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Herbal Medicine for Colorectal Cancer Treatment: Molecular Mechanisms and Clinical Applications

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ABSTRACT

Colorectal cancer (CRC) is one of the most common malignant tumours and is the second leading cause of cancer-related mortality worldwide. Despite the availability of preventative, diagnostic and treatment methods including endoscopic treatment, surgical intervention, radiotherapy, biologics, salvage therapy and immunotherapy, the mortality rate associated with CRC remains alarming. Consequently, there is a pressing need to search for medicines for the treatment of CRC. Phytomedicines have been shown to suppress the proliferation and metastasis of CRC through various mechanisms, including immune regulation, modulation of gut microbiota, targeting of stem cells, macrophage polarisation, glycolysis, ferroptosis induction, modulation of

Abbreviations: 5-HT3, 5-hydroxytryptamine receptor subtype 3; ABCG2, ATP binding cassette subfamily G member 2; ACF, aberrant crypt foci; ADCY4, adenylate cyclase 4; AIF, apoptosis-inducing factor; ALOX12B, arachidonate 12-lipoxygenase, 12R type; AOM, azoxymethane; Apaf-1, apoptotic protease activating factor-1; ARRC4, arrestin domain containing 4; CAC, colitis-associated colorectal cancer; CCL2, C–C motif chemokine ligand 2; CI, confidence interval; CRC, colorectal cancer; CSCs, cancer stem cells; CXB, celecoxib; CXCR5, C–X–C motif chemokine receptor 5; DCs, dendritic cells; DEPDC5, dishevelled, Egl-10 and pleckstrin domain-containing protein 5; DSS, dextran sulfate sodium; DT-13, saponin monomer 13 of the dwarf lilyturf tuber; EMT, epithelial–mesenchymal transition; FAK, focal adhesion kinase; FLIM, fluorescence lifetime imaging microscopy; GFP, green fluorescent protein; GLUT1, glucose transporter type 1; GPR81, G protein-coupled receptor 81; GRh3, ginsenoside Rh3; GRP78, glucose-regulated protein 78 kD; GSDMD, gasdermin D; HIF-1 α , hypoxia-inducible factor 1 subunit alpha; HPA, hypothalamic–pituitary–adrenal; ICIs, immune checkpoint inhibitors; ITGBL1, integrin subunit beta like 1; JAK2, Janus kinase 2; JNK-Mff, c-Jun N-terminal kinase–Mitochondrial fission factor; JPJDR, JianPi JieDu Recipe; KLT, Kanglaite; LDHA, lactate dehydrogenase A; LNT, lentinan; LPS, lipopolysaccharide; MDSCs, myeloid-derived suppressor cells; MMP, matrix metalloproteinases; MRP2, multidrug resistance proteins; MSD, the modified Shenlingbaizhu decoction; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NRF2, nuclear factor erythroid 2-related factor 2; PAD4, protein-arginine deiminase type-4; PD-1, programmed cell death protein 1; PKM2, pyruvate kinase M2; Poly E, polyphenon E; PRDX2, peroxiredoxin 2; ROS, reactive oxygen species; SLC7A11, suppressing solute carrier family 7 member 11; SP, side population; STAT4, signal transducer and activator of transcription 4; TAZ, transcriptional co-activator with PDZ-binding motif; TCM, Traditional Chinese Medicine; TER, triterpenoids; TIMP, tissue inhibitor of metalloproteinase; TLR4, Toll-like receptor 4; TNFAIP3, TNF-alpha-induced protein 3; TOX2, TOX high mobility group box family member 2; Tregs, regulatory T cells; TXYF, Tong-Xie-Yao-Fang; WMW, Wumei Wan; XIAP, X-linked inhibitor of apoptosis protein; YAP1, Yes-associated protein 1; YYFZBJS, Yi-Yi-Fu-Zi-Bai-Jiang-San; ZO-1, Zonula occludens-1.

Zuqing Su, Yanlin Li and Zihao Zhou have contributed equally to this study.

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extracellular vesicles, activation of mitochondria-induced apoptosis, inflammation reduction, oxidative stress management and intervention of autophagy. Furthermore, numerous studies have reported the anti-cancer and anti-metastatic effects of various phytomedicines, including curcumin, resveratrol, berberine, shikonin, dihydroartemisinin, fucoidan, luteolin, andrographolide, piperine, kaempferol, emodin, cannabidiol, tanshinone IIA and evodiamine. In this review, we sort out the effects and mechanisms of phytomedicines on CRC and outline the major phytomedicines commonly used in CRC treatment. We hope that these phytomedicines may serve as promising drugs or important lead compounds for the management of CRC.

1 | Introduction

Colorectal cancer (CRC) is a prevalent gastrointestinal tumour and the second deadliest cancer worldwide [1]. Recent epidemiological data show that poor dietary habits and a sedentary lifestyle, characterised by insufficient physical activity, have contributed to a year-on-year increase in the incidence rate of CRC, posing a significant threat to human health [2]. The incidence of CRC has declined in developed countries due to the ongoing promotion of CRC screening and advancements in screening technologies. While the 5-year survival rate for stage I CRC is 90%, this rate decreases to 72% for locally advanced CRC and drops to a mere 14% for patients with metastatic CRC [3]. Current clinical methods for treating CRC include surgical intervention, radiotherapy, biologics and immunotherapy. However, these approaches have various limitations. For example, endoscopic treatment is primarily suitable for early-stage tumours (non-metastatic), while radiation therapy can induce side effects such as gastrointestinal abnormalities and myelosuppression. Additionally, there is a limited population suitable for targeted therapy, and off-target effects can occur [4, 5]. Recently, the role of phytomedicines against CRC, whether as primary or adjunctive therapies, has received increasing attention. Research indicates that phytomedicines affect CRC through immune regulation (CD4⁺/CD8⁺ T lymphocytes, dendritic cells, Th17 cells and regulatory T cells), gut microbiota, colorectal cancer stem cells, macrophage polarisation, glycolysis, ferroptosis, extracellular vesicles, mitochondrial function, inflammation, oxidative stress and autophagy. Therefore, this review aims to outline the efficacy and molecular mechanisms of phytomedicines against CRC and summarise promising drug candidates, with the goal of identifying precursor drugs for future drug development.

2 | Cell Proliferation

2.1 | Immune Regulation

2.1.1 | CD4⁺/CD8⁺ T Lymphocytes

Currently, cancer immunotherapy represents one of the most innovative options for the treatment of CRC [6]. It has evolved from a basic adjuvant therapy into one of the most effective treatment modalities available. Compared to traditional therapies, immunotherapy overcomes the problems of radiotherapy and chemotherapy by regulating the patient's own immune system [7]. CD4⁺ and CD8⁺ T cells are crucial components of the cellular immune response. CD4⁺ T cells are important for regulating infections and are critical for the development of memory CD8⁺ T cells after stimulation [8, 9]. Insufficient CD4⁺ and CD8⁺ T cells can cause rapid growth and metastasis of tumours.

Conversely, enhancing the proportion of these cells within the tumour immune microenvironment can significantly improve the anti-cancer effects [10].

Wumei Wan (WMW) is a traditional Chinese medicine (TCM) prescription. In a male C57BL/6J mouse model of colitis-associated colorectal cancer (CAC) induced by azoxymethane (AOM) and dextran sulfate sodium (DSS), WMW effectively suppresses colonic inflammation and tumour growth during the early CAC. Additionally, WMW inhibits myeloid-derived suppressor cells (MDSCs) and enhances CD4⁺ and CD8⁺ T-cell populations in the spleen. Transcriptomic and serum metabolomic analyses indicate that amino acid metabolism and the PI3K/AKT signalling pathway are critical for WMW to exert an inhibitory effect on early-stage CAC [10]. However, the specific metabolites that ultimately influence the regulation of CD4⁺ and CD8⁺ T-cell function through the modulation of MDSCs and their mechanisms of action have not been addressed. In an AOM/DSS-induced CAC mouse model, Kimura and Sumiyoshi et al. explore the therapeutic effects of tetra- and pentahydroxyflavanones isolated from *Scutellariae* radix on CRC. They found that tetra- and pentahydroxyflavanones decreased the tumour volume by 60.6% and 72.9%, respectively, in the colons. Additionally, these compounds suppressed IL-10 and programmed cell death protein 1 (PD-1) expressions by inhibiting cyclooxygenase-2 (COX-2) and TOX/TOX2 expressions, which could transcriptionally and epigenetically induce CD8⁺ T-cell exhaustion. Therefore, tetra- and pentahydroxyflavanones inhibit AOM/DSS-induced CRC by downregulating COX-2 and TOX/TOX2 expressions, thereby decreasing IL-10 and PD-1 levels in tumour tissues [11]. Additional research is required to elucidate the impact of tetra- and pentahydroxyflavanones on the recovery from CD8⁺ T-cell exhaustion both in vivo and in vitro. Huang Qin Decoction (HQD), a traditional Chinese medicine, is utilised for the treatment of CRC. In an AOM/DSS-induced CAC mouse model, Pan et al. demonstrated that HQD significantly suppressed the incidence of colon cancers, alleviated intestinal inflammation and diminished neutrophil infiltration in the colon. Additionally, HQD restored intestinal mucosal permeability by enhancing intestinal tight junction protein (occludin and ZO-1) expressions and improved the immunosurveillance capacity of CD8⁺ T cells. Further analyses using network pharmacology, immunohistochemistry and immunoblotting indicated that HQD interfered with the initiation of CAC by modulating PAD4-dependent neutrophil extracellular traps [12]. HQD has been recognised for its efficacy in the management of gastrointestinal cancers. This article illustrates that HQD mitigates tumour-associated inflammation via the modulation of neutrophils; however, further investigation into the precise mechanisms underlying this effect is

warranted. Immune checkpoint inhibitors (ICIs) represent a significant advancement in cancer immunotherapy, in which ICIs intercept immune checkpoint proteins on immune cells, thereby preventing immune cells from recognising and killing cancer cells. By inhibiting these checkpoints, ICIs enable the immune system to effectively recognise and target cancer cells [13]. PD-1 is an important immune checkpoint protein primarily expressed on the surface of T lymphocytes, including CD8⁺ T cells. When the PD-1 protein on CD8⁺ T cells binds to PD-L1 on cancer cells, it signals the immune system to stop targeting and eliminating those cancer cells [14]. Evening primrose (*Oenothera biennis*) is used globally for the treatment of inflammatory and metabolic diseases. Lee et al. found that evening primrose root extract effectively blocked the molecular interaction between PD-L1 and PD-1, thereby increasing CD8⁺ T-cell-mediated tumour cytotoxicity and subsequently reducing tumour growth. Additionally, oenotherin B (an active compound derived from evening primrose) and FOLFOX (5-fluorouracil plus oxaliplatin) exhibited a synergistic effect in inhibiting hPD-L1-MC38 cell proliferation in an ex vivo model by activating CD8⁺ tumour-infiltrating T lymphocytes [14]. *Marsdenia tenacissima* (Roxb.) Wight et Arn. is a widely used Chinese herbal medicine. Yi et al. found that *Marsdenia tenacissima* tablets effectively elevated CD3⁺/CD8⁺ tumour-infiltrating T cells in 13 out of 17 CRC patients (76.5%). Additionally, *Marsdenia tenacissima* tablets suppressed TGF- β 1 and PD-L1 expressions in the CRC cell lines HCT116 and LoVo while enhancing the density of CD3⁺/CD8⁺ T cells and inhibiting tumour growth in CAC mouse models [15]. *Rhus chinensis* Mill., a medicinal plant belonging to the *Rhus* genus of the sumac family, is frequently utilised in the treatment of cancer in China, India and Japan. Wang et al. found that the triterpenoids of *Rhus chinensis* prevented CD8⁺ T-cell dysfunction and promoted glycolytic activation in these cells, which is beneficial for T cells in recognising and eliminating tumour cells [16]. Honeysuckle (*Lonicerae Japonicae* Flos) is a TCM with potent anti-inflammatory, antioxidant and anti-tumour properties. In a CT26 tumour-bearing C57BL/6 mouse model, both *Sid1*^{+/+} and *Sid1*^{-/-} mouse models, honeysuckle-derived microRNA2911 slowed CRC by promoting CD4⁺ and CD8⁺ T-cell infiltration and down-regulating the expression of TGF- β 1. As anticipated, the therapeutic effects of microRNA2911 were cancelled in T-cell-deficient mice, suggesting that microRNA2911 depends on functionally normal T cells to exert its anti-CRC effects [17]. It is widely recognised that honeysuckle contains a diverse array of microRNAs, including miR160, miR162, miR166, miR171, miR2914 and miR2910. The potential anti-tumour properties of these microRNAs merit further investigation. Additionally, the prospect of a synergistic effect among them in combating CRC appears to be highly promising. Yang et al. found that *Patrinia villosa* aqueous extract exhibited significant anti-proliferative and anti-metastatic effects by regulating the TGF- β R1-smad2/3-E-cadherin and FAK-RhoA-cofilin pathways. Additionally, it increased helper T cells (CD3⁺CD4⁺) and cytotoxic T lymphocytes (CD3⁺CD8⁺) percentages in spleen and thymus tissues [18]. Turmeric is the root of *Curcuma longa* L. and is used as a dietary supplement and a therapeutic drug for metabolic disorders and cancer [19]. Li et al. found that turmeric extract, which contains absorbable curcumin, inhibited tumour cell growth and liver and lung metastasis in

a xenograft model by targeting cofilin, FAK/pSrc, AKT, ERK and STAT3. Furthermore, it increased CD4⁺ helper T lymphocytes in the thymus and CD8⁺ cytotoxic T lymphocytes in tumour tissue [20]. Furthermore, the researchers also validated the reduction in immune function following FOLFOX treatment in a murine model. However, they found that turmeric extract enhanced the immune capacity of mice, indicating that turmeric extract is worth further research in conjunction with FOLFOX treatment. In a mouse xenograft model of CT26 tumours, Gegen Qinlian decoction, a TCM, combined with anti-mouse PD-1 significantly increased the proportion of CD8⁺ T cells in both peripheral blood and tumour tissues [21]. In conclusion, herbal medicines may be a promising strategy to significantly enhance anti-PD-1-mediated immunotherapy for CRC patients by modulating the percentages of CD4⁺ and CD8⁺ T lymphocytes (Figure 1).

2.1.2 | Dendritic Cells

Dendritic cells (DCs) derive their name from the numerous dendrites that extend from their cell membranes, resembling the structure of nerve cells. These cells hold significant potential for clinical applications in tumour treatment due to their unique anti-tumour responses and their role in regulating T-cell activity [22, 23]. While DCs do not directly attack CRC cells, they function as antigen-presenting cells that capture information from these cancer cells. This information is processed within the DCs, enabling them to effectively communicate their characteristics to T cells [24]. The ability of DCs to present antigens is crucial for the initiation of both innate and adaptive immunity. By targeting the potential influence of DCs on the tumour microenvironment in CRC, a novel approach to immunotherapy for this disease appears increasingly viable [25, 26].

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 polarise tumour-associated macrophages to the anti-tumorigenic M1 phenotype (CD11b⁺CD80⁺) in the CT26 CRC tumour model [27]. Furthermore, Huang and colleagues found that LNT suppressed tumour angiogenesis through interferon γ and in a T-cell-independent manner in the CT26 CRC tumour model [28]. Qizhen decoction is a traditional Chinese herbal formula used to treat CRC with significant efficacy [29]. In an AOM/DSS-induced CRC mouse model, QZD combined with a PD-1 inhibitor (InVivoMab) promoted DCs maturation, consequently releasing IL-12 and activating the JAK2/STAT4 pathway, which induced effector T-cell activation by increasing the abundance of *Akkermansia* [30]. Tong-Xie-Yao-Fang (TXYF) is a classical formula commonly used to treat intestinal disorders in China. TXYF was shown to suppress tumour growth in CRC mice with chronic restraint stress by inhibiting the hypothalamic–pituitary–adrenal axis and facilitating DCs maturation. This response was evidenced by an increase in the percentages of CD4⁺ T cells, CD4⁺/CD8⁺ T cells and Th1 cells [31]. The findings indicate that DCs may serve as a crucial intermediary in the exacerbation of CRC associated with depression. Consequently, targeting DCs could represent a novel approach in the clinical management of CRC (Figure 2).

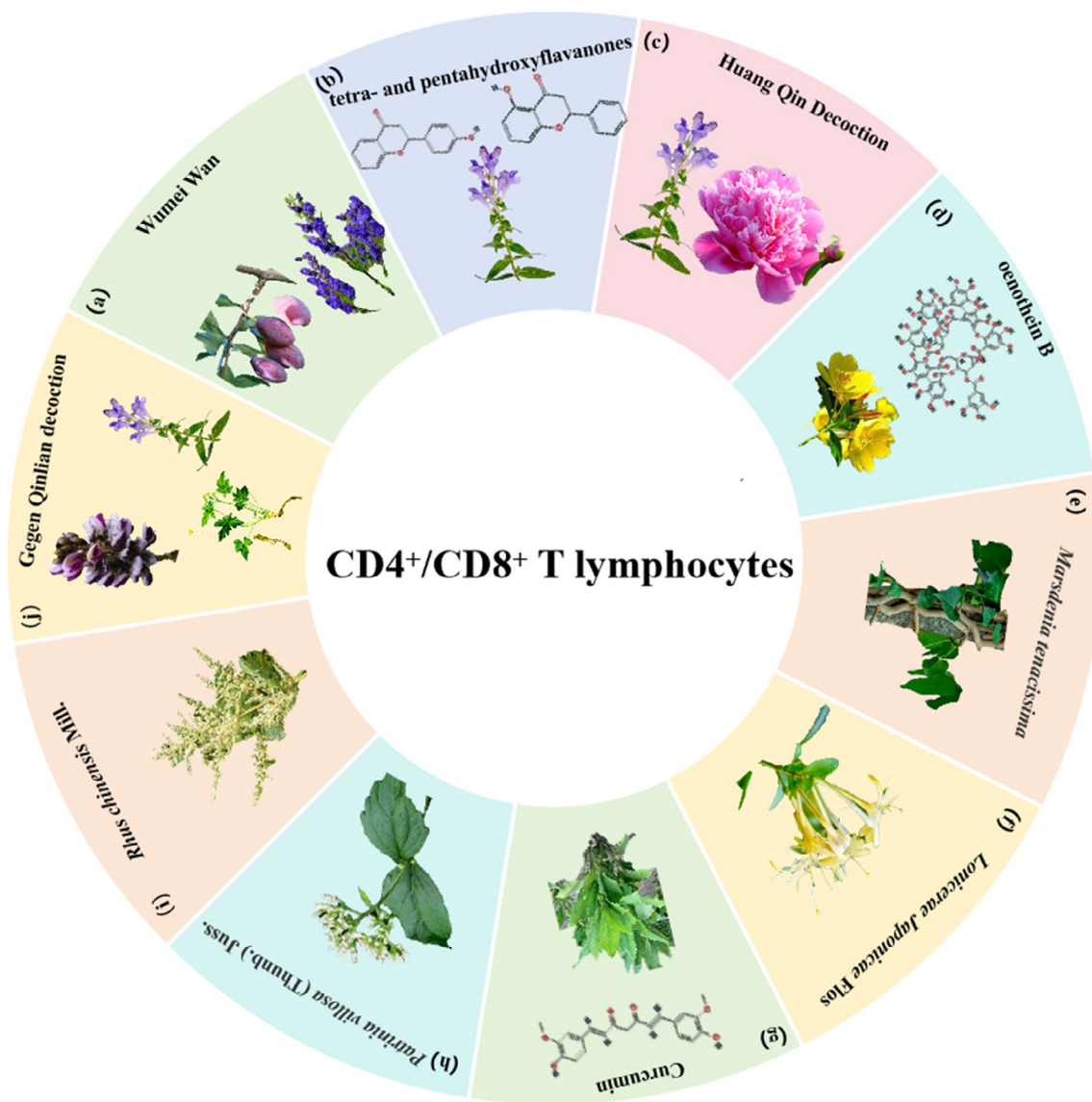


FIGURE 1 | Herbal medicine treats CRC by regulating CD4⁺/CD8⁺ T lymphocytes. (a) *Prunus mume* Siebold & Zucc. and *Aconitum carmichaelii* Debeaux. (b) *Scutellaria baicalensis* Georgi. (c) *Scutellaria baicalensis* Georgi and *Paeonia lactiflora* Pall. (d) *Oenothera biennis* L. (e) *Marsdenia tenacissima* (Roxb.) Wight et Arn. (f) *Lonicerae Japonicae* Flos. (g) *Curcuma longa* L. (h) *Patrinia villosa* (Thunb.) Juss. (i) *Rhus chinensis* Mill. (j) *Pueraria montana* (Lour.) Merr., *Scutellaria baicalensis* Georgi and *Coptis chinensis* Franch.

2.1.3 | Th17 Cells

Th17 cells are a subset of CD4⁺ T cells that secrete interleukin-17 and are considered protumorigenic immune cells in CRC. *Curcuma Longae* Rhizoma, the root of *Curcuma longa* L., has been used as a dietary supplement for thousands of years and is commonly employed to treat metabolic disorders and cancer [32]. The main components of *Curcuma Longae* Rhizoma are curcuminoids, with curcumin being the active ingredient. Wan et al. found that a novel surfactant-formulated curcumin inhibited SW480 cell proliferation by promoting cyclin B1-induced early apoptosis and inducing cell cycle arrest. Additionally, it suppressed Th17 cell differentiation to alleviate intestinal inflammation [32]. *Periploca sepium* periplosides, extracted from the dried root of *Periploca sepium* Bunge (*P. sepium*), are used to treat rheumatoid arthritis, dyspepsia and stomachache [33]. Lin et al. discovered that *Periploca sepium* periplosides improved the structure of gut

microbiota, thereby suppressing colitis and CAC by inhibiting the pathogenic Th17 cell population in both the DSS-induced acute colitis model and the DSS + AOM-induced CAC model (C57BL/6) [33]. This research possesses substantial scholarly value, and it is anticipated that future investigations will explore in greater depth the specific types of gut microbiota that affect the regulation of Th17 cells, along with the underlying mechanisms governing this regulatory process. Ginseng fruit (*Panax ginseng* C.A. Meyer), which encompasses both berries and seeds, is recognised for its immune-enhancing properties. Wang et al. found that while ginseng berry concentrate did not affect Th1 and Treg cell differentiation, it significantly inhibited Th17 cell differentiation, thereby regulating the Th17/Treg balance in adaptive immunity [34]. Future research is anticipated to investigate this mechanism using CRC animal models. Beyond that, there are numerous chemical compounds found in plants that have been shown to inhibit CRC by inhibiting Th17 cells, including dihydroartemisinin [35],

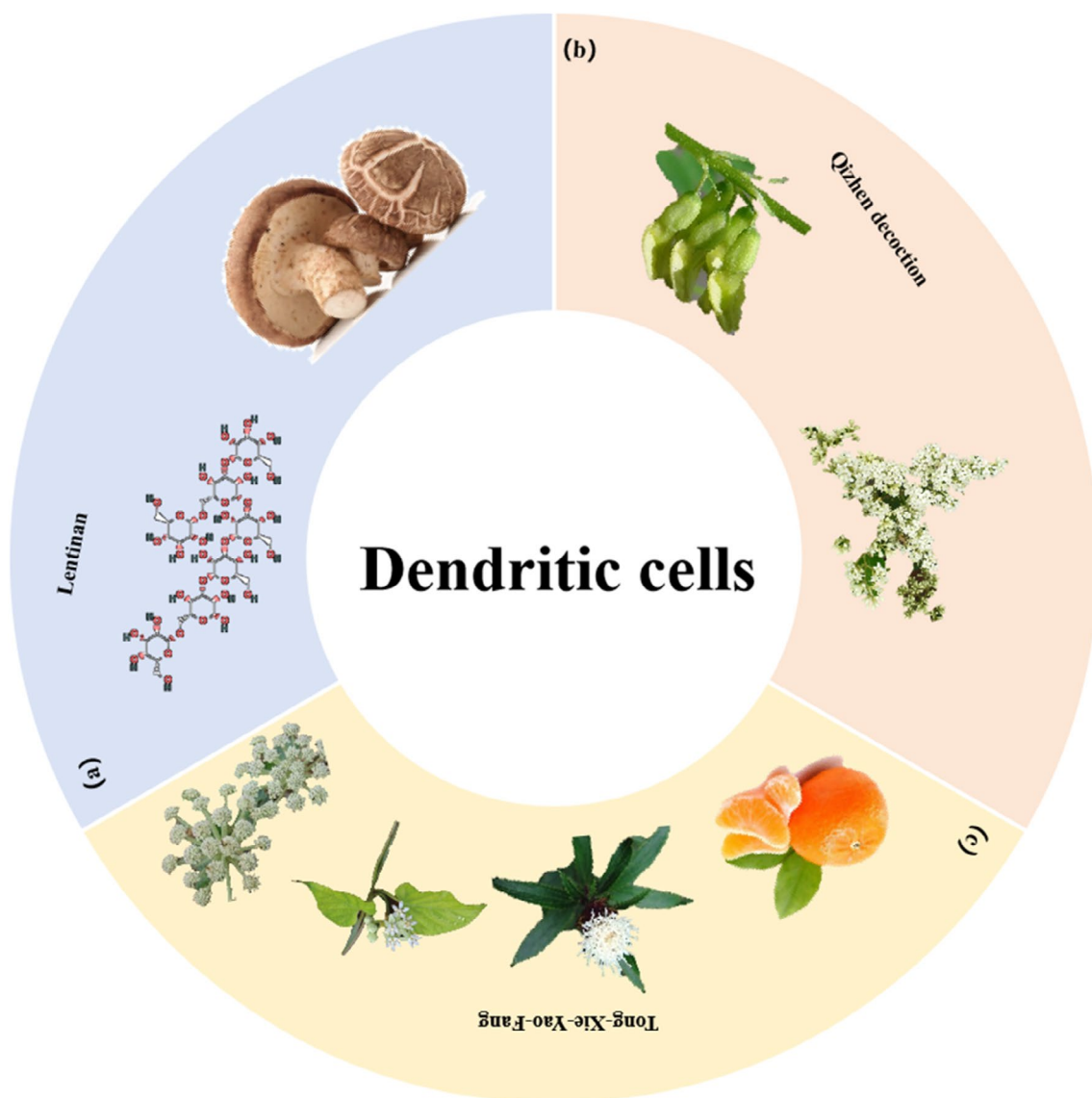


FIGURE 2 | Herbal medicine treats CRC by regulating dendritic cells. (a) *Lentinus edodes* (Berk.) Sing. (b) *Astragalus membranaceus* (Fisch.) Bunge and *Ligustrum lucidum* Ait. (c) *Citrus reticulata* Blanco, *Atractylodes macrocephala* Koidz., *Cynanchum otophyllum* Schneid. and *Saposhnikovia divaricata* (Turcz.) Schischk.

oleuropein [36] and YTE-17 (oblongifolin C and guttiferone K) [37] (Figure 3).

2.1.4 | Regulatory T Cells

Regulatory T cells (Tregs) are a subset of CD4⁺ T cells characterised by their low proliferation capacity and immunosuppressive effects. Considering that they break the immune responses of Th1, Th2 and Th17 cells through the secretion of IL-10 and TGF- β 1, Tregs are believed to contribute to CRC evasion of immune surveillance [38–40].

Yi-Yi-Fu-Zi-Bai-Jiang-San (YYFZBJS) is a commonly used herbal formulation for the treatment of gastrointestinal disorders in China. A study involving C57BL/6J *Apc*^{Min/+} mice demonstrated that YYFZBJS effectively regulated gut flora, including *Bacteroides fragilis* and *Lachnospiraceae*. Furthermore, when faeces from YYFZBJS-treated human volunteers were

administered to both conventional and germ-free mice, a significant inhibition of intestinal tumour growth was observed. Additional research indicated that the underlying mechanisms are associated with the regulation of gut microbiota, inhibition of CD4⁺CD25⁺Foxp3⁺ Tregs and a reduction in intestinal inflammation [41]. However, Zhang et al. further demonstrated that YYFZBJS suppressed tumour growth by promoting CD4⁺CD25⁺ Tregs-induced immunosuppression by targeting HIF-1 α -induced hypoxia in MC-38 cells and in AOM/DSS-induced CRC mice [42]. The aforementioned research findings prompt consideration of whether HIF-1 α serves as a primary target for the regulation of Tregs by intestinal microbiota. Additionally, it is essential to explore the mediators through which intestinal flora exerts this regulatory effect, including inflammatory metabolites and short-chain fatty acids. Quxie capsule is an herbal remedy used for the treatment of advanced CRC for over years. Chen et al. found that the Quxie capsule elevated the ratios of Th17/Tregs while inhibiting Foxp3 expression, an important moderator of Tregs, thereby suppressing colorectal tumorigenesis in CRC mice and in HCT26

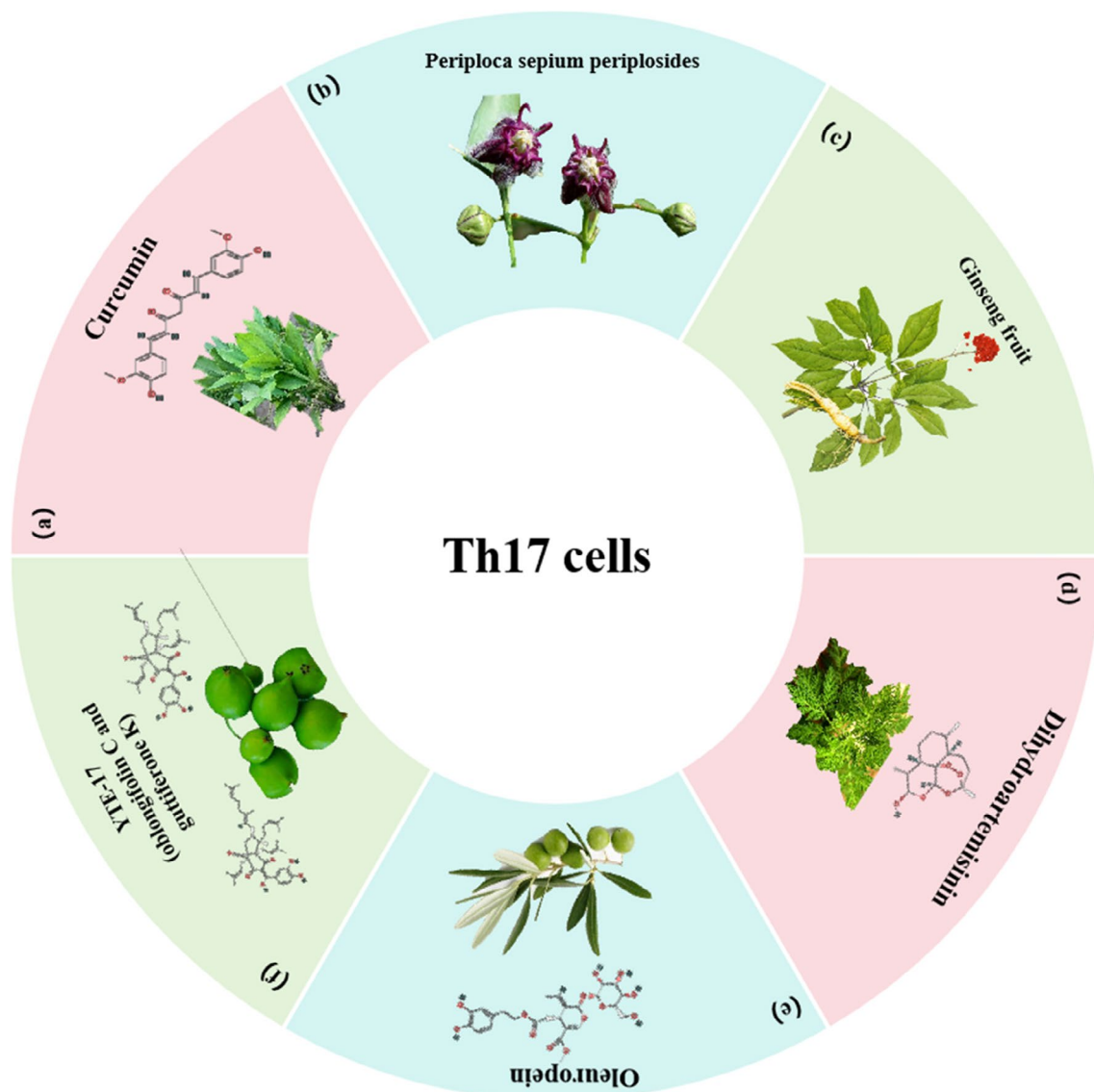


FIGURE 3 | Herbal medicine treats CRC by regulating Th17 cells. (a) *Curcuma longa* L. (b) *Periploca sepium* Bunge. (c) *Panax ginseng* C.A. Meyer. (d) *Artemisia caruifolia* Buch.-Ham. ex Roxb. (e) *Olea europaea* L. (f) *Garcinia yunnanensis* H. H. Hu.

and HCT116 cells [43]. Nonetheless, there have been sporadic instances of patients experiencing abdominal discomfort or diarrhoea potentially attributable to Quxie capsule, as it contains certain herbal components, such as *Crotonis fructus*, known to stimulate bowel activity [43]. It is important to note that these adverse effects are generally mild and manageable, and CRC patients often express a willingness to persist with Quxie capsule treatment. Rubiginosin B is obtained from *Rhododendron brachypodum* (R. brachypodum). Geng et al. found that rubiginosin B selectively suppressed TGF β -induced CD4⁺Foxp3⁺ Tregs cell differentiation, thereby enhancing the ability of the immune system to monitor and kill tumour cells by regulating the calcineurin-NFAT pathway in the CT26 and MC38 xenograft tumour models [44] (Figure 4).

