colorectal cancer through induction of ferroptosis and inhibition of M2 macrophage polarization via the MAPK signaling. Arch Biochem Biophys. 2024;758:110051.
36. Xun J, Hu Z, Wang M, et al. Hydroxygenkwanin suppresses peritoneal metastasis in colorectal cancer by modulating tumor-associated macrophages polarization. Chem Biol Interact. 2024;396:111038.
37. Che N, Li M, Liu X, Cui CA, Gong J, Xuan Y. Macelignan prevents colorectal cancer metastasis by inhibiting M2 macrophage polarization. Phytomedicine. 2024;122:155144.
38. Chang Y, Ou Q, Zhou X, et al. Jianpi Jiedu decoction suppresses colorectal cancer growth by inhibiting M2 polarization of TAMs through the tryptophan metabolism-AhR pathway. Int Immunopharmacol. 2024;138:112610.
39. Sougiannis AT, VanderVeen B, Chatzistamou I, et al. Emodin reduces tumor burden by diminishing M2-like macrophages in colorectal cancer. Am J Physiol Gastrointest Liver Physiol. 2022;322(3):G383-G395. doi:10.1152/ajpgi.00303.2021
40. Ge S, Sun X, Sang L, et al. Curcumin inhibits malignant behavior of colorectal cancer cells by regulating M2 polarization of tumor-associated macrophages and metastasis associated in colon cancer 1 (MACC1) expression. Chem Biol Drug Des. 2023;102(5):1202-1212. doi:10.1111/cbdd.14330
41. Fan Z, Cui Y, Chen L, Liu P, Duan W. 23-Hydroxybetulinic acid attenuates 5-fluorouracil resistance of colorectal cancer by modulating M2 macrophage polarization via STAT6 signaling. Cancer Immunol Immunother. 2024;73(5):83.
42. Zhang H, Zhao B, Wei H, Zeng H, Sheng D, Zhang Y. Cucurbitacin B controls M2 macrophage polarization to suppress metastasis via targeting JAK-2/STAT3 signalling pathway in colorectal cancer. J Ethnopharmacol. 2022;287:114915.
43. Kooshan Z, Cárdenas-Piedra L, Clements J, Batra J. Glycolysis, the sweet appetite of the tumor microenvironment. Cancer Lett. 2024;600:217156.
44. Wang G, Wang YZ, Yu Y, Wang JJ. Inhibitory ASIC2-mediated calcineurin/NFAT against colorectal cancer by triterpenoids extracted from Rhus chinensis Mill. J Ethnopharmacol. 2019;235:255-267.
45. Wang G, Wang YZ, Yu Y, Yin PH, Xu K, Zhang H. The anti-tumor effect and mechanism of triterpenoids in Rhus chinensis Mill. on reversing effector CD8+ T-cells dysfunction by targeting glycolysis pathways in colorectal cancer. Integr Cancer Ther. 2021;20:15347354211017219.
46. Wang K, Huang W, Sang X, et al. Atractylenolide I inhibits colorectal cancer cell proliferation by affecting metabolism and stemness via AKT/mTOR signaling. Phytomedicine. 2020;68:153191.
47. Li Y, Wang Y, Liu Z, Guo X, Miao Z, Ma S. Atractylenolide I induces apoptosis and suppresses glycolysis by blocking the JAK2/STAT3 signaling pathway in colorectal cancer cells. Front Pharmacol. 2020;11:273.
48. Wei X, Mao T, Li S, et al. DT-13 inhibited the proliferation of colorectal cancer via glycolytic metabolism and AMPK/mTOR signaling pathway. Phytomedicine. 2019;54:120-31.
49. Raina S, Hübner E, Samuel E, Nagel G, Fuchs H. DT-13 attenuates inflammation by inhibiting NLRP3-inflammasome related genes in RAW264.7 macrophages. Biochem Biophys Res Commun. 2024;708:149763.
50. 100. Xie G, Tong F, Xu M, Shu Y, Li Z. DT-13 inhibits the proliferation of pancreatic cancer by inducing apoptosis via AMPK-mTOR signaling. Biochem Biophys Res Commun.

