

Therapeutic potentials of plant-based antioxidants on colorectal cancer: Challenges and perspectives (Review)

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Abstract. Colorectal cancer (CRC) represents a major malignancy within the digestive tract, with its incidence and mortality rates steadily increasing annually, posing a severe threat to human health. Despite the extensive clinical utilization of diverse chemotherapeutic agents, their propensity for deleterious side effects and the emergence of drug resistance can impede patient compliance, consequently culminating in chemotherapy failure. Consequently, the quest for novel therapeutic agents with high efficacy and minimal toxicity has become increasingly urgent. To address this critical clinical dilemma, there is an imperative need to develop effective and well-tolerated anti-CRC drugs. Plant-based antioxidants (PBAs) are now understood to possess diverse biological activities, thereby offering significant advantages with respect to clinical anti-CRC applications. Compared with synthetic chemical agents, they are ubiquitous in natural sources, possess high safety profiles and can act as detoxifying or sensitizing agents when combined with conventional therapies in CRC, such as chemotherapy or radiotherapy. Hence, the present review systematically reviewed current research on PBAs for

CRC treatment from the perspective of bioactive compounds, with the aim of offering theoretical foundations and reference values for future studies and clinical applications of PBAs in CRC therapies.

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1. Introduction

Colorectal cancer (CRC) represents one of the most prevalent malignancies of the digestive tract. In 2020, CRC emerged as the third most diagnosed cancer worldwide and ranked second among global cancer mortality factors (1). Due to its insidious onset, most CRC patients present with advanced-stage disease at initial diagnosis, which limits opportunities for curative interventions such as surgical resection and local ablation (2). Consequently, the development and establishment of efficient multimodal therapeutic strategies have emerged as a research hotspot globally.

Current therapeutic modalities for CRC primarily encompass surgical resection, radiotherapy, chemotherapy and targeted therapy, which have demonstrably provided symptomatic relief, prolonged survival and improved the life quality of patients. However, adjuvant pharmacological treatment regimens for CRC, using chemotherapeutic agents such as irinotecan hydrochloride, 5-fluorouracil (5-FU), oxaliplatin and cetuximab, frequently induce irreversible damage to normal tissues and organs, accompanied by severe adverse

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reactions and toxic side effects (3). For instance, 5-FU administration may precipitate severe gastrointestinal reactions that exacerbate mucosal damage and related symptomatology (4). In addition, the emergence of drug resistance to cetuximab has progressively become a major clinical challenge requiring urgent attention (5). Therefore, developing effective yet low-toxicity therapeutic agents for CRC may constitute a pivotal strategy to enhance overall treatment efficacy.

Recent researches have elucidated that the pathogenesis of CRC involves the dysregulation of a number of cascading signaling pathways, including signal transducer and activator of transcription 3 (STAT3), transforming growth factor- β (TGF- β), phosphoinositide 3-kinase/protein kinase (PI3K/Akt) and Wnt/ β -catenin, characterized by aberrant silencing or activation of specific targets (6). However, current pharmacological interventions for CRC predominantly focus on single-target therapies. While acknowledging the clinical efficacy of specific single-target agents in CRC management (such as immune checkpoint inhibitors), monotherapy targeting individual signaling cascades or biological markers generally fail to achieve optimal therapeutic outcomes. Naturally derived phytochemicals exhibit marked advantages in modulating signal transduction cascades through multi-target, multi-pathway and multi-effect mechanisms, thereby enhancing treatment efficacy and quality of life in CRC patients while effectively preventing recurrence and potentiating targeted drug performance (7). Notable examples include paclitaxel, the first plant-derived chemotherapeutic agent and camptothecin, another plant-based antineoplastic alkaloid, have shown promising clinical applications. These instances underscore the growing significance of natural product-derived chemicals in anticancer drug discovery and research.

Chronic inflammation and oxidative stress-induced damage are closely implicated in the initiation and progression of CRC. Under physiological conditions, the balanced production of reactive oxygen species (ROS) and their elimination by endogenous antioxidants maintains the body's oxidative-antioxidant equilibrium. However, during pathological states, various environmental and endogenous stressors stimulate excessive ROS generation, disrupting this equilibrium and triggering oxidative stress. The resultant oxidative stress induces macromolecular oxidation of proteins, lipids and DNA/RNA, leading to lipid peroxidation of biomembranes, denaturation of intracellular proteins and enzymes and DNA damage. These alterations compromise intestinal mucosal barrier integrity, ultimately promoting mucosal injury, colitis and colorectal carcinogenesis (8,9).

Over the past decade, numerous plant-based antioxidants (PBAs) with anticancer properties have been identified, such as curcumin and epigallocatechin gallate (EGCG) (10). Chemically, PBAs under investigation for CRC therapy comprise diverse structural classes including phenolics, polysaccharides, alkaloids and terpenoids (Fig. 1). While these monomer compounds have demonstrated promising antitumor activities in epidemiological, *in vitro* and preclinical studies across various malignancies, their combinatorial application in CRC chemotherapy remains underexplored and the precise synergistic antitumor mechanisms remain incompletely elucidated (11). As oncology enters the era of precision medicine, effective integration of research on PBAs against CRC to

maximize their therapeutic potential represents an urgent priority in fundamental research.

The present review elucidated the preventive and therapeutic effects of PBAs on the occurrence and progression of CRC from the foundational cellular mechanisms and clinical research. Various types of PBAs play roles by regulating the signaling pathways related to CRC and modulating the expression of target genes involved in these pathways. Rather than focusing solely on a class of plant compounds or herbal medicines that modulate the gut microbiota of CRC (12,13), the present review comprehensively detailed the classification and therapeutic effects of various plant-derived antioxidant monomer components with anti-CRC properties. The present review also provided a more comprehensive theoretical basis for further understanding of the molecular mechanism of PBAs in the treatment of CRC. Additionally, there are few clinical studies on the prevention and treatment of CRC using PBAs and they are still facing bioavailability and safety problems. Different drug delivery strategies and individualized treatment concepts have been developed and the present review highlighted and emphasized the limitations and challenges of current progress. It requires further investigation to explore and promote the efficacy of PBAs in CRC.

2. Foundational mechanisms of plant-based antioxidants

Antioxidant and redox homeostasis. The mutation and transformation of normal tissue cells into cancerous cells can be triggered by the accumulation of free radicals during early stages, with oxygen-derived free radicals subsequently participating in cancer progression. Free radicals produced by *Enterococcus* bacteria in the colon may directly induce colonic DNA mutations, thereby contributing to CRC development (14). Oxidative stress is widely thought to promote intestinal epithelial cell damage by inducing genetic instability, specific gene alterations and aberrant methylation, creating opportunities for colorectal carcinogenesis. Excessive ROS generation triggers tissue or intracellular oxidative stress, further inducing oxidative DNA damage. Increased DNA damage stimulates the uptake of ω -polyunsaturated fatty acids as a compensatory response (15). Concurrently, ROS activates both intrinsic mitochondrial-mediated and extrinsic death receptor-mediated apoptosis pathways, thereby promoting CRC initiation and progression (16).