2.2 | Gut Microbiota

There is a consensus that dysbiosis of the gut microbiota is positively associated with CRC [45, 46]. The underlying mechanisms

include genotoxin-mediated promotion of mutagenesis, regulation of oncogenic signalling pathways, inflammation induction and immune evasion [45].

Cyasterone is a compound isolated from *Ajuga decumbens* Thunb (Labiatae) or *Cyathula officinalis* Kuan [47]. CRC with mutations in the *BRAF*^{V600E} gene is highly malignant and associated with poor outcomes and prognosis. In a *BRAF*^{V600E}-mutant mouse model of CRC, cyasterone enhanced gut microbiota diversity and beneficial bacteria abundance, including *Prevotellaceae*, *Muribaculaceae* and *Ruminococcaceae*. Although this study demonstrated that cyasterone modulates the abundance of several beneficial bacteria, its efficacy in *BRAF*^{V600E}-mutant CRC was not investigated, and the role of these probiotics remains unclear [47]. Huangqin decoction is often used to treat gastrointestinal symptoms in China for over years. Zhu et al. discovered that Huangqin decoction attenuated colitis and tumour volume, promoted apoptosis and inhibited the PI3K/AKT pathway in AOM/DSS-induced CRC mice, as well as in SW480 and HT-29 cells. This effect was associated

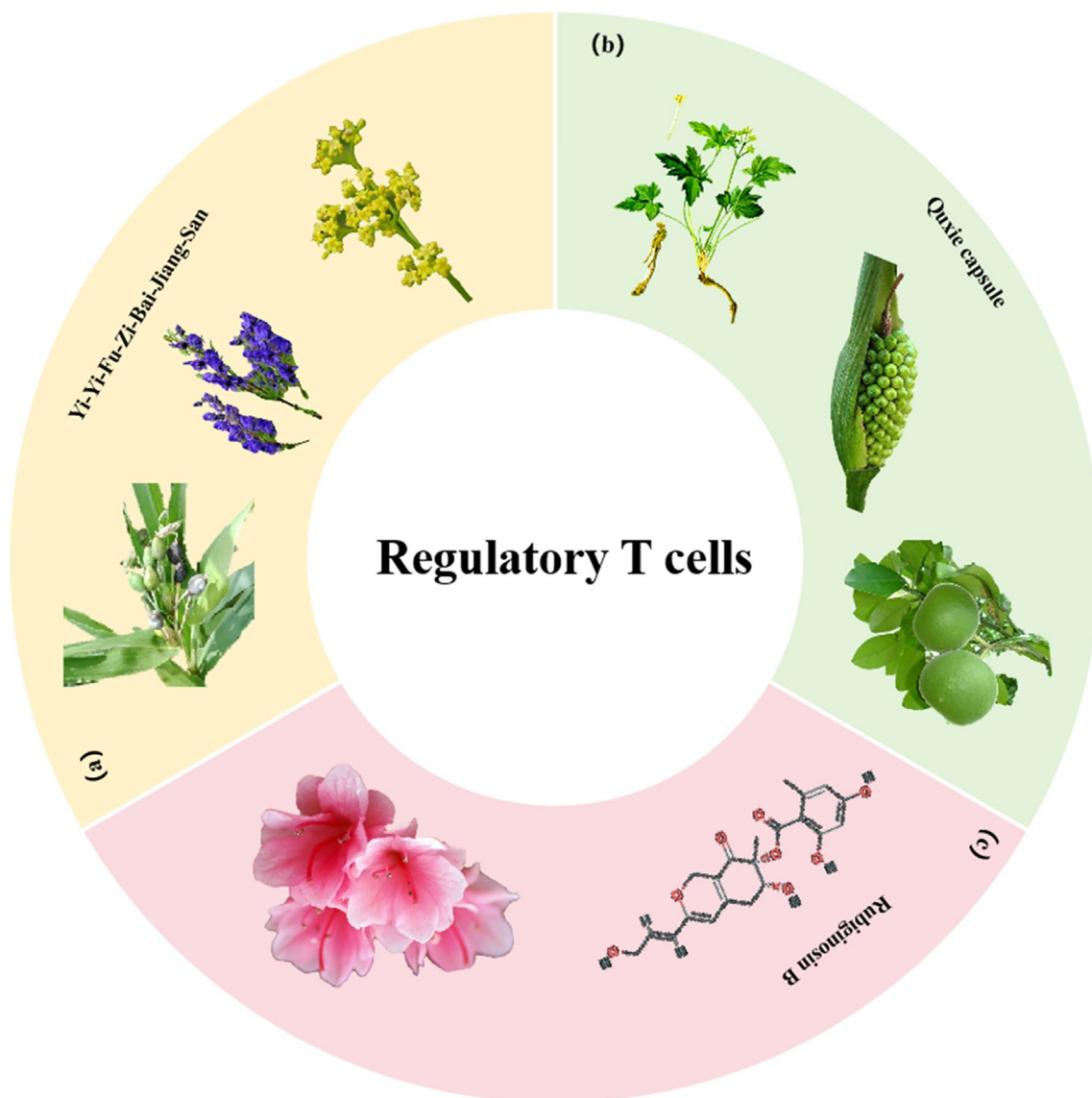


FIGURE 4 | Herbal medicine treats CRC by regulating regulatory T cells. (a) *Coix lacryma-jobi*, *Aconitum carmichaelii* Debeaux and *Patrinia scabiosifolia* Fisch. ex Trevir. (b) *Coptis chinensis* Franch., *Pinellia ternata* (Thunb.) Ten. ex Breitenb. and *Citrus grandis* 'Tomentosa'. (c) *Rhododendron brachypodum* Fang & P. S. Liu.

with an increased abundance of *Clostridium* and elevated levels of faecal butyric acid [48]. Additionally, Ji and colleagues further confirmed that Huangqin decoction enhanced the abundance of *Lachnospiraceae*, *Firmicutes*, *Fusobacteria* and *Clostridium*, while reducing the abundance of *Eggerthellales* in a deoxycholic acid-induced CRC mouse model [49]. Xiaoyaosan has been used to treat depression in China for hundreds of years. In a CRC xenograft mouse model with depression, Xiaoyaosan effectively suppressed tumour growth and prolonged overall survival by regulating the abundance of *Bacteroides*, *Lactobacillus*, *Desulfovibrio* and *Rikenellaceae* [50]. Shao et al. reported that Xiao-Chai-Hu-Tang, a well-known TCM prescription, inhibited tumour growth in CRC patients and in a subcutaneous tumour model in C57BL/6J (MC38 cells) under depression by regulating the gut microbiota-mediated TLR4/MyD88/NF- κ B pathway [51]. This finding may offer promising news for CRC patients suffering from depression. San-Wu-Huang-Qin decoction, a notable TCM prescription, effectively suppressed tumour growth and improved the mucosal barrier in CRC mice, partially by

regulating gut microbiota, specifically *Escherichia-Shigella*, a lipopolysaccharide (LPS)-producing bacterium [52]. Berberine, a compound derived from *Coptis chinensis*, might impede CRC by suppressing the Hedgehog pathway and modulating gut microbiota in CRC mice. Additionally, 5-fluorouracil has been shown to reduce the α -diversity of the microbial community in CRC mice [53]. Multiple studies have confirmed that berberine decreases the diversity of intestinal flora in mice with CRC [54–57]. However, several investigations have suggested that berberine does not have an impact on the diversity of the intestinal microbiota in mice with CRC [58–60]. Even some studies have found that berberine can significantly increase the diversity of the intestinal microbiota in mice with CRC [61–63]. The conflicting results may be related to inconsistencies in the preparation protocols for CRC in mice, the sampling sites of intestinal flora, dosing cycles and the presence or absence of environmental contamination during sampling. Cheng et al. found that Xianlian Jiedu decoction, a well-known TCM prescription, could inhibit tumour growth in CRC mice. Mechanistically, Xianlian Jiedu

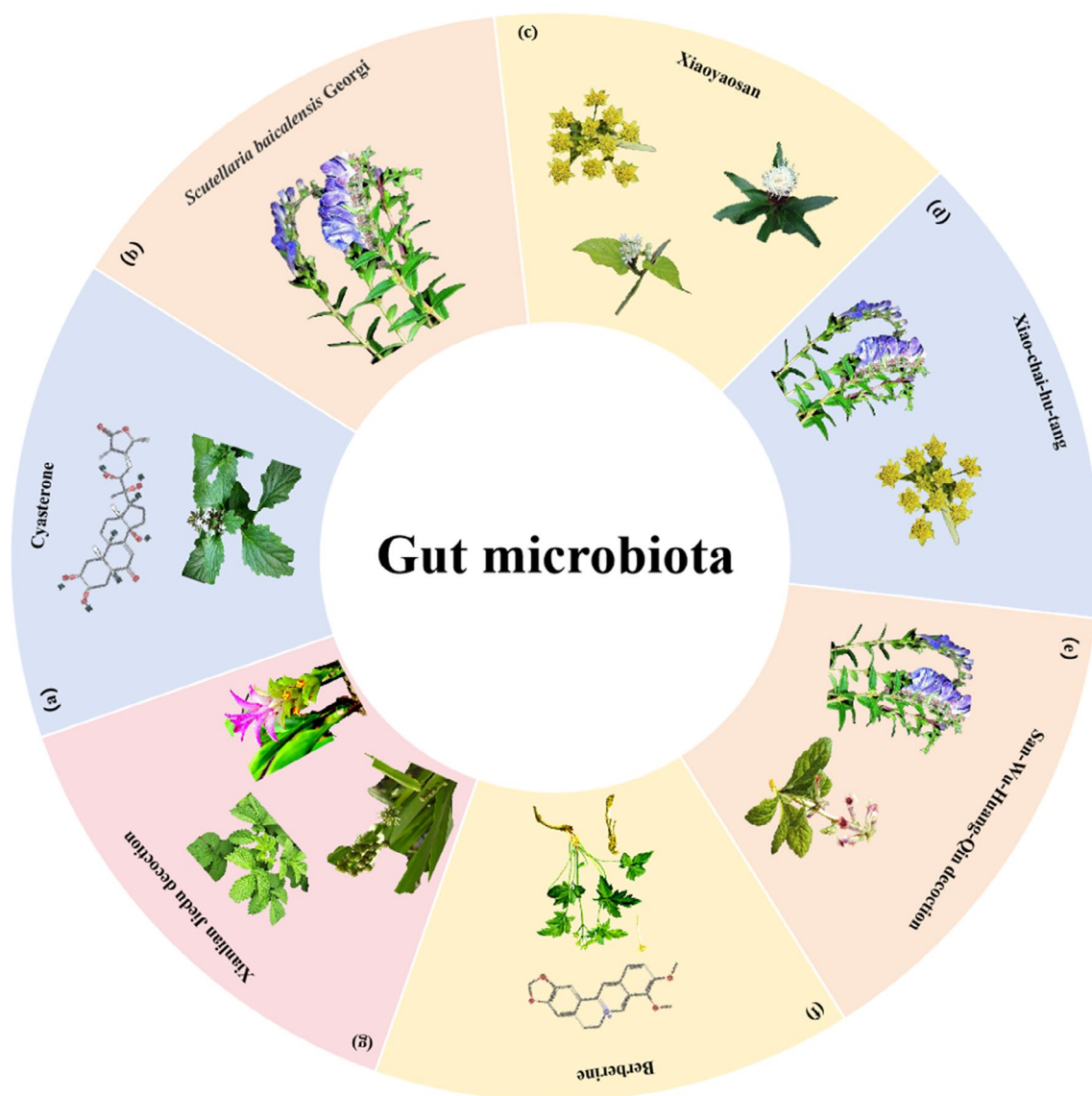


FIGURE 5 | Herbal medicine treats CRC by regulating gut microbiota. (a) *Ajuga decumbens* Thunb. (b) *Scutellaria baicalensis* Georgi. (c) *Bupleurum chinense* DC., *Atractylodes macrocephala* Koidz. and *Cynanchum otophyllum* Schneid. (d) *Scutellaria baicalensis* Georgi, and *Bupleurum chinense* DC. (e) *Scutellaria baicalensis* Georgi, and *Rehmanniaglutinosa* (Gaertn.) Libosch. ex Fisch. & C. A. Mey. (f) *Coptis chinensis* Franch. (g) *Sparganium stoloniferum* (Buch.-Ham. ex Graebn.) Buch.-Ham. ex Juz., *Agrimonia pilosa* Ledeb. and *Curcuma phaeocaulis* Valetton.

decoction restored gut microbiota homeostasis and increased levels of short-chain fatty acids, sphingolipids and glycerophospholipids by inhibiting the abundance of *Turicibacter* and *Clostridium_sensu_stricto_1* [64] (Figure 5).

A comprehensive analysis of the available literature reveals that most research investigating the role of herbal medicine in the treatment of CRC through the modulation of intestinal flora is relatively simplistic. These studies primarily describe changes in the abundance of relevant intestinal flora in CRC models following the application of herbal medicine, often lacking validation experiments and separate investigations into the role of the predominant flora alone. Additionally, it is important to acknowledge that the outcomes of certain animal studies frequently diverge from those observed in clinical trials, particularly with respect to alterations in the composition of intestinal microbiota and the levels of metabolic byproducts. In general, mice exhibit heightened sensitivity to the modulation of intestinal

microbiota, likely due to the controlled nature of their living conditions and dietary intake, in contrast to the variable living environments and dietary practices of humans. Consequently, when developing therapeutic strategies for CRC that target gut microbiota, it is essential to meticulously evaluate the influence of diverse dietary habits on the effectiveness of these treatments.

2.3 | Cancer Stem Cells

Cancer stem cells (CSCs) are unique cells located within tumour tissues with the ability to self-renew and differentiate into various cell types. They can replicate indefinitely, giving rise to new CSCs. CSCs contribute to cellular heterogeneity, lineage plasticity and drug resistance [65]. Identifying molecular markers and signalling pathways associated with CSCs in CRC can help develop more precisely targeted therapies [66, 67]. Given their significant role in the development

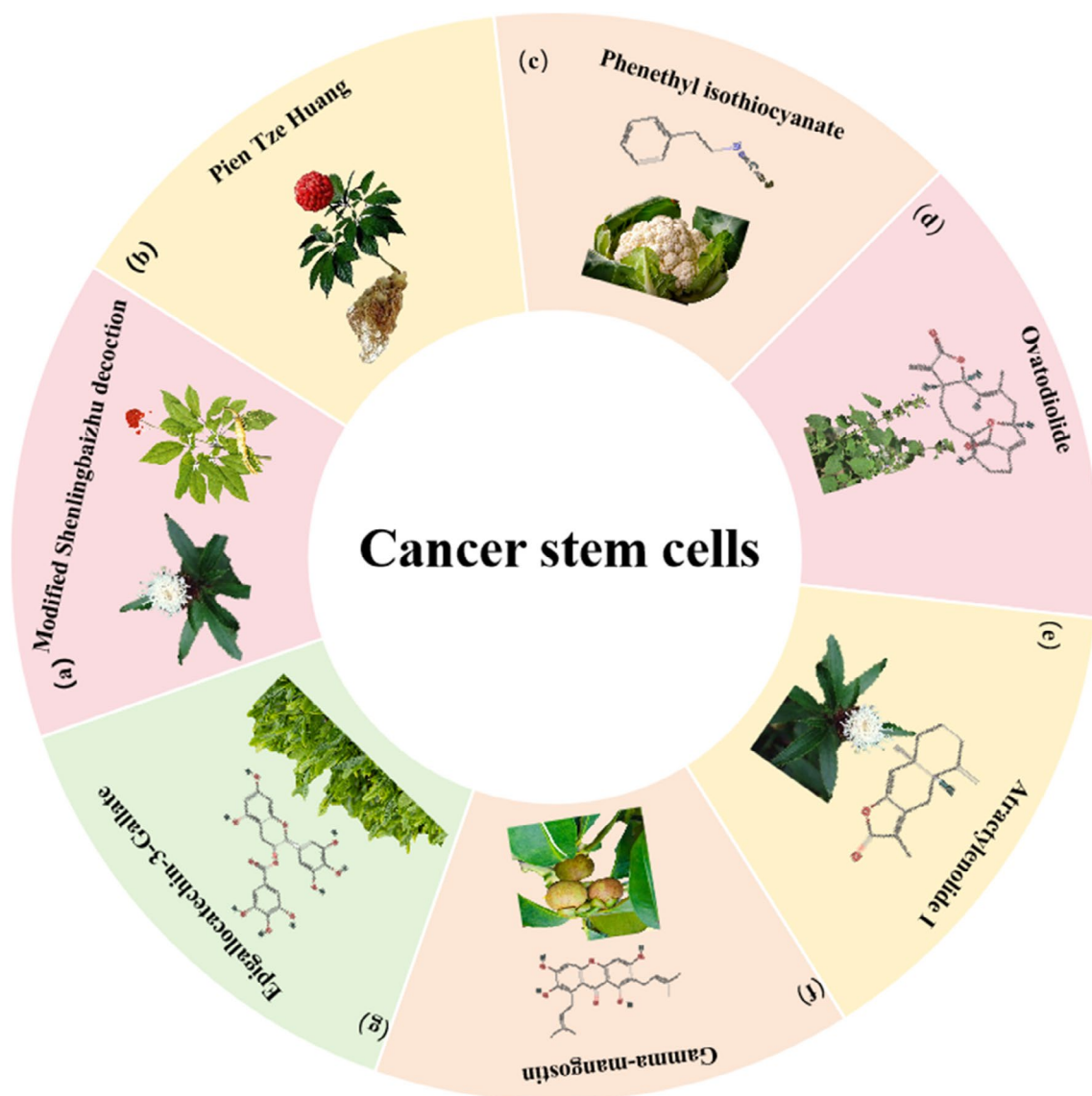


FIGURE 6 | Herbal medicine treats CRC by regulating cancer stem cells. (a) *Panax ginseng* C. A. Mey., *Atractylodes macrocephala* Koidz. (b) *Panax notoginseng* (Burkill) F. H. Chen ex C. H. Chow. (c) *Brassica oleracea* var. *botrytis* Linnaeus. (d) *Anisomeles indica* (L.) O.Ktze. (e) *Atractylodes macrocephala* Koidz. (f) *Garcinia mangostana* L. (g) Green Tea polyphenols.

of CRC, targeting CSCs has become a vital therapeutic strategy [68].

The modified Shenlingbaizhu decoction (MSD), a TCM formula, has been utilised for cancer treatment for several years at Nanfang Hospital in China. Dai proved that MSD significantly inhibited tumours and CD133⁺ CSCs in the tumour tissues of CRC mice. Furthermore, MSD suppressed the pluripotency of CRC cells primarily by inhibiting the epithelial-mesenchymal transition (EMT) induced by TGF- β /Smad [69]. Pien Tze Huang (PZH), a TCM formula, notably decreased the proportion of CRC stem-like side population cells and diminished the sphere-forming capacity of HT-29 cells, which is beneficial to the treatment of CRC [70]. Peng et al. further demonstrated that PZH exerts a negative regulatory effect on the properties of CSCs in SW480 cells by inhibiting the Notch1 signalling pathway [71]. Additionally, Cao et al. found that PZH augments T-cell-mediated cytotoxicity by suppressing the

expression of cancer stem cell markers in HCT15, HCT116, as well as in SW480 cells and CRC patient-derived organoids [72]. These findings underscore the necessity of conducting clinical trials to evaluate the efficacy of PZH in the treatment of CRC. Chu Won Nho et al. found that phenethyl isothiocyanate, a glucosinolate derived from cruciferous vegetables, could prevent CRC growth by inhibiting CSCs in HCT116 cells and a mouse xenograft model by partially regulating inflammation-mediated tumour microenvironments, although the precise role of inflammation requires further investigation [73]. Han et al. also demonstrated that phenethyl isothiocyanate exerts an inhibitory effect on CSCs in DLD-1 and SW480 cell lines through the suppression of the Wnt/ β -catenin signalling pathway [74]. Additionally, numerous chemical compounds derived from plants have been shown to inhibit CRC by targeting CSCs, including ovatodioid [75], atractylolide I [76], ginsenoside Rg3 [77], epigallocatechin-3-gallate [78] and gamma-mangostin [79] (Figure 6).

2.4 | Macrophage Polarisation

Macrophages can polarise into M1 and M2 phenotypes within the tumour microenvironment. M1 macrophages exhibit anti-tumour properties and promote tumour immunotherapy, whereas M2 macrophages facilitate tumorigenesis and metastasis [80]. Furthermore, macrophages are involved not only in tumour immunity but also in the inflammatory environment that precedes tumour formation. This has led to the recognition of macrophages as a significant target for immunotherapy of CRC [81].

Vitexin (apigenin-8-C-glucoside) is found in various edible and medicinal plants, such as *Crataegus pinnatifida* Bge. and *Vigna radiata* (L.) Wilczek [82]. In AOM/DSS-induced CRC mice, vitexin has been shown to suppress chronic CAC partly by up-regulating M1 macrophage polarisation, which triggers inflammation in colonic tumour tissue. Simultaneously, it significantly inhibits M1 macrophage polarisation in adjacent non-cancerous tissues, thereby reducing inflammation-induced carcinogenesis [83]. Tang and colleagues discovered that vitexin targeted the vitamin D receptor (VDR) and influenced macrophage polarisation via the VDR/PBLD (phenazine biosynthesis-like domain protein) signalling pathway, consequently mitigating the progression from chronic colitis to CRC [84]. This helps us better understand the mechanisms by which vitexin inhibits the development of chronic colitis to CRC. Jiedu Xiaozheng Yin, composed of *Hedyotis diffusa* Willd., *Spica prunellae*, *Pseudobulbus cremastrae* and *Sophora flavescens*, decreases tumour growth by inducing M1 macrophage polarisation through the TLR4 pathway and inhibiting M2 macrophage polarisation in the tumour tissue of CRC mice [85]. Dictamnine, extracted from *Dictamnus dasycarpus* Turcz., inhibits CRC tumour growth by inducing ferroptosis and suppressing M2 macrophage polarisation by regulating the MAPK pathway in DLD-1 xenograft mice [86]. Additionally, hydroxygenkwanin [87], macelignan [88], Jianpi Jiedu decoction [89], emodin [90], curcumin [91], 23-hydroxybetulinic acid [92] and cucurbitacin B [93] have also been shown to inhibit M2 macrophage polarisation, thereby contributing to their anti-metastatic and anti-proliferative effects against CRC (Figure 7).

2.5 | Glycolysis

The Warburg effect refers to the phenomenon in which cancer cells primarily obtain energy through glycolysis, a characteristic of tumour metabolism. Furthermore, studies have shown that glycolysis produces various metabolites that favour tumour cell proliferation and metastasis [94]. In recent years, targeting glycolysis has emerged as a significant strategy for exploring treatment options for CRC.

Rhus chinensis Mill., a medicinal plant belonging to the *Rhus* genus of the sumac family, is frequently utilised in cancer treatment in China, India and Japan. Wang et al. demonstrated that the triterpenoids (TER) from *Rhus chinensis* Mill. inhibited glycolysis by suppressing glucose uptake and lactate acid production by inhibiting glycolysis gene expressions, including GLUT1, LDHA and PKM2, in SW620 and HCT116 cells [95]. Furthermore, Wang et al. identified that TER not only suppressed glycolysis and glutaminolysis [96] but also promoted

glycolytic gene expression in CD8⁺ T cells, thereby enhancing T-cells recognition and significantly inhibiting CRC tumour growth [16]. Atractylenolide I is a natural compound derived from *Atractylodes Macrocephalae* Rhizoma. Wang et al. found that atractylenolide I significantly affected the Warburg effect and disrupted stemness maintenance by suppressing the AKT/mTOR pathway, which induced cell apoptosis and inhibited invasion in COLO205 and HCT116 cells, as well as in HCT116 xenografted nude mice [76]. Ma et al. provided additional evidence that atractylenolide I induced apoptosis and inhibited glycolysis by obstructing the JAK2/STAT3 signalling pathway in HCT116 and SW480 cells, as well as in HCT116 xenografted nude mouse models [97]. Saponin monomer 13 of the dwarf lilyturf tuber (DT-13) is a natural product extracted from *Liriope Radix*, and its anti-inflammatory and antitumor activities have been reported in several publications [98–101]. DT-13 has been shown to block GLUT1-mediated glycolysis in HCT-15 and HT-29 CRC cells, as well as in an HCT-15 orthotopic nude mouse model of CRC. Additionally, DT-13 inhibited the number of spontaneous adenomas in the intestines of APC^{min} mice, a model of familial adenomatous polyposis that exhibits a phenotype similar to the human disease, by regulating the AMPK/mTOR pathway [98]. The findings from the orthotopic xenograft implantation mouse model indicated that DT-13 exhibited a superior anti-tumor effect at a dosage of 1.25 mg/kg compared to 2.5 mg/kg. This interesting result may be attributed to factors such as the drug's absorption and metabolism, as well as its specific targets and mechanisms of action. Future investigations should focus on elucidating its intrinsic mechanisms by examining its pharmacokinetic and pharmacodynamic properties, conducting molecular target and pathway analyses, validating findings through cell and animal models and assessing metabolism and potential toxicity accumulation. Furthermore, various botanical drugs have been demonstrated to regulate glycolysis to inhibit CRC cell growth, including diosgenin [102], epigallocatechin-3-gallate [103], kaempferol [104], curcumol [105], naringin [106], cannabidiol [107] and Quxie capsule [108] (Figure 8).

At present, the detection of tumour glycolysis levels primarily relies on the measurement of glycolytic enzymes and their associated products. However, these methods do not fully capture the true state of glycolysis. As technology continues to advance, it is essential to integrate metabolite quantification, enzyme activity analysis and cutting-edge techniques in the assessment of tumour glycolysis levels, such as Seahorse XF, fluorescence lifetime imaging microscopy (FLIM) and ¹³C metabolic flux analysis.

2.6 | Ferroptosis

Ferroptosis is a type of cell death that relies on iron and is marked by the accumulation of lipid peroxides, resulting in harm to the membranes of tumour cells. This process leads to several phenomena, including increased lipid peroxidation, failure of antioxidant defences, elevated ROS, mitochondrial atrophy and cell membrane rupture [109–111]. As the investigation of ferroptosis as a potential treatment for CRC is still in its early stages, further investigation is needed to determine how to effectively trigger ferroptosis in CRC cells while minimising disruption to normal cells [112]. Ginsenoside Rh3 (GRh3), a bacterial byproduct of

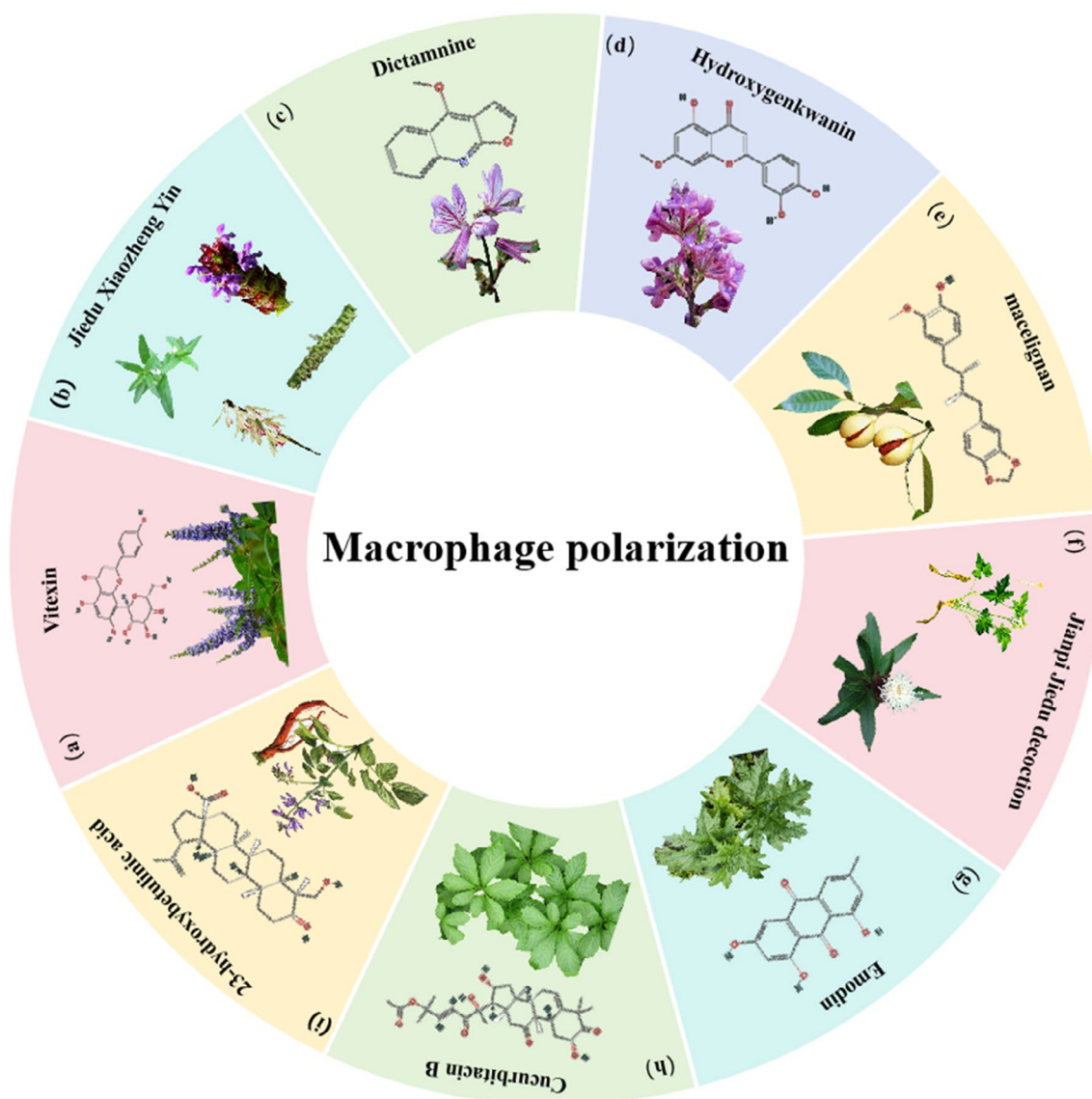


FIGURE 7 | Herbal medicine treats CRC by regulating macrophage polarisation. (a) *Vitex negundo* L. var. *cannabifolia* (Sieb. et Zucc.) Hand.-Mazz. (b) *Hedyotis diffusa* Willd, *Spica prunellae*, *Cremastra appendiculata* (D. Don) Makino and *Sophora Flavescens*. (c) *Dictamnus dasycarpus* Turcz. (d) *Daphne genkwa* Siebold & Zucc. (e) *Myristica fragrans* Houtt. (f) *Coptis chinensis* Franch., and *Atractylodes macrocephala* Koidz. (g) *Rheum palmatum* L. (h) *Gynostemma pentaphyllum* (Thunb.) Makino. (i) *Salvia miltiorrhiza* Bunge.

ginsenoside Rg5, induces ferroptosis via triggering gasdermin D-dependent pyroptosis and suppressing solute carrier family 7 member 11. This inhibition activates ferroptosis through the Stat3/p53/NRF2 pathway in HT29 and HCT116 cells, as well as in HT29 and HCT116 xenograft models in nude mice [113]. In vivo studies have indicated that GRh3 does not cause substantial harm to hepatic and renal tissues. Furthermore, in vitro investigations have revealed that GRh3 does not exert a significant inhibitory effect on normal colorectal cells [113]. Therefore, the current research data indicate that GRh3 can significantly inhibit CRC and has no toxic or side effects on normal tissues. Solanine, a steroidal alkaloid, is the main chemical component of *Solanum nigrum* L [114]. Lu et al. found that solanine could induce ferroptotic cell death through the ALOX12B/ADCY4 molecular axis in HCT116 and SW480 cells [115]. Curcumin, the main component of *Curcumae Longae* Rhizoma, is proven to trigger ferroptosis by regulating the JNK signalling pathway

[116], suppressing glutathione peroxidase-4 and ferroptosis suppressor protein-1 (in combination with andrographis) [117], inhibiting the PI3K/AKT/mTOR signalling pathway [118] and regulating the p53 and solute carrier family 7 member 11/glutathione/glutathione peroxidase 4 signalling axis [119]. Studies have demonstrated that curcumin can synergistically enhance the anti-tumour efficacy of chemotherapeutic agents (e.g., 5-fluorouracil) and natural compounds (e.g., andrographolide) while exhibiting low toxicity toward normal tissues. However, its clinical application is hindered by poor bioavailability, primarily attributed to low water solubility, which limits drug absorption and accelerates metabolic clearance. To address this challenge, research efforts are focused on developing advanced delivery systems, such as nanomaterial-based carriers or plant extracellular vesicles. These technologies aim to improve drug solubility, enable targeted delivery and enhance in vivo stability, thereby unlocking the full therapeutic potential of curcumin.