2024;695:149451.
51. Wang C, He H, Liu G, et al. DT-13 induced apoptosis and promoted differentiation of acute myeloid leukemia cells by activating AMPK-KLF2 pathway. Pharmacol Res. 2020;158:104864.
52. Li SY, Shang J, Mao XM, et al. Diosgenin exerts anti-tumor effects through inactivation of cAMP/PKA/CREB signaling pathway in colorectal cancer. Eur J Pharmacol. 2021;908:174370.
53. Chen S, Nishi M, Morine Y, et al. Epigallocatechin-3-gallate hinders metabolic coupling to suppress colorectal cancer malignancy through targeting aerobic glycolysis in cancer-associated fibroblasts. Int J Oncol. 2022;60(2):19.
54. Wu H, Cui M, Li C, et al. Kaempferol reverses aerobic glycolysis via miR-339-5p-mediated PKM alternative splicing in colon cancer cells. J Agric Food Chem. 2021;69(10):3060-8.
55. Gan Y, Zhou L, Wang R, et al. Curcumol reduces aerobic glycolysis and overcomes chemoresistance by inducing Cdh1-mediated Skp2 ubiquitination. Am J Chin Med. 2023;51(3):723-40.
56. Pan G, Zhang P, Chen A, et al. Aerobic glycolysis in colon cancer is repressed by naringin via the HIF1A pathway. J Zhejiang Univ Sci B. 2023;24(3):221-31.
57. Sun X, Zhou L, Wang Y, et al. Single-cell analyses reveal cannabidiol rewires tumor microenvironment via inhibiting alternative activation of macrophage and synergizes with anti-PD-1 in colon cancer. J Pharm Anal. 2023;13(7):726-44.
58. Zhang Z, Chen Y, Zheng Y, et al. Quxie capsule alleviates colitis-associated colorectal cancer through modulating the gut microbiota and suppressing A. fumigatus-induced aerobic glycolysis. Integr Cancer Ther. 2022;21:15347354221138534.
59. Zhang Q, Deng T, Zhang H, et al. Adipocyte-derived exosomal MTTP suppresses ferroptosis and promotes chemoresistance in colorectal cancer. Adv Sci. 2022;9(28):e2203357.
60. Li H, Yu K, Hu H, et al. METTL17 coordinates ferroptosis and tumorigenesis by regulating mitochondrial translation in colorectal cancer. Redox Biol. 2024;71:103087.
61. Singhal R, Mitta SR, Das NK, et al. HIF-2α activation potentiates oxidative cell death in colorectal cancers by increasing cellular iron. J Clin Invest. 2021;131(12):e143691. doi:10.1172/JCI143691.
62. Yan H, Talty R, Aladelokun O, Bosenberg M, Johnson CH. Ferroptosis in colorectal cancer: a future target? Br J Cancer. 2023;128(8):1439-51.
63. Wu Y, Pi D, Zhou S, et al. Ginsenoside Rh3 induces pyroptosis and ferroptosis through the Stat3/p53/NRF2 axis in colorectal cancer cells. Acta Biochim Biophys Sin (Shanghai). 2023;55(4):587-600.
64. Luo S, Tian GJ, Yu FX, Wen ZD. A narrative review of the antitumor studies of solanine. Transl Cancer Res. 2021;10(3):1578-82.
65. Xin W, Zhang Y. Curcumin activates the JNK signaling pathway to promote ferroptosis in colon cancer cells. Chem Biol Drug Des. 2024;103(3):e14468.
66. Miyazaki K, Xu C, Shimada M, Goel A. Curcumin and Andrographis exhibit anti-tumor effects in colorectal cancer via activation of ferroptosis and dual suppression of glutathione peroxidase-4 and ferroptosis suppressor protein-1. Pharmaceuticals (Basel). 2023;16(3):383.
67. Chen M, Tan AH, Li J. Curcumin represses colorectal cancer cell proliferation by triggering ferroptosis via PI3K/Akt/mTOR signaling. Nutr Cancer. 2023;75(2):726-33.