Gingerol (6-Shogaol, 20 mg/kg/day, orally), compared with the control group [a mouse colorectal adenoma model induced by Azoxymethane (AOM) and dextran sulfate sodium (DSS)], reportedly demonstrates significant antioxidant stress effects by reducing levels of interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), lipid peroxidation, myeloperoxidase (MPO) and nitric oxide (NO), while markedly enhancing activities of superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) (17). These effects collectively promote redox homeostasis restoration in colonic tissues. Curcumin activates intracellular redox reactions to induce ROS generation, which upregulates apoptotic receptors on tumor cell membranes. In addition, curcumin enhances the expression and activity of p53, a tumor suppressor that inhibits proliferation and promotes apoptosis. This compound also potentially inhibits NF- κ B and COX-2 activities, both linked to overexpression

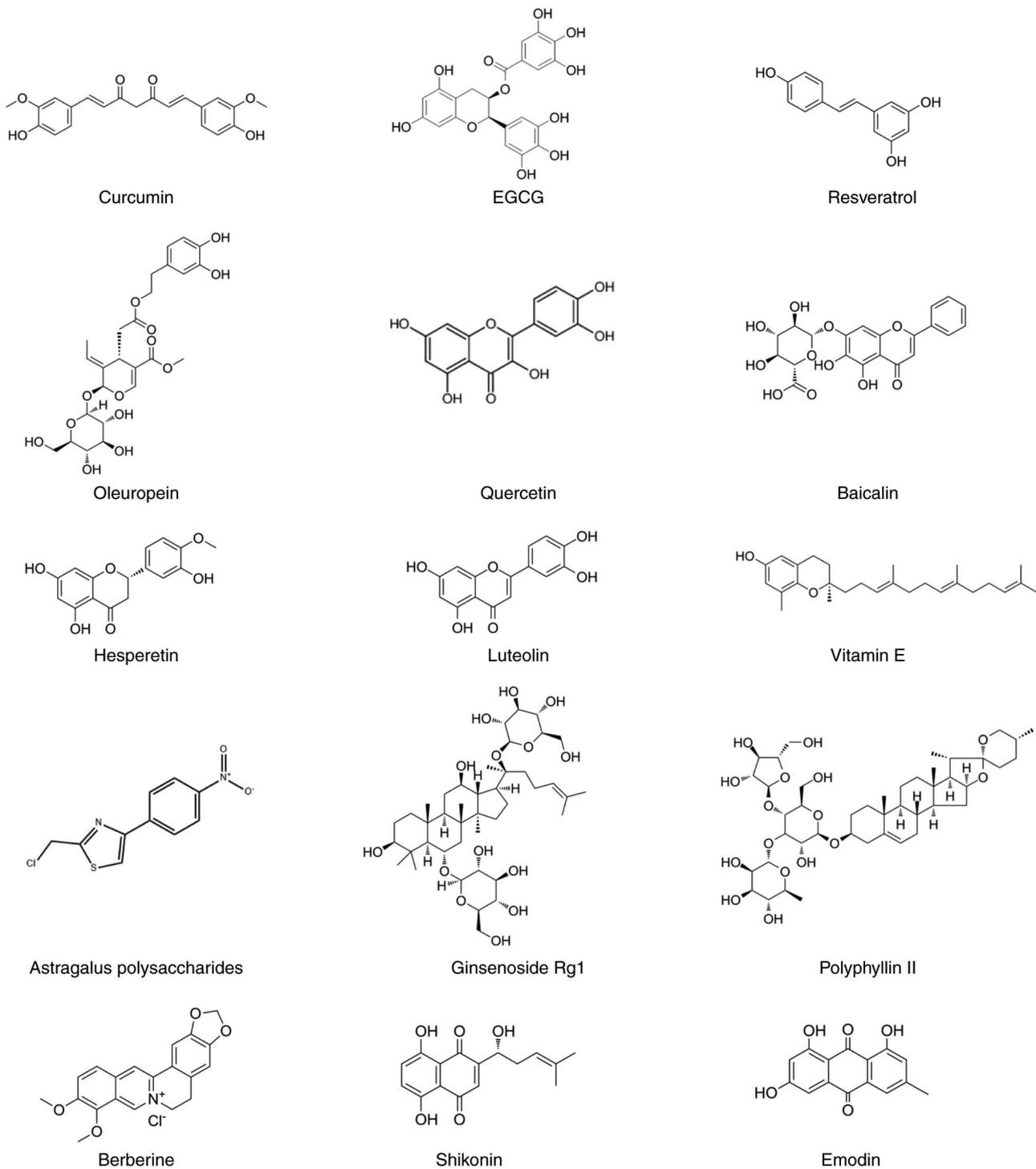


Figure 1. Representative plant-based antioxidants with anti-CRC effects. Polyphenols: Curcumin, EGCG, resveratrol, oleuropein, quercetin, baicalin, hesperetin, luteolin; Vitamins: Vitamin E; Polysaccharides: Astragalus polysaccharides; Saponins: Ginsenoside Rg1, polyphyllin II; Alkaloids: Berberine; Quinones: Shikonin, emodin.

of anti-apoptotic genes such as *Bcl-2*. Curcumin further attenuates pro-survival PI3K signaling while increasing mitogen-activated protein kinase (MAPK) expression, stimulating endogenous ROS production, which may activate a ROS/KEAP1/NRF2/miR-34a/b/c cascade to suppress colorectal cancer metastasis (18).

Anti-inflammatory and immunomodulatory effects. Colitis-associated CRC (CAC) is now understood to develop

from chronic inflammatory bowel disease (IBD) (19). During early intestinal inflammation and mucosal barrier disruption, luminal microbial antigens trigger immune cell chemotaxis to the colonic mucosa. These infiltrating cells secrete pro-inflammatory cytokines including IL-6, IL-1 β , TNF- α and interferon- γ (IFN- γ), establishing a chronic inflammatory microenvironment. Concurrently, immune-derived reactive oxygen/nitrogen species, such as inducible nitric oxide synthase (iNOS), induce colonic epithelial DNA damage (20).

Nuclear factor- κ B (NF- κ B) serves as a master regulator of inflammatory mediator production, with its hyperactivation critical for maintaining colonic inflammation and promoting epithelial dysplasia (21). Upon activation, inhibitors of NF- κ B (κ Bs) undergo phosphorylation and degradation, releasing the p65 subunit for nuclear translocation and pro-inflammatory gene transcription (22). To investigate the effect of Berberine (BBR) on intestinal inflammatory response in AOM/DSS-induced CAC mice, BBR (daily gavage of 100 mg/kg) markedly decreased the colonic levels of TNF α , IL-6 and IL-1 β compared with the CAC group (daily gavage of 100 μ l PBS). Furthermore, compared with the CAC group, the zonula occludens-1 (ZO-1), occludin and mucin-2 (MUC-2) mRNAs were markedly upregulated in response to BBR (23). These results indicated that BBR could improve colitis symptoms and epithelial injury in inflamed mucosa, inhibiting CAC development. Toll-like receptor 4 (TLR4), a pathogen recognition receptor expressed in colonic epithelia and lamina propria immune cells, activates downstream inflammatory pathways that exacerbate IBD-associated inflammation and tumorigenesis (24). Compared with the control group (constituting AOM/DSS-induced CAC mouse model), Rosmarinic acid (30 mg/kg/day; orally) markedly decreased 83.3% of the polypoid tumor number and inhibited COX-2 and iNOS protein levels *in vivo*. Furthermore, Rosmarinic acid (25 μ M) competitively antagonizes TLR4, blocking NF- κ B and STAT3 activation in HCT116 cells and HT29 cells exposed to the inflammatory microenvironment (25). This suppression reduces inflammatory mediator levels and confers chemo-preventive effects against CAC.

The intestine constitutes the most significant component of the human immune system, making the modulation of intestinal immune status to restore homeostasis a promising therapeutic approach for treating IBD and preventing CAC development. During intestinal inflammation, myeloid-derived suppressor cells (MDSCs) are recruited and activated in gut tissues, where they suppress dendritic cell antigen uptake/processing and subsequent CD4⁺ T cell proliferation/activation. This impairment compromises pathogen clearance at bacterial penetration sites, perpetuating chronic inflammatory stimuli (26). The resultant shift from acute to chronic inflammation creates a permissive microenvironment for tumor initiation.

Madecassic acid (MA), a triterpenoid compound isolated from *Centella asiatica*, blocks MDSC migration by inhibiting γ δ T17 cell activation and related chemokine expression. Compared with the control group (AOM/DSS mouse model) and the positive control group (5-amino-o-hydroxybenzoic acid, 5-ASA; 75 mg/kg/day, orally), orally administered of MA (25 mg/kg/day) can markedly weaken the severity of CAC and reduce the incidence of tumors and 5-ASA only delays the progression of tumors (27). This intervention enhances anti-tumor immunity and suppresses CAC progression. Curcumin (20 μ M) exerts dual actions by inducing CT26 tumor cell apoptosis and heat shock protein 70 expression while recruiting CD3⁺ T cells and F4/80⁺ macrophages to inhibit CRC growth (28). In addition, tumors from curcumin-treated rats (750 μ g/kg, i.p. on days 21 and 26) were infiltrated with numerous activated lymphocytes, compared with the control group (untreated). The proteome alterations showed that curcumin suppresses Foxp3 expression while enhancing

type II interferon production, skewing T cell differentiation toward Th1 phenotype and counteracting tumor immune evasion (29).