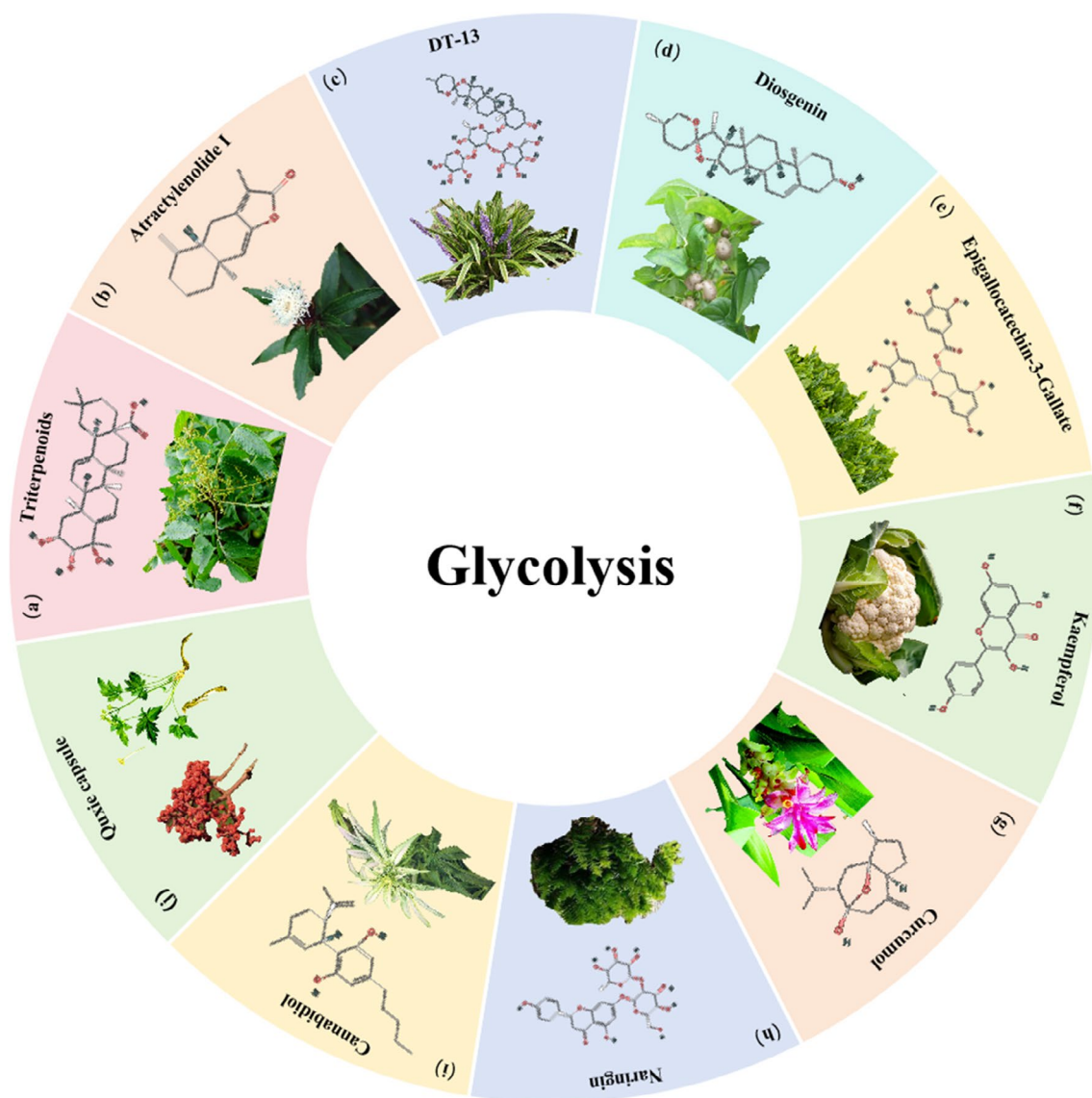


FIGURE 8 | Herbal medicine treats CRC by regulating glycolysis. (a) *Rhus chinensis* Mill. (b) *Atractylodes macrocephala* Koidz. (c) *Liriodopsis Radix*. (d) *Dioscorea polystachya* Turcz. (e) Green Tea polyphenols. (f) *Brassica oleracea* var. *botrytis* Linnaeus. (g) *Curcuma phaeocaulis* Valetton. (h) *Drynaria roosii* Nakaike. (i) *Cannabis sativa* L. (j) *Evodiae fructus*, and *Coptis chinensis* Franch.

The role of ferroptosis in CRC has garnered increasing attention and has been demonstrated in the mechanisms of action of various botanicals, including tagitinin C [120], emodin [121], baicalin [122], coumestrol [123], erianin [124], luteolin [125], osthole [126], puerarin [127], punicic acid [128], rosmarinic acid [129], ginsenoside Rh4 [130] and gambogenic acid [131] (Figures 9 and 10).

Currently, investigations into ferroptosis predominantly rely on in vitro experiments, with a limited number of associated animal models. This disparity arises from the significantly more intricate metabolic processes that occur in vivo compared to those observed in cellular studies. Furthermore, existing research utilising animal models primarily distinguishes between control and drug treatment groups, with a notable absence of positive control groups. Future studies on the mechanisms underlying ferroptosis should aim to enhance the validation of findings through in vivo experimentation.

2.7 | Extracellular Vesicles

An exosome is a membrane-bound vesicle released from a cell through the fusion of an intracellular multivesicular body with the cell membrane. Exosomes transport nucleic acids, proteins, lipids and other biological macromolecules. They bind to surface receptors on recipient cells via specific surface molecules, facilitating the delivery of their contents for intercellular communication. Increasing evidence indicates that exosomal miRNAs serve as crucial mediators of communication between tumour cells and the tumour microenvironment [132, 133]. The modulation of exosome levels containing specific contents represents a promising approach for CRC treatment [134, 135]. JianPi JieDu Recipe (JPJDR), a TCM prescription, has been frequently utilised to treat gastrointestinal tumours. Ji and colleagues discovered that JPJDR suppressed the growth and migration of CRC cells by modulating the ITGBL1-rich extracellular vesicle-mediated TNFAIP3-NF- κ B pathway, which subsequently inhibited fibroblast activation [136].

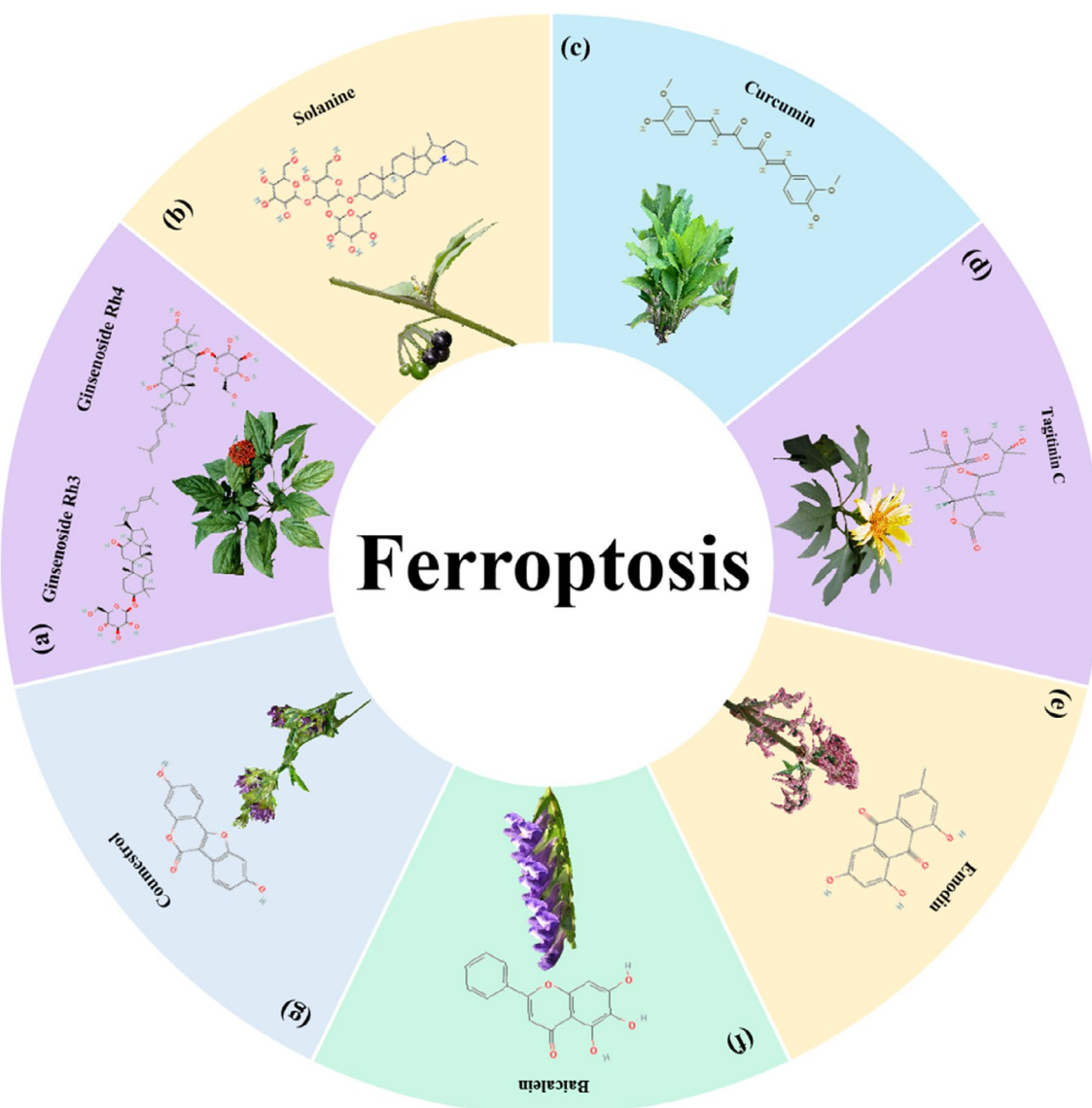


FIGURE 9 | Herbal medicine treats CRC by regulating ferroptosis. (a) *Panax ginseng* C. A. Mey. (b) *Solanum nigrum* L. (c) *Curcuma longa* L. (d) *Tithonia diversifolia* (Hemsl.) A. Grey. (e) *Rheum palmatum* L. (f) *Scutellaria baicalensis* Georgi. (g) *Medicago sativa* L.

Paris polyphylla, an herbal medicine, has demonstrated various physiological activities, including antifungal, antidiabetic, anti-inflammatory, antioxidant and immunomodulatory effects and potential benefits against digestive tract cancers [137–141]. Tai and colleagues found that pennogenin 3-O-beta-chacotrioside and polyphyllin VI, both extracted from *Paris polyphylla*, could inhibit the release of extracellular vesicles from *Fusobacterium nucleatum*, an intestinal bacterium enriched in CRC lesions and associated with CRC proliferation and metastasis, thereby interfering with the invasion of Caco-2 and HT-29 cells [142]. Furthermore, various chemical compounds derived from plants have been found to regulate extracellular vesicles to inhibit CRC tumour growth or metastasis. For example, matrine inhibits the secretion of exosomal circSLC7A6 by regulating CXCR5 [143]; salvianolic acid A inhibits the amount of GRP78 in exosomes [144]; Dahuang Zhechong Pill ameliorates exosomal CCL2 primed pre-metastatic niche [145]; and total coumarins extracted from *Pileostegia tomentella* Hand. Mazz (Saxifragaceae) upregulate exosomal miR-375-3p [146] (Figure 11).

Current research on the molecular mechanisms by which herbal medicines exert therapeutic effects against CRC through extracellular vesicle modulation remains in its early stages. Specifically, the upstream and downstream regulatory mechanisms by which certain drugs inhibit CRC are not yet fully elucidated. Furthermore, many studies lack validation in animal models and subsequent verification of clinical efficacy. Additionally, the active components of herbal formulations and the synergistic effects of component combinations remain unclear. Further investigation is also required to evaluate drug bioavailability, in vivo metabolic stability and long-term toxicity.

2.8 | Mitochondrial Function

Abnormal mitochondrial function can lead to metabolic imbalances and altered redox status, which may promote the development of cancer. Conversely, mitochondria can also influence cancer progression by participating in processes such

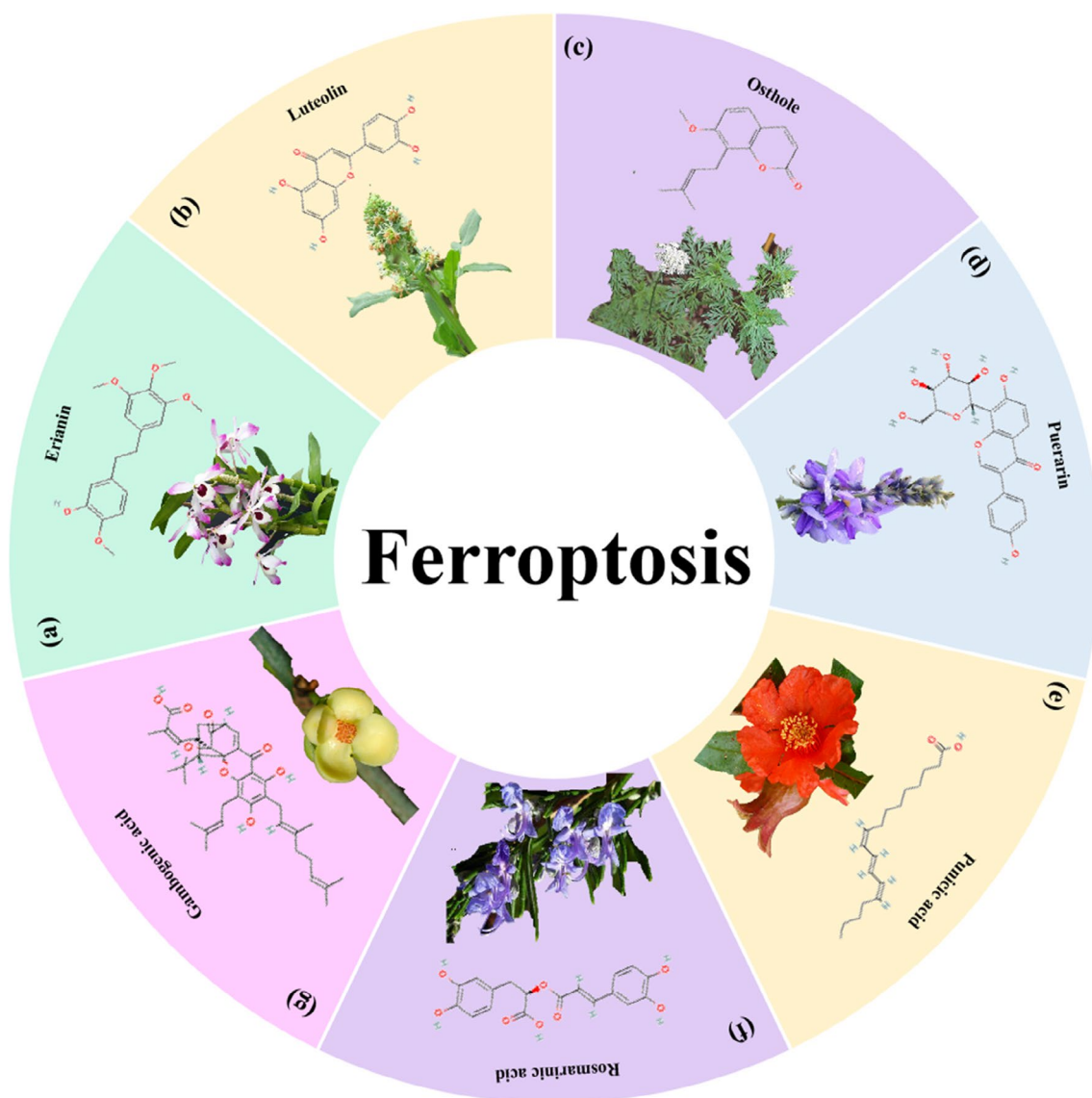


FIGURE 10 | Herbal medicine treats CRC by regulating ferroptosis. (a) *Dendrobium nobile* Lindl. (b) *Reseda odorata* L. (c) *Cnidium monnieri* (L.) Spreng. (d) *Pueraria lobata* (Willd) Ohwi. (e) *Punica granatum* L. (f) *Rosmarinus officinalis* L. (g) *Garcinia hanburyi* Hook.f.

as apoptosis. Given the important role of mitochondria in CRC, treatment strategies targeting mitochondrial function are gaining increasing attention [147, 148]. Coptisine is an isoquinoline alkaloid extracted from *Coptis chinensis* Franch. Han et al. proved that coptisine significantly suppressed cytoactive and migration in HCT-116 cells by disrupting mitochondrial function, which was indicated by a lower mitochondrial membrane potential (MMP) and increased levels of ROS. Consequently, Han et al. speculated that coptisine promoted HCT-116 cell apoptosis via activating mitochondrial-related apoptotic pathways [149]. Furthermore, an analysis of the visceral index and mortality rates in the coptisine-treated animals revealed no indications of drug-related toxicity. These results collectively support the conclusion that coptisine is a compound characterised by low toxicity and possesses anti-tumour properties [149]. Tanshinone IIA, a main natural product derived from *Salvia miltiorrhiza* Bunge, has demonstrated a range of physiological activities, including effects on hepatic steatosis, insulin resistance, cardiovascular disorders and cancers [150–152]. Recent

evidence suggests that excessive mitochondrial fission disrupts mitochondrial physiological function, leading to a decrease in MMP, an increase in mitochondrial ROS level and ultimately triggering mitochondria-mediated apoptosis [153]. Li et al. found that tanshinone IIA inhibited the proliferation and migration of SW837 cells by triggering the JNK-Mff pathway, which mediates mitochondrial fission [153]. Huo et al. demonstrated that tanshinone IIA promotes IL2-mediated SW480 cell apoptosis through the activation of INF2-mediated mitochondrial fission and the stimulation of the Mst1-Hippo signalling pathway [154]. However, all of the aforementioned research results are based on cell experiments, and further animal experiments and clinical trials are necessary to support these findings. Piperine is the major bioactive compound found in black pepper (*Piper nigrum*). Srikanta Kumar Rath et al. found that piperine enhanced the oral bioavailability of CXB (a selective COX-2 inhibitor) by 129% in adult female BALB/c mice. Additionally, piperine increased the toxicity of CXB to HT-29 cells, but not to IEC-6 cells, by inducing mitochondria-mediated apoptosis. This was evidenced

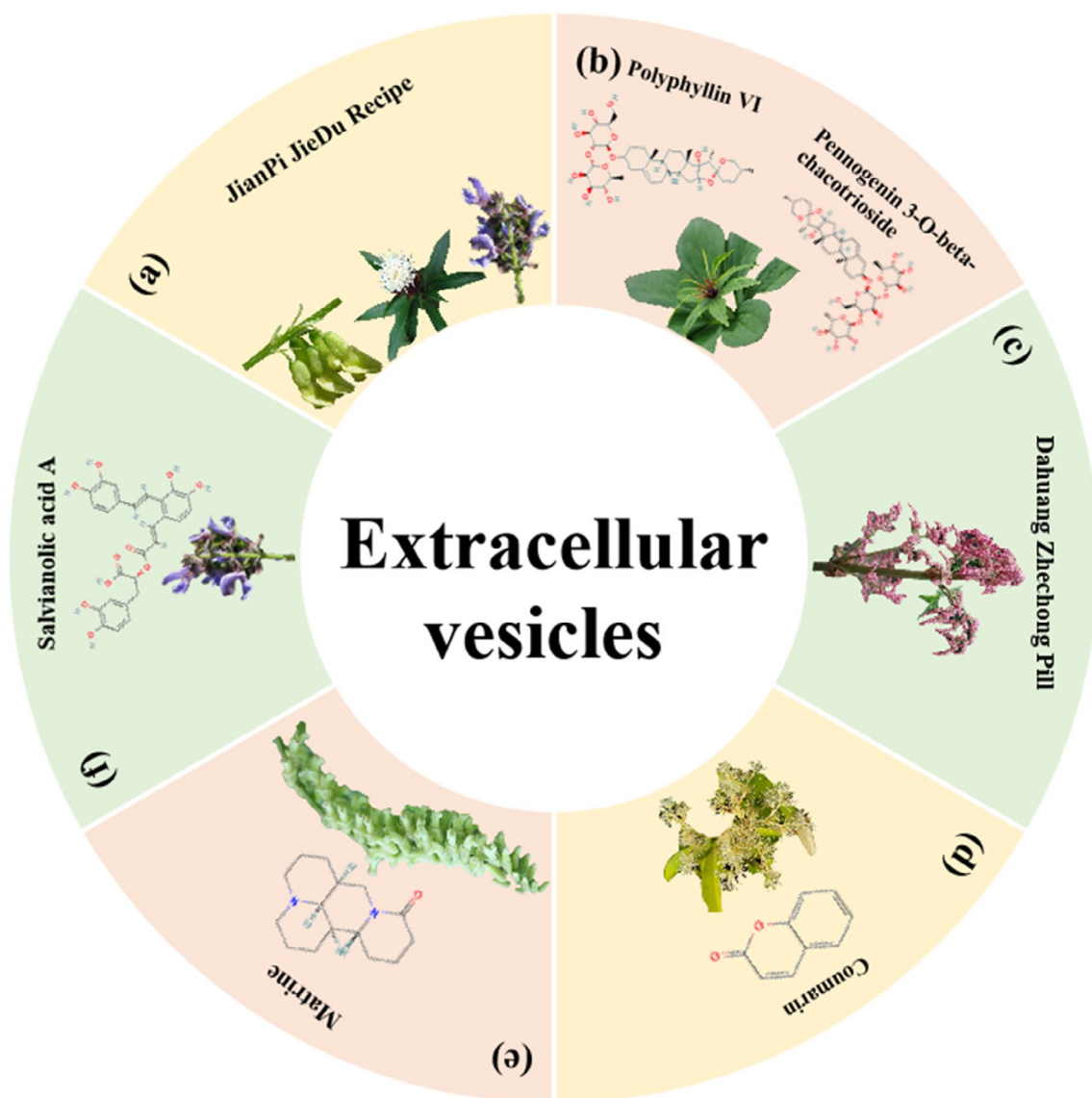


FIGURE 11 | Herbal medicine treats CRC by regulating extracellular vesicles. (a) *Astragalus membranaceus* (Fisch.) Bunge, *Atractylodes macrocephala* Koidz. and *Salvia miltiorrhiza* Bunge. (b) *Paris polyphylla* Sm. (c) *Rheum palmatum* L. (d) *Pileostegia tomentella* Hand. Mazz (Saxifragaceae). (e) *Sophora flavescens* Ait. (f) *Salvia miltiorrhiza* Bunge.

by higher ROS levels, caspase activation and increased apoptotic protein expressions. Furthermore, the combination of piperine and CXB reduced the population of CD133⁺/CD44⁺ CSCs and stemness-related protein expressions. In the CT26 xenograft BALB/c mouse model, piperine and CXB synergistically suppressed tumour growth, as indicated by the tumour volume in the piperine and CXB group, which increased by 20.9% compared to the vehicle group (77.9%), the CXB group (66.9%) and the piperine group (75.4%). Mechanistically, piperine synergizes with CXB to suppress CRC cell proliferation by regulating the Wnt/ β -catenin pathway and inducing mitochondria-mediated apoptosis in HT-29 cells [155]. The role of piperine in inhibiting the proliferation of CRC by regulating mitochondrial-mediated apoptosis has also been confirmed by multiple studies [156–159]. However, all the above research results are based on in vitro cell experiments, and further animal experiments are necessary to validate these findings. What is more, considering that pepper is commonly used as a flavouring agent, its consumption may influence the bioavailability, efficacy and even toxicity of certain

drugs. Therefore, more comprehensive studies are necessary. Mitochondrial-associated apoptosis is a crucial mechanism involved in the action of various compounds against CRC, including curcumin [160], magnolol [161], resveratrol [162], atractylenolide I [163], tangeretin [164], shikonin [165], oxymatrine [166], naringin [167], baicalin [168], luteolin [169] and *Thymus vulgaris* [170] (Figures 12 and 13).

2.9 | Inflammation

Chronic inflammatory stimulation is a significant contributor to CRC, which accounts for the heightened risk of CRC in individuals with ulcerative colitis (UC) [171]. The secretion of pro-inflammatory cytokines is a hallmark of the chronic inflammatory response and accelerates tumour growth and metastasis [172]. Exploring botanical treatments for CRC may be beneficial, and increasing the intake of an anti-inflammatory diet is also an effective strategy for preventing CRC in patients with UC

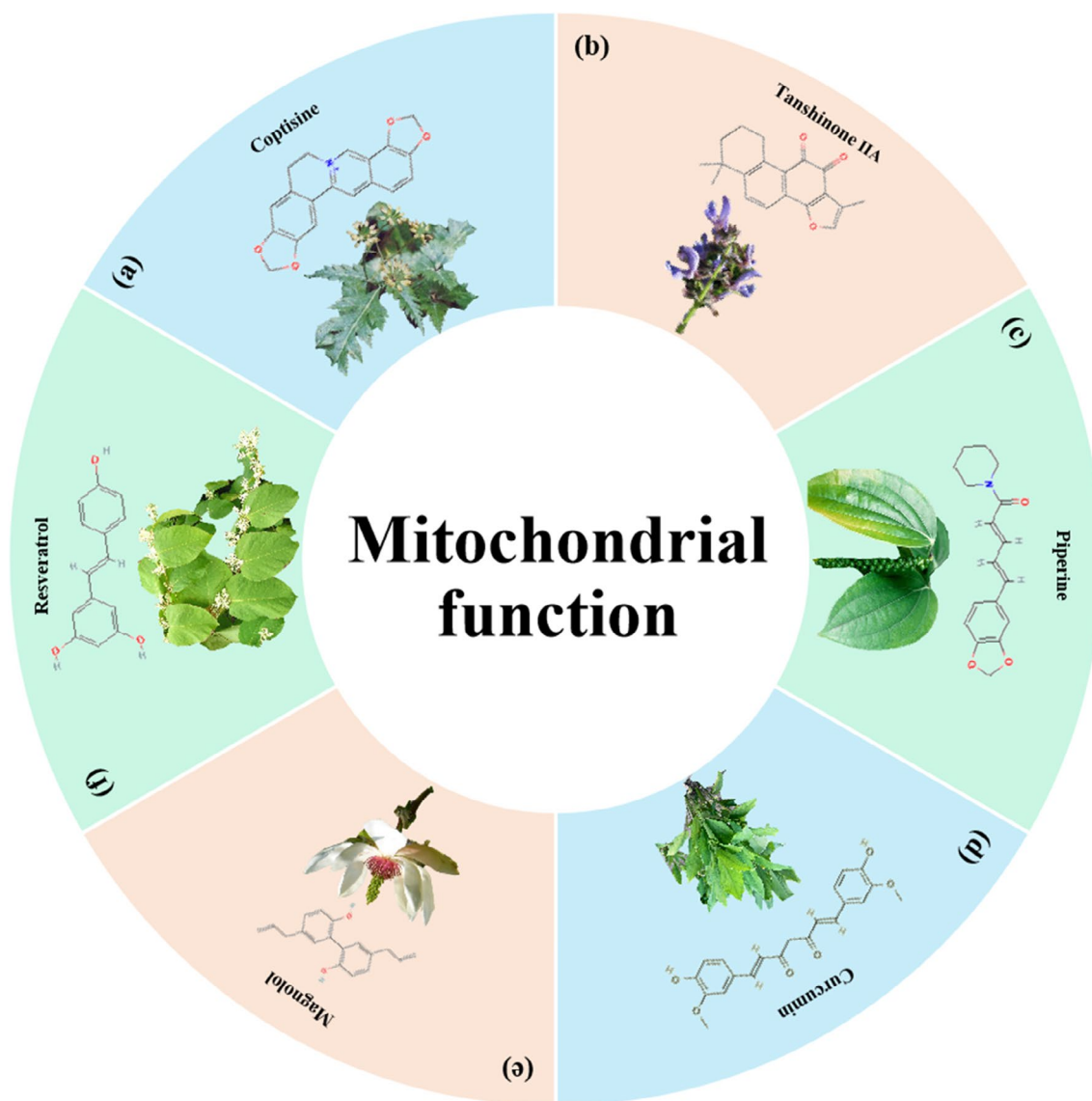


FIGURE 12 | Herbal medicine treats CRC by regulating mitochondrial function. (a) *Coptis chinensis* Franch. (b) *Salvia miltiorrhiza* Bunge. (c) *Piper nigrum* L. (d) *Curcuma longa* L. (e) *Magnolia officinalis* Rehd. et Wils. (f) *Polygonum cuspidatum* Sieb. et Zucc.