68. Ming T, Lei J, Peng Y, et al. Curcumin suppresses colorectal cancer by induction of ferroptosis via regulation of p53 and solute carrier family 7 member 11/glutathione/glutathione peroxidase 4 signaling axis. Phytother Res. 2024;38(8):3954-72.
69. Lin LT, Shi YC, Choong CY, Tai CJ. The fruits of Paris polyphylla inhibit colorectal cancer cell migration induced by Fusobacterium nucleatum-derived extracellular vesicles. Molecules. 2021;26(13):4081.
70. Han B, Jiang P, Li Z, et al. Coptisine-induced apoptosis in human colon cancer cells (HCT-116) is mediated by PI3K/Akt and mitochondrial-associated apoptotic pathway. Phytomedicine. 2018;48:152-60.
71. Zheng L, Li B, Yuan A, et al. TFEB activator tanshinone IIA and derivatives derived from Salvia miltiorrhiza Bge. attenuate hepatic steatosis and insulin resistance. J Ethnopharmacol. 2024;335:118662.
72. Ma L, Zhang T, Wang R, et al. Sodium tanshinone IIA sulfonate protects primary cardiomyocytes against radiation-induced myocardial injury via the p38 pathway. Int Heart J. 2024;65(4):730-7.
73. Rafter J. Probiotics and colon cancer. Best Pract

Res Clin Gastroenterol. 2003;17(5):849-859.
74. Wollowski I, Rechkemmer G, Pool-Zobel BL. Protective role of probiotics and prebiotics in colon cancer. Am J Clin Nutr. 2001;73(2 Suppl):451S-455S.
75. O'Keefe SJ. Diet, microorganisms and their metabolites, and colon cancer. Nat Rev Gastroenterol Hepatol. 2016;13(12):691-706.
76. Eslami M, Yousefi B, Kokhaei P, et al. Importance of probiotics in the prevention and treatment of colorectal cancer. J Cell Physiol. 2019;234(10):17127-17143.
77. Chen HL, Tsai TC, Wu YH, et al. Kefir improves fatty liver syndrome by inhibiting lipid accumulation and oxidative stress. J Dairy Sci. 2014;97(2):879-888.
78. de Moreno de LeBlanc A, Matar C, Farnworth E, Perdigón G. Study of immune cells involved in the antitumor effect of kefir in a murine breast cancer model. J Dairy Sci. 2007;90(4):1920-1928.
79. Rowland IR. The role of gastrointestinal microbiota in colorectal cancer. Curr Pharm Des. 2009;15(13):1524-1531.
80. Zeng X, Zhang Y, Kwok LY, Sun J. Synergistic effects of probiotics and phytochemicals in cancer prevention. Nutrients. 2021;13(1):243.
81. Cao L, Qin Z, Yu T, et al. Tanshinone IIA acts as a regulator of lipogenesis to overcome osimertinib acquired resistance in lung cancer. Biochem Pharmacol. 2024;224:116207.
82. Jieensinue S, Zhu H, Li G, Dong K, Liang M, Li Y. Tanshinone IIA reduces SW837 colorectal cancer cell viability via the promotion of mitochondrial fission by activating JNK-Mff signaling pathways. BMC Cell Biol. 2018;19(1):21.
83. Qian J, Fang D, Lu H, et al. Tanshinone IIA promotes IL2-mediated SW480 colorectal cancer cell apoptosis by triggering INF2-related mitochondrial fission and activating the Mst1-Hippo pathway. Biomed Pharmacother. 2018;108:1658-69.
84. Srivastava S, Dewangan J, Mishra S, et al. Piperine and celecoxib synergistically inhibit colon cancer cell proliferation via modulating Wnt/β-catenin signaling pathway. Phytomedicine. 2021;84:153484.
85. Yaffe PB, Doucette CD, Walsh M, Hoskin DW. Piperine impairs cell cycle progression and causes reactive oxygen species-dependent apoptosis in rectal cancer cells. Exp Mol Pathol. 2013;94(1):109-14.
86. Yaffe PB, Power Coombs MR, Doucette CD, Walsh M, Hoskin DW. Piperine, an alkaloid from black pepper, inhibits growth of human colon cancer cells via G1 arrest and apoptosis triggered by endoplasmic reticulum stress. Mol Carcinog. 2015;54(10):1070-85.