Cell cycle and apoptosis regulation. Dysregulation of cell cycle progression represents a critical mechanism underlying uncontrolled proliferation and malignant transformation of tumor cells, with aberrant activation of cell cycle checkpoints playing a pivotal role in this process. Overexpression of Cyclin D1 and Cyclin B1, key rate-limiting regulators for G₁/S and G₂/M phase transitions, respectively, disrupts cellular proliferation control, impairs differentiation and facilitates oncogenic progression (30). Consequently, targeted cell cycle arrest has emerged as a promising therapeutic avenue for cancer cell elimination. EGCG has been shown to downregulate mRNA expression of several cell cycle-related genes while enhancing expression of the cyclin-dependent kinase inhibitor p21 and apoptosis-associated death receptor 5 (31). Disrupted apoptotic processes compromise the equilibrium between apoptosis and proliferation in colonic epithelial cells, ultimately contributing to CRC development. It demonstrates that various PBAs exert anti-apoptotic effects via mitochondria-dependent apoptotic pathways, primarily by modulating the expression of cysteine-aspartic acid protease (caspase) family members and Bcl-2 family proteins (Fig. 2).

The cell viability assay showed that curcumin analogue, MS13 (1,5-Bis(4-hydroxy-3-methoxyphenyl)-1,4-pentadien e-3-one) has a greater cytotoxicity effect on SW480 (EC₅₀: 7.5 \pm 2.8 μ M) and SW620 (EC₅₀: 5.7 \pm 2.4 μ M), compared with curcumin (SW480, EC₅₀: 30.6 \pm 1.4 μ M) and SW620, EC₅₀: 26.8 \pm 2.1 μ M). Subsequent analysis indicated that MS13 induced apoptosis by enhancing caspase-3 activity while reducing Bcl-2 protein levels, thereby suppressing CRC cell growth (32). Furthermore, a significant proportion of these phytochemicals activate mitochondrial apoptosis by targeting aberrant signaling cascades within cancer cells, including the PI3K/Akt, MAPK/extracellular signal-regulated kinase (ERK) and p38 MAPK pathways (Fig. 2). In addition, it has been established that EGCG inhibits tumor cell growth and apoptosis through the PI3K-Akt-Cyclin D1 and p53 signaling axes. Its pro-apoptotic mechanism also involves suppression of fasciclin-like arabinogalactan protein-mediated Jun N-terminal kinase (JNK) signaling, leading to increased BAX/Bcl-2 ratio (31). These findings collectively underscore the multi-targeted therapeutic potential of PBAs in CRC management through coordinated regulation of apoptosis-related proteins and oncogenic signaling networks.

Epigenetic modifications and miRNA regulation. Recent investigations have elucidated the biological activities of EGCG in inhibiting DNA methyltransferase (DNMT) and microRNA expression, which play pivotal roles in cancer therapeutics (31). EGCG reportedly suppresses DNMT activity via radical scavenging and antioxidant mechanisms, leading to demethylation and upregulated expression of tumor suppressor genes *P16* and *P21*, ultimately inducing apoptosis and inhibiting tumorigenesis. Notably, treatment of EGCG (20 μ g/ml) to head and neck cancer cell lines markedly reduced DNMT activity to 60% in SCC-1 and 80% in FaDu cells. An *in vivo* study demonstrated that administration of EGCG (0.5%, w/w)

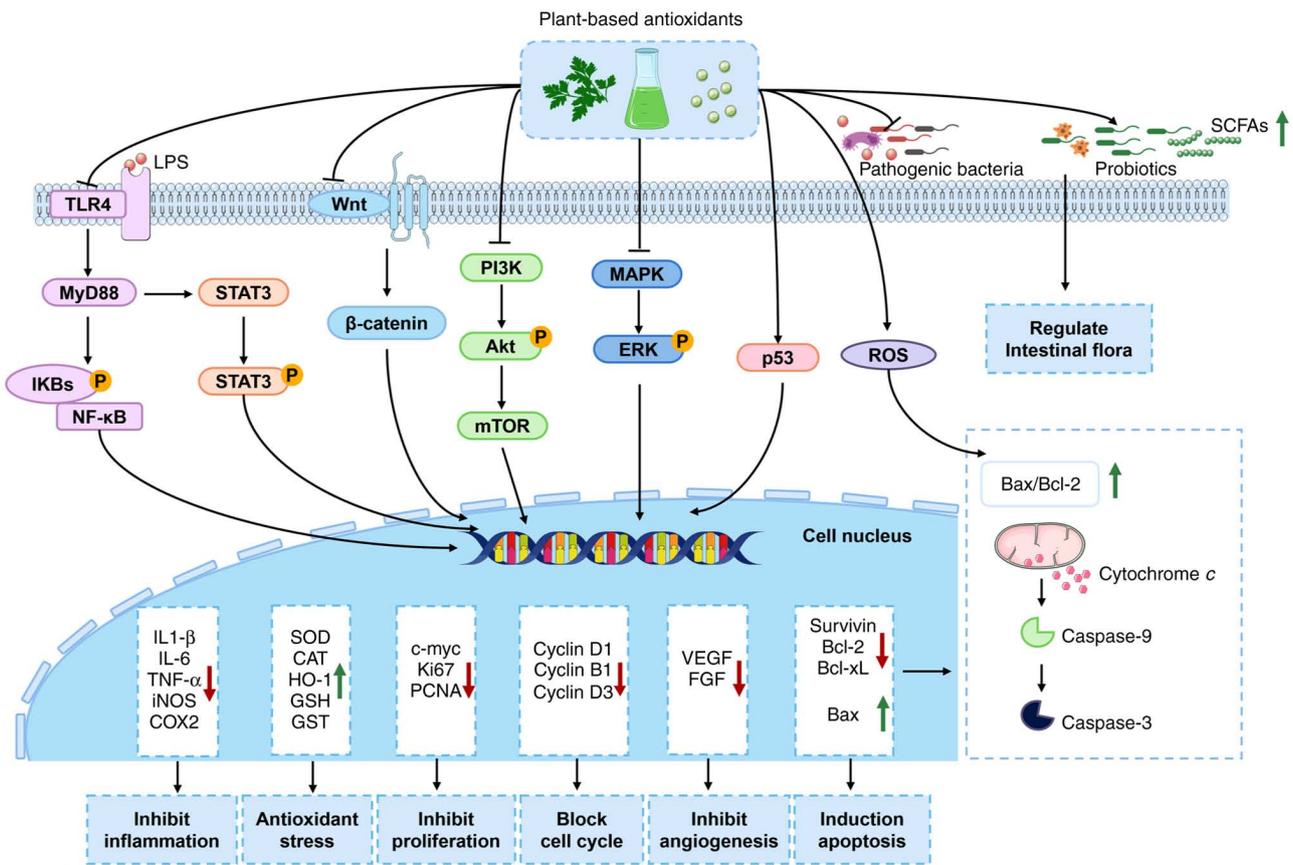


Figure 2. Signaling pathway diagram illustrating the mechanisms of plant-based antioxidants against CRC. Plant-based antioxidants exhibit significant efficacy in the prevention and treatment of CRC. Its molecular mechanisms of action encompass multi-targets, including NF- κ B, TLR4, Wnt/ β -catenin, PI3K/Akt and MAPK/ERK signaling pathways, which suppress chronic inflammation, alleviate oxidative stress, inhibit cell proliferation and angiogenesis, induce cell apoptosis and cell cycle arrest and regulate gut microbiota composition. CRC, colorectal cancer; NF- κ B, nuclear factor kappa-B; TLR4, toll-like receptor 4; PI3K/Akt, phosphoinositide 3-kinase/protein kinase; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinase; LPS, lipopolysaccharide; IKBs, inhibitors of NF- κ B; STAT3, signal transducer and activator of transcription 3; mTOR, mammalian target of rapamycin; ROS, reactive oxygen species; SCFAs, short chain fatty acids; iNOS, inducible nitric oxide synthase; COX2, cyclooxygenase-2; SOD, superoxide dismutase; CAT, catalase; HO-1, heme oxygenase 1; GSH, glutathione; GST, glutathione S-transferase; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor.

inhibited tumor growth in xenografts in nude mice (80%) compared with non-EGCG-treated controls (33).