[173, 174]. Curcumin, a flavonoid derived from *Curcuma longa* L., is proven to promote SW480 and HCT116 cell apoptosis by activating the NLRP3 inflammasome. However, the mechanisms underlying the promotion of apoptosis in LoVo and HT-29 cells remain unclear, suggesting that NLRP3 inflammasome activation is only one of the pathways by which curcumin causes CRC cell apoptosis [175]. The role of curcumin in inducing apoptosis in CRC cells by regulating inflammation has been confirmed by multiple studies [176, 177]. Although several Phase I clinical studies have clearly demonstrated the safety of oral curcumin, high concentrations of curcumin have been found to potentially provoke glutathione depletion and caspase-3 activation, which may cause hepatocytotoxicity in rat hepatocytes [178]. Furthermore, Torti and colleagues discovered that curcumin could induce iron depletion in mice with low iron content in the body by inhibiting hepcidin. This might be an important consideration when curcumin is used to treat patients with borderline iron deficiency or those exhibiting anaemia due to diseases [179]. Kanglaite injection is an extract derived from *Coix lacryma-jobi* (adlay) seed. Wang et al. demonstrated that Kanglaite enhanced

the sensitivity of CRC cells to Taxol by suppressing NF- κ B and promoting connexin 43 in a mouse model with subcutaneous tumours [180]. Shi et al. also proposed that Kanglaite inhibits EMT by inhibiting NF- κ B in CRC cells as well as in a mouse model with subcutaneous tumours using CT26 cells [181]. Evodiamine is an anti-tumour active ingredient extracted from *Tetradium ruticarpum* (A. Juss.) T. G. Hartley [182]. Sui et al. found that evodiamine could inhibit ABCG2-mediated drug resistance by suppressing NF- κ B in HCT-116/L-OHP cells and in a colorectal multidrug-resistant cancer xenograft model in nude mice [182]. Zhao et al. also found that evodiamine promoted apoptosis and suppressed migration of HCT-116 cells by suppressing the JAK2/STAT3 pathway, which activates NF- κ B [183]. The effect of evodiamine in regulating inflammation against CRC has also been supported by numerous studies [184–187]. Scutellarin, a phytochemical flavonoid derived from *Scutellaria altissima* L., inhibits CAC by suppressing the Hedgehog pathway and the NF- κ B-mediated inflammatory response in mice with AOM/DSS-induced CRC [188]. Xu and colleagues further discovered that scutellarin suppressed serum TNF- α and IL-6 levels in mice,

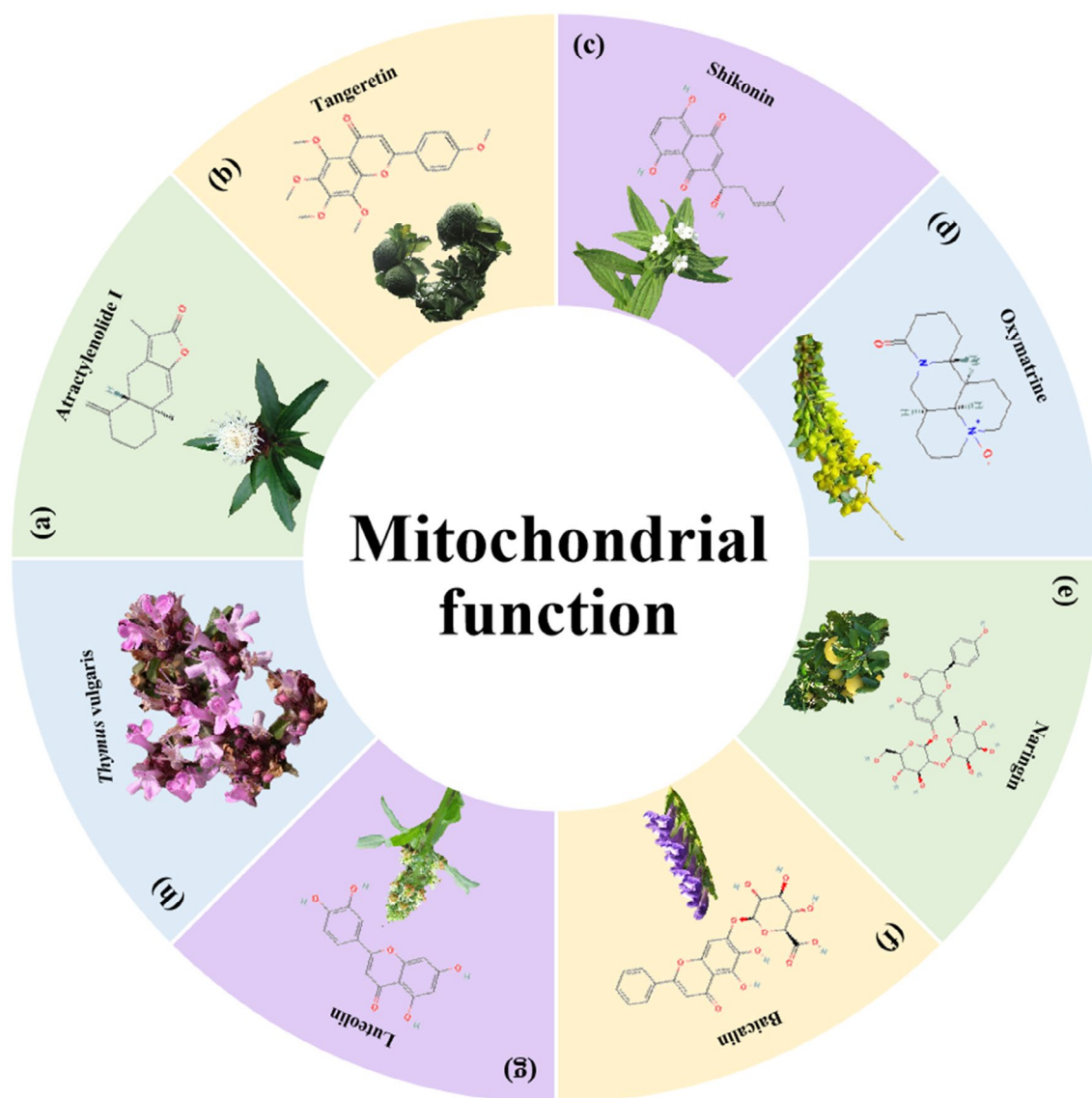


FIGURE 13 | Herbal medicine treats CRC by regulating mitochondrial function. (a) *Atractylodes macrocephala* Koidz. (b) *Citrus aurantium* L. (c) *Lithospermum erythrorhizon* Siebold & Zucc. (d) *Sophora tonkinensis* Gagnep. (e) *Citrus paradisi* Macf. (f) *Scutellaria baicalensis* Georgi. (g) *Reseda odorata* L. (h) *Thymus mongolicus* (Ronniger) Ronniger.

increased the expression of Bax and decreased the levels of Bcl-2 in the CAC tissues by inhibiting the Wnt/ β -catenin signalling pathway. These findings suggest that scutellarin may mitigate inflammation through multiple mechanisms, thereby exerting a therapeutic effect on CAC [189]. Jujube (*Ziziphus jujuba* Mill.), a common fruit in the Rhamnaceae family, has been used for decades to treat CRC. Ruan et al. found that the bioactive triterpenes in jujube prevented CRC by inhibiting the PI3K/AKT/NF- κ B pathway. Various triterpenes were identified in this study, which significantly contributed to subsequent development efforts [190]. Pristimerin is a triterpenoid derived from the *Celastraceae* and *Hippocrateaceae* families. Yousef et al. found that pristimerin prevented CRC growth by inhibiting the NF- κ B pathway in HCT-116 cells and in a BALB/c nude mouse model with HCT-116 xenografts [191, 192]. Kim and colleagues further discovered that the administration of pristimerin resulted in a reduction in inflammation and cellular proliferation triggered by AOM/DSS in colonic tissue. Additionally, pristimerin promoted apoptosis and modulated the AKT/FOXO3a

signalling pathway [193]. Puerarin is an isoflavone isolated from *Pueraria lobata* (Willd.) Ohwi, with significant anti-CRC activity [127, 194–197]. Nonetheless, the clinical efficacy of puerarin is limited due to its poor solubility and low bioavailability. Deng et al. prepared colon-specific microspheres loaded with puerarin by emulsification/internal gelation, which inhibited tumorigenesis and metastasis in CRC, partly by suppressing inflammation [198]. However, the mechanism by which puerarin exerts its therapeutic effects on CRC by regulating inflammation still requires further research for confirmation. Cryptotanshinone, a natural ingredient derived from *Salvia miltiorrhiza* Bunge, has been shown to significantly suppress the proliferation and growth of CRC [199–201]. Li et al. confirmed that cryptotanshinone induced CRC cell apoptosis by inhibiting Stat3, a known NF- κ B activator [199]. Zhang et al. found that cryptotanshinone prevented the proliferation and metastasis of CRC by inhibiting inflammation and angiogenesis by the regulation of the MMP/TIMP system, the PI3K/AKT/mTOR pathway and the HIF-1 α pathway in CT26 cells and a CT26 xenograft model using

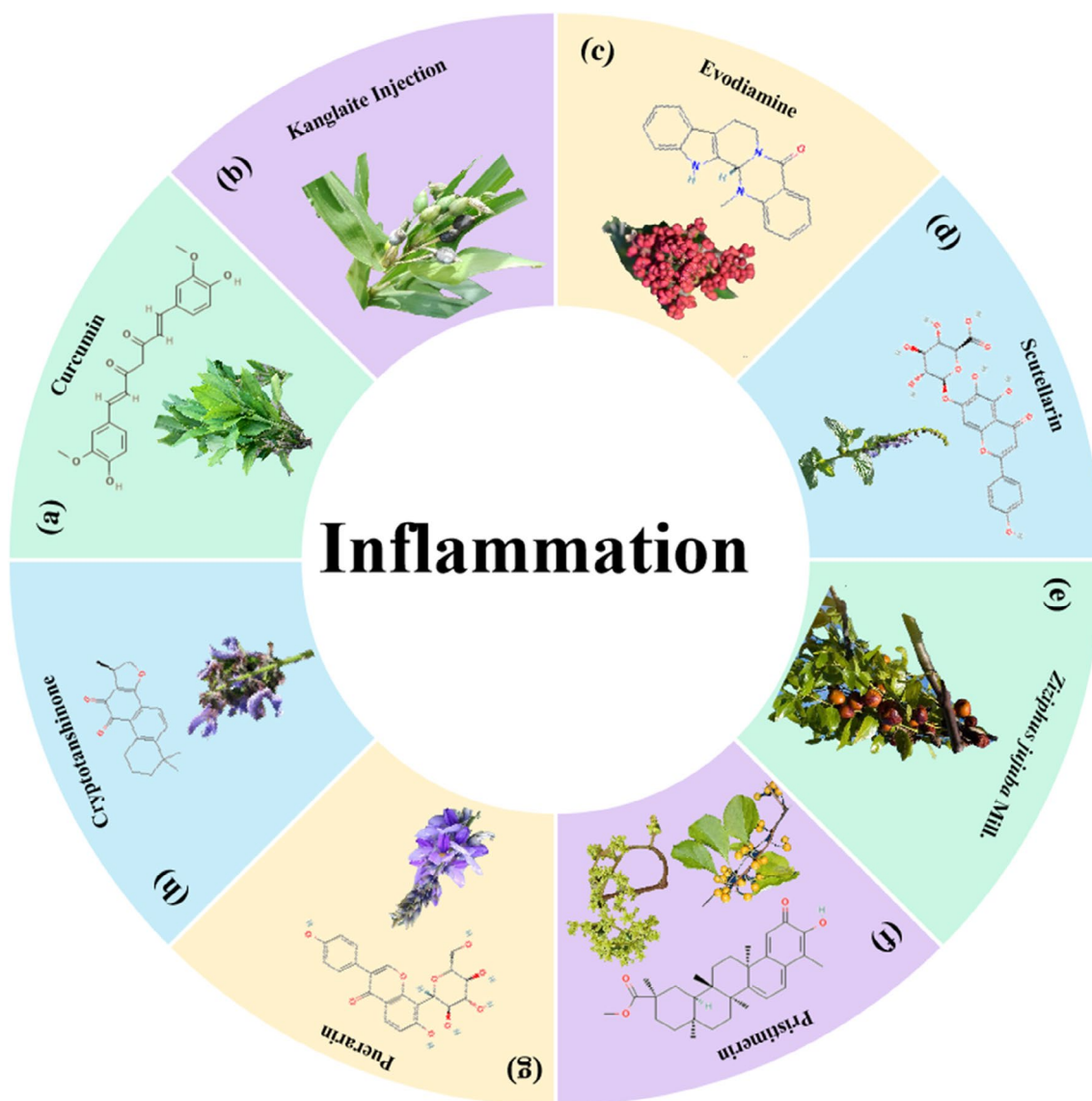


FIGURE 14 | Herbal medicine treats CRC by regulating inflammation. (a) *Curcuma longa* L. (b) *Coix lacryma-jobi* (adlay) seed. (c) *Tetradium ruticarpum* (A. Juss.) T. G. Hartley. (d) *Scutellaria altissima* L. (e) *Ziziphus jujuba* Mill. (f) *Celastraceae* and *Hippocrateaceae* families. (g) *Pueraria lobata* (Willd.) Ohwi. (h) *Salvia miltiorrhiza* Bunge.

BALB/c mice [202]. These findings further suggest that the inflammatory response plays a crucial role in CRC treatment through the action of cryptotanshinone (Figure 14).

2.10 | Oxidative Stress

Growing evidence indicates that chronic oxidative stress can activate inflammatory signalling pathways, which may subsequently trigger various transcription factors or lead to the deregulation of gene expression, thereby influencing tumour development and the survival of cancer cells. Additionally, oxidative stress causes excessive lipid peroxidation, and several lipid peroxidation products, including 4-hydroxynonenal and acrolein, have been implicated in the development of CRC [203, 204]. Zerumbone, a sesquiterpene derived from the edible ginger (*Zingiber zerumbet* Smith), has been shown to suppress CRC by various mechanisms, including the modulation of oxidative stress, gut microbiota and inflammation [205–212].

Memari et al. also found that zerumbone promoted apoptosis and suppressed metastasis in HT-29 cells by elevating ROS levels [210]. Sithara et al. demonstrated that zerumbone induces apoptosis in SW480 cells, partly by increasing cellular ROS levels and decreasing antioxidant levels [213]. Dihydroartemisinin is a well-known antimalarial drug derived from *Artemisia caruifolia* Buch.-Ham. ex Roxb. Yu et al. found that dihydroartemisinin promoted the anti-tumour activity of oxaliplatin by altering the PRDX2-ROS pathways in HCT116 and RKO cells, as well as in an HCT116 xenograft model using nude mice [214]. Additionally, Yao et al. found that dihydroartemisinin promoted the antitumor capacity of 5-fluorouracil against the resistant HCT116 TP53^{-/-} cells through ROS-mediated apoptosis [215]. However, the mechanisms by which dihydroartemisinin exerts its therapeutic effects on CRC by regulating oxidative stress still require more research data from various cell lines and animal models for confirmation. Dihydromyricetin is a flavonoid compound extracted from the leaves of *Vitis heyneana* Roem. et Schult. Wang et al. found that dihydromyricetin counteracted

multidrug resistance caused by MRP2 by inhibiting the NF- κ B-Nrf2 pathway in HCT116 and HCT8 cells, as well as in a xenograft model using BALB/c mice with NF- κ B/p65-overexpressing HCT116/OXA cells [216]. Zhang et al. believed that the involvement of semaphoring 4D is essential for the initiation of the antioxidant and anti-inflammatory properties of dihydromyricetin in colon cancer [217]. Andrographolide is a bicyclic diterpenoid lactone extracted from *Andrographis paniculata* (Burm.f.) Nees. Khan and colleagues discovered that andrographolide suppressed the proliferation of SW-480, DLD-1, HT-29 and HCT-116 cells via augmenting intracellular ROS generation [218–221]. Additionally, Banerjee et al. reported that andrographolide induced apoptosis in T84 and COLO205 cells by triggering ROS [222]. Andrographolide could also enhance the anti-tumour capacity of melatonin and cisplatin through ROS-mediated ER stress [223, 224].

Furthermore, numerous phytomedicines have been shown to regulate oxidative stress to inhibit CRC growth, including

granatin B, punicalagin, *imperata cylindrical* L. Raeusch (IMP), macrostemonoside A, auricularin, conferone, gambogenic acid, *Angelica dahurica*, Shaoyao decoction and astragaloside IV [225–234] (Figures 15 and 16).

2.11 | Autophagy

Autophagy is a cellular degradation process observed in eukaryotic cells that plays a crucial role in preserving metabolic homeostasis by facilitating the breakdown of misfolded or aggregated proteins, as well as damaged organelles [235]. Autophagy exhibits a multifaceted and dual role in the progression of CRC, with its mechanisms differing based on tumour stage, micro-environment and genetic context. These mechanisms can be categorised into the following primary aspects: inhibiting early carcinogenesis and maintaining genomic stability [236]; promoting advanced tumour survival and metabolic adaptation [237]; regulating metastasis and drug resistance [238, 239]; and

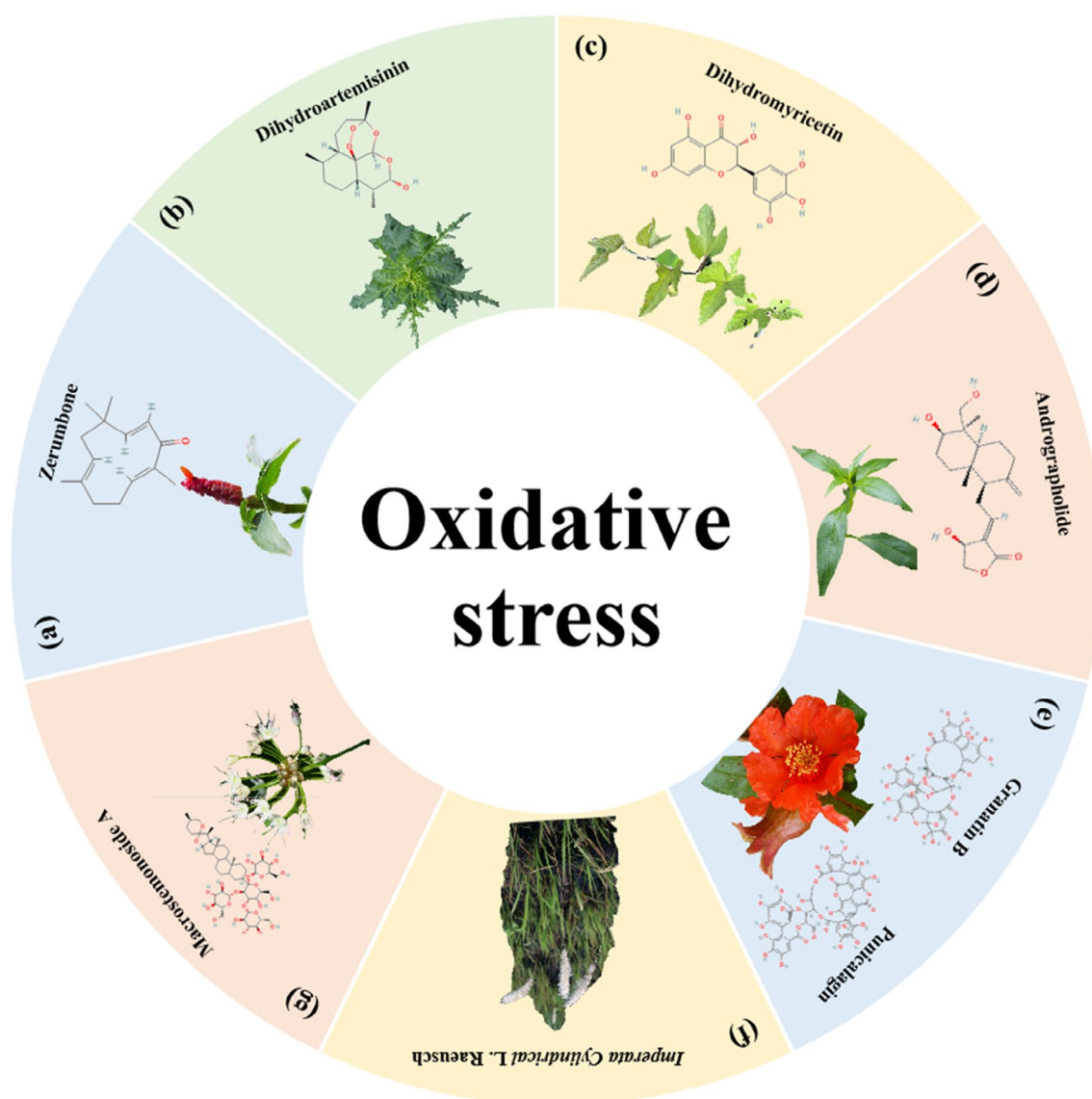


FIGURE 15 | Herbal medicine treats CRC by regulating oxidative stress. (a) *Zingiber zerumbet* Smith. (b) *Artemisia annua* L. (c) *Vitis heyneana* Roem. et Schult. (d) *Andrographis paniculata* (Burm. f.) Nees. (e) *Punica granatum* L. (f) *Imperata Cylindrical* L. Raeusch. (g) *Allium macrostemon* Bunge.

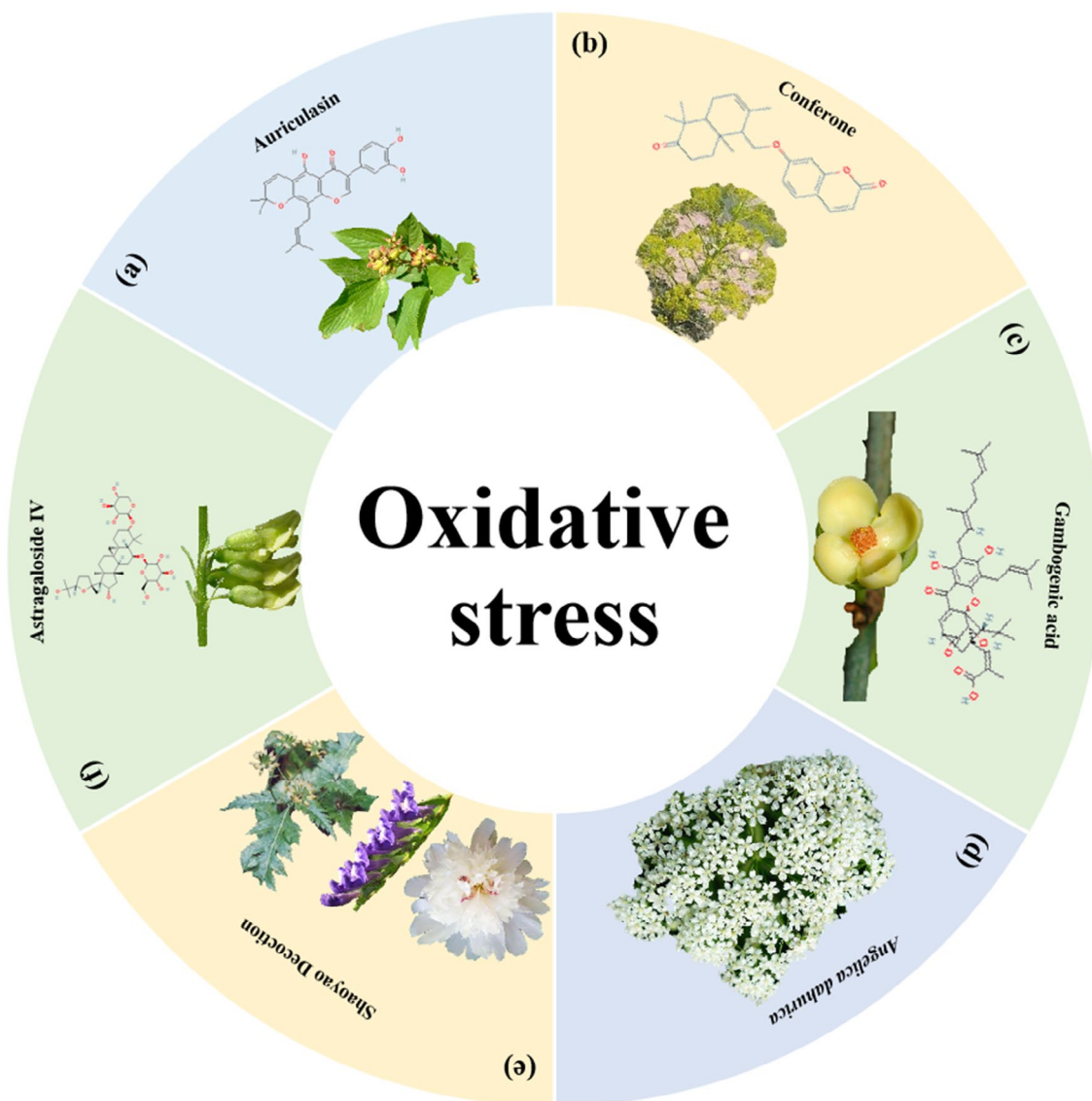


FIGURE 16 | Herbal medicine treats CRC by regulating oxidative stress. (a) *Flemingia prostrata* Roxb. f. ex Roxb. (b) *Ferula fukanensis* K. M. Shen. (c) *Garcinia hanburyi* Hook.f. (d) *Angelica dahurica* (Fisch. ex Hoffm.) Benth. et Hook. f. (e) *Paeonia lactiflora* Pall., *Scutellaria baicalensis* Georgi and *Coptis chinensis* Franch. (f) *Astragalus membranaceus* (Fisch.) Bunge.

modulating the immune microenvironment [240]. In conclusion, autophagy exhibits spatiotemporal dynamics in CRC, and targeting autophagy should be integrated with tumour staging and molecular characteristics. For instance, inhibiting autophagy in advanced CRC may enhance sensitivity to chemotherapy, while early intervention may necessitate the activation of autophagy to prevent carcinogenesis.

Rhus coriaria, commonly known as sumac, is a member of the Anacardiaceae family [241]. Research conducted by Ali Eid et al. has demonstrated that *Rhus coriaria* extract exhibited significant anti-CRC properties, primarily through the stimulation of proteolysis and the induction of autophagic and apoptotic cell death, as evidenced by studies involving HT-29 and Caco-2 cells [241]. The resistance to 5-fluorouracil is a critical factor that influences the effectiveness of treatments for CRC [242]. In their further investigations, Ali Eid et al. found that *Rhus coriaria* inhibited the viability, colony formation, and growth of HCT-116-WT and HCT-116-5FU-R cells by triggering autophagic cell

death. These findings suggest that *Rhus coriaria* may represent a promising and valuable source for the development of novel therapeutic agents for CRC [243]. *Origanum majorana* is an herbaceous plant found in southern Europe and the Mediterranean area. Research conducted by Ali Eid and colleagues has demonstrated that *Origanum majorana* ethanolic extract displayed significant anti-proliferative effects on HT-29 and Caco-2 cells, primarily through the mechanisms of autophagy and apoptosis induction [244]. Furthermore, their studies indicated that the essential oil of *Origanum majorana* triggered p38 MAPK-mediated autophagy, apoptosis and caspase-dependent cleavage of P70S6K, thereby inhibiting cellular viability and colony growth in HT-29 cells [245]. Dehydroevodiamine is a quinazoline alkaloid derived from *Tetradium ruticarpum* (A. Juss.) T. G. Hartley. A study conducted by Seung-Heon Hong and colleagues demonstrated that dehydroevodiamine inhibited the cell viability of HCT116, CT26, SW480 and LoVo cells by inducing caspase-dependent apoptosis and autophagy. In this study, dehydroevodiamine was also proved to inhibit the

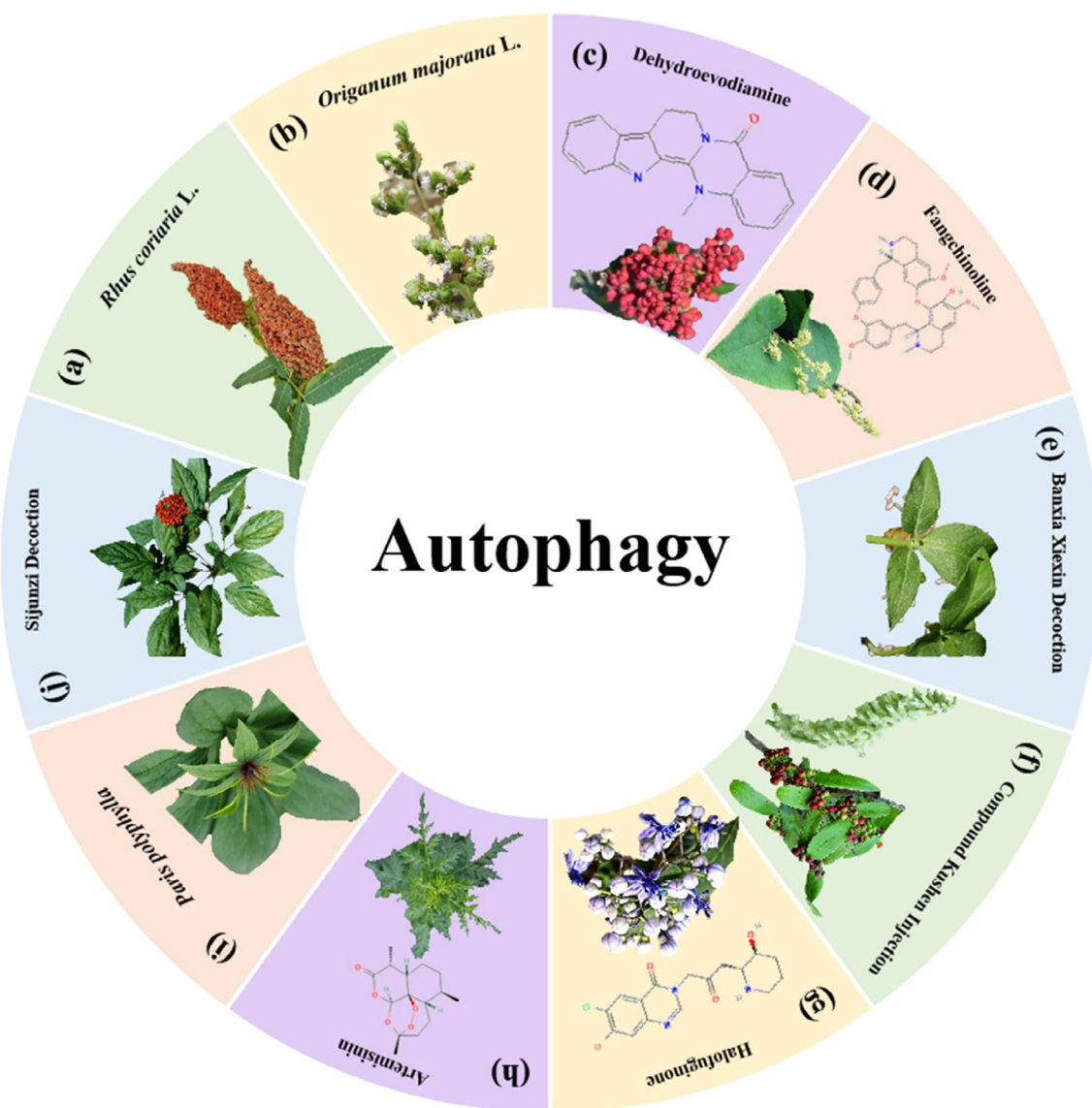


FIGURE 17 | Herbal medicine treats CRC by regulating autophagy. (a) *Rhus coriaria* L. (b) *Origanum majorana* L. (c) *Tetradium ruticarpum* (A. Juss.) T. G. Hartley. (d) *Stephaniae tetrandine* S. Moore. (e) *Pinellia ternata* (Thunb.) Ten. ex Breitenb. (f) *Sophora flavescens* Ait. and *Smilax glabra* Roxb. (g) *Dichroa febrifuga* Lour. (h) *Artemisia annua* L. (i) *Paris polyphylla* Sm. (j) *Panax ginseng* C. A. Mey.

lung metastasis of CT26 cells in an in vivo model by regulating EMT [246]. Fangchinoline is an isoquinoline alkaloid isolated from *Stephaniae tetrandine* S. Moore (Menispermaceae). Feng et al. found that fangchinoline induced apoptosis in HT29 and HCT116 cells, and HT29 xenograft model by activating AMPK/mTOR/ULK1-mediated autophagy [247]. Furthermore, numerous phytomedicines have been shown to regulate autophagy to inhibit CRC growth, including Banxia Xiexin decoction [248], compound Kushen injection [249], halofuginone and artemisinin [250], *Paris polyphylla* [251] and Sijunzi Decoction [252] (Figure 17).

3 | CRC Metastasis

Metastasis remains the primary reason for mortality in individuals with solid tumours, such as CRC [253]. Despite significant advancements in our understanding of CRC, its metastasis continues to pose a considerable challenge, primarily due to limited

treatment options and a poor prognosis [254]. Wogonin, a flavonoid derived from the herbal medicine *Scutellaria baicalensis*, has also been found to suppress the proliferation of SW620 and RKO cells and to inhibit EMT by downregulating AKT expression. The inhibitory effect of Wogonin on SW620 or HCT-29 xenograft BALB/c nude mouse model is confirmed; however, its impact on EMT remains unclear [255]. Gentisic acid, a phenolic acid and a minor product of salicylic acid metabolism, has also been investigated. Feng et al. developed an animal model of lung metastasis by injecting MC38 cells into the tail vein. They showed that gentisic acid suppressed lung metastasis of CRC by impacting GPR81-mediated DEPDC5 degradation [256]. Yiqi Huayu Jiedu Decoction, a TCM compound, is proven to inhibit liver metastasis by promoting the function of natural killer cells in a mouse model of CRC liver metastasis, which was prepared by injecting CT26-GFP cells under the spleen envelope [257]. Echinacoside, a natural polyphenol compound, inhibits CRC liver metastasis by benefiting butyrate-producing gut bacteria, thereby suppressing the PI3K/AKT signalling pathway

and EMT in a mouse model of liver metastasis induced by intrasplenic injection [258]. Macelignan, a type of lignan isolated from *Myristica fragrans*, prevents CRC metastasis by inhibiting macrophage M2 polarisation through the ROS-mediated PI3K/AKT pathway in a nude mouse model of CRC liver metastases [88]. Brusatol, a primary quassinoid extracted from *Brucea Fructus*, suppresses the proliferation and lung metastasis of HCT116, HT29 and SW480 cells, as well as in the HCT116 and HT29 xenograft BALB/c nude mouse model, by activating ARDC4 through modulation of the PI3K/YAP1/TAZ pathway [259]. *Astragalus mongholicus* Bunge-*Curcuma aromatica* Salisb. (AC), a TCM combination, is frequently employed to treat CRC. Tang et al. found that AC inhibited liver metastasis in CRC through modulating EMT by CXCL8/CXCR2 and PI3K/AKT/mTOR pathways [260, 261]. Yi Ai Fang, a TCM formula, influences the formation of vasculogenic mimicry in CRC by modulating HIF-1 α and EMT in HCT-116 cells, as well as in an HCT-116 xenograft nude mouse model. These findings suggest that Yi Ai Fang may possess the potential to inhibit tumour migration [262]. Ji et al. found that resveratrol suppressed lung metastases of LoVo cells in a mouse tail vein injection model, as well as lung and liver metastases in a mouse orthotopic transplantation tumour model. Resveratrol inhibited cell invasion by suppressing EMT through the TGF- β 1/Smads pathway, which regulated Snail/E-cadherin expression [263]. Although many herbs have been shown to inhibit EMT, their anti-metastatic effects require further validation through additional animal and human studies, such as lycorine [264], asperuloside [265], glabridin [266], ginsenoside Rb2 [267], physciosporin [268], fucoidan [269] and Danggui-Sayuk-Ga-Osuyu-Senggang-Tang [270].