87. Shaheer K, Somashekarappa HM, Lakshmanan MD. Piperine sensitizes radiation-resistant cancer cells towards radiation and promotes intrinsic pathway of apoptosis. J Food Sci. 2020;85(11):4070-9.
88. Tak JK, Lee JH, Park JW. Resveratrol and piperine enhance radiosensitivity of tumor cells. BMB Rep. 2012;45(4):242-6.
89. Wang Y, Zhang C, Zhang S, et al. Kanglaite sensitizes colorectal cancer cells to Taxol via NF-κB inhibition and Connexin 43 upregulation. Sci Rep. 2017;7(1):1280.
90. Shi G, Zheng X, Zhang S, et al. Kanglaite inhibits EMT caused by TNF-α via NF-κB inhibition in colorectal cancer cells. Oncotarget. 2018;9(6):6771-9.
91. Sui H, Zhou LH, Zhang YL, et al. Evodiamine suppresses ABCG2 mediated drug resistance by inhibiting p50/p65 NF-κB pathway in colorectal cancer. J Cell Biochem. 2016;117(6):1471-81.
92. Zhao LC, Li J, Liao K, et al. Evodiamine induces apoptosis and inhibits migration of HCT-116 human colorectal cancer cells. Int J Mol Sci. 2015;16(11):27411-21.
93. Zhang Y, Zhang Y, Zhao Y, et al. Protection against ulcerative colitis and colorectal cancer by evodiamine via anti-inflammatory effects. Mol Med Rep. 2022;25(5):188.
94. Wang M, Zhou B, Cong W, et al. Amelioration of AOM/DSS-induced murine colitis-associated cancer by evodiamine intervention is primarily associated with gut microbiota-metabolism-inflammatory signaling axis. Front Pharmacol. 2021;12:797605.
95. Lu Y, Dong K, Yang M, Liu J. Network pharmacology-based strategy to investigate the bioactive ingredients and molecular mechanism of Evodia rutaecarpa in colorectal cancer. BMC Complement Med Ther. 2023;23(1):433.
96. Zhou P, Li XP, Jiang R, et al. Evodiamine inhibits migration and invasion by Sirt1-mediated post-translational modulations in colorectal cancer. Anticancer Drugs. 2019;30(6):611-7.
97. Ruan J, Li H, Lu M, et al. Bioactive triterpenes of jujube in the prevention of colorectal cancer and their molecular mechanism research.

Phytomedicine. 2023;110:154639.
98. Yousef BA, Hassan HM, Zhang LY, Jiang ZZ. Pristimerin exhibits in vitro and in vivo anticancer activities through inhibition of nuclear factor-κB signaling pathway in colorectal cancer cells. Phytomedicine. 2018;40:140-7.
99. Yousef BA, Guerram M, Hassan HM, Hamdi AM, Zhang LY, Jiang ZZ. Pristimerin demonstrates anticancer potential in colorectal cancer cells by inducing G1 phase arrest and apoptosis and suppressing various pro-survival signaling proteins. Oncol Rep. 2016;35(2):1091-100.
100. Park JH, Kim JK. Pristimerin, a naturally occurring triterpenoid, attenuates tumorigenesis in experimental colitis-associated colon cancer. Phytomedicine. 2018;42:164-71.
101. Yu Z, Li W. Induction of apoptosis by puerarin in colon cancer HT-29 cells. Cancer Lett. 2006;238(1):53-60.
102. Luo J, Qu J, Yang R, et al. Phytochemicals mediate the expression and activity of OCTN2 as activators of the PPARγ/RXRα pathway. Front Pharmacol. 2016;7:189.
103. Li J, Guo C, Lu X, Tan W. Anti-colorectal cancer biotargets and biological mechanisms of puerarin: study of molecular networks. Eur J Pharmacol. 2019;858:172483.
104. Wang Y, Ma Y, Zheng Y, et al. In vitro and in vivo anticancer activity of a novel puerarin nanosuspension against colon cancer, with high efficacy and low toxicity. Int J Pharm. 2013;441(1-2):728-35.