During the progression of IBD, numerous miRNAs exhibit altered expression patterns and regulate the expression of related tumor suppressor genes and proto-oncogenes, exerting pro-carcinogenic effects by disrupting intestinal homeostasis. Substantial evidence supports the association between CAC and inflammation-induced aberrant miRNA expression. Pristimerin, a natural triterpenoid compound isolated from *Celastraceae* plants, alleviates intestinal inflammation symptoms in DSS-induced colitis models through intraperitoneal injection of 0.4 mg/kg daily for 5 days compared with the untreated model mice (34). This effect is mediated by inhibiting intestinal miRNA-155 expression and suppressing the NF- κ B signaling pathway. Resveratrol, a naturally occurring stilbene compound, has been reported to markedly inhibit LoVo and SW480 cell viability by 50% at the concentration of 50 μ M. Compared with control groups, Resveratrol treatment led to increased miR-769-5p expression and decreased MSI1 expression in CRC cells (35). This indicates that Resveratrol inhibits CRC cell proliferation and migration by activating the miR-769-5p/MSI1 pathway. The aforementioned studies overlap in their assertion that PBAs can attenuate intestinal

inflammation and suppress CRC by targeting miRNAs, highlighting the need for developing more miRNA-targeted small molecule therapeutics to expand clinical treatment options.

Gut microbiota regulation. CRC patients exhibit marked alterations in gut microbiota composition and distribution, characterized by reduced beneficial bacteria and increased pathogenic species. Pathogens such as *Escherichia coli*, *Fusobacterium*, *Streptococcus* and *Enterococcus* promote colorectal carcinogenesis by secretion of oncogenic metabolites that induce DNA damage, amplify inflammation and activate proliferative signaling pathways (36). Conversely, probiotics and their metabolites (such as short-chain fatty acids, SCFAs) exert chemopreventive effects via anti-mutagenesis, proliferation suppression, apoptosis induction, mucosal barrier enhancement, inflammatory microenvironment modulation and immune activation (37,38). Gut microbiota can produce ROS or stimulate intestinal epithelial cells to produce ROS, thereby promoting tumorigenesis and development (39).

PBAs have shown promise in alleviating gut dysbiosis in CRC animal models. Compared with the NC group, an AOM/DSS induced CRC model group (PBS, 150 mg/kg/day) exhibited a marked reduction in colon length and an

obvious increase in tumor count, while the curcumin treatment groups (CRC-Cur, 150 mg/kg/day) increased the length of the colon and markedly reduced the number of tumors. The intestinal flora and intestinal metabolites analysis showed that curcumin educed harmful bacteria (such as *Ileibacterium*, *Monoglobus* and *Desulfovibrio*) and increased the abundance of *Clostridia_UCG-014*, *Bifidobacterium* and *Lactobacillus* in AOM/DSS-induced CRC model mice (40). Patchouli essential oil (40 mg/kg/day) markedly reduced the number of polyps (47.14±15.66) compared with the control group (vehicle 0.5% carboxymethyl cellulose + 1% DMSO, 81.86±12.36) in Apc^{Min/+} mice while enhancing intestinal barrier integrity and alleviating the inflammatory microenvironment. This effect was associated with decreased abundance of pathogenic bacteria (*Desulfovibrio*, *Mycoplasma genitalium* and *Clostridium difficile*) and elevated fecal SCFAs, which upregulated SCFA receptors (GPR41, GPR43 and GPR109a) and peroxisome proliferator-activated receptor γ expression (41). Compared with a dextran sulfate sodium (DSS)-induced colitis group (daily gavage of PBS for 3 weeks with 2.5% DSS in drinking water for the last 6 days), an EGCG group (50 mg/kg) altered the gut microbiome of DSS-treated mice by increasing *Akkermansia* abundance and butyrate production. The alteration of gut microbiome further promotes anti-inflammatory effects and colonic barrier integrity (42). Current research on plant-based CRC prevention has mainly focused on microbiota modulation and metabolite production, with little emphasis on host-microbiota crosstalk mechanisms involving antitumor immunity and epithelial cell signaling. Accordingly, further investigations are warranted to elucidate these interactive pathways.

3. Unique anti-tumor effects of key plant-based antioxidants in CRC

Polyphenols

Curcumin. Curcumin, derived from the rhizome of *Curcuma longa* (turmeric), exhibits diverse biological activities including anti-cancer, antimicrobial, anti-inflammatory, antiviral, antioxidant, anti-aging, anti-diabetic and cardiovascular protective properties (43). Systematic meta-analyses show that curcumin has therapeutic potential for CRC, improves survival rates and enhances quality of life (44-46). Curcumin targets proliferating cancer stem-like cells (CSCs) within CRC premalignant adenoma and early-stage cancer tissues. Curcumin decreases the proportion of proliferating CSCs by direct binding to NANOG, thereby inhibiting tumor development (47). Moreover, Curcumin can inhibit CRC growth by inducing ferroptosis via regulation of p53 and SLC7A11/glutathione/GPX4 axis (48). Combining curcumin (50 μ M) and metformin (40 μ M) markedly suppresses the migration ability of HCT116 cells and promote ROS-induced cell death (49), which provides a potential option for CRC treatment. Overall, these findings indicate that curcumin plays an effective adjunct therapy for CRC on a number of molecular targets. However, its low bioavailability and rapid metabolism limit its clinical translation (46). Addressing these challenges through more studies, determining effective doses and improving formulations to enhance absorption is essential.

EGCG. The anti-cancer mechanisms of EGCG encompass angiogenesis inhibition, induction of tumor cell death and suppression of tumor growth.

EGCG downregulates the expression of HIF-1 α , HIF-1 β and VEGF in CRC cells, reducing tumor vascular density and effectively controlling tumor cell metastasis while inhibiting the PI3K/Akt signaling pathway (31). Furthermore, EGCG inhibits CRC cell proliferation and induces apoptosis by blocking the activation of the receptor tyrosine kinases family members EGFR, IGF-1R and VEGFR2 (50). In the Caco-2 cell line, EGCG (15 μ M) downregulates the expression of MMP-2 and MMP-9 through a NOX1/EGFR signaling pathway-dependent mechanism, while directly inhibiting the enzymatic activity of MMPs, thereby effectively suppressing tumor cell invasion and metastasis (51). A fibril composed of EGCG and lysozyme (EGCG-LYS) demonstrated excellent siRNA delivery efficiency in *in vitro* experiments. It could effectively silence the expression of circMAP2K2 (hsa_circRNA_102415), thereby inhibiting the epithelial-mesenchymal transition (EMT)-like phenotype generated by circMAP2K2 through the protease-mediated PCBP1/GPX1 axis, inhibiting the activated AKT/GSK3 β signaling pathway and achieving the goal of inhibiting the proliferation and metastasis of gastric cancer cells, which provides a new tool for the treatment of gastric cancer (52). Collectively, these findings demonstrate that EGCG effectively alleviates tumor angiogenesis and metastasis.