4 | Clinical Applications

4.1 | Curcumin

Curcumin is a flavonoid derived from *Curcuma longa* L. Y. Panahi and colleagues conducted a double-blind, placebo-controlled trial involving patients with stage 3 CRC aged ≥ 20 years who received postoperative chemotherapy. A total of 72 patients were randomly divided into curcuminoids capsules (500 mg/day) or placebo capsules, with 36 patients in each group, for 8 weeks. Although three subjects in the curcuminoids group and two in the placebo group were lost to follow-up, the curcuminoids group showed significant improvements in serum C-reactive protein levels ($p=0.002$), erythrocyte sedimentation rate ($p=0.0001$), function ($p=0.002$) and overall quality of life ($p=0.020$) [271]. Wang and colleagues conducted a clinical trial involving 126 patients with CRC who were randomly divided into curcumin capsule group (360 mg/day, three times/day) for 10–30 days (10–15 days: 12 cases, 16–20 days: 15 cases, 21–25 days: 18 cases and 26–30 days: 18 cases) and placebo capsule group before surgery [272]. The results of this study indicated that curcumin supplementation led to an increase in body weight among CRC patients, as well as an increase in p53 expression, DNA fragmentation and Bax levels, while Bcl-2 expression decreased in CRC tissues [272]. MB-6 is a botanical product composed of fermented soybean extract, green tea extract, *Antrodia camphorata* mycelia, spirulina, grape seed extract and curcumin extract. In a proof-of-concept clinical study, 72 patients with metastatic CRC received FOLFOX4 chemotherapy

in combination with either MB-6 ($n=34$) or a placebo ($n=38$) for 16 weeks. Although there were no notable differences between the MB-6 and placebo groups in terms of the best overall response rate and overall survival, patients receiving MB-6 exhibited a reduced rate of disease progression (0.0% vs. 15.8%, $p=0.026$). Additionally, patients in the placebo group experienced a greater proportion of adverse events of at least grade 4 (28.9% vs. 2.9%, $p=0.004$) and a higher incidence of increased serum creatinine levels (29% vs. 5.9%, $p=0.014$) [273]. Because cancer patients need to take drugs for a long time, the safety of these drugs is of great concern. Multiple Phase I clinical trials of oral curcumin have shown that curcumin, whether administered alone or in combination with FOLFOX chemotherapy, is reliable in the effective dose range [274–277].

4.2 | Resveratrol

A clinical pharmacological investigation was conducted to evaluate the effects of resveratrol and its metabolites in CRC patients. The study involved 20 participants who ingested eight daily doses of resveratrol at dosages of either 0.5 g or 1.0 g prior to surgical resection. The findings indicated that although resveratrol could reduce tumour cell proliferation by 5%, this reduction was not statistically significant ($p=0.05$). Furthermore, orally 0.5 g or 1.0 g resveratrol daily is adequate to elicit anti-cancer effects in the human gastrointestinal tract [278]. Despite resveratrol having shown significant efficacy in animal models of CRC, its clinical effectiveness is significantly hindered by its low bioavailability. In order to address this limitation, Gescher and colleagues developed a micronised formulation of resveratrol and assessed its safety, pharmacokinetics and pharmacodynamics in CRC patients with hepatic metastases who were scheduled for hepatectomy (5.0 g daily for 14 days) [279]. Research indicated that plasma micronised resveratrol levels were 3.6-fold higher than non-micronised resveratrol and treatment with micronised resveratrol resulted in a significant 39% increase in cleaved caspase-3 levels in malignant hepatic tissue. In summary, although resveratrol has shown remarkable efficacy in preclinical models of CRC, further clinical exploration is warranted to fully assess its potential clinical utility.

4.3 | Berberine

Berberine is an alkaloid derived from *Coptis chinensis*. Approximately 90% of CRC cases arise from adenomatous lesions, particularly advanced colorectal adenomas [280]. A double-blind, randomised, placebo-controlled trial was performed involving patients aged 18 to 75 years who had undergone complete polypectomy within the preceding 6 months and presented with a minimum of one and a maximum of six colorectal adenomas. Participants were randomly assigned (1:1) to receive either berberine (0.3 g twice daily) or placebo tablets. In the two-year observational study, it was observed that 36% of participants in the berberine group experienced recurrent adenomas, compared to 47% in the placebo group (unadjusted relative risk ratio for recurrence: 0.77, 95% CI 0.66–0.91; $p=0.001$), without CRC development. The most frequently reported adverse event was constipation (1% in the berberine group, <0.5% in the placebo group) without serious adverse events [280].

4.4 | Fucoidan

Fucoidan is a [sulfated polysaccharide](#) that is naturally extracted from various species of brown, green and red seaweeds, predominantly composed of L-fucose and sulfate groups [281]. A double-blind, randomised, placebo-controlled study was conducted involving 87 patients with locally advanced rectal cancer. Participants were randomly assigned to either the fucoidan group ($n=44$) or the placebo group ($n=43$). Those in the fucoidan group orally received 4 g of low-molecular-weight fucoidan (twice a day, 3 months). This fucoidan was obtained through enzyme hydrolysis of the original substance, and participants also underwent neoadjuvant concurrent chemoradiotherapy. In contrast, participants in the placebo group orally received 4 g of cellulose powder (twice a day, 3 months). Although enhanced physical well-being was observed at 2 and 3 months (both $p < 0.0125$), along with improvements in skin rash, itching and fatigue (both $p < 0.05$) and an increase in the abundance of the genus *Parabacteroides* in the gut microbiota in the fucoidan group, the improvements in the functional assessment of cancer therapy for patients with CRC were not statistically significant [282]. However, a prospective, randomised, double-blind, controlled trial conducted by the same research team confirmed the efficacy of low-molecular-weight fucoidan as a chemotherapy-targeted drug supplement in patients with metastatic CRC [283]. In this clinical trial, 54 patients with metastatic CRC were randomly assigned to either the fucoidan group ($n=28$) or the Control group ($n=26$). Participants in the fucoidan group orally received 4 g of low-molecular-weight fucoidan (twice a day, 6 months). In contrast, participants in the Control group orally received 4 g of cellulose powder (twice a day, 6 months). All patients underwent chemotherapy with targeted therapy. The disease control rates for the primary endpoint were 92.8% in the fucoidan group and 69.2% in the Control group, respectively ($p = 0.026$). However, secondary endpoints, including the overall response rate, progression-free survival, overall survival, adverse effects and quality of life, were not statistically significant. In summary, the studies indicate that low-molecular-weight fucoidan exhibits varying effects in different disease states of CRC, highlighting the need for additional clinical data to confirm its clinical efficacy.

4.5 | Epigallocatechin-3-Gallate

Epigallocatechin 3-gallate is one of the most important and abundant polyphenols found in green tea [284]. In order to examine the potential biological preventive effects of flavonoids, a study was conducted to assess the recurrence risk of neoplasia in patients who had undergone resection for CRC [285]. A total of 36 patients were included in the study, all of whom had resected colon cancer. The participants were categorised into two groups: one group received a flavonoid mixture consisting of a daily dose of 20 mg of apigenin and 20 mg of epigallocatechin-3-gallate ($n=14$), while the other group served as a matched control ($n=22$) for a duration of 3–4 years. A total of 29 patients underwent surveillance colonoscopy. Among those who received flavonoid treatment, there was no recurrence of cancer, and only one adenoma was identified. In contrast, the control group experienced three instances of cancer recurrence and four adenomas. The overall recurrence rate for

neoplasia was 7% (1 out of 14) in the treated cohort, compared to 47% (7 out of 15) in the control group, with a statistically significant difference observed ($p=0.027$).

CRC typically follows an ‘adenoma-cancer’ sequence, in which colorectal adenomas represent the stage preceding the occurrence of CRC. Colorectal adenomas are benign tumours that originate from the glandular epithelium of the colorectal mucosa and are the most prevalent precancerous lesions associated with CRC, accounting for approximately 85% to 90% of all cases. A randomised clinical trial was conducted involving 176 patients who underwent complete resection of colorectal adenomas through endoscopic polypectomy [286]. The participants were randomly assigned to one of two groups: the supplementation group (0.9 g of green tea extract tablets daily for 12 months) or the control group without green tea extract tablets. Each green tea extract tablet (500 mg) contained 225 mg of green tea extract, comprising 51.5 mg of (–)-epigallocatechin-3-gallate, 11.6 mg of (–)-epicatechin, 65.5 mg of (–)-epigallocatechin, 5.7 mg of (–)-epicatechin gallate and 10.9 mg of caffeine. A follow-up colonoscopy was performed 12 months later on 143 patients (71 in the control group and 72 in the green tea extract tablet group). The incidence of metachronous adenomas was found to be 42.3% (30 out of 71) in the control group, compared to 23.6% (17 out of 72) in the green tea extract tablet group (relative risk, 0.56; 95% confidence interval, 0.34–0.92). Additionally, the mean number of relapsed adenomas was significantly lower in the green tea extract tablet group than in the control group (0.7 ± 1.1 vs. 0.3 ± 0.6 , $p = 0.010$). However, no significant differences were observed between the two groups regarding body mass index, dietary intakes, serum lipid profiles, fasting serum glucose levels and serum C-reactive protein levels ($p > 0.05$).

Aberrant crypt foci (ACF) are the earliest morphologically detectable lesions in the colorectal mucosa and are believed to be precursors to adenomas and cancers [287]. Stephen Sontag and colleagues conducted a randomised phase II trial evaluating polyphenon E (Poly E) in patients at high risk of recurrent colonic neoplasia. A total of 39 participants with a history of colorectal adenomas or cancers, who exhibited five or more rectal aberrant crypt foci (ACF), were assigned to either the Poly E group oral Poly E (780 mg of epigallocatechin-3-gallate) or a placebo group. Of these, 32 out of 39 participants successfully completed the 6-month treatment period. Poly E demonstrated a favourable tolerance profile and exhibited no significant toxicity at the doses utilised in the study. However, it did not demonstrate a statistically significant reduction in the number of rectal ACF when compared to the placebo group [287].

4.6 | Quxie Capsule

Quxie capsule, consisting of *Croton tiglium*, *Evodia rutaecarpa*, *Rhizoma zingiberis*, *Cinnamomum cassia* Presl, *Radix aconiti*, *Pinellia ternata* and *Pericarpium citri* Reticulatae, is an herbal formulation that has been utilised for the treatment of CRC for more than 10 years. A block-randomised, double-blind, placebo-controlled trial involving 60 patients with metastatic CRC was conducted by YANG and colleagues. Participants were assigned to either the Quxie capsule group or the Control group. The

patients assigned to the Quxie capsule group underwent standard treatment protocols, which encompassed chemotherapy, radiotherapy, targeted therapy and supportive care. Additionally, they received Chinese herbal medicine in conjunction with the Quxie capsule (50 mg/kg twice daily from day 1 to day 20, over a 30-day treatment cycle) for a duration of 3 months. The participants in the control group were administered standard therapeutic interventions alongside Chinese herbal medicine in conjunction with a placebo for a duration of 3 months. The findings of this study showed that Quxie capsule significantly increased the median overall survival to 23.9 months, compared to 14.3 months in the Control group ($p < 0.05$), without significant differences between the two groups in progression-free survival [288]. YANG and colleagues also investigated the safety of the Quxie capsule in patients with metastatic CRC, and the results showed no severe haematological toxicity or liver and renal function injury [289]. In summary, Quxie capsule prolongs the overall survival of patients with metastatic CRC without serious complications.

4.7 | Jianpi Jiedu Formula

Over the past few years, TCM has received more recognition for its effectiveness and safety in treating CRC. Many Chinese patients with CRC seek assistance from TCM during or after first-line treatment [290]. Jianpi Jiedu formula is a TCM formula, consisting of *Radix Astragali*, *Radix Ginseng*, *Rhizoma Atractylodis Macrocephalae*, *Poria*, *Semen Coicis*, *Rhizoma Smilacis Chinensis*, *Herba Hedyotis Diffusae*, *Herba Scutellariae Barbatae*, *Rhizoma Paridis* and *Radix Actinidiae Chinensis*. In comparison to the chemotherapy group ($n = 295$), the Jianpi Jiedu formula combined with chemotherapy prolonged the mean survival time by 5.594 months and the median survival time by 6 months for patients with stage II and III CRC ($n = 171$, $p = 0.004$) [291]. However, the study was a retrospective clinical investigation rather than a controlled trial and it lacked a placebo control group. Consequently, the clinical efficacy of the Jianpi Jiedu formula on CRC still requires validation through additional controlled clinical studies.

4.8 | Hezhong Granules

Hezhong granules, consisting of *Pinellia ternata* (Thunb.) Makino, *Zingiber officinale* Roscoe, *Scutellaria baicalensis* Georgi, *Coptis chinensis* Franch., *Evodia rutaecarpa* (Juss.) Benth, *Panax ginseng* C. A. Mey, *Poria cocos* (Schw.) Wolf and *Cinnamomum verum* J. Presl, is an herbal formulation that has been utilised to treat CRC. A prospective randomised controlled trial enrolling 112 patients with advanced CRC was carried out from October 2020 to February 2022 across 12 hospitals in southwestern China. Compared to patients in the placebo group (a 5-HT₃-receptor antagonist, dexamethasone and a placebo), the incidence of chemotherapy-induced nausea and vomiting was significantly lower in those from the Hezhong granules group (a 5-HT₃-receptor antagonist, dexamethasone and Hezhong granules). Furthermore, Hezhong granules did not cause serious adverse events, indicating that they are both effective and well-tolerated for preventing nausea and vomiting caused by chemotherapy in patients with advanced CRC [292].

4.9 | Shenbai Granules

Shenbai granules, consisting of *Sophorae flavescens* radix, *Hedyotis diffusa*, *Codonopsis* radix, *Atractylodis macrocephalae* rhizoma, *Coicis* semen, *Coptidis* rhizoma, *Mume* fructus and *Zingiberis rhizoma* praeparatum, have been utilised for the management of CRC for several years. Cheng and colleagues conducted a multicentre, randomised, double-blind, placebo-controlled clinical trial with a follow-up period of 2 years, involving 400 patients with adenomas who had undergone complete polypectomy within the preceding 6 months. The results of this study demonstrated that Shenbai granules significantly decreased the recurrence rate of adenomas. This was evidenced by notable differences between the Shenbai granules group and the placebo group regarding the proportion of patients experiencing at least one recurrent adenoma (42.5% vs. 58.6%; OR, 0.47; 95% CI, 0.29–0.74; $p = 0.001$) and sessile serrated lesion (1.8% vs. 8.3%; OR, 0.20; 95% CI, 0.06–0.72; $p = 0.01$). However, Shenbai granules had no significant effect on the proportion of patients who developed polypoid lesions or high-risk adenomas [293].

Although recent years have witnessed an increasing number of herbal medicines and their active ingredients demonstrated to have therapeutic effects on CRC, these remedies are primarily regarded as important adjuvant therapies rather than primary treatments. However, many clinical studies conducted to date are retrospective rather than randomised controlled trials, indicating that numerous research findings require validation through higher-quality and rigorously designed randomised controlled trials. It is hoped that the discovery of the anti-tumour efficacy of paclitaxel, along with its widespread clinical application, will reinforce our belief in the significant developmental potential of herbal medicines.

5 | Reproducibility Analysis

The pertinent literature for the last 5 years were gathered from several databases such as PubMed, Google Scholar, Medline, ScienceDirect, Springer Link and Web of Science, using the following keywords: ‘phytomedicine’, ‘botanical drug’, ‘herbal medicine’, ‘natural medicine’, ‘natural drug’ and ‘colorectal cancer’. Non-experimental articles, such as reviews and meta-analyses, were excluded from this study (Table 1). In Table 2, we present the frequency of different botanicals reported for the treatment of CRC. Due to the extensive number of references, only the frequency of reported botanicals is provided (see Table S1 for details on specific references). Curcumin, resveratrol, berberine, shikonin, dihydroartemisinin, fucoidan, luteolin, andrographolide, piperine, kaempferol, emodin, cannabidiol, tanshinone IIA and evodiamine have consistently been reported to exhibit therapeutic effects on CRC. These compounds may hold significant potential for the development of future anti-CRC drugs or precursor agents.

6 | Discussion on Challenges and Future Perspectives

This review aims to consolidate the current understanding of the anti-cancer and anti-metastatic properties, as well as the underlying mechanisms of phytochemicals in CRC. Recent investigations

TABLE 1 | The efficacy and mechanism of herbal medicine in the treatment of CRC.

Herbal medicine	Plant origin	Model	Effects	Molecular mechanisms	References
Wumei Wan	<i>Prunus mume</i> (Siebold) Siebold & Zucc., <i>Coptis chinensis</i> Franch., <i>Neolitsea cassia</i> (L.) Kosterm., <i>Codonopsis pilosula</i> (Franch.) Nannf., <i>Zanthoxylum bungeanum</i> Maxim., <i>Zingiber officinale</i> Roscoe, <i>Aconitum carmichaelii</i> Debeaux, <i>Phellodendron amurense</i> Rupr., <i>Asarum heterotropoides</i> F. Schmidt and <i>Angelica sinensis</i> (Oliv.) Diels.	● AOM/DSS-induced CAC mouse model (C57BL/6J)	● Inhibits tumour growth	● Suppresses intestinal inflammation (IL-1 β , IL-6 and TNF- α) ● Suppresses myeloid-derived suppressor cells and increase CD4 ⁺ T and CD8 ⁺ T cells in spleen	[10]
Tetra- and pentahydroxyflavanones	<i>Scutellaria baicalensis</i> Georgi.	● AOM/DSS-induced CAC mouse model (C57BL/6J)	● Inhibits tumour growth	● Suppresses IL-10 and PD-1 through inhibiting COX-2 and CD8 ⁺ T-cell exhaustion by TOX/TOX2	[11]
Huang Qin decoction	<i>S. baicalensis</i> , <i>P. lactiflora</i> , <i>G. uralensis</i> and <i>Z. jujuba</i>	● AOM/DSS-induced CAC mouse model (C57BL/6J)	● Inhibits tumour growth	● Suppresses intestinal inflammation (TNF- α and IL-1 β) ● Neutrophil infiltration in colon ● Restores intestinal mucosal permeability (occludin and ZO-1) ● Improves the immunosurveillance of CD8 ⁺ T cells ● Modulates PAD4-dependent neutrophil extracellular traps	[12]

(Continues)

TABLE 1 | (Continued)

Herbal medicine	Plant origin	Model	Effects	Molecular mechanisms	References
Evening primrose root extract and oenothien B	Evening primrose (<i>Oenothera biennis</i>)	● Co-culture system using human PD-L1-expressed murine MC38 cells and CD8 ⁺ tumour-infiltrating T lymphocytes expressing humanised PD-1 ● CRC C57BL/6J mouse model bearing MC38 cells expressing humanised PD-L1 and PD-1 proteins	● Inhibits tumour growth	● Suppresses the binding between PD-L1 and PD-1 to increase CD8 ⁺ T cell-mediated tumour cytotoxicity	[14]
Marsdenia tenacissima tablet	<i>Marsdenia tenacissima</i> (Roxb.) Wight et Arn.	● CRC patients ● HCT116 and LoVo cells ● AOM/DSS-induced CAC mouse model (BALB/c) ● Subcutaneous CT26 tumour model (BALB/c)	● Inhibits tumour growth ● Inhibits the immune escape of cancer cells	● Increases the number of CD3 ⁺ /CD8 ⁺ tumour-infiltrating T cells ● Suppresses TGF-β1 and PD-L1 expressions	[15]
Triterpenoids of <i>Rhus chinensis</i>	<i>Rhus chinensis</i> Mill.	● DLD1 and CT26 cells ● Subcutaneous CT26 tumour model (BALB/c)	● Inhibits tumour growth	● Prevents CD8 ⁺ T-cell dysfunction by enhancing mTOR and glycolytic gene expression	[16]
Honeysuckle-derived microRNA2911	<i>Lonicerae Japonicae</i> Flos	● CT26 tumour-bearing C57BL/6, Sidt1 ^{+/+} and Sidt1 ^{-/-} mouse models	● Inhibits tumour growth	● Increases T lymphocytes (CD4 ⁺ T cells and CD8 ⁺ T cells) infiltration ● Suppresses TGF-β1 expression	[17]
<i>Patrinia villosa</i> aqueous extract	<i>Patrinia villosa</i> Juss.	● HCT116, SW480, colon 26-luc cells ● Xenograft HCT116 tumour model (nude mice) ● Zebrafish model	● Inhibits tumour growth ● Inhibits tumour metastasis	● Regulates TGF-β R1-smad2/3-E-cadherin and FAK-RhoA-cofilin pathways ● Increases helper T (CD3 ⁺ CD4 ⁺) and cytotoxic T lymphocytes (CD3 ⁺ CD8 ⁺) percentage ● Increases the relative abundance of gut microbiota	[18]
Turmeric extract, with absorbable curcumin	<i>Curcuma longa</i> L.	● HCT116, HT-29 and colon 26, colon 26-M01 cells ● Orthotopic xenografts colon 26-M01 tumour model (BALB/c)	● Inhibits tumour growth ● Inhibits tumour metastasis (liver and lung)	● Regulates cofilin, FAK/pSrc, AKT, Erk and STAT3 ● Increases CD4 ⁺ helper T lymphocytes in thymus and CD8 ⁺ cytotoxic T lymphocytes in tumour tissue	[20]

(Continues)

TABLE 1 | (Continued)

Herbal medicine	Plant origin	Model	Effects	Molecular mechanisms	References
Gegen Qinlian decoction	<i>Radix Puerariae</i> , <i>Scutellariae Radix</i> , <i>Coptidis Rhizoma</i> and <i>liquorice</i>	● Xenograft CT26 tumour model (BALB/c)	● Inhibits tumour growth	● Increases the proportion of CD8 ⁺ T cells in peripheral blood and tumour tissues ● Remodels gut microbiota	[21]
Lentinan	<i>Lentinus edodes</i> (Berk.) sing.	● Xenograft CT26 tumour model (BALB/c) ● AOM/DSS-induced CAC mouse model (BALB/c)	● Inhibits tumour growth	● Promotes dendritic cell maturation ● Polarises tumour-associated macrophage from a pro-tumorigenic M2 to an anti-tumorigenic M1 phenotype (CD11b ⁺ CD80 ⁺)	[27]
Qizhen decoction	<i>Astragali Radix</i> , <i>Ligustri Lucidi Fructus</i> , <i>Codonopsis Radix</i> , <i>Salviae Miltiorrhizae Radix</i> Et Rhizoma, <i>Radix Paeoniae Alba</i> , <i>Herba Hedyotidis</i> <i>Diffusae, Polygoni Cuspidati Rhizoma</i> Et Radix, <i>Fiveleaf Gynostemma</i> Herb	● Xenograft CT26 tumour model (BALB/c) ● HCT26 cells ● AOM/DSS-induced CRC mouse model (C57BL/6J)	● Inhibits tumour growth ● Inhibits tumour growth	● Promotes tumour infiltration of CD4 ⁺ , CD8 ⁺ , NK1.1 ⁺ cells, monocytes and neutrophils ● Suppresses tumour-associated macrophages ● Promotes the maturation of dendritic cells to release IL-12 and activate the JAK2/STAT4 pathway to induce effector T-cell activation by increasing the abundance of Akkermansia	[28] [30]

(Continues)

TABLE 1 | (Continued)

Herbal medicine	Plant origin	Model	Effects	Molecular mechanisms	References
Tong-Xie-Yao-Fang	<i>Atractylodes macrocephala</i> Koidz., <i>Paeonia lactiflora</i> Pall., <i>Citrus reticulata</i> Blanco, <i>Saposhnikovia divaricata</i> (Turcz.) Schischk	● Mouse model of chronic stress by chronic restraint stress and subcutaneous injection of CT26-Luc cells (BALB/c)	● Inhibits tumour growth	● Suppresses the HPA axis ● Facilitates dendritic cells maturation, thereby triggering T-cell-mediated immune response, evidenced by increased CD4+ T cells, CD4+/CD8+ T cells and Th1 cells percentage ● Promotes serum IFN- γ , IL-18, IL-2 and IL-12 levels ● Suppresses serum IL-4 and IL-10 levels	[31]
Curcumin	<i>Curcuma Longae</i> Rhizoma	● SW480 cells	● Inhibits tumour growth	● Suppresses early apoptosis and arrested ● Suppresses cell cycle in G2/M phase via increasing cyclin B1 ● Suppresses Th17 cell differentiation	[32]
Periploca sepium periplosides	<i>Cortex Periplocae</i>	● DSS/AOM induced-CAC model (C57BL/6)	● Inhibits tumour growth	● Modulates the gut microbiota structure ● Suppresses pathogenic Th17 cell population	[33]
Ginseng berry	<i>Panax ginseng</i> C.A. Meyer	● HCT116 and HT29 cells	● Inhibits tumour growth	● Suppresses Th17 cell differentiation and thus regulates the balance of Th17/Treg	[34]
Yi-Yi-Fu-Zi-Bai-Jiang-San	<i>Semen Coicis</i> , <i>monkshood</i> and <i>Herba Patriniae</i>	● <i>Apc</i> ^{Min/+} mice (C57BL/6J)	● Inhibits tumour growth	● Regulates gut flora, including <i>Bacteroides fragilis</i> and <i>Lachnospiraceae</i> ● Suppresses CD4 ⁺ CD25 ⁺ Foxp3 ⁺ Tregs by regulating gut microbiota	[41]
		● MC-38 and IEC-6 cells ● AOM/DSS-induced CRC mice (C57BL/6J)	● Inhibits tumour growth	● Promotes Tregs-induced immunosuppression through HIF-1 α -mediated hypoxia	[42]

(Continues)

TABLE 1 | (Continued)

Herbal medicine	Plant origin	Model	Effects	Molecular mechanisms	References
Quxie capsule	<i>Evodiae fructus</i> , <i>Zingiberis rhizoma</i> , <i>Cortex cinnamomi</i> , <i>Radix aconiti</i> , <i>Coptis chinensis</i> , <i>Pinelliae rhizoma</i> , <i>Citri grandis exocarpium</i> , <i>Poria</i> , <i>Arecae semen</i> , <i>Magnoliae officinalis</i> , <i>Aurantii fructus immaturus</i> , <i>Acori tatarinowii rhizoma</i> , <i>Corydalis rhizoma</i> , <i>Panax Ginseng</i> , <i>Lignum aquilariae resinatum</i> , <i>Radix platycodonis</i> , <i>Succinum</i> , <i>Crotonis fructus</i> , <i>Galli Gigerii endothelium corneum</i> , <i>Hordei fructus germinatus</i> and <i>Gleditsiae fructus abnormalis</i>	● Xenograft HCT26 tumour model ● HCT26 and HCT116 cells	● Inhibits tumour growth	● Increases the ratios of Th1/Th2 and Th17/Treg cells ● Suppresses the level of Foxp3 (the key regulator of Treg cells)	[43]
Rubiginosin B	<i>Rhododendron brachypodium</i> (R. brachypodium)	● CT26 and MC38 xenograft tumour model	● Inhibits tumour growth	● Suppresses TGFβ-induced CD4 ⁺ Foxp3 ⁺ regulatory T cells differentiation	[44]
Cyasterone	<i>Ajuga decumbens</i> Thunb (Labiateae) or <i>Cyathula officinalis</i> Kuan	● <i>BRAF^{V600E}</i> -mutant mouse model with CRC	● Inhibits tumour growth	● Enhances the diversity of the gut microbiota ● Elevates the abundance of beneficial bacteria, including <i>Prevotellaceae</i> , <i>Muribaculaceae</i> and <i>Ruminococcaceae</i>	[47]

(Continues)

TABLE 1 | (Continued)

Herbal medicine	Plant origin	Model	Effects	Molecular mechanisms	References
Huangqin decoction	<i>Scutellaria baicalensis</i>	● AOM/DSS-induced CRC mice (C57BL/6J)	● Inhibits tumour growth	● Microbial butyrate mediated PI3K/AKT Pathway suppression	[48]
	Georgi, <i>Paeonia lactiflora</i> Pall,	● SW480 and HT-29 cells			
	<i>Ziziphus jujuba</i> Mill and <i>Glycyrrhiza uralensis</i> Fisch	● Deoxycholic acid-induced <i>Apc^{Min/+}</i> mice	● Inhibits tumour growth	● Increases the abundance of <i>Lachnospiraceae</i> , <i>Firmicutes</i> , <i>Fusobacteria</i> and <i>Clostridium Eggerthellales</i>	[49]
Xiaoyaosan	<i>Angelica sinensis</i> ,	● CRC xenograft model in mice with chronic restraint stress (athymic nude mice)	● Inhibits tumour growth	● Regulates the abundance of <i>Bacteroides</i> , <i>Lactobacillus</i> , <i>Desulfovibrio</i> and <i>Rikenellaceae</i>	[50]
	<i>Paeonia lactiflora</i> ,				
	<i>Bupleuri Radix</i> , <i>Atractylodis Macrocephalae</i> Rhizoma, <i>Glycyrrhizae Radix</i> , Poria, <i>Zingiberis Rhizoma</i> Recens, <i>Menthae Haplocalycis</i> Herba				
Xiao-Chai-Hu-Tang	<i>Bupleuri Radix</i> ,	● CRC patients	● Inhibits tumour growth	● Regulates gut microbiota-mediated TLR4/MyD88/NF-κB pathway	[51]
	<i>Scutellariae Radix</i> , <i>Ginseng Radix</i> et Rhizoma, <i>Pinelliae</i> Rhizoma, <i>Glycyrrhizae Radix</i> et Rhizoma, <i>Zingiberis Rhizoma</i> Recens and <i>Jujubae Fructus</i>	● MC38 xenograft model in mice under depression (C57BL/6J)			
	<i>Scutellariae Radix</i> , <i>Sophorae Flavescentis Radix</i> and <i>Rehmanniae Radix</i>				
San-Wu-Huang-Qin decoction	<i>Scutellariae Radix</i> , <i>Sophorae Flavescentis Radix</i> and <i>Rehmanniae Radix</i>	● AOM/DSS-induced CRC mouse model (C57BL/6J)	● Inhibits tumour growth	● Improves mucosal barrier partially by targeting gut microbiota: <i>Escherichia-Shigella</i>	[52]
Berberine	<i>Coptis chinensis</i>	● AOM/DSS-induced CRC mouse model (C57BL/6) ● HT-29 cells	● Inhibits tumour growth	● Suppresses Hedgehog pathway ● Modulates gut microbiota	[53]

(Continues)

TABLE 1 | (Continued)

Herbal medicine	Plant origin	Model	Effects	Molecular mechanisms	References
Xianlian Jiedu decoction	<i>Agrimoniae Herba</i> , <i>Coptidis Rhizoma</i> , <i>Sophorae Flavescentis</i> Radix, <i>Coicis Semen</i> , <i>Sparganii Rhizoma</i> , <i>Curcumae Rhizoma</i> , <i>Astragali Radix</i> and <i>Atractylodis</i> <i>Macrocephalae Rhizoma</i>	● AOM/DSS-induced CRC mouse model (C57BL/6)	● Inhibits tumour growth	● Improves gut microbiota disorders and associated short-chain fatty acids, sphingolipid and glycerophospholipid levels by inhibiting the abundance of <i>Turicibacter</i> and <i>Clostridium_sensu_stricto_1</i>	[64]
	<i>Panax ginseng</i> C. A. Mey, <i>Wolfiporia</i> cocos (F.A. Wolf) Ryvarden & Gilb, <i>Wikstroemia indica</i> (L.) C. A. Mey, <i>Atractylodes</i> <i>macrocephala</i> Koidz, <i>Ficus hirta</i> Vahl, <i>Polygonum chinense</i> L, <i>Kalopanax septemlobus</i> (Thunb.) Koidz, <i>Curcuma zedoaria</i> (Christm) Roscoe, <i>Coix lacryma-jobi</i> L, <i>Ailanthus altissima</i> (Mill.) Swingle	● Orthotopic tumour ● SW480 and MC38 cells	● Inhibits tumour growth	● Suppresses the pluripotency of colorectal cancer stem cells by inhibiting TGF- β mediated EMT program	[69]
Modified Shenlingbaizhu decoction					
Pien Tze Huang	<i>Moschus, Calculus</i> <i>Bovis, Snake Gall</i> and <i>Radix Notoginseng</i>	● HT-29 SP cells ● SW480 cells	● Inhibits cell proliferation ● Inhibits cell proliferation	● Suppresses stem-like side population ● Suppresses stem-like side population ● Suppresses the Notch1 signalling pathway	[70] [71]
		● HCT116, SW480 and HCT15 cells ● MC38 xenograft tumour mouse model (C57BL/6) ● CRC patient-derived organoids	● Inhibits tumour growth	● Promotes T cell-mediated killing of CRC by inhibiting stemness and PD-L1 expression	[72]

(Continues)

TABLE 1 | (Continued)