105. Deng XQ, Zhang HB, Wang GF, et al. Colon-specific microspheres loaded with puerarin reduce tumorigenesis and metastasis in colitis-associated colorectal cancer. Int J Pharm. 2019;570:118644.
106. Li W, Saud SM, Young MR, Colburn NH, Hua B. Cryptotanshinone, a Stat3 inhibitor, suppresses colorectal cancer proliferation and growth in vitro. Mol Cell Biochem. 2015;406(1-2):63-73.
107. Su YS, Kuo MZ, Kuo YT, et al. Diterpenoid anthraquinones as chemopreventive agents altered microRNA and transcriptome expressions in cancer cells. Biomed Pharmacother. 2021;136:111260.
108. Vundavilli H, Datta A, Sima C, Hua J, Lopes R, Bittner M. Targeting oncogenic mutations in colorectal cancer using cryptotanshinone. PLoS One. 2021;16(2):e0247190.
109. Zhang L, Chen C, Duanmu J, et al. Cryptotanshinone inhibits the growth and invasion of colon cancer by suppressing inflammation and tumor angiogenesis through modulating MMP/TIMP system, PI3K/Akt/mTOR signaling and HIF-1α nuclear translocation. Int Immunopharmacol. 2018;65:429-37.
110. Deorukhkar A, Ahuja N, Mercado AL, et al. Zerumbone increases oxidative stress in a thiol-dependent ROS-independent manner to increase DNA damage and sensitize colorectal cancer cells to radiation. Cancer Med. 2015;4(2):278-92.
111. Dehghan R, Najafi R, Azizi Jalilian F, et al. A promising effect of zerumbone with improved anti-tumor-promoting inflammation activity of miR-34a in colorectal cancer cell lines. Mol Biol Rep. 2021;48(1):203-18.
112. Cho HW, Rhee KJ, Eom YB. Zerumbone restores gut microbiota composition in ETBF colonized AOM/DSS mice. J Microbiol Biotechnol. 2020;30(11):1640-50.
113. Hosseini N, Khoshnazar A, Saidijam M, et al. Zerumbone suppresses human colorectal cancer invasion and metastasis via modulation of FAK/PI3K/NFκB-uPA pathway. Nutr Cancer. 2019;71(1):159-71.
114. Radaei Z, Zamani A, Najafi R, et al. Promising effects of zerumbone on the regulation of tumor-promoting cytokines induced by TNF-α-activated fibroblasts. Curr Med Sci. 2020;40(6):1075-84.
115. Yodkeeree S, Sung B, Limtrakul P, Aggarwal BB. Zerumbone enhances TRAIL-induced apoptosis through the induction of death receptors in human colon cancer cells: evidence for an essential role of reactive oxygen species. Cancer Res. 2009;69(16):6581-9.
116. Hwang S, Jo M, Hong JE, Park CO, Lee CG, Rhee KJ. Protective effects of zerumbone on colonic tumorigenesis in Enterotoxigenic Bacteroides fragilis (ETBF)-colonized AOM/DSS BALB/c mice. Int J Mol Sci. 2020;21(3):857.
117. Memari F, Mirzavi F, Jalili-Nik M, Afshari AR, Ghorbani A, Soukhtanloo M. Tumor-inhibitory effects of zerumbone against HT-29 human colorectal cancer cells. Int J Toxicol. 2022;41(5):402-11.
118. Sithara T, Dhanya BP, Arun KB, et al. Zerumbone, a cyclic sesquiterpene from Zingiber zerumbet induces apoptosis, cell cycle arrest, and antimigratory effects in SW480 colorectal cancer cells. J Agric Food Chem. 2018;66(3):602-12. doi:10.1021/acs.jafc.7b04472.
119. Yu Y, Chen D, Wu T, et al. Dihydroartemisinin enhances the anti-tumor activity of oxaliplatin in colorectal cancer cells by altering PRDX2–

reactive oxygen species–mediated multiple signaling pathways. Phytomedicine. 2022;98:153932.