Apoptosis, a programmed cellular protective mechanism, represents the primary pathway for eliminating tumor cells through the induction of their programmed death. EGCG induces apoptosis in gastrointestinal tumor cells in a dose-dependent manner without affecting normal cell growth and it triggers cancer cell death through a number of pathways (31). Specifically, EGCG enhances the translocation of cytochrome *c* from the mitochondrial inner membrane to the cytoplasm, inhibits ATP synthesis, disrupts mitochondrial membrane potential, activates caspase cascades and promotes tumor cell apoptosis (53). Moreover, treatment with 10 μ g/ml EGCG for 24 h induced apoptosis and markedly suppressed the proliferation in CACO-2 and CW-2 cells. The miRNA analysis showed that the expression of hsa-miR-187-5p in CW-2 cells was markedly downregulated following EGCG treatment (54). An *in vitro* dosage of 6 μ M EGCG has an initial antagonistic effect on oxaliplatin cytotoxicity and increases the sensitivity of HCT116 and HT29 cells to subsequent oxaliplatin administration, which provides an adjunctive treatment for CRC with lower and safer doses of EGCG (55). EGCG also inhibits gastric cancer cell proliferation by targeting STAT3 to inhibit M2 macrophages polarization induced by PLXNC1-mediated exosomes (56). In an *in vivo* study, mice received intraperitoneal injections of EGCG at a dose of 50 μ g/kg (0.1 ml) developed markedly smaller tumors than the control group treated with 0.1 ml PBS alone (54). While EGCG primarily antagonizes gastrointestinal tumors by inducing tumor cell apoptosis, the methods of triggering such apoptosis are complex and diverse, with a number of underlying mechanisms remaining unclear. Elucidating the molecular mechanisms of tumor apoptosis represents one of the significant future directions in cancer research to more effectively induce this process. Furthermore, EGCG can be

administered orally or injected with an acceptable safety profile and its safe dose of antitumor effects still needs more reports.

Resveratrol. Resveratrol exerts multi-faceted effects on CRC through various mechanisms, including suppression of cell proliferation, inhibition of metastasis, induction of apoptosis, stimulation of autophagy, modulation of immune responses, alleviation of inflammation, regulation of gut microbiota and enhancement of other anticancer drug efficacy (57). The expression of pro-inflammatory cytokine tumor necrosis factor- β and its receptor activates nuclear transcription factor NF- κ B, which participates in CRC cell growth and proliferation. Compared with HCT116 and SW480 cells in the control groups, resveratrol (5 μ M) suppressed the cancer cell proliferation with the regulation of β 1-integrin/FAK/p65-NF- κ B pathway and cyclin D1-signaling. CRC cells treated with resveratrol markedly inhibited β 1-integrin expression and reduced the distribution of β 1-integrin receptors on the cell surface (58). In addition, high concentration (>10 μ M) of resveratrol disrupted interactions between CRC cells and stromal cells within the multicellular tumor microenvironment, triggering apoptosis through promoting hyperacetylation of p53 and FOXO3a as post-translational substrates of Sirt-1 in the CRC tumor microenvironment (59). Furthermore, resveratrol markedly reduced serine/threonine kinase 1/2/3 (Akt1/2/3) phosphorylation, downregulated bone morphogenetic protein expression via PI3K/Akt signaling inhibition, upregulated STATB2 to promote Bax-Caspase 3/9 apoptotic pathway protein expression in HCT116 cells and induced CRC cell apoptosis (60).

Oxidative stress has been established as a pro-carcinogenic factor and resveratrol alleviates oxidative stress by up-regulating antioxidant enzymes. Reports suggest that resveratrol achieves therapeutic efficacy by inhibiting SOD activity or activating Nrf2-mediated antioxidant signaling pathways, thereby suppressing oxidative stress in CRC. Resveratrol (10 μ mol/l) was found to activate Nrf2 and Sirt-1 to regulate cellular oxidation, reducing 5-FU-induced oxidative stress damage in normal cells at a 5 μ g/ml concentration, demonstrating a dose-response relationship (61). Furthermore, in a murine cardiotoxicity model established via intraperitoneal injection of 5-FU at 15, 30 and 60 mg/kg, resveratrol was found to attenuate myocardial cell toxicity induced by 5-FU, showing potential in mitigating cardiac damage associated with long-term high-dose 5-FU treatment for CRC (62). Sprague-Dawley rats that received oxaliplatin (2 mg/kg/day, cumulative dose: 6 mg/kg, i.p.) and oral resveratrol (7.14 mg/kg/day) was found not to develop mechanical allodynia or hypersensitivity, which inhibited upregulation of NF- κ B, TNF- α , AIF3 and excitatory neuronal promoter c-fos, while increasing expression of Nrf2, NQO-1, HO-1 and Sirt1. This combination restored the GSH/GSSG ratio, preventing and antagonizing chemotherapy-induced peripheral neuropathic pain (63).

Oleuropein. Oleuropein represents one of the primary phenolic compounds in olive leaf extracts. It has demonstrated that oleuropein exerts protective effects in acetic acid-induced ulcerative colitis in rats by inhibiting the production of intestinal inflammatory factors (64). There were three groups: Normal control, positive control (ulcerative colitis and untreated) and

oleuropein group (treated with intrarectal oleuropein at a dose of 350 mg/kg). Compared with the positive control group, oleuropein resulted in a significant reduction of MPO and NO levels and increased SOD, CAT and GPX levels in colon tissues. Moreover, the expression levels of pro-inflammatory cytokines (IL-1 β , TNF- α , IL-10, COX-2, iNOS and NF- κ B) were also decreased in the oleuropein group. In the intestinal tissues of rats treated with oleuropein, expression of the pro-apoptotic gene Bcl-2-associated X protein was reduced, while the anti-apoptotic gene *Bcl-2* was upregulated. These findings indicate that oleuropein alleviates inflammation by suppressing aberrant apoptosis of intestinal cells.

Flavonoids. Flavonoids represent a class of plant secondary metabolites characterized by a basic structure comprising two benzene rings interconnected via a three-carbon bridge, establishing a C6-C3-C6 configuration (65). Baicalin, a natural flavonoid, has been found to possess remarkable anti-CRC properties. Studies have revealed its capacity (at 100 μ g/ml) to induce cell cycle G₁ phase arrest in CRC cells, promote p53-independent apoptosis and suppress both endogenous and exogenous TGF- β 1-induced EMT via inhibition of the TGF- β /Smad pathway (66). In an *in vivo* test, orthotopic transplanted colon tumor model mice were randomly divided into negative control, positive control (25 mg/kg of 5-FU), low dose group (100 mg/kg of baicalin) and high dose group (200 mg/kg baicalin), respectively. The low-dose baicalin group exhibited markedly tumor inhibition rates (ratios of average tumor size of treated groups and negative control group) compared with those in both positive control and high-dose baicalin groups. Hesperetin, a flavonoid primarily derived from citrus fruits, has been reported to prevent DSS-induced colitis. The mice were randomly divided into four groups: control group, DSS group, hesperetin treated group (20 mg/kg, injected daily intraperitoneally) and DSS with hesperetin treated group (20 mg/kg, injected daily intraperitoneally). The DSS group showed a lower weight and colon length compared with the control group, while these changes were rescued by hesperetin treatment. Hesperetin enhances intestinal expression of ZO-1, occludin and MUC-2, while reducing TNF- α , IL-6, IL-18, HMGB1 and IL-1 β levels to exert intestinal protective effects (67). Further investigation revealed hesperetin's ability to decrease expression of receptor-interacting protein kinase 3 (RIPK3) and mixed lineage kinase domain-like protein (MLKL), two critical mediators of necroptosis pathways, suggesting its capacity to ameliorate DSS-induced intestinal inflammation through suppression of the RIPK3/MLKL necroptosis signaling cascade (67). This anti-inflammatory action preserves intestinal barrier homeostasis and inhibits intestinal tissue carcinogenesis driven by persistent inflammatory stimuli. Moreover, 50 or 100 mg/kg of luteolin has been found to markedly attenuate DSS-induced murine colitis symptoms compared with a DSS group, primarily by inhibiting JNK1/2, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling, NF- κ B and STAT3 pathways to exert anti-inflammatory, anti-apoptotic and anti-autophagic effects for colonic homeostasis restoration (68).