Herbal medicine	Plant origin	Model	Effects	Molecular mechanisms	References
Phenethyl isothiocyanate	Cruciferous vegetables	● HCT116 cells	● Inhibits tumour growth	● Suppresses cancer stem cell properties	[73]
		● HCT116 xenograft tumour mouse model			
		● DLD-1 and SW480 cells			
Vitexin	<i>Crataegus pinnatifida</i> Bge. and <i>Vigna radiata</i> (L.) Wilczek	● AOM/DSS-induced CRC mouse model (BALB/c)	● Inhibits tumour growth	● Suppresses cancer stem cell properties by inhibiting the Wnt/ β -catenin signalling pathway	[74]
				● Increases M1 macrophage polarisation in colonic tumour tissue	
				● Suppresses M1 macrophage polarisation in adjacent noncancerous tissues	
Jiedu Xiaozheng Yin	<i>Hedyotis diffusa</i> Willd., <i>Spica prunellae</i> , <i>Pseudobulbus</i> Cremastrae and <i>Sophora Flavescens</i>	● THP-1, RAW 264.7, CT26. WT and HCT 116 cells	● Inhibits the transition from chronic colitis to colorectal cancer	● Targets macrophage polarisation via the VDR/PBLD signalling pathway	[84]
		● AOM/DSS-induced CRC mouse model (C57BL/6)			
		● AOM/DSS-induced CRC mouse model (BALB/c)			
		● RAW264.7 cells			
				● Increases M1 macrophage polarisation through TLR4 pathway in colonic tumour tissue	
Dictamnine	<i>Dictamnus dasycarpus</i> Turcz.	● DLD-1 xenograft mouse model (BALB/c nude mice)	● Inhibits tumour growth	● Increases ferroptosis and suppressing M2 macrophage polarisation via the MAPK signalling	[86]
		● DLD-1 and LoVo cells			
		● THP-1 cells			
Triterpenoids of <i>Rhus chinensis</i> Mill.	<i>Rhus chinensis</i> Mill	● SW620 and HCT116 cells	● Inhibits cell growth and invasion	● Inhibits the ASIC2-induced calcineurin/NFAT pathway	[95]
				● Suppresses glycolysis	
		● SW620 cells		● Suppresses glycolysis and glutaminolysis	
		● Co-culture CD8 ⁺ T cells and CT26 cells	● Inhibits cell proliferation	● Promotes glycolysis in CD8 ⁺ T-cells	[16]

(Continues)

TABLE 1 | (Continued)

Herbal medicine	Plant origin	Model	Effects	Molecular mechanisms	References
Atractylenolide I	<i>Atractylodes</i> <i>Macrocephalae</i> Rhizoma	● HCT116, COLO205, SW480 and LOVO cells	● Inhibits tumour growth	● Suppresses glycolysis	[76]
		● HCT116 xenograft tumour mouse model (Balb/c-nu/nu nude mice)		● Suppresses AKT/mTOR pathway	
				● Suppresses stemness maintenance	
Saponin monomer 13 of the dwarf lilyturf tuber (DT-13)	<i>Liriodops</i> Radix	● HCT116 and SW480 cells	● Inhibits tumour growth	● Promotes apoptosis	[97]
		● HCT116 xenograft tumour mouse model (nude mice)		● Suppresses glycolysis	
				● Suppresses the JAK2/STAT3 pathway	
Ginsenoside Rh3	Hot-processed ginseng	● HCT-15, HCT-116, COLO205, HT-29, SW620 and SW480 cells	● Inhibits tumour growth	● Suppresses glycolysis	[98]
		● Orthotopic mouse model (HCT-15, BALB/c nude mice)		● Activates AMPK and inhibited m-TOR	
		● HT29, HCT116, SW620, DLD1 and RKO cells	● Inhibits tumour growth	● Activates pyroptosis and ferroptosis	
Solanine	<i>Solanum nigrum</i> L	● HT29 and HCT116 xenograft mouse model (BALB/c nude mouse)		● Regulates the Stat3/p53/NRF2 axis	[113]
		● HCT116 and SW480 cells	● Inhibits cell proliferation	● Activates ferroptosis by increasing ALOX12B/ADCY4	
			● Inhibits cell proliferation	● Activates JNK-mediated ferroptosis	
Curcumin	<i>Curcuma Longae</i> Rhizoma	● SW480 cells	● Inhibits cell proliferation	● Activates ferroptosis by inhibiting PI3K/AKT/mTOR Signalling	[116]
		● HCT-8 cells			
		● SW620 cells and LoVo	● Inhibits tumour cell growth	● Activates ferroptosis by regulating p53 and solute carrier family 7 member 11/glutathione/glutathione peroxidase 4 signalling axis	

(Continues)

TABLE 1 | (Continued)

Herbal medicine	Plant origin	Model	Effects	Molecular mechanisms	References
JianPi JieDu Recipe	<i>Radix Astragal</i> , <i>Rhizoma Atractylodis</i> Macrocephala, wild grapevines, <i>Fructus</i> <i>Akebia</i> , <i>Salvia</i> <i>chinensis</i> Benth. and <i>Evodia rutaecarpa</i> .	● LoVo, HCT116 and MC-38 cells ● Liver metastasis model (MC38 cells on C57BL/6 mouse)	● Inhibits tumour growth ● Inhibits colorectal cancer liver metastasis	● Regulates ITGBL1-rich extracellular vesicles-mediated activation of cancer-associated fibroblasts	[136]
Pennogenin 3-O-beta-chacotrioside and polyphyllin VI	<i>Paris polyphylla</i>	● Caco-2 and HT-29 cells	● Inhibits CRC cell invasion	● Inhibits the release of extracellular vesicles from <i>Fusobacterium nucleatum</i>	[142]
Coptisine	<i>Coptis chinensis</i> Franch.	● HCT-116 cells ● HCT-116 xenograft mouse model (BALB/c nude mouse)	● Inhibits tumour growth	● Inhibits the PI3K/AKT pathway ● Activates mitochondrial-associated apoptosis	[149]
Tanshinone IIA	<i>Salvia miltiorrhiza</i> Bunge	● SW837 and SW480 cells	● Inhibits cell proliferation	● Increases mitochondrial fission by activating JNK-Mff signalling pathways	[153]
		● SW480 cells	● Inhibits cell proliferation	● Activates INF2-mediated mitochondrial fission ● Activates Mst1-Hippo pathway	[154]
Piperine	Black (<i>Piper nigrum</i>) and long pepper (<i>Piper longum</i>)	● HT-29 cells ● CT26 xenograft tumour mouse model (BALB/c)	● Inhibits tumour growth	● Synergistically with Celecoxib to inhibit CRC cell proliferation via modulating Wnt/ β -catenin signalling pathway	[155]
Curcumin	<i>Curcuma longa</i> L.	● SW480 and HCT116 cells	● Inhibits tumour cell growth	● Increases apoptosis ● Activates NLRP3 inflammasome-dependent pyroptosis	[175]
Kanglaite (KLT) injection	<i>Coix lacryma-jobi</i> (adlay) seed	● HCT106, HCT116, LoVo and CT26 cells ● CT26 xenograft tumour mouse model (BALB/c)	● Inhibits tumour growth	● Suppresses NF- κ B ● Promotes connexin 43	[180]
		● HCT106, HCT116, LoVo and CT26 cells ● CT26 xenograft tumour mouse model (BALB/c)	● Inhibits tumour growth	● Suppresses NF- κ B	[181]

(Continues)

TABLE 1 | (Continued)

Herbal medicine	Plant origin	Model	Effects	Molecular mechanisms	References
Evodiamine	<i>Tetradium ruticarpum</i> (A. Juss.) T. G. Hartley	● HCT-116, HCT-116/L-OHP cells	● Inhibits tumour growth	● Suppresses the p50/p65 NF- κ B pathway	[182]
		● HCT-116/L-OHP xenograft tumour mouse model (athymic nude mice)			
		● HCT-116 cells	● Inhibits tumour growth	● Suppresses the JAK2/STAT3 pathway	[183]
Scutellarin	<i>Scutellaria alba</i> L.	● SW480 cells	● Inhibits tumour growth	● Suppresses Hedgehog pathway and NF- κ B-mediated inflammation	[188]
		● AOM/DSS-induced CRC mouse model (C57BL/6)			
		● HT-29 cells	● Inhibits tumour growth	● Suppresses serum TNF- α and IL-6 levels	[189]
Triterpenes of jujube	<i>Ziziphus jujuba</i> Mill.	● AOM/DSS-induced CRC mouse model (C57BL/6)	● Inhibits tumour growth	● Suppresses the PI3K/AKT/NF- κ B pathway	[190]
		● HCT-116 cells	● Inhibits tumour growth	● Suppresses the NF- κ B pathway	[191]
		● HCT-116 xenograft mouse model (BALB/c nude mouse)			
Puerarin	<i>Celastraceae</i> and <i>Hippocrateaceae</i> families	● AOM/DSS-induced CRC mouse model (BALB/c)	● Inhibits tumour growth	● Suppresses the NF- κ B pathway	[193]
		● AOM/DSS-induced CRC mouse model (BALB/c)	● Inhibits tumour growth	● Suppresses inflammation	[198]
		● CT26 cells	● Inhibits tumour growth	● Suppresses inflammation and angiogenesis by regulating MMP/TIMP system, PI3K/AKT/mTOR and HIF-1 α pathway	[202]
Cryptotanshinone	<i>Salvia miltiorrhiza</i> Bunge	● CT26 xenograft mouse model (BALB/c)			
		● SW480 cells	● Inhibits tumour cell growth	● Increases cellular ROS levels and decreases antioxidant levels	[213]
		● HT-29 cells	● Inhibits tumour cell growth and metastasis	● Increases ROS level	[210]
Dihydroartemisinin	<i>Artemisia caruifolia</i> Buch.-Ham. ex Roxb	● HCT116 and RKO	● Promotes the anti-tumour activity of oxaliplatin	● Increases PRDX2-reactive oxygen species-mediated multiple signalling pathways	[214]
		● HCT116 xenograft mouse model (BALB/c nude mice)			

(Continues)

TABLE 1 | (Continued)

Herbal medicine	Plant origin	Model	Effects	Molecular mechanisms	References
Dihydromyricetin	<i>Vitis heyneana</i>	● HCT116 cells (TP53 ^{-/-})	● Inhibits tumour cell growth	● Activates ROS-mediated apoptosis	[215]
		● HCT116, HCT8 and HCT116/OXA cells	● Inhibits tumour growth	● Suppresses NF- κ B-Nrf2 signalling	[216]
		● NF- κ B/p65-overexpressed HCT116/OXA cells xenograft mouse model (BALB/c)	● Reverses MRP2-induced multidrug resistance		
Andrographolide	<i>Andrographis paniculata</i> (Burm.f.) Nees	● COLO205 cells	● Inhibits tumour growth	● Semaphoring 4D is essential for anti-oxidant and anti-inflammatory properties	[217]
		● COLO205 xenograft mouse model (BALB/c nude mouse)			
		● SW-480, DLD-1, HT-29 and HCT-116 cells	● Inhibits tumour cell growth	● Increases intracellular ROS	[218–221]
<i>Rhus coriaria</i> extract	<i>Rhus coriaria</i>	● T84 and COLO205 cells	● Inhibits tumour cell growth	● Increases intracellular ROS	[222]
		● HT-29 and Caco-2 cells	● Inhibits cell proliferation	● Activates autophagic and apoptotic cell death	[241]
		● HCT-116-WT and HCT-116-5FU-R cells	● Inhibits cell proliferation	● Activates autophagic and apoptotic cell death	[243]
<i>Origanum majorana</i> ethanolic extract	<i>Origanum majorana</i>	● HT-29 and Caco-2 cells	● Inhibits cell proliferation	● Activates autophagic and apoptotic cell death	[244]
<i>Origanum majorana</i> essential oil	<i>Origanum majorana</i>	● HT-29 cells	● Inhibits cell proliferation	● Activates p38 MAPK-mediated autophagy, apoptosis and caspase-dependent cleavage of P70S6K	[245]
Dehydroevodiamine	<i>Tetradium ruticarpum</i> (A. Juss.) T. G. Hartley	● HCT116, CT26, SW480 and LoVo cells	● Inhibits cell proliferation	● Activates caspase-dependent apoptosis and autophagy	[246]
			● Inhibits lung metastasis	● Regulating epithelial to mesenchymal transition	
Fangchinoline	<i>Stephania tetrandine</i> S. Moore (Menispermaceae)	● HT29 and HCT116 cells ● HT29 xenograft mouse model (BALB/c nude mice)	● Inhibits tumour cell growth	● Activates AMPK/mTOR/ULK1-mediated autophagy	[247]

TABLE 2 | Herbal medicine for CRC treatment.

Number	Herbal medicine	Number of reported
1	Curcumin	176
2	Resveratrol	50
3	Berberine	40
4	Shikonin	20
5	Dihydroartemisinin	18
6	Fucoidan	16
7	Luteolin	14
8	Andrographolide	14
9	Piperine	13
10	Kaempferol	12
11	Emodin	11
12	Cannabidiol	11
13	Tanshinone IIA	11
14	Evodiamine	10
15	Pien Tze Huang	7
16	Baicalein	7
17	Matrine	7
18	Oxymatrine	7
19	Cryptotanshinone	7
20	Oleuropein	7
21	Epigallocatechin-3-gallate	6
22	Astragaloside IV	6
23	Ginsenoside Rg3	5
24	Rosmarinic acid	5
25	Zerumbone	5
26	Baicalin	5
27	Quxie capsule	5
28	Phenethyl isothiocyanate	4
29	Wogonin	4
30	Tetrandrine	3
31	Diosgenin	3
32	Lentianan	2

have increasingly concentrated on phytochemicals due to their protective attributes, therapeutic efficacy and favourable safety profiles, positioning them as promising candidates for CRC intervention. Phytochemicals exert their inhibitory effects on CRC tumour growth through a variety of mechanisms, which include immune system modulation (involving CD4⁺/CD8⁺ T lymphocytes, dendritic cells, Th17 cells and regulatory T cells), alteration of gut microbiota, targeting of colorectal cancer stem cells,

macrophage polarisation, regulation of glycolysis, induction of ferroptosis, involvement of extracellular vesicles, modulation of mitochondrial function, management of inflammation and oxidative stress and autophagy. Furthermore, several phytochemicals, such as curcumin, resveratrol, berberine, shikonin, dihydroartemisinin, fucoidan, luteolin, andrographolide, piperine, kaempferol, emodin, cannabidiol, tanshinone IIA and evodiamine, have consistently exhibited anti-CRC effects. Consequently, these phytochemicals may represent promising therapeutic agents or significant lead compounds for the treatment of CRC. Nevertheless, despite the demonstrated effects of these phytochemicals in both in vitro and in vivo studies, further clinical research is essential to substantiate their anti-cancer and anti-metastatic efficacy.

Author Contributions

Zuqing Su: writing – original draft, writing – review and editing, visualisation. **Yanlin Li:** writing – review and editing. **Zihao Zhou:** writing – review and editing. **Bing Feng:** supervision, validation, funding acquisition. **Haiming Chen:** supervision, validation, funding acquisition. **Guangjuan Zheng:** supervision, validation, funding acquisition.

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Ethics Statement

This article does not contain any studies with human or animal subjects.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. F. Bray, M. Laversanne, H. Sung, et al., “Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries,” *CA: A Cancer Journal for Clinicians* 74, no. 3 (2024): 229–263.
2. S. G. Patel, J. J. Karlitz, T. Yen, C. H. Lieu, and C. R. Boland, “The Rising Tide of Early-Onset Colorectal Cancer: A Comprehensive Review of Epidemiology, Clinical Features, Biology, Risk Factors, Prevention,

- and Early Detection,” *Lancet Gastroenterology & Hepatology* 7, no. 3 (2022): 262–274.
3. Q. Wang, X. Shen, G. Chen, and J. Du, “Drug Resistance in Colorectal Cancer: From Mechanism to Clinic,” *Cancers (Basel)* 14, no. 12 (2022): 2928.
 4. R. Abedizadeh, F. Majidi, H. R. Khorasani, H. Abedi, and D. Sabour, “Colorectal Cancer: A Comprehensive Review of Carcinogenesis, Diagnosis, and Novel Strategies for Classified Treatments,” *Cancer Metastasis Reviews* 43, no. 2 (2024): 729–753.
 5. E. Dekker, P. J. Tanis, J. L. A. Vleugels, P. M. Kasi, and M. B. Wallace, “Colorectal Cancer,” *Lancet* 394, no. 10207 (2019): 1467–1480.
 6. M. Al Zein, M. Boukhoudou, H. Shammaa, et al., “Immunotherapy and Immuno-evasion of Colorectal Cancer,” *Drug Discovery Today* 28, no. 9 (2023): 103669.
 7. J. F. Chen, S. W. Wu, Z. M. Shi, and B. Hu, “Traditional Chinese Medicine for Colorectal Cancer Treatment: Potential Targets and Mechanisms of Action,” *Chinese Medicine* 18, no. 1 (2023): 14.
 8. D. S. M. Chatzileontiadou, H. Sloane, A. T. Nguyen, S. Gras, and E. J. Grant, “The Many Faces of CD4(+) T Cells: Immunological and Structural Characteristics,” *International Journal of Molecular Sciences* 22, no. 1 (2020): 1–27.
 9. B. J. Laidlaw, J. E. Craft, and S. M. Kaech, “The Multifaceted Role of CD4+ T Cells in CD8+ T Cell Memory,” *Nature Reviews. Immunology* 16, no. 2 (2016): 102–111.
 10. Z. H. Lu, Y. Ding, Y. J. Wang, et al., “Early Administration of Wumei Wan Inhibit Myeloid-Derived Suppressor Cells via PI3K/Akt Pathway and Amino Acids Metabolism to Prevent Colitis-Associated Colorectal Cancer,” *Journal of Ethnopharmacology* 333 (2024): 118260.
 11. Y. Kimura and M. Sumiyoshi, “Two Hydroxyflavanones Isolated From *Scutellaria Baicalensis* Roots Prevent Colitis-Associated Colon Cancer in C57BL/6 J Mice by Inhibiting Programmed Cell Death-1, Interleukin 10, and Thymocyte Selection-Associated High Mobility Group Box Proteins TOX/TOX2,” *Phytomedicine* 100 (2022): 154076.
 12. Z. Pan, X. Xie, Y. Chen, et al., “Huang Qin Decoction Inhibits the Initiation of Experimental Colitis Associated Carcinogenesis by Controlling the PAD4 Dependent NETs,” *Phytomedicine* 107 (2022): 154454.
 13. M. S. Carlino, J. Larkin, and G. V. Long, “Immune Checkpoint Inhibitors in Melanoma,” *Lancet* 398, no. 10304 (2021): 1002–1014.
 14. E. J. Lee, Y. S. Kim, J. H. Kim, et al., “Uncovering the Colorectal Cancer Immunotherapeutic Potential: Evening Primrose (*Oenothera biennis*) Root Extract and Its Active Compound Oenothien B Targeting the PD-1/PD-L1 Blockade,” *Phytomedicine* 125 (2024): 155370.
 15. B. Yi, S. Zhang, S. Yan, et al., “Marsdenia Tenacissima Enhances Immune Response of Tumor Infiltrating T Lymphocytes to Colorectal Cancer,” *Frontiers in Immunology* 14 (2023): 1238694.
 16. G. Wang, Y. Z. Wang, Y. Yu, P. H. Yin, K. Xu, and H. Zhang, “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,” *Integrative Cancer Therapies* 20 (2021): 15347354211017219.
 17. C. Liu, M. Xu, L. Yan, et al., “Honeysuckle-Derived MicroRNA2911 Inhibits Tumor Growth by Targeting TGF- β 1,” *Chinese Medicine* 16, no. 1 (2021): 49.
 18. H. Yang, G. G. Yue, K. K. Yuen, et al., “Mechanistic Insights Into the Anti-Tumor and Anti-Metastatic Effects of *Patrinia villosa* Aqueous Extract in Colon Cancer via Modulation of TGF- β R1-smad2/3-E-Cadherin and FAK-RhoA-Cofilin Pathways,” *Phytomedicine* 117 (2023): 154900, <https://doi.org/10.1016/j.phymed.2023.154900>.
 19. F. Yuan, W. Wu, L. Ma, et al., “Turmeric and Curcuminoids Ameliorate Disorders of Glycometabolism Among Subjects With Metabolic Diseases: A Systematic Review and Meta-Analysis of Randomized Controlled Trials,” *Pharmacological Research* 177 (2022): 106121.
 20. M. Li, G. G. Yue, S. K. Tsui, K. P. Fung, and C. B. Lau, “Turmeric Extract, With Absorbable Curcumin, has Potent Anti-Metastatic Effect In Vitro and In Vivo,” *Phytomedicine* 46 (2018): 131–141.
 21. J. Lv, Y. Jia, J. Li, et al., “Gegen Qinlian Decoction Enhances the Effect of PD-1 Blockade in Colorectal Cancer With Microsatellite Stability by Remodelling the Gut Microbiota and the Tumour Microenvironment,” *Cell Death & Disease* 10, no. 6 (2019): 415.
 22. C. Guo, Z. You, H. Shi, et al., “SLC38A2 and Glutamine Signalling in cDC1s Dictate Anti-Tumour Immunity,” *Nature* 620, no. 7972 (2023): 200–208.
 23. I. Heras-Murillo, I. Adán-Barrientos, M. Galán, S. K. Wculek, and D. Sancho, “Dendritic Cells as Orchestrators of Anticancer Immunity and Immunotherapy,” *Nature Reviews. Clinical Oncology* 21, no. 4 (2024): 257–277.
 24. M. J. Pittet, M. di Pilato, C. Garriss, and T. R. Mempel, “Dendritic Cells as Shepherds of T Cell Immunity in Cancer,” *Immunity* 56, no. 10 (2023): 2218–2230.
 25. L. Hato, A. Vizcay, I. Eguren, et al., “Dendritic Cells in Cancer Immunology and Immunotherapy,” *Cancers (Basel)* 16, no. 5 (2024): 981.
 26. H. Ma, W. Fang, Q. Li, Y. Wang, and S. X. Hou, “Arf1 Ablation in Colorectal Cancer Cells Activates a Super Signal Complex in DC to Enhance Anti-Tumor Immunity,” *Advanced Science* 10, no. 32 (2023): e2305089.
 27. Q. Mao, J. Min, R. Zeng, et al., “Self-Assembled Traditional Chinese Nanomedicine Modulating Tumor Immunosuppressive Microenvironment for Colorectal Cancer Immunotherapy,” *Theranostics* 12, no. 14 (2022): 6088–6105.
 28. S. Deng, G. Zhang, J. Kuai, et al., “Lentian Inhibits Tumor Angiogenesis via Interferon γ and in a T Cell Independent Manner,” *Journal of Experimental & Clinical Cancer Research* 37, no. 1 (2018): 260.
 29. X. Kong, C. Liu, P. Lu, 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* 6, no. 22 (2021): 14341–14360.
 30. X. Kong, Q. Li, D. Wang, M. Wang, F. Yang, and J. Meng, “Mechanism of Qizhen Decoction-Mediated Maturation of DC Cells to Activate the IL-12/JAK2/STAT4 Pathway to Sensitize PD-1 Inhibitors in the Treatment of Colorectal Cancer,” *Journal of Ethnopharmacology* 320 (2024): 117399.
 31. Y. Jiang, Y. Hu, Y. Yang, et al., “Tong-Xie-Yao-Fang Promotes Dendritic Cells Maturation and Retards Tumor Growth in Colorectal Cancer Mice With Chronic Restraint Stress,” *Journal of Ethnopharmacology* 319, no. Pt 1 (2024): 117069.
 32. C. Wan, Q. Ma, S. Anderson, et al., “Effects of Curcuminoids and Surfactant-Formulated Curcumin on Chemo-Resistant Colorectal Cancer,” *American Journal of Chinese Medicine* 51, no. 6 (2023): 1577–1594, <https://doi.org/10.1142/S0192415X23500714>.
 33. Z. Lin, L. Chen, M. Cheng, et al., “Cortex Periplocae Modulates the Gut Microbiota to Restrict Colitis and Colitis-Associated Colorectal Cancer via Suppression of Pathogenic Th17 Cells,” *Biomedicine & Pharmacotherapy* 153 (2022): 113399.
 34. C. Z. Wang, C. Wan, Y. Luo, et al., “Ginseng Berry Concentrate Prevents Colon Cancer via Cell Cycle, Apoptosis Regulation, and Inflammation-Linked Th17 Cell Differentiation,” *Journal of Physiology and Pharmacology* 72, no. 2 (2021): 225–237.
 35. C. Z. Wang, C. Wan, Y. Luo, et al., “Effects of Dihydroartemisinin, a Metabolite of Artemisinin, on Colon Cancer Chemoprevention and

- Adaptive Immune Regulation,” *Molecular Biology Reports* 49, no. 4 (2022): 2695–2709.
36. E. Giner, M. C. Recio, J. L. Ríos, J. M. Cerdá-Nicolás, and R. M. Giner, “Chemopreventive Effect of Oleuropein in Colitis-Associated Colorectal Cancer in c57bl/6 Mice,” *Molecular Nutrition & Food Research* 60, no. 2 (2016): 242–255.
 37. H. Sui, W. Deng, Q. Chai, et al., “YTE-17 Inhibits Colonic Carcinogenesis by Resetting Antitumor Immune Response via Wnt5a/JNK Mediated Metabolic Signaling,” *Journal of Pharmaceutical Analysis* 14, no. 4 (2024): 100901.
 38. H. Nishikawa and S. Koyama, “Mechanisms of Regulatory T Cell Infiltration in Tumors: Implications for Innovative Immune Precision Therapies,” *Journal for Immunotherapy of Cancer* 9, no. 7 (2021): e002591, <https://doi.org/10.1136/jitc-2021-002591>.
 39. W. Fong, Q. Li, F. Ji, et al., “*Lactobacillus gallinarum*-Derived Metabolites Boost Anti-PD1 Efficacy in Colorectal Cancer by Inhibiting Regulatory T Cells Through Modulating IDO1/Kyn/AHR Axis,” *Gut* 72, no. 12 (2023): 2272–2285.
 40. Z. Liu, N. Zheng, J. Li, et al., “N6-Methyladenosine-Modified Circular RNA QSOX1 Promotes Colorectal Cancer Resistance to Anti-CTLA-4 Therapy Through Induction of Intratumoral Regulatory T Cells,” *Drug Resistance Updates* 65 (2022): 100886.
 41. H. Sui, L. Zhang, K. Gu, et al., “YYFZBJS Ameliorates Colorectal Cancer Progression in Apc (Min/+) Mice by Remodeling Gut Microbiota and Inhibiting Regulatory T-Cell Generation,” *Cell Communication and Signaling* 18, no. 1 (2020): 113.
 42. Y. Zhang, N. Chai, Z. Wei, et al., “YYFZBJS Inhibits Colorectal Tumorigenesis by Enhancing Tregs-Induced Immunosuppression Through HIF-1 α Mediated Hypoxia In Vivo and In Vitro,” *Phytomedicine* 98 (2022): 153917.
 43. D. Chen, Y. Yang, and P. Yang, “Quxie Capsule Inhibits Colon Tumor Growth Partially Through Foxo1-Mediated Apoptosis and Immune Modulation,” *Integrative Cancer Therapies* 18 (2019): 1534735419846377.
 44. C. A. Geng, F. Y. Chen, J. B. Zheng, et al., “Rubiginosin B Selectively Inhibits Treg Cell Differentiation and Enhances Anti-Tumor Immune Responses by Targeting Calcineurin-NFAT Signaling Pathway,” *Phytomedicine* 116 (2023): 154898.
 45. C. C. Wong and J. Yu, “Gut Microbiota in Colorectal Cancer Development and Therapy,” *Nature Reviews. Clinical Oncology* 20, no. 7 (2023): 429–452.
 46. F. Karam, Y. El Deghel, R. Iratni, A. H. Dakroub, and A. H. Eid, “The Gut Microbiome and Colorectal Cancer: An Integrative Review of the Underlying Mechanisms,” *Cell Biochemistry and Biophysics* (2025).
 47. Y. Xiong, X. Zheng, Y. Xie, Y. Gong, and Y. I. Luo, “Effect of Cyasterone on Intestinal Flora in a (BRAF)V600E-Mutant Mouse Model of Colorectal Cancer,” *Die Pharmazie* 77, no. 10 (2022): 291–294.
 48. J. J. Zhu, H. Y. Liu, L. J. Yang, et al., “Anti-Tumour Effect of Huangqin Decoction on Colorectal Cancer Mice Through Microbial Butyrate Mediated PI3K/Akt Pathway Suppression,” *Journal of Medical Microbiology* 72, no. 5 (2023): 1–13.
 49. Y. Liu, Q. Zhang, L. Lu, et al., “Huang-Qin Decoction Alleviates Deoxycholic Acid-Induced Colorectal Cancer in Mice by Regulating Gut Microbiota,” *Journal of Ethnopharmacology* 346 (2025): 119715.
 50. Z. Zhang, S. Shao, Y. Zhang, et al., “Xiaoyaosan Slows Cancer Progression and Ameliorates Gut Dysbiosis in Mice With Chronic Restraint Stress and Colorectal Cancer Xenografts,” *Biomedicine & Pharmacotherapy* 132 (2020): 110916.
 51. S. Shao, R. Jia, L. Zhao, et al., “Xiao-Chai-Hu-Tang Ameliorates Tumor Growth in Cancer Comorbid Depressive Symptoms via Modulating Gut Microbiota-Mediated TLR4/MyD88/NF- κ B Signaling Pathway,” *Phytomedicine* 88 (2021): 153606.
 52. Y. Zhou, Y. Feng, R. Cen, et al., “San-Wu-Huang-Qin Decoction Attenuates Tumorigenesis and Mucosal Barrier Impairment in the AOM/DSS Model by Targeting Gut Microbiome,” *Phytomedicine* 98 (2022): 153966.
 53. Q. Sun, H. Yang, M. Liu, et al., “Berberine Suppresses Colorectal Cancer by Regulation of Hedgehog Signaling Pathway Activity and Gut Microbiota,” *Phytomedicine* 103 (2022): 154227.
 54. H. Wang, L. Guan, J. Li, M. Lai, and X. Wen, “The Effects of Berberine on the Gut Microbiota in Apc (Min/+) Mice Fed With a High Fat Diet,” *Molecules* 23, no. 9 (2018): 2298.
 55. M. Wang, Y. Ma, G. Yu, et al., “Integration of Microbiome, Metabolomics and Transcriptome for In-Depth Understanding of Berberine Attenuates AOM/DSS-Induced Colitis-Associated Colorectal Cancer,” *Biomedicine & Pharmacotherapy* 179 (2024): 117292.
 56. H. Chen, C. Ye, C. Wu, et al., “Berberine Inhibits High Fat Diet-Associated Colorectal Cancer Through Modulation of the Gut Microbiota-Mediated Lysophosphatidylcholine,” *International Journal of Biological Sciences* 19, no. 7 (2023): 2097–2113.
 57. H. Chen, C. Ye, B. Cai, et al., “Berberine Inhibits Intestinal Carcinogenesis by Suppressing Intestinal Pro-Inflammatory Genes and Oncogenic Factors Through Modulating Gut Microbiota,” *BMC Cancer* 22, no. 1 (2022): 566.
 58. S. Yan, J. Chang, X. Hao, et al., “Berberine Regulates Short-Chain Fatty Acid Metabolism and Alleviates the Colitis-Associated Colorectal Tumorigenesis Through Remodeling Intestinal Flora,” *Phytomedicine* 102 (2022): 154217.
 59. H. Chen, F. Zhang, J. Zhang, X. Zhang, Y. Guo, and Q. Yao, “A Holistic View of Berberine Inhibiting Intestinal Carcinogenesis in Conventional Mice Based on Microbiome-Metabolomics Analysis,” *Frontiers in Immunology* 2020 (2020): 11.
 60. X. Wang, A. Peng, and C. Huang, “Suppression of Colon Cancer Growth by Berberine Mediated by the Intestinal Microbiota and the Suppression of DNA Methyltransferases (DNMTs),” *Molecular and Cellular Biochemistry* 479, no. 8 (2024): 2131–2141.
 61. C. Wu, J. Yang, C. Ye, et al., “Berberine Attenuates 5-Fluorouracil-Induced Intestinal Mucosal Injury by Modulating the Gut Microbiota Without Compromising Its Anti-Tumor Efficacy,” *Heliyon* 10, no. 14 (2024): e34528.
 62. J. Deng, L. Zhao, X. Yuan, et al., “Pre-Administration of Berberine Exerts Chemopreventive Effects in AOM/DSS-Induced Colitis-Associated Carcinogenesis Mice via Modulating Inflammation and Intestinal Microbiota,” *Nutrients* 14, no. 4 (2022): 726.
 63. W. Yang, T. Yang, B. Huang, Z. Chen, H. Liu, and C. Huang, “Berberine Improved the Microbiota in Lung Tissue of Colon Cancer and Reversed the Bronchial Epithelial Cell Changes Caused by Cancer Cells,” *Heliyon* 10, no. 2 (2024): e24405.
 64. K. Cai, X. Y. Cao, F. Chen, et al., “Xianlian Jiedu Decoction Alleviates Colorectal Cancer by Regulating Metabolic Profiles, Intestinal Microbiota and Metabolites,” *Phytomedicine* 128 (2024): 155385.
 65. H. Zheng, H. Liu, H. Li, et al., “Characterization of Stem Cell Landscape and Identification of Stemness-Relevant Prognostic Gene Signature to Aid Immunotherapy in Colorectal Cancer,” *Stem Cell Research & Therapy* 13, no. 1 (2022): 244.
 66. Y. Zhu, S. Huang, S. Chen, et al., “SOX2 Promotes Chemoresistance, Cancer Stem Cells Properties, and Epithelial-Mesenchymal Transition by β -Catenin and Beclin1/Autophagy Signaling in Colorectal Cancer,” *Cell Death & Disease* 12, no. 5 (2021): 449.
 67. F. Wei, T. Zhang, S. C. Deng, et al., “PD-L1 Promotes Colorectal Cancer Stem Cell Expansion by Activating HMGA1-Dependent Signaling Pathways,” *Cancer Letters* 450 (2019): 1–13.
 68. S. K. Fey, N. Vaquero-Siguero, and R. Jackstadt, “Dark Force Rising: Reawakening and Targeting of Fetal-Like Stem Cells in Colorectal Cancer,” *Cell Reports* 43, no. 6 (2024): 114270.