120. Yao Z, Bhandari A, Wang Y, et al. Dihydroartemisinin potentiates antitumor activity of 5-fluorouracil against a resistant colorectal cancer cell line. Biochem Biophys Res Commun. 2018;501(3):636-42.
121. Wang Z, Sun X, Feng Y, et al. Dihydromyricetin reverses MRP2-induced multidrug resistance by preventing NF-κB–Nrf2 signaling in colorectal cancer cell. Phytomedicine. 2021;82:153414.
122. Liang J, Wu J, Wang F, Zhang P, Zhang X. Semaphorin 4D is required for the induction of antioxidant stress and anti-inflammatory effects of dihydromyricetin in colon cancer. Int Immunopharmacol. 2019;67:220-30.
123. Andrographolide inhibits proliferation of colon cancer SW-480 cells via downregulating Notch signaling pathway. Anticancer Agents Med Chem. 2021;21(4):487-97.
124. Khan I, Mahfooz S, Ansari IA. Antiproliferative and apoptotic properties of andrographolide against human colon cancer DLD1 cell line. Endocr Metab Immune Disord Drug Targets. 2020;20(6):930-42.
125. Khan I, Khan F, Farooqui A, Ansari IA. Andrographolide exhibits anticancer potential against human colon cancer cells by inducing cell cycle arrest and programmed cell death via augmentation of intracellular reactive oxygen species level. Nutr Cancer. 2018;70(5):787-803.
126. Khan I, Mahfooz S, Faisal M, Alatar AA, Ansari IA. Andrographolide induces apoptosis and cell cycle arrest through inhibition of aberrant Hedgehog signaling pathway in colon cancer cells. Nutr Cancer. 2021;73(11-12):2428-46.
127. Banerjee A, Banerjee V, Czinn S, Blanchard T. Increased reactive oxygen species levels cause ER stress and cytotoxicity in andrographolide treated colon cancer cells. Oncotarget. 2017;8(16):26142-53.
128. Sharda N, Ikuse T, Hill E, et al. Impact of andrographolide and melatonin combinatorial drug therapy on metastatic colon cancer cells and organoids. Clin Med Insights Oncol. 2021;15:11795549211012672.
129. Athamneh K, Hasasna HE, Samri HA, et al. Rhus coriaria increases protein ubiquitination, proteasomal degradation and triggers non-canonical Beclin-1-independent autophagy and apoptotic cell death in colon cancer cells. Sci Rep. 2017;7(1):11633.
130. Hamze K, Abdallah RH, Younis NK, et al. 2-Nucleobase-substituted 4,6-diaminotriazine analogs: synthesis and anti-cancer activity in 5-fluorouracil-sensitive and resistant colorectal cancer cells. Curr Med Chem. 2023;30(26):3032-49.
131. Nizami ZN, Al Azzani M, Khaldi S, et al. Rhus coriaria (sumac) induces autophagic cell death and inhibits mTOR, p38MAPK and STAT3 pathways in 5-fluorouracil-resistant colorectal cancer cells. Front Pharmacol. 2025;16:1542204.
132. Benhalilou N, Alsamri H, Alneyadi A, et al. Origanum majorana ethanolic extract promotes colorectal cancer cell death by triggering abortive autophagy and activation of the extrinsic apoptotic pathway. Front Oncol. 2019;9:2019.
133. Athamneh K, Alneyadi A, Alsamri H, et al. Origanum majorana essential oil triggers p38 MAPK-mediated protective autophagy, apoptosis, and caspase-dependent cleavage of P70S6K in colorectal cancer cells. Biomolecules. 2020;10(3):412.
134. Jeon HD, Han YH, Mun JG, et al. Dehydroevodiamine inhibits lung metastasis by suppressing survival and metastatic abilities of colorectal cancer cells. Phytomedicine. 2022;96:153809.
135. Xiang X, Tian Y, Hu J, et al. Fangchinoline exerts anticancer effects on colorectal cancer by inducing autophagy via regulation of AMPK/mTOR/ULK1 pathway. Biochem Pharmacol. 2021;186:114475.
136. Liu Y, Lu L, Cheng P, et al. Wogonin inhibits colorectal cancer proliferation and epithelial mesenchymal transformation by suppressing phosphorylation in the AKT pathway. Am J Chin Med. 2024;52(4):1155-72. doi:10.1142/S0192415X24500460.