Vitamins. Defects in intestinal mucosal antioxidant defense constitute the initiating factor in the pathogenesis of IBD, with oxidative imbalance in the intestinal mucosa further associated

with disease activity and progression. Reduced plasma levels of vitamins A, E and β -carotene, coupled with decreased antioxidant enzyme activity in the intestinal mucosa, correlate with IBD severity and may serve as indicators of disease activity (69). Notably, vitamin E (δ -tocotrienol), a natural antioxidant, protects phagocytes and surrounding tissues from oxidative assault by free radicals generated from neutrophils and macrophages (70). This compound inhibits the elevation of free radicals produced during lipid and lipoprotein oxidative damage in IBD.

Polysaccharides. Polysaccharides, complex carbohydrate macromolecules formed through condensation and dehydration of a number of monosaccharide units, have recently attracted significant interest in their anti-CRC effects. Tao *et al.* (71) investigated the anti-tumor activities of *Dendrobium officinale* polysaccharides, *Astragalus* polysaccharides and *Lentinus edodes* polysaccharides with varying molecular weights using a zebrafish xenograft model. Compared with the model group (inhibition $0\pm 5.09\%$), the results indicated that all three polysaccharides inhibited the growth of HT29 cells in the xenograft model, with *Dendrobium officinale* polysaccharides ($250\ \mu\text{g/ml}$) exhibiting the most significant inhibitory effect on CRC ($67.91\pm 1.69\%$). Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis suggested that their primary mechanisms may involve immunomodulation and induction of apoptosis. *Astragalus* polysaccharides, a major bioactive component in *Astragalus membranaceus*, primarily consist of arabinose, galactose, glucose, xylose and mannose (72). Compared with the AOM/DSS control group, *in vivo* studies revealed that middle doses ($200\ \text{mg/kg}$) of *Astragalus* polysaccharides effectively improved CD8⁺ T cell function through modulation of the STAT3/Gal-3/LAG3 pathway to inhibit CRC development (73). These findings suggest that *Astragalus* polysaccharides may exert anti-CRC effects as a novel strategy for future clinical development of natural anti-tumor drugs.

Saponins. Ginsenoside Rg1, a bioactive component derived from the traditional Chinese medicine *Panax ginseng*, exerts therapeutic effects via modulation of various metabolic pathways of the gut microbiota, primarily by enhancing tryptophan metabolite levels to influence microbial tryptophan metabolism, thereby alleviating intestinal inflammation (74). Polyphyllin, a natural steroidal saponin derived from the traditional Chinese medicine *Paris polyphylla*, encompasses compounds such as Polyphyllin I, II, VI and VII, demonstrating significant anti-tumor, antimicrobial, antioxidant, sedative, analgesic, hemostatic, immunomodulatory and organ-protective effects, with particularly notable anti-tumor activities (75). Li *et al.* (76) found that the percentages of the apoptotic cells for HCT116 cells increased from 4.7-35.2% in the control group and the Polyphyllin II treated group ($4\ \mu\text{M}$) and for SW620 cells from 4.6-27.3% in the control group and the Polyphyllin II treated group. *In vivo* study showed Polyphyllin II (0.5 or $1\ \text{mg/kg}$, i.p. once every 3 days) suppressed HCT116 tumor growth in nude mice. Further mechanism study revealed that Polyphyllin II markedly induced G₂/M-phase cell cycle arrest and apoptosis and reduced the expression levels of phosphorylated (p-)PI3K, p-Akt and p-mTOR in HCT116 and SW620 cells, promoting

the expression of autophagy-related protein LC3B-II. Further increases in LC3B-II expression were observed upon treatment with the mTOR inhibitor rapamycin, indicating that Polyphyllin II induces tumor cell autophagy by inhibiting the PI3K/Akt/mTOR signaling pathway. Moreover, Polyphyllin II was found to induce tumor cell apoptosis by suppressing the Janus kinase 2/signal transducer and activator of STAT3 signaling pathway, exerting anti-CRC effects (76).

Alkaloids. Alkaloids are organic compounds containing one or more basic nitrogen atoms arranged in cyclic structures. Berberine, also known as berberrubine, is a quaternary ammonium isoquinoline alkaloid isolated from the traditional Chinese medicine *Coptis chinensis*, demonstrating diverse biological activities including anti-tumor, anti-oxidant, anti-inflammatory, cholesterol-lowering, anti-diabetic, anti-obesity and anti-microbial properties (77). Its anti-cancer effects and mechanisms have been extensively studied, establishing it as a potential anti-cancer drug candidate. It has been reported that berberine alleviates AOM/DSS-induced intestinal barrier damage in mice, thereby reducing microbial invasion (78). In the AOM/DSS mice model, berberine was daily administered with a dose of 50 and 100 mg/kg and aspirin was the positive control. Compared with the AOM/DSS model group, berberine markedly reduced the number and load of tumors in mice. Furthermore, berberine suppressed inflammation and CRC development by increasing the abundance of short-chain fatty acid-producing bacteria and decreasing pathogenic bacterial populations (78). By reshaping the gut microbiota composition, berberine increased the expression of occludin and ZO-1, inhibited the activation of the p-NF- κ B/p-STAT3 pathway, consequently impeding colorectal adenocarcinoma progression. Berberine's restorative mechanisms against oxidative stress-induced DNA damage have been demonstrated across murine models. In adenovirus-infected AOM/DSS mice administered with 28 mg/kg berberine for 5 weeks, berberine enhanced Dicer expression and reduced IL-6 expression, mitigating intestinal injury (79). Collectively, these findings indicate that berberine suppresses CRC progression by reducing inflammation-related chemotactic factors, enhancing antioxidant radical scavenging capacity and repairing DNA damage.

Terpenoids. Terpenoids represent a class of compounds composed of five-carbon isoprene units (C₅H₈), categorized based on the number of isoprene units into monoterpenes, sesquiterpenes, diterpenes, sesterterpenes, triterpenes, tetraterpenes and polyterpenes (80). Zingiberene, a sesquiterpene compound and the primary constituent of ginger essential oil, exhibits anti-cancer, antioxidant, antibacterial, anti-inflammatory and anti-angiogenic activities. In the aberrant crypt focus (ACF) rat model induced with 1.2 Dimethylhydrazine (DMH) at a 20 mg/kg dose, the experimental treatment group (DMH + Zingiberene at a 300 mg/kg concentration) showed decreased amount of AC in the distal region compared with the positive induction control group (81). It also has shown that zingiberene demonstrates specific activity against HT-29 cells with minimal effects on non-cancerous cells. It promotes the formation of autophagosomes in tumor cells, increasing

LC3-II expression and decreasing p62 expression to induce autophagy (82).

Quinones. There has been burgeoning research interest in the potential of various plant-based quinone bioactive compounds for CRC drug development due to their promising therapeutic efficacy. Shikonin, a naphthoquinone component primarily sourced from the traditional Chinese medicinal herb *Lithospermumerythrorhizon*, activates ROS-mediated endoplasmic reticulum stress to notably inhibit HCT116 cell proliferation. In addition, 1.5 μ M shikonin markedly inhibited the HCT116 cell colonies compared with the control group. In the HCT116 xenograft mouse model, a dose of 3 mg/kg (i.p.) shikonin effectively inhibited tumor growth by 52.3% *in vivo*. Moreover, shikonin downregulates Bcl-2 expression and activates cleavage of caspase3/9 and PARP to induce apoptosis (83). Emodin is a natural anthraquinone compound with antioxidant, anti-inflammatory and anti-tumor properties. In AOM/DSS-induced models, emodin (50 mg/kg) reduced recruitment of inflammatory cells, expression of cytokines and pro-inflammatory enzymes in the tumor microenvironment while enhancing CD3⁺ T lymphocyte levels. In addition, emodin decreased viability, migration and fibroblast-induced invasion capacity of SW-620 and HCT116 cells *in vitro* (84).