69. Y. Dai, H. Wang, R. Sun, et al., "Modified Shenlingbaizhu Decoction Represses the Pluripotency of Colorectal Cancer Stem Cells by Inhibiting TGF- β Mediated EMT Program," *Phytomedicine* 103 (2022): 154234.
70. L. Wei, P. Chen, Y. Chen, et al., "Pien Tze Huang Suppresses the Stem-Like Side Population in Colorectal Cancer Cells," *Molecular Medicine Reports* 9, no. 1 (2014): 261–266.
71. F. Qi, L. Wei, A. Shen, 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," *Oncology Reports* 35, no. 1 (2016): 511–517.
72. Q. Lu, Z. Zhang, S. Liu, et al., "Inhibition of Stemness and PD-L1 Expression by Pien Tze Huang Enhances T Cell-Mediated Killing of Colorectal Cancer," *Journal of Ethnopharmacology* 343 (2025): 119447.
73. J. M. Shin, E. Lim, Y. S. Cho, and C. W. Nho, "Cancer-Preventive Effect of Phenethyl Isothiocyanate Through Tumor Microenvironment Regulation in a Colorectal Cancer Stem Cell Xenograft Model," *Phytomedicine* 84 (2021): 153493.
74. Y. Chen, Y. Li, X. Q. Wang, et al., "Phenethyl Isothiocyanate Inhibits Colorectal Cancer Stem Cells by Suppressing Wnt/ β -Catenin Pathway," *Phytotherapy Research* 32, no. 12 (2018): 2447–2455.
75. Y. J. Huang, C. K. Yang, P. L. Wei, et al., "Ovatodiolide Suppresses Colon Tumorigenesis and Prevents Polarization of M2 Tumor-Associated Macrophages Through YAP Oncogenic Pathways," *Journal of Hematology & Oncology* 10, no. 1 (2017): 60.
76. K. Wang, W. Huang, X. Sang, et al., "Atractylenolide I Inhibits Colorectal Cancer Cell Proliferation by Affecting Metabolism and Stemness via AKT/mTOR Signaling," *Phytomedicine* 68 (2020): 153191.
77. Y. C. Tang, Y. Zhang, J. Zhou, et al., "Ginsenoside Rg3 Targets Cancer Stem Cells and Tumor Angiogenesis to Inhibit Colorectal Cancer Progression In Vivo," *International Journal of Oncology* 52, no. 1 (2018): 127–138.
78. Y. Chen, X. Q. Wang, Q. Zhang, et al., "(–)-Epigallocatechin-3-Gallate Inhibits Colorectal Cancer Stem Cells by Suppressing Wnt/ β -Catenin Pathway," *Nutrients* 9, no. 6 (2017): 572.
79. A. T. Wu, Y. C. Yeh, Y. J. Huang, N. Mokgautsi, B. Lawal, and T. H. Huang, "Gamma-Mangostin Isolated From *garcinia mangostana* Suppresses Colon Carcinogenesis and Stemness by Downregulating the GSK3 β / β -Catenin/CDK6 Cancer Stem Pathway," *Phytomedicine* 95 (2022): 153797.
80. M. Zhang, X. Li, Q. Zhang, J. Yang, and G. Liu, "Roles of Macrophages on Ulcerative Colitis and Colitis-Associated Colorectal Cancer," *Frontiers in Immunology* 14 (2023): 1103617.
81. H. Wang, T. Tian, and J. Zhang, "Tumor-Associated Macrophages (TAMs) in Colorectal Cancer (CRC): From Mechanism to Therapy and Prognosis," *International Journal of Molecular Sciences* 22, no. 16 (2021): 8470.
82. M. He, J. W. Min, W. L. Kong, X. H. He, J. X. Li, and B. W. Peng, "A Review on the Pharmacological Effects of Vitexin and Isovalexin," *Fitoterapia* 115 (2016): 74–85.
83. Y. Chen, B. Wang, X. Yuan, et al., "Vitexin Prevents Colitis-Associated Carcinogenesis in Mice Through Regulating Macrophage Polarization," *Phytomedicine* 83 (2021): 153489.
84. Y. Chen, J. Liang, S. Chen, et al., "Discovery of Vitexin as a Novel VDR Agonist That Mitigates the Transition From Chronic Intestinal Inflammation to Colorectal Cancer," *Molecular Cancer* 23, no. 1 (2024): 196.
85. H. Liu, S. Yan, R. Yang, 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," *Integrative Cancer Therapies* 23 (2024): 15347354241247061.
86. X. Zuo, H. Lin, Z. Song, B. Yu, and C. Zhao, "Antitumor Activity of Dictamnine Against Colorectal Cancer Through Induction of Ferroptosis and Inhibition of M2 Macrophage Polarization via the MAPK Signaling," *Archives of Biochemistry and Biophysics* 758 (2024): 110051.
87. J. Xun, Z. Hu, M. Wang, et al., "Hydroxyginkwanin Suppresses Peritoneal Metastasis in Colorectal Cancer by Modulating Tumor-Associated Macrophages Polarization," *Chemico-Biological Interactions* 396 (2024): 111038.
88. N. Che, M. Li, X. Liu, C. A. Cui, J. Gong, and Y. Xuan, "Macelignan Prevents Colorectal Cancer Metastasis by Inhibiting M2 Macrophage Polarization," *Phytomedicine* 122 (2024): 155144.
89. Y. Chang, Q. Ou, X. Zhou, et al., "Jianpi Jiedu Decoction Suppresses Colorectal Cancer Growth by Inhibiting M2 Polarization of TAMs Through the Tryptophan Metabolism-AhR Pathway," *International Immunopharmacology* 138 (2024): 112610.
90. A. T. Sougiannis, B. VanderVeen, I. Chatzistamou, et al., "Emodin Reduces Tumor Burden by Diminishing M2-Like Macrophages in Colorectal Cancer," *American Journal of Physiology. Gastrointestinal and Liver Physiology* 322, no. 3 (2022): G383–G395, <https://doi.org/10.1152/ajpgi.00303.2021>.
91. S. Ge, X. Sun, L. Sang, 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," *Chemical Biology & Drug Design* 102, no. 5 (2023): 1202–1212, <https://doi.org/10.1111/cbdd.14330>.
92. Z. Fan, Y. Cui, L. Chen, P. Liu, and W. Duan, "23-Hydroxybetulinic Acid Attenuates 5-Fluorouracil Resistance of Colorectal Cancer by Modulating M2 Macrophage Polarization via STAT6 Signaling," *Cancer Immunology, Immunotherapy* 73, no. 5 (2024): 83.
93. H. Zhang, B. Zhao, H. Wei, H. Zeng, D. Sheng, and Y. Zhang, "Cucurbitacin B Controls M2 Macrophage Polarization to Suppresses Metastasis via Targeting JAK-2/STAT3 Signalling Pathway in Colorectal Cancer," *Journal of Ethnopharmacology* 287 (2022): 114915.
94. Z. Kooshan, L. Cárdenas-Piedra, J. Clements, and J. Batra, "Glycolysis, the Sweet Appetite of the Tumor Microenvironment," *Cancer Letters* 600 (2024): 217156.
95. G. Wang, Y. Z. Wang, Y. Yu, and J. J. Wang, "Inhibitory ASIC2-Mediated Calcineurin/NFAT Against Colorectal Cancer by Triterpenoids Extracted From *Rhus chinensis* Mill," *Journal of Ethnopharmacology* 235 (2019): 255–267.
96. G. Wang, Y. Z. Wang, Y. Yu, J. J. Wang, P. H. Yin, and K. Xu, "Triterpenoids Extracted From *Rhus chinensis* Mill Act Against Colorectal Cancer by Inhibiting Enzymes in Glycolysis and Glutaminolysis: Network Analysis and Experimental Validation," *Nutrition and Cancer* 72, no. 2 (2020): 293–319.
97. Y. Li, Y. Wang, Z. Liu, X. Guo, Z. Miao, and S. Ma, "Atractylenolide I Induces Apoptosis and Suppresses Glycolysis by Blocking the JAK2/STAT3 Signaling Pathway in Colorectal Cancer Cells," *Frontiers in Pharmacology* 11 (2020): 273.
98. X. Wei, T. Mao, S. Li, et al., "DT-13 Inhibited the Proliferation of Colorectal Cancer via Glycolytic Metabolism and AMPK/mTOR Signaling Pathway," *Phytomedicine* 54 (2019): 120–131.
99. S. Raina, E. Hübner, E. Samuel, G. Nagel, and H. Fuchs, "DT-13 Attenuates Inflammation by Inhibiting NLRP3-Inflammasome Related Genes in RAW264.7 Macrophages," *Biochemical and Biophysical Research Communications* 708 (2024): 149763.
100. G. Xie, F. Tong, M. Xu, Y. Shu, and Z. Li, "DT-13 Inhibits the Proliferation of Pancreatic Cancer by Inducing Apoptosis via AMPK-mTOR Signaling," *Biochemical and Biophysical Research Communications* 695 (2024): 149451.

101. C. Wang, H. He, G. Liu, et al., "DT-13 Induced Apoptosis and Promoted Differentiation of Acute Myeloid Leukemia Cells by Activating AMPK-KLF2 Pathway," *Pharmacological Research* 158 (2020): 104864.
102. S. Y. Li, J. Shang, X. M. Mao, et al., "Diosgenin Exerts Anti-Tumor Effects Through Inactivation of cAMP/PKA/CREB Signaling Pathway in Colorectal Cancer," *European Journal of Pharmacology* 908 (2021): 174370.
103. S. Chen, M. Nishi, Y. Morine, et al., "Epigallocatechin-3-Gallate Hinders Metabolic Coupling to Suppress Colorectal Cancer Malignancy Through Targeting Aerobic Glycolysis in Cancer-Associated Fibroblasts," *International Journal of Oncology* 60, no. 2 (2022): 19.
104. H. Wu, M. Cui, C. Li, et al., "Kaempferol Reverses Aerobic Glycolysis via miR-339-5p-Mediated PKM Alternative Splicing in Colon Cancer Cells," *Journal of Agricultural and Food Chemistry* 69, no. 10 (2021): 3060–3068.
105. Y. Gan, L. Zhou, R. Wang, et al., "Curcumol Reduces Aerobic Glycolysis and Overcomes Chemoresistance by Inducing Cdh1-Mediated Skp2 Ubiquitination," *American Journal of Chinese Medicine* 51, no. 3 (2023): 723–740.
106. G. Pan, P. Zhang, A. Chen, et al., "Aerobic Glycolysis in Colon Cancer Is Repressed by Naringin via the HIF1A Pathway," *Journal of Zhejiang University. Science. B* 24, no. 3 (2023): 221–231.
107. X. Sun, L. Zhou, Y. Wang, 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," *Journal of Pharmaceutical Analysis* 13, no. 7 (2023): 726–744.
108. Z. Zhang, Y. Chen, Y. Zheng, et al., "Quxie Capsule Alleviates Colitis-Associated Colorectal Cancer Through Modulating the Gut Microbiota and Suppressing *A. fumigatus*-Induced Aerobic Glycolysis," *Integrative Cancer Therapies* 21 (2022): 15347354221138534.
109. Q. Zhang, T. Deng, H. Zhang, et al., "Adipocyte-Derived Exosomal MTTP Suppresses Ferroptosis and Promotes Chemoresistance in Colorectal Cancer," *Advanced Science* 9, no. 28 (2022): e2203357.
110. H. Li, K. Yu, H. Hu, et al., "METTL17 Coordinates Ferroptosis and Tumorigenesis by Regulating Mitochondrial Translation in Colorectal Cancer," *Redox Biology* 71 (2024): 103087.
111. R. Singhal, S. R. Mita, N. K. Das, et al., "HIF-2 α Activation Potentiates Oxidative Cell Death in Colorectal Cancers by Increasing Cellular Iron," *Journal of Clinical Investigation* 131, no. 12 (2021): e143691, <https://doi.org/10.1172/JCI143691>.
112. H. Yan, R. Talty, O. Aladelokun, M. Bosenberg, and C. H. Johnson, "Ferroptosis in Colorectal Cancer: A Future Target?," *British Journal of Cancer* 128, no. 8 (2023): 1439–1451.
113. Y. Wu, D. Pi, S. Zhou, et al., "Ginsenoside Rh3 Induces Pyroptosis and Ferroptosis Through the Stat3/p53/NRF2 Axis in Colorectal Cancer Cells," *Acta Biochimica et Biophysica Sinica* 55, no. 4 (2023): 587–600.
114. S. Luo, G.-J. Tian, F.-X. Yu, and Z.-D. Wen, "A Narrative Review of the Antitumor Studies of Solanine," *Translational Cancer Research* 10, no. 3 (2021): 1578–1582.
115. X. Ma, Y. Li, D. Liang, et al., "Solanine Induces Ferroptosis in Colorectal Cancer Cells Through ALOX12B/ADCY4 Molecular Axis," *Journal of Pharmacy and Pharmacology* 76, no. 3 (2024): 224–235.
116. W. Xin and Y. Zhang, "Curcumin Activates the JNK Signaling Pathway to Promote Ferroptosis in Colon Cancer Cells," *Chemical Biology & Drug Design* 103, no. 3 (2024): e14468.
117. K. Miyazaki, C. Xu, M. Shimada, and A. Goel, "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)* 16, no. 3 (2023): 383.
118. M. Chen, A. H. Tan, and J. Li, "Curcumin Represses Colorectal Cancer Cell Proliferation by Triggering Ferroptosis via PI3K/Akt/mTOR Signaling," *Nutrition and Cancer* 75, no. 2 (2023): 726–733.
119. T. Ming, J. Lei, Y. Peng, 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," *Phytotherapy Research* 38, no. 8 (2024): 3954–3972.
120. R. Wei, Y. Zhao, J. Wang, et al., "Tagitinin C Induces Ferroptosis Through PERK-Nrf2-HO-1 Signaling Pathway in Colorectal Cancer Cells," *International Journal of Biological Sciences* 17, no. 11 (2021): 2703–2717.
121. Z. Shen, L. Zhao, S. A. Yoo, et al., "Emodin Induces Ferroptosis in Colorectal Cancer Through NCOA4-Mediated Ferritinophagy and NF- κ B Pathway Inactivation," *Apoptosis* 29, no. 9–10 (2024): 1810–1823.
122. J. Q. Lai, L. L. Zhao, C. Hong, et al., "Baicalein Triggers Ferroptosis in Colorectal Cancer Cells via Blocking the JAK2/STAT3/GPX4 Axis," *Acta Pharmacologica Sinica* 45, no. 8 (2024): 1715–1726.
123. J. Geng, Y. Wang, F. Lv, et al., "Coumestrol Facilitates Apoptosis in Colorectal Cancer Cells by Interacting With ZIP8 Protein via the Ferroptosis Pathway," *Journal of Cancer* 15, no. 14 (2024): 4656–4667.
124. Q. Miao, W. Q. Deng, W. Y. Lyu, et al., "Erianin Inhibits the Growth and Metastasis Through Autophagy-Dependent Ferroptosis in KRAS(G13D) Colorectal Cancer," *Free Radical Biology & Medicine* 204 (2023): 301–312.
125. Y. Zheng, L. Li, H. Chen, et al., "Luteolin Exhibits Synergistic Therapeutic Efficacy With Erastin to Induce Ferroptosis in Colon Cancer Cells Through the HIC1-Mediated Inhibition of GPX4 Expression," *Free Radical Biology & Medicine* 208 (2023): 530–544.
126. X. Zhou, J. Kang, L. Zhang, and Y. Cheng, "Osthole Inhibits Malignant Phenotypes and Induces Ferroptosis in KRAS-Mutant Colorectal Cancer Cells via Suppressing AMPK/Akt Signaling," *Cancer Chemotherapy and Pharmacology* 92, no. 2 (2023): 119–134.
127. G. Lian, X. X. Huang, and Y. Zeng, "Puerarin Induces Ferroptosis in Colorectal Cancer Cells via Triggering NCOA4 Upregulation," *Nutrition and Cancer* 75, no. 7 (2023): 1571–1578.
128. P. Vermonden, M. Vancoppenolle, E. Dierge, et al., "Punicic Acid Triggers Ferroptotic Cell Death in Carcinoma Cells," *Nutrients* 13, no. 8 (2021): 2751.
129. J. Y. Huang, T. W. Hsu, Y. R. Chen, and S. H. Kao, "Rosmarinic Acid Potentiates Cytotoxicity of Cisplatin Against Colorectal Cancer Cells by Enhancing Apoptotic and Ferroptosis," *Life* 14, no. 8 (2024): 1017, <https://doi.org/10.3390/life14081017>.
130. Y. Wu, D. Pi, Y. Chen, Q. Zuo, S. Zhou, and M. Ouyang, "Ginsenoside Rh4 Inhibits Colorectal Cancer Cell Proliferation by Inducing Ferroptosis via Autophagy Activation," *Evidence-Based Complementary and Alternative Medicine* 2022 (2022): 6177553.
131. X. Ma, M. Xu, X. Zhang, et al., "Gambogic Acid Inhibits Proliferation and Ferroptosis by Targeting the miR-1291/FOXA2 and AMPK α /SLC7A11/GPX4 Axis in Colorectal Cancer," *Cell Biology International* 47, no. 11 (2023): 1813–1824.
132. S. Zhao, Y. Mi, B. Guan, et al., "Tumor-Derived Exosomal miR-934 Induces Macrophage M2 Polarization to Promote Liver Metastasis of Colorectal Cancer," *Journal of Hematology & Oncology* 13, no. 1 (2020): 156.
133. Y. Liang, J. Li, Y. Yuan, et al., "Exosomal miR-106a-5p From Highly Metastatic Colorectal Cancer Cells Drives Liver Metastasis by Inducing Macrophage M2 Polarization in the Tumor Microenvironment," *Journal of Experimental & Clinical Cancer Research* 43, no. 1 (2024): 281.
134. Y. Yin, B. Liu, Y. Cao, et al., "Colorectal Cancer-Derived Small Extracellular Vesicles Promote Tumor Immune Evasion by Upregulating PD-L1 Expression in Tumor-Associated Macrophages," *Advanced Science* 9, no. 9 (2022): 2102620.

135. A. Prakash, T. Gates, X. Zhao, D. Wangmo, and S. Subramanian, "Tumor-Derived Extracellular Vesicles in the Colorectal Cancer Immune Environment and Immunotherapy," *Pharmacology & Therapeutics* 241 (2023): 108332.
136. R. Li, J. Zhou, X. Wu, et al., "Jianpi Jiedu Recipe Inhibits Colorectal Cancer Liver Metastasis via Regulating ITGBL1-Rich Extracellular Vesicles Mediated Activation of Cancer-Associated Fibroblasts," *Phytomedicine* 100 (2022): 154082.
137. Y. Chen, Q. Yan, Y. Ji, et al., "Unraveling the Serial Glycosylation in the Biosynthesis of Steroidal Saponins in the Medicinal Plant *Paris polyphylla* and Their Antifungal Action," *Acta Pharmaceutica Sinica B* 13, no. 11 (2023): 4638–4654.
138. H. Hao and A. Sha, "Study on Anti-Fatigue Effects and Mechanisms of Polysaccharide From *Paris polyphylla*," *Doklady. Biochemistry and Biophysics* 516, no. 1 (2024): 58–65.
139. V. Kshetrimayum, K. D. Chanu, T. Biona, et al., "*Paris polyphylla* Sm. Characterized Extract Infused Ointment Accelerates Diabetic Wound Healing in In-Vivo Model," *Journal of Ethnopharmacology* 331 (2024): 118296.
140. L. Li, J. Zhang, W. Cheng, F. Di, C. Wang, and Q. An, "Saponins of *Paris polyphylla* for the Improvement of Acne: Anti-Inflammatory, Antibacterial, Antioxidant and Immunomodulatory Effects," *Molecules* 29, no. 8 (2024): 1793.
141. J. Wang, B. Y. Ni, J. Wang, et al., "Research Progress of *Paris polyphylla* in the Treatment of Digestive Tract Cancers," *Discover Oncology* 15, no. 1 (2024): 31.
142. L. T. Lin, Y. C. Shi, C. Y. Choong, and C. J. Tai, "The Fruits of *Paris polyphylla* Inhibit Colorectal Cancer Cell Migration Induced by *Fusobacterium nucleatum*-Derived Extracellular Vesicles," *Molecules* 26, no. 13 (2021): 4081.
143. C. Gu, H. Lu, and Z. Qian, "Matrine Reduces the Secretion of Exosomal circSLC7A6 From Cancer-Associated Fibroblast to Inhibit Tumorigenesis of Colorectal Cancer by Regulating CXCR5," *Biochemical and Biophysical Research Communications* 527, no. 3 (2020): 638–645.
144. Y. Yang, L. Zhang, X. La, Z. Li, H. Li, and S. Guo, "Salvianolic Acid A Inhibits Tumor-Associated Angiogenesis by Blocking GRP78 Secretion," *Naunyn-Schmiedeberg's Archives of Pharmacology* 392, no. 4 (2019): 467–480.
145. C. Chen, X. Yao, Y. Xu, et al., "Dahuang Zhechong Pill Suppresses Colorectal Cancer Liver Metastasis via Ameliorating Exosomal CCL2 Primed Pre-Metastatic Niche," *Journal of Ethnopharmacology* 238 (2019): 111878.
146. Y. Liu, D. H. Cheng, Z. Y. Su, et al., "Effects of Total Coumarins From *Pileostegia tomentella* on Exosomal miRNA Expression and Angiogenesis in Colorectal Cancer Cells," *Pharmaceutical Biology* 62, no. 1 (2024): 153–161.
147. J. Chen, S. Duan, Y. Wang, et al., "MYG1 Drives Glycolysis and Colorectal Cancer Development Through Nuclear-Mitochondrial Collaboration," *Nature Communications* 15, no. 1 (2024): 4969.
148. S. Taha-Mehlitz, G. Bianco, M. Coto-Llerena, et al., "Adenylosuccinate Lyase Is Oncogenic in Colorectal Cancer by Causing Mitochondrial Dysfunction and Independent Activation of NRF2 and mTOR-MYC-Axis," *Theranostics* 11, no. 9 (2021): 4011–4029.
149. B. Han, P. Jiang, Z. Li, et al., "Coptisine-Induced Apoptosis in Human Colon Cancer Cells (HCT-116) is Mediated by PI3K/Akt and Mitochondrial-Associated Apoptotic Pathway," *Phytomedicine* 48 (2018): 152–160.
150. L. Zheng, B. Li, A. Yuan, et al., "TFEB Activator Tanshinone IIA and Derivatives Derived From *Salvia miltiorrhiza* Bge. Attenuate Hepatic Steatosis and Insulin Resistance," *Journal of Ethnopharmacology* 335 (2024): 118662.
151. L. Ma, T. Zhang, R. Wang, et al., "Sodium Tanshinone IIA Sulfonate Protects Primary Cardiomyocytes Against Radiation-Induced Myocardial Injury via the p38 Pathway," *International Heart Journal* 65, no. 4 (2024): 730–737.
152. L. Cao, Z. Qin, T. Yu, et al., "Tanshinone IIA Acts as a Regulator of Lipogenesis to Overcome Osimertinib Acquired Resistance in Lung Cancer," *Biochemical Pharmacology* 224 (2024): 116207.
153. S. Jiensinue, H. Zhu, G. Li, K. Dong, M. Liang, and Y. Li, "Tanshinone IIA Reduces SW837 Colorectal Cancer Cell Viability via the Promotion of Mitochondrial Fission by Activating JNK-Mff Signaling Pathways," *BMC Cell Biology* 19, no. 1 (2018): 21.
154. J. Qian, D. Fang, H. Lu, et al., "Tanshinone IIA Promotes IL2-Mediated SW480 Colorectal Cancer Cell Apoptosis by Triggering INF2-Related Mitochondrial Fission and Activating the Mst1-Hippo Pathway," *Biomedicine & Pharmacotherapy* 108 (2018): 1658–1669.
155. S. Srivastava, J. Dewangan, S. Mishra, et al., "Piperine and Celecoxib Synergistically Inhibit Colon Cancer Cell Proliferation via Modulating Wnt/ β -Catenin Signaling Pathway," *Phytomedicine* 84 (2021): 153484.
156. P. B. Yaffe, C. D. Doucette, M. Walsh, and D. W. Hoskin, "Piperine Impairs Cell Cycle Progression and Causes Reactive Oxygen Species-Dependent Apoptosis in Rectal Cancer Cells," *Experimental and Molecular Pathology* 94, no. 1 (2013): 109–114.
157. P. B. Yaffe, M. R. Power Coombs, C. D. Doucette, M. Walsh, and D. W. Hoskin, "Piperine, an Alkaloid From Black Pepper, Inhibits Growth of Human Colon Cancer Cells via G1 Arrest and Apoptosis Triggered by Endoplasmic Reticulum Stress," *Molecular Carcinogenesis* 54, no. 10 (2015): 1070–1085.
158. K. Shaheer, H. M. Somashekarappa, and M. D. Lakshmanan, "Piperine Sensitizes Radiation-Resistant Cancer Cells Towards Radiation and Promotes Intrinsic Pathway of Apoptosis," *Journal of Food Science* 85, no. 11 (2020): 4070–4079.
159. J. K. Tak, J. H. Lee, and J. W. Park, "Resveratrol and Piperine Enhance Radiosensitivity of Tumor Cells," *BMB Reports* 45, no. 4 (2012): 242–246.
160. M. Guéguinou, S. Ibrahim, J. Bourgeais, et al., "Curcumin and NCLX Inhibitors Share Anti-Tumoral Mechanisms in Microsatellite-Instability-Driven Colorectal Cancer," *Cellular and Molecular Life Sciences* 79, no. 6 (2022): 284.
161. C. M. Su, Y. S. Weng, L. Y. Kuan, J. H. Chen, and F. T. Hsu, "Suppression of PKC δ /NF- κ B Signaling and Apoptosis Induction Through Extrinsic/Intrinsic Pathways Are Associated Magnolol-Inhibited Tumor Progression in Colorectal Cancer In Vitro and In Vivo," *International Journal of Molecular Sciences* 21, no. 10 (2020): 3527.
162. Y. Fu, Y. Ye, G. Zhu, et al., "Resveratrol Induces Human Colorectal Cancer Cell Apoptosis by Activating the Mitochondrial Pathway via Increasing Reactive Oxygen Species," *Molecular Medicine Reports* 23, no. 3 (2021): 1–7.
163. Y. Qin, Y. Yu, C. Yang, et al., "Atractylenolide I Inhibits NLRP3 Inflammasome Activation in Colitis-Associated Colorectal Cancer via Suppressing Drp1-Mediated Mitochondrial Fission," *Frontiers in Pharmacology* 12 (2021): 674340.
164. Y. Bai, Y. Xiong, Y. Y. Zhang, et al., "Tangeretin Synergizes With 5-Fluorouracil to Induce Autophagy Through MicroRNA-21 in Colorectal Cancer Cells," *American Journal of Chinese Medicine* 50, no. 6 (2022): 1681–1701.
165. L. Long, W. Xiong, F. Lin, et al., "Regulating Lactate-Related Immunometabolism and EMT Reversal for Colorectal Cancer Liver Metastases Using Shikonin Targeted Delivery," *Journal of Experimental & Clinical Cancer Research* 42, no. 1 (2023): 117.
166. L. Liang, W. Sun, X. Wei, et al., "Oxymatrine Suppresses Colorectal Cancer Progression by Inhibiting NLRP3 Inflammasome Activation