137. Feng G, Zhang L, Bao W, et al. Gentisic acid prevents colorectal cancer metastasis via blocking GPR81-mediated DEPDC5 degradation. Phytomedicine. 2024;129:155615.
138. Zhou JY, Wu C, Shen Z, et al. Yiqi Huayu Jiedu decoction inhibits liver metastasis of colorectal cancer via enhancing natural killer cells function. J Ethnopharmacol. 2024;318(Pt A):116915.
139. 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. 2024;318(Pt A):116866.
140. Huang QH, Zhang J, Cho WCS, et al. Brusatol

suppresses the tumor growth and metastasis of colorectal cancer via upregulating ARRDC4 expression through modulating PI3K/YAP1/TAZ pathway. Phytomedicine. 2023;109:154567.
141. Ji Q, Liu X, Han Z, et al. Resveratrol suppresses epithelial-to-mesenchymal transition in colorectal cancer through TGF-β1/Smads signaling pathway mediated Snail/E-cadherin expression. BMC Cancer. 2015;15:97.
142. Kong X, Liu C, Lu P, et al. Combination of UPLC-Q-TOF/MS and network pharmacology to reveal the mechanism of Qizhen Decoction in the treatment of colon cancer. ACS Omega. 2021;6(22):14341-60.
143. Kong X, Li Q, Wang D, Wang M, Yang F, Meng J. Mechanism of Qizhen Decoction-mediated maturation of DC cells to activate the IL-12/JAK2/STAT4 pathway to sensitise PD-1 inhibitors in the treatment of colorectal cancer. J Ethnopharmacol. 2024;320:117399.
144. Jiang Y, Hu Y, Yang Y, et al. Tong-Xie-Yao-Fang promotes dendritic cells maturation and retards tumor growth in colorectal cancer mice with chronic restraint stress. J Ethnopharmacol. 2024;319(Pt 1):117069.
145. 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.
146. Zhang Y, Chai N, Wei Z, et al. YYFZBJS inhibits colorectal tumorigenesis by enhancing Tregs-induced immunosuppression through HIF-1α mediated hypoxia in vivo and in vitro. Phytomedicine. 2022;98:153917.
147. Chen D, Yang Y, Yang P. Quxie capsule inhibits colon tumor growth partially through Foxo1-mediated apoptosis and immune modulation. Integr Cancer Ther. 2019;18:1534735419846377.
148. Zhu JJ, Liu HY, Yang LJ, et al. Anti-tumour effect of Huangqin decoction on colorectal cancer mice through microbial butyrate mediated PI3K/Akt pathway suppression. J Med Microbiol. 2023;72(5):1-13.
149. Liu Y, Zhang Q, Lu L, et al. Huang-Qin decoction alleviates deoxycholic acid-induced colorectal cancer in mice by regulating gut microbiota. J Ethnopharmacol. 2025;346:119715.
150. 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.
151. 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-κB signaling pathway. Phytomedicine. 2021;88:153606.
152. Zhou Y, Feng Y, Cen R, et al. San-Wu-Huang-Qin decoction attenuates tumorigenesis and mucosal barrier impairment in the AOM/DSS model by targeting gut microbiome. Phytomedicine. 2022;98:153966.
153. Cai K, Cao XY, Chen F, et al. Xianlian Jiedu decoction alleviates colorectal cancer by regulating metabolic profiles, intestinal microbiota and metabolites. Phytomedicine. 2024;128:155385.
154. Dai Y, Wang H, Sun R, et al. Modified Shenlingbaizhu decoction represses the pluripotency of colorectal cancer stem cells by inhibiting TGF-β mediated EMT program. Phytomedicine. 2022;103:154234.
155. Wei L, Chen P, Chen Y, et al. Pien Tze Huang suppresses the stem-like side population in colorectal cancer cells. Mol Med Rep. 2014;9(1):261-6.
156. Qi F, Wei L, Shen A, et al. Pien Tze Huang inhibits the proliferation, and induces the apoptosis and differentiation of colorectal cancer stem cells via suppression of the Notch1 pathway. Oncol Rep. 2016;35(1):511-7.