4. Current challenges and progress in clinical research

PBAs have shown promising therapeutic effects in CRC cell lines and animal models. Several clinical trials investigating the prevention and treatment of CRC with PBAs have been conducted (Table I). Carroll *et al* (85) assessed the effects of oral curcumin (2 g/day or 4 g/day for 30 days) on PGE2 within ACF in a nonrandomized, open-label clinical trial. Colonoscopy revealed no significant ACF reduction in the 2 g/day group, whereas the 4 g/day group showed a 40% reduction. Cruz-Correa *et al* (86) evaluated the regress adenomas effects of curcumin (480 mg/day) and quercetin (20 mg/day) in 5 post-colectomy familial adenomatous polyposis (FAP) patients. Colonoscopy demonstrated a 60.4% reduction in polyp number and a 50.9% decrease in size compared with baseline. While this study showed prominent therapeutic effects, a subsequent larger trial involving 44 FAP patients found no significant differences in polyp number or size (87). Panahi *et al* (88) assessed the effects of curcumin in 67 stage III CRC patients with chemotherapy after the surgery. The results demonstrated that 8-week curcuminoids capsules (500 mg daily) improved erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) levels, while also enhancing the quality of life in stage III CRC patients compared with the control group taking placebo capsules. The effect of curcumin on the prognosis of CRC patients remains unclear. Several completed clinical trials (NCT02439385, NCT01490996 and NCT01948661) are expected to provide further elucidation upon publication of their results.

Patel *et al* (89) enrolled 20 CRC patients who received 0.5 g or 1.0 g/day resveratrol for 8 days before surgery intervention. Post-intervention tissue analysis revealed a 5% reduction in tumor cell proliferation. Further clinical trials (NCT00256334 and NCT00433576) have been conducted, with the results eagerly expected.

Seufferlein *et al* (90) investigated EGCG's preventive effects on CRC, with 1,001 colon adenoma patients randomized to EGCG (150 mg/day) or placebo groups. At 3 years, colonoscopy showed adenoma recurrence rates of 55.7% (placebo) vs. 51.1% (EGCG), with no statistical significance. Sinicrope *et al* (91) also studied EGCG's effects on 39 patients with 35 rectal ACFs, with no significant differences in ACF number, total ACF burden and adenoma recurrence observed. Several clinical trials (NCT02891538 and NCT01360320) investigating the preventive effects of EGCG have been completed, though their results remain unpublished.

The clinical evidence regarding vitamin supplementation for CRC prevention remains contradictory. Bonelli *et al* (92) demonstrated in a double-blind randomized trial that vitamins A, C and E could markedly reduce intestinal adenoma recurrence in patients with prior polypectomy. However, Oliai *et al* (93) reported that vitamin B12 could potentially increase risk of CRC. A number of relevant clinical trials have demonstrated no significant effects of vitamins on CRC outcomes. In Greenberg *et al*'s study (94) of 864 adenoma patients, vitamin C and E supplementation showed no difference in adenoma incidence compared with placebo groups. Gaziano *et al*'s large-scale trial (95) involving 14,641 male physicians found no effect of vitamin E and C on CRC incidence. Similarly, Wang *et al* (96) analyzed antioxidant vitamin C and E intake in 816 CRC patients vs. 815 controls, showing no association with cancer risk. Ng *et al* (97) evaluated vitamin D3 supplementation in advanced/metastatic CRC, revealing no significant improvement in progression-free survival (PFS) between high-dose and standard-dose groups. Ongoing clinical trials (NCT02969681, NCT01574027, NCT00905918 and NCT02603757) are currently underway, whose findings are expected to further clarify the role of vitamins in CRC.

A multicenter, double-blind, randomized controlled trial has demonstrated berberine's efficacy in CRC prevention. In this study, Chen *et al* (98) enrolled 1,108 patients with colorectal adenomas, which were randomly allocated to the berberine group (n=553, 0.3 g twice daily) and placebo group (n=555). Colonoscopy evaluation after a 2-year's follow-up revealed lower adenoma recurrence in the berberine group (n=155, 36%) compared with the placebo group (n=216, 47%). These results warrant validation through ongoing clinical trials (NCT03281096, NCT02226185 and NCT03333265).

Despite the potential anticancer effects demonstrated in preclinical studies, PBAs have not shown clear clinical benefits in CRC and their clinical translation faces a number of challenges. Indeed, low bioavailability is a critical limiting factor. For example, bioavailability of oral curcumin is <1% (99), with resulting concentrations in plasma much lower than the doses *in vitro*. Second, the core roles of PBAs in CRC remain unclear. While current research reveals a number of anti-tumor mechanisms (gene expression, signaling pathways and epigenetics) of PBAs in CRC, the heterogeneity across models (cell lines, animal species) and differences between models and human obscure the core mechanisms. Third, clinical trial design requires optimization. Dose selection lacks standardization: Carroll *et al* (85) found efficacy with 4 g/day curcumin, whereas a larger trial by Cruz-Correa *et al* (87) showed no benefit at 480 mg/day, highlighting the need for pharmacokinetic-guided individualized dosing. Moreover,

Table I. Clinical researches of PBAs.

First author/s, year	Type of PBA	Type of study	Patients	Group	Outcomes	(Refs.)
Carroll <i>et al</i> , 2011	Curcumin	Open-label trial	44 eligible smokers with 8 or more ACF on screening colonoscopy	2 g/day or 4 g/day for 30 days	No significant ACF reduction in the 2 g/day group, 40% reduction in ACF number in the 4 g/day group	(85)
Cruz-Correa <i>et al</i> , 2006	Curcumin	Single-arm trial	5 post-colectomy FAP patients	Curcumin (480 mg/day) and quercetin (20 mg/day)	60.4% reduction in polyp number and 50.9% decrease in size compared with baseline	(86)
Cruz-Correa <i>et al</i> , 2018	Curcumin	Randomized controlled trial	44 FAP patients who had not undergone colectomy	Curcumin (1,500 mg orally, twice per day) or identical-appearing placebo capsules for 12 months	No significant difference in mean polyp size between the curcumin group and the placebo group	(87)
Panahi <i>et al</i> , 2021	Curcumin	Randomized controlled trial	67 stage III CRC patients with chemotherapy after the surgery	Treatment group receiving curcuminoids capsules (500 mg/day) (n=36), or the control group taking placebo capsules (n=36) for 8 weeks	A significant change in CRP and ESR in treatment group. A significant improvement in functional and global quality of life in treatment group	(88)
Patel <i>et al</i> , 2010	Resveratrol	Single-arm trial	20 CRC patients before surgical resection	0.5 or 1g daily for 8 days	5% reduction in tumor cell proliferation	(89)
Seufferlein <i>et al</i> , 2022	EGCG	Randomized controlled trial	1,001 patients with colon adenomas	EGCG (150 mg/day) or placebo groups over 3 years	No significant difference in adenoma rate between the EGCG group and the placebo group	(90)
Sinicrope <i>et al</i> , 2021	EGCG	Randomized controlled trial	39 patients with at least 5 rectal ACF	EGCG (780 mg/day) or placebo groups over 6 months	No significant differences in ACF number, total ACF burden and adenoma recurrence	(91)
Bonelli <i>et al</i> , 2013	Vitamin	Randomized controlled trial	411 post-polypectomy patients	Active compound (200 µg selenium, 30 mg zinc, 2 mg vitamin A, 180 mg vitamin C, 30 mg vitamin E) or a placebo daily for 5 years	39% reduction of the risk of recurrence in the intervention group Compared with the placebo group	(92)
Oliai Araghi <i>et al</i> , 2019	Vitamin	Randomized controlled trial	2,524 Participants aged 65 years and over with an elevated homocysteine Level	Folic acid (400 µg/day) and vitamin B12 (500 µg/day) vs. placebo over 2 to 3 years	Vitamin B12 were markedly associated with a higher risk of CRC	(93)

Table I. Continued.