- Through Mitophagy Induction In Vitro and In Vivo,” *Phytotherapy Research* 37, no. 8 (2023): 3342–3362.
167. J. N. Zeng, J. Y. Tan, and L. Mo, “Naringin Inhibits Colorectal Carcinogenesis by Inhibiting Viability of Colorectal Cancer Cells,” *Chinese Journal of Integrative Medicine* 29, no. 8 (2023): 707–713.
 168. R. Cai, Y. P. Zhou, Y. H. Li, J. J. Zhang, and Z. W. Hu, “Baicalin Blocks Colon Cancer Cell Cycle and Inhibits Cell Proliferation Through miR-139-3p Upregulation by Targeting CDK16,” *American Journal of Chinese Medicine* 51, no. 1 (2023): 189–203.
 169. D. Özerkan, “The Determination of Cisplatin and Luteolin Synergistic Effect on Colorectal Cancer Cell Apoptosis and Mitochondrial Dysfunction by Fluorescence Labelling,” *Journal of Fluorescence* 33, no. 3 (2023): 1217–1225.
 170. A. Al-Menhali, A. Al-Rumaihi, H. Al-Mohammed, et al., “*Thymus vulgaris* (Thyme) Inhibits Proliferation, Adhesion, Migration, and Invasion of Human Colorectal Cancer Cells,” *Journal of Medicinal Food* 18, no. 1 (2015): 54–59.
 171. J. Chen, E. Pitmon, and K. Wang, “Microbiome, Inflammation and Colorectal Cancer,” *Seminars in Immunology* 32 (2017): 43–53.
 172. A. E. V. Quaglio, T. G. Grillo, E. C. S. de Oliveira, L. C. di Stasi, and L. Y. Sasaki, “Gut Microbiota, Inflammatory Bowel Disease and Colorectal Cancer,” *World Journal of Gastroenterology* 28, no. 30 (2022): 4053–4060.
 173. W. Weng and A. Goel, “Curcumin and Colorectal Cancer: An Update and Current Perspective on This Natural Medicine,” *Seminars in Cancer Biology* 80 (2022): 73–86.
 174. N. Shivappa, J. Godos, J. R. Hébert, et al., “Dietary Inflammatory Index and Colorectal Cancer Risk-A Meta-Analysis,” *Nutrients* 9, no. 9 (2017): 1043.
 175. Z. Dal and B. Aru, “The Role of Curcumin on Apoptosis and NLRP3 Inflammasome-Dependent Pyroptosis on Colorectal Cancer In Vitro,” *Turkish Journal of Medical Sciences* 53, no. 4 (2023): 883–893.
 176. N. Seiwert, J. Fahrner, G. Nagel, J. Frank, D. Behnam, and B. Kaina, “Curcumin Administered as Micellar Solution Suppresses Intestinal Inflammation and Colorectal Carcinogenesis,” *Nutrition and Cancer* 73, no. 4 (2021): 686–693.
 177. J. Sun, Z. Zhao, J. Lu, et al., “The Tumor Microenvironment Mediates the HIF-1 α /PD-L1 Pathway to Promote Immune Escape in Colorectal Cancer,” *International Journal of Molecular Sciences* 25, no. 7 (2024): 3735.
 178. A. I. Ghoneim, “Effects of Curcumin on Ethanol-Induced Hepatocyte Necrosis and Apoptosis: Implication of Lipid Peroxidation and Cytochrome c,” *Naunyn-Schmiedeberg's Archives of Pharmacology* 379, no. 1 (2009): 47–60.
 179. Y. Jiao, J. Wilkinson, X. Di, et al., “Curcumin, a Cancer Chemopreventive and Chemotherapeutic Agent, Is a Biologically Active Iron Chelator,” *Blood* 113, no. 2 (2009): 462–469, <https://doi.org/10.1182/blood-2008-05-155952>.
 180. Y. Wang, C. Zhang, S. Zhang, et al., “Kanglaite Sensitizes Colorectal Cancer Cells to Taxol via NF- κ B Inhibition and Connexin 43 Upregulation,” *Scientific Reports* 7, no. 1 (2017): 1280.
 181. G. Shi, X. Zheng, S. Zhang, et al., “Kanglaite Inhibits EMT Caused by TNF- α via NF- κ B Inhibition in Colorectal Cancer Cells,” *Oncotarget* 9, no. 6 (2018): 6771–6779.
 182. H. Sui, L. H. Zhou, Y. L. Zhang, et al., “Evodiamine Suppresses ABCG2 Mediated Drug Resistance by Inhibiting p50/p65 NF- κ B Pathway in Colorectal Cancer,” *Journal of Cellular Biochemistry* 117, no. 6 (2016): 1471–1481.
 183. L. C. Zhao, J. Li, K. Liao, et al., “Evodiamine Induces Apoptosis and Inhibits Migration of HCT-116 Human Colorectal Cancer Cells,” *International Journal of Molecular Sciences* 16, no. 11 (2015): 27411–27421.
 184. Y. Zhang, Y. Zhang, Y. Zhao, et al., “Protection Against Ulcerative Colitis and Colorectal Cancer by Evodiamine via Anti-Inflammatory Effects,” *Molecular Medicine Reports* 25, no. 5 (2022): 188.
 185. M. Wang, B. Zhou, W. Cong, et al., “Amelioration of AOM/DSS-Induced Murine Colitis-Associated Cancer by Evodiamine Intervention Is Primarily Associated With Gut Microbiota-Metabolism-Inflammatory Signaling Axis,” *Frontiers in Pharmacology* 12 (2021): 797605.
 186. Y. Lu, K. Dong, M. Yang, and J. Liu, “Network Pharmacology-Based Strategy to Investigate the Bioactive Ingredients and Molecular Mechanism of Evodia Rutaecarpa in Colorectal Cancer,” *BMC Complementary Medicine and Therapies* 23, no. 1 (2023): 433.
 187. P. Zhou, X. P. Li, R. Jiang, et al., “Evodiamine Inhibits Migration and Invasion by Sirt1-Mediated Post-Translational Modulations in Colorectal Cancer,” *Anti-Cancer Drugs* 30, no. 6 (2019): 611–617.
 188. S. Zeng, L. Tan, Q. Sun, et al., “Suppression of Colitis-Associated Colorectal Cancer by Scutellarin Through Inhibiting Hedgehog Signaling Pathway Activity,” *Phytomedicine* 98 (2022): 153972.
 189. S. Zeng, L. Chen, Q. Sun, et al., “Scutellarin Ameliorates Colitis-Associated Colorectal Cancer by Suppressing Wnt/ β -Catenin Signaling Cascade,” *European Journal of Pharmacology* 906 (2021): 174253.
 190. J. Ruan, H. Li, M. Lu, et al., “Bioactive Triterpenes of Jujube in the Prevention of Colorectal Cancer and Their Molecular Mechanism Research,” *Phytomedicine* 110 (2023): 154639.
 191. B. A. Yousef, H. M. Hassan, L. Y. Zhang, and Z. Z. Jiang, “Pristimerin Exhibits In Vitro and In Vivo Anticancer Activities Through Inhibition of Nuclear Factor- κ B Signaling Pathway in Colorectal Cancer Cells,” *Phytomedicine* 40 (2018): 140–147.
 192. B. A. Yousef, M. Guerram, H. M. Hassan, A. M. Hamdi, L. Y. Zhang, and Z. Z. Jiang, “Pristimerin Demonstrates Anticancer Potential in Colorectal Cancer Cells by Inducing G1 Phase Arrest and Apoptosis and Suppressing Various Pro-Survival Signaling Proteins,” *Oncology Reports* 35, no. 2 (2016): 1091–1100.
 193. J. H. Park and J. K. Kim, “Pristimerin, a Naturally Occurring Triterpenoid, Attenuates Tumorigenesis in Experimental Colitis-Associated Colon Cancer,” *Phytomedicine* 42 (2018): 164–171.
 194. Z. Yu and W. Li, “Induction of Apoptosis by Puerarin in Colon Cancer HT-29 Cells,” *Cancer Letters* 238, no. 1 (2006): 53–60.
 195. J. Luo, J. Qu, R. Yang, et al., “Phytochemicals Mediate the Expression and Activity of OCTN2 as Activators of the PPAR γ /RXR α Pathway,” *Frontiers in Pharmacology* 7 (2016): 189.
 196. J. Li, C. Guo, X. Lu, and W. Tan, “Anti-Colorectal Cancer Biotargets and Biological Mechanisms of Puerarin: Study of Molecular Networks,” *European Journal of Pharmacology* 858 (2019): 172483.
 197. Y. Wang, Y. Ma, Y. Zheng, et al., “In Vitro and In Vivo Anticancer Activity of a Novel Puerarin Nanosuspension Against Colon Cancer, With High Efficacy and Low Toxicity,” *International Journal of Pharmaceutics* 441, no. 1–2 (2013): 728–735.
 198. X. Q. Deng, H. B. Zhang, G. F. Wang, et al., “Colon-Specific Microspheres Loaded With Puerarin Reduce Tumorigenesis and Metastasis in Colitis-Associated Colorectal Cancer,” *International Journal of Pharmaceutics* 570 (2019): 118644.
 199. W. Li, S. M. Saud, M. R. Young, N. H. Colburn, and B. Hua, “Cryptotanshinone, a Stat3 Inhibitor, Suppresses Colorectal Cancer Proliferation and Growth In Vitro,” *Molecular and Cellular Biochemistry* 406, no. 1–2 (2015): 63–73.
 200. Y. S. Su, M. Z. Kuo, Y. T. Kuo, et al., “Diterpenoid Anthraquinones as Chemopreventive Agents Altered microRNA and Transcriptome

- Expressions in Cancer Cells,” *Biomedicine & Pharmacotherapy* 136 (2021): 111260.
201. H. Vundavilli, A. Datta, C. Sima, J. Hua, R. Lopes, and M. Bittner, “Targeting Oncogenic Mutations in Colorectal Cancer Using Cryptotanshinone,” *PLoS One* 16, no. 2 (2021): e0247190.
202. L. Zhang, C. Chen, J. Duanmu, 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-1 α Nuclear Translocation,” *International Immunopharmacology* 65 (2018): 429–437.
203. D. Y. Lee, M. Y. Song, and E. H. Kim, “Role of Oxidative Stress and Nrf2/KEAP1 Signaling in Colorectal Cancer: Mechanisms and Therapeutic Perspectives With Phytochemicals,” *Antioxidants* 10, no. 5 (2021): 743, <https://doi.org/10.3390/antiox10050743>.
204. A. Bardelčíková, J. Šoltys, and J. Mojžiš, “Oxidative Stress, Inflammation and Colorectal Cancer: An Overview,” *Antioxidants* 12, no. 4 (2023): 901, <https://doi.org/10.3390/antiox12040901>.
205. A. Deorukhkar, N. Ahuja, A. L. Mercado, 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 Medicine* 4, no. 2 (2015): 278–292.
206. R. Dehghan, R. Najafi, F. Azizi Jalilian, et al., “A Promising Effect of Zerumbone With Improved Anti-Tumor-Promoting Inflammation Activity of miR-34a in Colorectal Cancer Cell Lines,” *Molecular Biology Reports* 48, no. 1 (2021): 203–218.
207. H. W. Cho, K. J. Rhee, and Y. B. Eom, “Zerumbone Restores Gut Microbiota Composition in ETBF Colonized AOM/DSS Mice,” *Journal of Microbiology and Biotechnology* 30, no. 11 (2020): 1640–1650.
208. N. Hosseini, A. Khoshnazar, M. Saidijam, et al., “Zerumbone Suppresses Human Colorectal Cancer Invasion and Metastasis via Modulation of FAK/PI3k/NF κ B-uPA Pathway,” *Nutrition and Cancer* 71, no. 1 (2019): 159–171.
209. Z. Radaei, A. Zamani, R. Najafi, et al., “Promising Effects of Zerumbone on the Regulation of Tumor-Promoting Cytokines Induced by TNF- α -Activated Fibroblasts,” *Current Medical Science* 40, no. 6 (2020): 1075–1084.
210. F. Memari, F. Mirzavi, M. Jalili-Nik, A. R. Afshari, A. Ghorbani, and M. Soukhtanloo, “Tumor-Inhibitory Effects of Zerumbone Against HT-29 Human Colorectal Cancer Cells,” *International Journal of Toxicology* 41, no. 5 (2022): 402–411.
211. S. Yodkeeree, B. Sung, P. Limtrakul, and B. B. Aggarwal, “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 Research* 69, no. 16 (2009): 6581–6589.
212. S. Hwang, M. Jo, J. E. Hong, C. O. Park, C. G. Lee, and K. J. Rhee, “Protective Effects of Zerumbone on Colonic Tumorigenesis in Enterotoxigenic *Bacteroides fragilis* (ETBF)-Colonized AOM/DSS BALB/c Mice,” *International Journal of Molecular Sciences* 21, no. 3 (2020): 857.
213. T. Sithara, B. P. Dhanya, K. B. Arun, et al., “Zerumbone, a Cyclic Sesquiterpene From *Zingiber zerumbet* Induces Apoptosis, Cell Cycle Arrest, and Antimigratory Effects in SW480 Colorectal Cancer Cells,” *Journal of Agricultural and Food Chemistry* 66, no. 3 (2018): 602–612, <https://doi.org/10.1021/acs.jafc.7b04472>.
214. Y. Yu, D. Chen, T. Wu, 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* 98 (2022): 153932.
215. Z. Yao, A. Bhandari, Y. Wang, et al., “Dihydroartemisinin Potentiates Antitumor Activity of 5-Fluorouracil Against a Resistant Colorectal Cancer Cell Line,” *Biochemical and Biophysical Research Communications* 501, no. 3 (2018): 636–642.
216. Z. Wang, X. Sun, Y. Feng, et al., “Dihydromyricetin Reverses MRP2-Induced Multidrug Resistance by Preventing NF- κ B-Nrf2 Signaling in Colorectal Cancer Cell,” *Phytomedicine* 82 (2021): 153414.
217. J. Liang, J. Wu, F. Wang, P. Zhang, and X. Zhang, “Semaphoring 4D Is Required for the Induction of Antioxidant Stress and Anti-Inflammatory Effects of Dihydromyricetin in Colon Cancer,” *International Immunopharmacology* 67 (2019): 220–230.
218. I. Khan, S. Mahfooz, M. Saeed, I. Ahmad, and I. A. Ansari, “Andrographolide Inhibits Proliferation of Colon Cancer SW-480 Cells via Downregulating Notch Signaling Pathway,” *Anti-Cancer Agents in Medicinal Chemistry* 21, no. 4 (2021): 487–497.
219. I. Khan, S. Mahfooz, and I. A. Ansari, “Antiproliferative and Apoptotic Properties of Andrographolide Against Human Colon Cancer DLD1 Cell Line,” *Endocrine, Metabolic & Immune Disorders Drug Targets* 20, no. 6 (2020): 930–942.
220. I. Khan, F. Khan, A. Farooqui, and I. A. Ansari, “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,” *Nutrition and Cancer* 70, no. 5 (2018): 787–803.
221. I. Khan, S. Mahfooz, M. Faisal, A. A. Alatar, and I. A. Ansari, “Andrographolide Induces Apoptosis and Cell Cycle Arrest Through Inhibition of Aberrant Hedgehog Signaling Pathway in Colon Cancer Cells,” *Nutrition and Cancer* 73, no. 11–12 (2021): 2428–2446.
222. A. Banerjee, V. Banerjee, S. Czinn, and T. Blanchard, “Increased Reactive Oxygen Species Levels Cause ER Stress and Cytotoxicity in Andrographolide Treated Colon Cancer Cells,” *Oncotarget* 8, no. 16 (2017): 26142–26153.
223. N. Sharda, T. Ikuse, E. Hill, et al., “Impact of Andrographolide and Melatonin Combinatorial Drug Therapy on Metastatic Colon Cancer Cells and Organoids,” *Clinical Medicine Insights: Oncology* 15 (2021): 11795549211012672.
224. H. Hong, W. Cao, Q. Wang, C. Liu, and C. Huang, “Synergistic Antitumor Effect of Andrographolide and Cisplatin Through ROS-Mediated ER Stress and STAT3 Inhibition in Colon Cancer,” *Medical Oncology* 39, no. 5 (2022): 101.
225. X. X. Chen, S. Khyeam, Z. J. Zhang, and K. Y. Zhang, “Granatin B and Punicalagin From Chinese Herbal Medicine Pomegranate Peels Elicit Reactive Oxygen Species-Mediated Apoptosis and Cell Cycle Arrest in Colorectal Cancer Cells,” *Phytomedicine* 97 (2022): 153923.
226. A. H. Kwok, Y. Wang, and W. S. Ho, “Cytotoxic and Pro-Oxidative Effects of *Imperata cylindrica* Aerial Part Ethyl Acetate Extract in Colorectal Cancer In Vitro,” *Phytomedicine* 23, no. 5 (2016): 558–565, <https://doi.org/10.1016/j.phymed.2016.02.015>.
227. Y. Wang, Q. Tang, S. Jiang, M. Li, and X. Wang, “Anti-Colorectal Cancer Activity of Macrostemnoside A Mediated by Reactive Oxygen Species,” *Biochemical and Biophysical Research Communications* 441, no. 4 (2013): 825–830.
228. C. X. Wang, L. H. Chen, H. B. Zhuang, et al., “Auricularin Enhances ROS Generation to Regulate Colorectal Cancer Cell Apoptosis, Ferroptosis, Oxidative Stress, Invasion and Colony Formation,” *Biochemical and Biophysical Research Communications* 587 (2022): 99–106.
229. O. Cheraghi, G. Dehghan, M. Mahdavi, et al., “Potent Anti-Angiogenic and Cytotoxic Effect of Conferone on Human Colorectal Adenocarcinoma HT-29 Cells,” *Phytomedicine* 23, no. 4 (2016): 398–405.
230. Q. Zhao, J. Zhong, Y. Bi, et al., “Gambogic Acid Induces Noxa-Mediated Apoptosis in Colorectal Cancer Through ROS-Dependent Activation of IRE1 α /JNK,” *Phytomedicine* 78 (2020): 153306.
231. Y. M. Zheng, J. Z. Shen, Y. Wang, A. X. Lu, and W. S. Ho, “Anti-Oxidant and Anti-Cancer Activities of *Angelica dahurica* Extract via

- Induction of Apoptosis in Colon Cancer Cells,” *Phytomedicine* 23, no. 11 (2016): 1267–1274.
232. J. Liang, C. Yang, P. Li, et al., “Astragaloside IV Inhibits AOM/DSS-Induced Colitis-Associated Tumorigenesis via Activation of PPAR γ Signaling in Mice,” *Phytomedicine* 121 (2023): 155116.
233. X. Wang, S. M. Saud, X. Zhang, W. Li, and B. Hua, “Protective Effect of Shaoyao Decoction Against Colorectal Cancer via the Keap1-Nrf2-ARE Signaling Pathway,” *Journal of Ethnopharmacology* 241 (2019): 111981.
234. X. Wang, S. M. Saud, F. Wang, et al., “Protective Effect of ShaoYao Decoction on Colitis-Associated Colorectal Cancer by Inducing Nrf2 Signaling Pathway,” *Journal of Ethnopharmacology* 252 (2020): 112600.
235. H. Li, Z. Ye, G. Zheng, and Z. Su, “Polysaccharides Targeting Autophagy to Alleviate Metabolic Syndrome,” *International Journal of Biological Macromolecules* 283, no. Pt 1 (2024): 137393.
236. Z. Zhang, Y. Zhao, Y. Wang, Y. Zhao, and J. Guo, “Autophagy/Ferroptosis in Colorectal Cancer: Carcinogenic View and Nanoparticle-Mediated Cell Death Regulation,” *Environmental Research* 238, no. Pt 2 (2023): 117006.
237. S. N. Devenport, R. Singhal, M. D. Radyk, et al., “Colorectal Cancer Cells Utilize Autophagy to Maintain Mitochondrial Metabolism for Cell Proliferation Under Nutrient Stress,” *JCI Insight* 6, no. 14 (2021): e138835.
238. Y. Xuan, S. Zhao, X. Xiao, L. Xiang, and H. C. Zheng, “Inhibition of Chaperone-Mediated Autophagy Reduces Tumor Growth and Metastasis and Promotes Drug Sensitivity in Colorectal Cancer,” *Molecular Medicine Reports* 23, no. 5 (2021): 360.
239. F. Burada, E. R. Nicoli, M. E. Ciurea, D. C. Uscatu, M. Ioana, and D. I. Gheonea, “Autophagy in Colorectal Cancer: An Important Switch From Physiology to Pathology,” *World Journal of Gastrointestinal Oncology* 7, no. 11 (2015): 271–284.
240. Y. Wu, J. Yao, J. Xie, et al., “The Role of Autophagy in Colitis-Associated Colorectal Cancer,” *Signal Transduction and Targeted Therapy* 3, no. 1 (2018): 31.
241. K. Athamneh, H. E. Hasasna, H. A. Samri, 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,” *Scientific Reports* 7, no. 1 (2017): 11633.
242. K. Hamze, R. H. Abdallah, N. K. Younis, et al., “2-Nucleobase-Substituted 4,6-Diaminotriazine Analogs: Synthesis and Anti-Cancer Activity in 5-Fluorouracil-Sensitive and Resistant Colorectal Cancer Cells,” *Current Medicinal Chemistry* 30, no. 26 (2023): 3032–3049.
243. Z. N. Nizami, M. Al Azzani, S. Khaldi, et al., “*Rhus coriaria* (Sumac) Induces Autophagic Cell Death and Inhibits mTOR, p38MAPK and STAT3 Pathways in 5-Fluorouracil-Resistant Colorectal Cancer Cells,” *Frontiers in Pharmacology* 16 (2025): 1542204.
244. N. Benhalilou, H. Alsamri, A. Alneyadi, et al., “*Origanum majorana* Ethanolic Extract Promotes Colorectal Cancer Cell Death by Triggering Abortive Autophagy and Activation of the Extrinsic Apoptotic Pathway,” *Frontiers in Oncology* 2019 (2019): 9.
245. K. Athamneh, A. Alneyadi, H. Alsamri, et al., “*Origanum majorana* Essential Oil Triggers p38 MAPK-Mediated Protective Autophagy, Apoptosis, and Caspase-Dependent Cleavage of P70S6K in Colorectal Cancer Cells,” *Biomolecules* 10, no. 3 (2020): 412.
246. H. D. Jeon, Y. H. Han, J. G. Mun, et al., “Dehydroevodiamine Inhibits Lung Metastasis by Suppressing Survival and Metastatic Abilities of Colorectal Cancer Cells,” *Phytomedicine* 96 (2022): 153809.
247. X. Xiang, Y. Tian, J. Hu, et al., “Fangchinoline Exerts Anticancer Effects on Colorectal Cancer by Inducing Autophagy via Regulation AMPK/mTOR/ULK1 Pathway,” *Biochemical Pharmacology* 186 (2021): 114475.
248. Y. Wang, T. Zhao, C. Huang, et al., “Effect and Mechanism of Banxia Xiexin Decoction in Colorectal Cancer: A Network Pharmacology Approach,” *Phytomedicine* 123 (2024): 155174.
249. J. Sun, M. Li, T. Lin, et al., “Cell Cycle Arrest Is an Important Mechanism of Action of Compound Kushen Injection in the Prevention of Colorectal Cancer,” *Scientific Reports* 12, no. 1 (2022): 4384.
250. R. H. Gong, D. J. Yang, H. Y. Kwan, A. P. Lyu, G. Q. Chen, and Z. X. Bian, “Cell Death Mechanisms Induced by Synergistic Effects of Halofuginone and Artemisinin in Colorectal Cancer Cells,” *International Journal of Medical Sciences* 19, no. 1 (2022): 175–185.
251. L. T. Lin, W. C. Uen, C. Y. Choong, et al., “Paris Polyphylla Inhibits Colorectal Cancer Cells via Inducing Autophagy and Enhancing the Efficacy of Chemotherapeutic Drug Doxorubicin,” *Molecules* 24, no. 11 (2019): 2102.
252. L. Shang, Y. Wang, J. Li, et al., “Mechanism of Sijunzi Decoction in the Treatment of Colorectal Cancer Based on Network Pharmacology and Experimental Validation,” *Journal of Ethnopharmacology* 302, no. Pt A (2023): 115876.
253. X. Zhu, S. Q. Lin, J. Xie, et al., “Biomarkers of Lymph Node Metastasis in Colorectal Cancer: Update,” *Frontiers in Oncology* 14 (2024): 1409627.
254. A. Cañellas-Socias, E. Sancho, and E. Batlle, “Mechanisms of Metastatic Colorectal Cancer,” *Nature Reviews. Gastroenterology & Hepatology* 21, no. 9 (2024): 609–625.
255. Y. Liu, L. Lu, P. Cheng, et al., “Wogonin Inhibits Colorectal Cancer Proliferation and Epithelial Mesenchymal Transformation by Suppressing Phosphorylation in the AKT Pathway,” *American Journal of Chinese Medicine* 52, no. 4 (2024): 1155–1172, <https://doi.org/10.1142/S0192415X24500460>.
256. G. Feng, L. Zhang, W. Bao, et al., “Gentisic Acid Prevents Colorectal Cancer Metastasis via Blocking GPR81-Mediated DEPDC5 Degradation,” *Phytomedicine* 129 (2024): 155615.
257. J. Y. Zhou, C. Wu, Z. Shen, et al., “Yiqi Huayu Jiedu Decoction Inhibits Liver Metastasis of Colorectal Cancer via Enhancing Natural Killer Cells Function,” *Journal of Ethnopharmacology* 318, no. Pt A (2024): 116915.
258. J. Wei, Z. Zheng, X. Hou, et al., “Echinacoside Inhibits Colorectal Cancer Metastasis via Modulating the Gut Microbiota and Suppressing the PI3K/AKT Signaling Pathway,” *Journal of Ethnopharmacology* 318, no. Pt A (2024): 116866.
259. Q. H. Huang, J. Zhang, W. C. S. Cho, et al., “Brusatol Suppresses the Tumor Growth and Metastasis of Colorectal Cancer via Upregulating ARDC4 Expression Through Modulating PI3K/YAP1/TAZ Pathway,” *Phytomedicine* 109 (2023): 154567.
260. Z. Q. Liang, Y. Bian, J. F. Gu, 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* 114 (2023): 154772.
261. F. Liu, Y. Liang, R. Sun, 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,” *Chinese Medicine* 17, no. 1 (2022): 91, <https://doi.org/10.1186/s13020-022-00641-4>.
262. F. Hou, W. Li, Q. Shi, et al., “Yi Ai Fang, a Traditional Chinese Herbal Formula, Impacts the Vasculogenic Mimicry Formation of Human Colorectal Cancer Through HIF-1 α and Epithelial Mesenchymal Transition,” *BMC Complementary and Alternative Medicine* 16, no. 1 (2016): 428.
263. Q. Ji, X. Liu, Z. Han, et al., “Resveratrol Suppresses Epithelial-To-Mesenchymal Transition in Colorectal Cancer Through TGF- β 1/Smads Signaling Pathway Mediated Snail/E-Cadherin Expression,” *BMC Cancer* 15 (2015): 97.
264. L. Gao, Y. Feng, C. Ge, et al., “Identification of Molecular Anti-Metastasis Mechanisms of Lycorine in Colorectal Cancer by RNA-Seq Analysis,” *Phytomedicine* 85 (2021): 153530.

265. Y. Lu, T. Guan, S. Xu, et al., "Asperuloside Inhibited Epithelial-Mesenchymal Transition in Colitis Associated Cancer via Activation of Vitamin D Receptor," *Phytomedicine* 101 (2022): 154070.
266. R. Li, H. Chi, X. Liao, S. Cen, and Y. Zou, "The Glabridin From Huangqin Decoction Prevents the Development of Ulcerative Colitis Into Colitis-Associated Colorectal Cancer by Modulating MMP1/MMP3 Activity," *International Immunopharmacology* 135 (2024): 112262.
267. G. Dai, B. Sun, T. Gong, Z. Pan, Q. Meng, and W. Ju, "Ginsenoside Rb2 Inhibits Epithelial-Mesenchymal Transition of Colorectal Cancer Cells by Suppressing TGF- β /Smad Signaling," *Phytomedicine* 56 (2019): 126–135.
268. İ. Taş, J. Han, S. Y. Park, et al., "Physciosporin Suppresses the Proliferation, Motility and Tumourigenesis of Colorectal Cancer Cells," *Phytomedicine* 56 (2019): 10–20.
269. C. H. Chan, Y. H. Deng, B. Y. Peng, et al., "Anti-Colorectal Cancer Effects of Fucoidan Complex-Based Functional Beverage Through Retarding Proliferation, Cell Cycle and Epithelial-Mesenchymal Transition Signaling Pathways," *Integrative Cancer Therapies* 22 (2023): 15347354231213613.
270. K. Lee, S. G. Cho, Y. K. Choi, et al., "Herbal Prescription, Danggui-Sayuk-Ga-Osuyu-Senggang-Tang, Inhibits TNF- α -Induced Epithelial-Mesenchymal Transition in HCT116 Colorectal Cancer Cells," *International Journal of Molecular Medicine* 41, no. 1 (2018): 373–380.
271. Y. Panahi, M. Saberi-Karimian, O. Valizadeh, et al., "Effects of Curcuminoids on Systemic Inflammation and Quality of Life in Patients With Colorectal Cancer Undergoing Chemotherapy: A Randomized Controlled Trial," *Advances in Experimental Medicine and Biology* 1328 (2021): 1–9.
272. Z. Y. He, C. B. Shi, H. Wen, F. L. Li, B. L. Wang, and J. Wang, "Upregulation of p53 Expression in Patients With Colorectal Cancer by Administration of Curcumin," *Cancer Investigation* 29, no. 3 (2011): 208–213.
273. W. T. Chen, T. S. Yang, H. C. Chen, et al., "Effectiveness of a Novel Herbal Agent MB-6 as a Potential Adjunct to 5-Fluoracil-Based Chemotherapy in Colorectal Cancer," *Nutrition Research* 34, no. 7 (2014): 585–594, <https://doi.org/10.1016/j.nutres.2014.06.010>.
274. G. R. Irving, L. M. Howells, S. Sale, et al., "Prolonged Biologically Active Colonic Tissue Levels of Curcumin Achieved After Oral Administration—A Clinical Pilot Study Including Assessment of Patient Acceptability," *Cancer Prevention Research* 6, no. 2 (2013): 119–128, <https://doi.org/10.1158/1940-6207.CAPR-12-0281>.
275. R. A. Sharma, S. A. Euden, S. L. Platton, et al., "Phase I Clinical Trial of Oral Curcumin: Biomarkers of Systemic Activity and Compliance," *Clinical Cancer Research* 10, no. 20 (2004): 6847–6854.
276. M. I. James, C. Iwuji, G. Irving, et al., "Curcumin Inhibits Cancer Stem Cell Phenotypes in Ex Vivo Models of Colorectal Liver Metastases, and Is Clinically Safe and Tolerable in Combination With FOLFOX Chemotherapy," *Cancer Letters* 364, no. 2 (2015): 135–141.
277. L. M. Howells, C. O. O. Iwuji, G. R. B. Irving, et al., "Curcumin Combined With FOLFOX Chemotherapy Is Safe and Tolerable in Patients With Metastatic Colorectal Cancer in a Randomized Phase IIa Trial," *Journal of Nutrition* 149, no. 7 (2019): 1133–1139.
278. K. R. Patel, V. A. Brown, D. J. Jones, et al., "Clinical Pharmacology of Resveratrol and Its Metabolites in Colorectal Cancer Patients," *Cancer Research* 70, no. 19 (2010): 7392–7399, <https://doi.org/10.1158/0008-5472.CAN-10-2027>.
279. L. M. Howells, D. P. Berry, P. J. Elliott, et al., "Phase I Randomized, Double-Blind Pilot Study of Micronized Resveratrol (SRT501) in Patients With Hepatic Metastases—Safety, Pharmacokinetics, and Pharmacodynamics," *Cancer Prevention Research* 4, no. 9 (2011): 1419–1425.
280. Y. X. Chen, Q. Y. Gao, T. H. Zou, et al., "Berberine Versus Placebo for the Prevention of Recurrence of Colorectal Adenoma: A Multicentre, Double-Blinded, Randomised Controlled Study," *Lancet Gastroenterology & Hepatology* 5, no. 3 (2020): 267–275.
281. J. Venkatesan, S. S. Murugan, and G. H. Seong, "Fucoidan-Based Nanoparticles: Preparations and Applications," *International Journal of Biological Macromolecules* 217 (2022): 652–667.
282. H. L. Tsai, Y. S. Yeh, P. J. Chen, et al., "The Auxiliary Effects of Low-Molecular-Weight Fucoidan in Locally Advanced Rectal Cancer Patients Receiving Neoadjuvant Concurrent Chemoradiotherapy Before Surgery: A Double-Blind, Randomized, Placebo-Controlled Study," *Integrative Cancer Therapies* 22 (2023): 15347354231187153, <https://doi.org/10.1177/15347354231187153>.
283. H. L. Tsai, C. J. Tai, C. W. Huang, F. R. Chang, and J. Y. Wang, "Efficacy of Low-Molecular-Weight Fucoidan as a Supplemental Therapy in Metastatic Colorectal Cancer Patients: A Double-Blind Randomized Controlled Trial," *Marine Drugs* 15, no. 4 (2017): 122.
284. J. Levin, S. Maaß, M. Schuberth, et al., "Safety and Efficacy of Epigallocatechin Gallate in Multiple System Atrophy (PROMESA): A Randomised, Double-Blind, Placebo-Controlled Trial," *Lancet Neurology* 18, no. 8 (2019): 724–735.
285. H. Hoensch, B. Groh, L. Edler, and W. Kirch, "Prospective Cohort Comparison of Flavonoid Treatment in Patients With Resected Colorectal Cancer to Prevent Recurrence," *World Journal of Gastroenterology* 14, no. 14 (2008): 2187–2193.
286. C. M. Shin, D. H. Lee, A. Y. Seo, et al., "Green Tea Extracts for the Prevention of Metachronous Colorectal Polyps Among Patients Who Underwent Endoscopic Removal of Colorectal Adenomas: A Randomized Clinical Trial," *Clinical Nutrition* 37, no. 2 (2018): 452–458.
287. F. A. Sinicrope, T. R. Viggiano, N. S. Buttar, et al., "Randomized Phase II Trial of Polyphenon E Versus Placebo in Patients at High Risk of Recurrent Colonic Neoplasia," *Cancer Prevention Research* 14, no. 5 (2021): 573–580.
288. T. Zhang, Y. Xu, L. Y. Sun, et al., "Efficacy of Quxie Capsule in Metastatic Colorectal Cancer: Long-Term Survival Update of A Double-Blind, Randomized, Placebo Controlled Trial," *Chinese Journal of Integrative Medicine* 28, no. 11 (2022): 971–974.
289. T. Zhang, Y. F. Yang, B. He, D. H. Yi, J. Hao, and D. Zhang, "Efficacy and Safety of Quxie Capsule () in Metastatic Colorectal Cancer: A Double-Blind Randomized Placebo Controlled Trial," *Chinese Journal of Integrative Medicine* 24, no. 3 (2018): 171–177.
290. X. Geng, Z. Wang, L. Feng, et al., "Efficacy and Safety of Xian-Lian-Jie-Du Optimization Decoction as an Adjuvant Treatment for Prevention of Recurrence in Patients With Stage IIIB/IIIC Colon Cancer: Study Protocol for a Multicentre, Randomized Controlled Trial," *BMC Complementary Medicine and Therapies* 23, no. 1 (2023): 239.
291. F. X. Lin, L. F. Tian, C. Y. Lei, C. C. Ding, L. Shi, and S. F. Zhang, "Chinese Medicine for Outcomes in Colorectal Cancer Patients: A Retrospective Clinical Study," *Chinese Journal of Integrative Medicine* 23, no. 9 (2017): 648–653.
292. Z. Wu, X. Fu, H. Jing, et al., "Herbal Medicine for the Prevention of Chemotherapy-Induced Nausea and Vomiting in Patients With Advanced Colorectal Cancer: A Prospective Randomized Controlled Trial," *Journal of Ethnopharmacology* 325 (2024): 117853.
293. M. Ni, Y. Zhang, Z. Sun, et al., "Efficacy and Safety of Shenbai Granules for Recurrent Colorectal Adenoma: A Multicenter Randomized Controlled Trial," *Phytomedicine* 127 (2024): 155496.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.