157. Lu Q, Zhang Z, Liu S, et al. Inhibition of stemness and PD-L1 expression by Pien Tze Huang enhances T cell-mediated killing of colorectal cancer. J Ethnopharmacol. 2025;343:119447.
158. Shin JM, Lim E, Cho YS, Nho CW. Cancer-preventive effect of phenethyl isothiocyanate through tumor microenvironment regulation in a colorectal cancer stem cell xenograft model. Phytomedicine. 2021;84:153493
159. Zhao S, Mi Y, Guan B, et al. Tumor-derived exosomal miR-934 induces macrophage M2 polarization to promote liver metastasis of colorectal cancer. J Hematol Oncol. 2020;13(1):156.
160. Liang Y, Li J, Yuan Y, et al. Exosomal miR-106a-5p from highly metastatic colorectal cancer cells drives liver metastasis by inducing macrophage M2 polarization in the tumor microenvironment. J Exp Clin Cancer Res. 2024;43(1):281.
161. Yin Y, Liu B, Cao Y, et al. Colorectal cancer-derived small extracellular vesicles promote tumor

immune evasion by upregulating PD-L1 expression in tumor-associated macrophages. Adv Sci. 2022;9(9):2102620.
162. Prakash A, Gates T, Zhao X, Wangmo D, Subramanian S. Tumor-derived extracellular vesicles in the colorectal cancer immune environment and immunotherapy. Pharmacol Ther. 2023;241:108332.
163. Li R, Zhou J, Wu X, et al. Jianpi Jiedu recipe inhibits colorectal cancer liver metastasis via regulating ITGBL1-rich extracellular vesicles mediated activation of cancer-associated fibroblasts. Phytomedicine. 2022;100:154082.
164. Chen Y, Yan Q, Ji Y, et al. Unraveling the serial glycosylation in the biosynthesis of steroidal saponins in the medicinal plant Paris polyphylla and their antifungal action. Acta Pharm Sin B. 2023;13(11):4638-54.
165. Hao H, Sha A. Study on anti-fatigue effects and mechanisms of polysaccharide from Paris polyphylla. Dokl Biochem Biophys. 2024;516(1):58-65.
166. Kshetrimayum V, Chanu KD, Biona T, et al. Paris polyphylla Sm. characterized extract infused ointment accelerates diabetic wound healing in in-vivo model. J Ethnopharmacol. 2024;331:118296.
167. Li L, Zhang J, Cheng W, Di F, Wang C, An Q. Saponins of Paris polyphylla for the improvement of acne: anti-inflammatory, antibacterial, antioxidant and immunomodulatory effects. Molecules. 2024;29(8):1793.
168. Wang J, Ni BY, Wang J, et al. Research progress of Paris polyphylla in the treatment of digestive tract cancers. Discover Oncol. 2024;15(1):31.
169. Zhou JY, Wu C, Shen Z, et al. Yiqi Huayu Jiedu decoction inhibits liver metastasis of colorectal cancer via enhancing natural killer cells function. J Ethnopharmacol. 2024;318(Pt A):116915.
170. Liang ZQ, Bian Y, Gu JF, et al. Exploring the anti-metastatic effects of Astragalus mongholicus Bunge-Curcuma aromatica Salisb. on colorectal cancer: a network-based metabolomics and pharmacology approach. Phytomedicine. 2023;114:154772.
171. Liu F, Liang Y, Sun R, et al. Astragalus mongholicus Bunge and Curcuma aromatica Salisb. inhibits liver metastasis of colon cancer by regulating EMT via the CXCL8/CXCR2 axis and PI3K/AKT/mTOR signaling pathway. Chin Med. 2022;17(1):91. doi:10.1186/s13020-022-00641-4.
172. Hou F, Li W, Shi Q, et al. Yi Ai Fang, a traditional Chinese herbal formula, impacts the vasculogenic mimicry formation of human colorectal cancer through HIF-1α and epithelial mesenchymal transition. BMC Complement Altern Med. 2016;16(1):428.