First author/s, year	Type of PBA	Type of study	Patients	Group	Outcomes	(Refs.)
Greenberg <i>et al</i> , 1994	Vitamin	Randomized controlled trial	864 patients who had at least one histologically confirmed adenoma removed from the large bowel	Beta carotene (25 mg daily); vitamin C (1 g daily) and vitamin E (400 mg daily); or the beta carotene plus vitamins C and E; placebo	There was no evidence that either beta carotene or vitamins C and E reduced the incidence of adenomas	(94)
Gaziano <i>et al</i> , 2009	Vitamin	Randomized controlled trial	14,641 male physicians aged 50 years or older	400 IU of vitamin E every other day and 500 mg of vitamin C daily; placebo	Neither vitamin E nor vitamin C had a significant effect on CRC incidence	(95)
Wang <i>et al</i> , 2012	Vitamin	Randomized controlled trial	816 CRC patients and 815 controls	Dietary intakes of vitamin C and vitamin E were assessed by a PC-assisted interview regarding 148 food items	Intake of vitamin C and vitamin E were not related to CRC risk in either men or women	(96)
Ng <i>et al</i> , 2019	Vitamin	Randomized controlled trial	139 patients with advanced or metastatic CRC	mFOLFOX6 plus bevacizumab chemotherapy every 2 weeks and either high-dose vitamin D3 (n=69) or standard-dose vitamin D3 (n=70) daily	No significant improvement in progression-free survival between high-dose and standard-dose groups	(97)
Chen <i>et al</i> , 2020	Berberine	Randomized controlled trial	553 participants who had colorectal adenomas that had undergone complete polypectomy	Berberine (0.3 g twice daily) or placebo	Lower adenoma recurrence in the berberine group vs. the placebo group	(98)

PBAs, plant-based antioxidants; ACF, aberrant crypt focus; FAP, familial adenomatous polyposis; CRC, colorectal cancer; ESR, erythrocyte sedimentation rate; EGCG, epigallocatechin gallate.

the influence of patient heterogeneity on the anticancer effects of PBAs warrants further confirmation. For example, genetic backgrounds of FAP patients may affect curcumin response (86,87).

5. Directions for future research

Improving bioavailability represents the central goal for clinical translation of PBAs. Nano-drug delivery system has become a research focus in the context of PBAs given its

ability to improve drug solubility, prolong circulation time and enhance tumor targeting (100,101). Currently, nanoparticles, nano micelles and liposomes are relatively reliable nano-drug delivery systems to improve the bioavailability of PBAs (Fig. 3).

Nanoparticles are generally classified into three classes: Inorganic, organic and carbon-based. Various strategies such as surface modification of nanoparticles with synthetic polymer polyethylene glycol (PEG) can improve the water solubility of nanoparticles (101). Zhang *et al* (102) developed erythrocyte

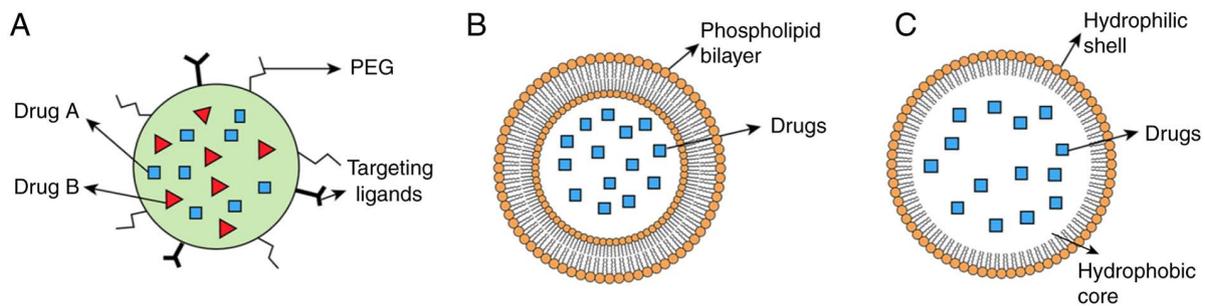


Figure 3. Nano-drug delivery systems for plant-based antioxidants. (A) Drugs are encapsulated in nanoparticles. Surface modification of nanoparticles with PEG and ligands enhances their water solubility and targeting capability. (B) Liposomes have hydrophobic phospholipid bilayer and encapsulate drugs in central cavity. (C) Nano-micelles have hydrophilic shell and hydrophobic core, with drugs encapsulated in central cavity (101). PEG, polyethylene glycol.

membrane-coated resveratrol nanoparticles modified with PCL-PEG, markedly prolonging half-life of resveratrol. Sun *et al* (103) designed PEG-modified amphiphilic cyclodextrin nanoparticles for co-delivery of ginsenoside and quercetin, enhancing duration of drug in CRC models. In addition, designing nanoparticles according to the characteristics of PBAs represents an effective way to improve bioavailability.

Nanomicelles, self-assembled amphiphilic polymer structures, feature a hydrophilic shell to enhance pharmacokinetics and a hydrophobic core to encapsulate the drug and control release (104). Ran *et al* (105) encapsulated ginsenoside compound K in nanomicelles fabricated via ultrasonic self-assembly of O-carboxymethyl chitosan, N-isopropylacrylamide and thermoresponsive IR820. The nanomicelles markedly improved water solubility and bioavailability of ginsenoside. Zhu *et al* (106) incorporated silybin into Soluplus-PVPVA nanomicelles, enhancing the pharmacokinetics of silybin.

Liposomes are biocompatible and biodegradable spherical vesicles with hydrophilic cores and lipid bilayers (107). These structures serve as effective carriers for the delivery of PBAs. Notably, curcumin liposomes exhibit improved solubility and anticancer activity against CRC cell lines (82,108), with clinical studies confirming safety and tolerability in CRC patients (109).

Developing nano-drug delivery systems combining PBAs with chemotherapeutics is another direction of further research. Curcumin can reportedly reverse the resistance of CRC cell lines to 5-FU, irinotecan and oxaliplatin through a number of mechanisms (110,111). Quercetin can synergistically enhance the killing effect of doxorubicin, 5-FU and oxaliplatin on CRC cells (112-114). Rutin can alleviate ensartinib-induced hepatotoxicity (115). Howells *et al* (116) conducted a study of 28 patients with metastatic CRC receiving either FOLFOX alone or FOLFOX combined with curcumin. The results showed that the curcumin-FOLFOX combination exhibited favorable safety and superior clinical outcomes compared with FOLFOX. Therefore, the combination of PBAs and chemotherapeutic drugs may enhance the therapeutic effect of chemotherapeutic drugs and appropriate nano-drug delivery systems can further improve the utilization and targeting of drugs. Sen *et al* (117) developed a liposome containing both apigenin and 5-FU, which demonstrated improved anti-tumor effects than 5-FU. Liu *et al* (118) designed a nanoparticle loaded with irinotecan and quercetin

with Conatumumab modified to target CRC cells, with the nanoparticle yielding improved anti-tumor effects without systemic toxicity.

Personalized treatment involving PBAs in CRC will contribute to its clinical translation. First, the mechanism underlying the efficacy of different PBAs in treating CRC needs to be elucidated. Integrating single-cell sequencing or spatial transcriptome technology will help to identify the core targets of specific cell subsets (119). The core targets can subsequently be harnessed to identify populations that benefit from PBAs or those for whom they are unsuitable. For instance, microsatellite-stable CRC cell lines are more sensitive to curcumin (120), while EGCG may restore TCF4-chromatin interactions and activate the Wnt pathway in p53-mutant models, paradoxically promoting tumorigenesis (121). Thus, microsatellite-stable CRC patients could be potential beneficiaries of curcumin, while EGCG should be avoided in patients with p53 mutations. Future efforts should focus on integrating molecular subtyping and biomarkers to identify the potential population, thereby advancing the clinical application of PBAs in CRC treatment.

6. Conclusion

CRC remains a formidable global health challenge, with conventional therapies often limited by toxicity, drug resistance and poor patient compliance. PBAs, characterized by their multi-target, multi-pathway mechanisms, have emerged as promising candidates for CRC prevention and treatment. Preclinical studies highlight their ability to modulate oxidative stress, inflammation, apoptosis, epigenetic dysregulation and gut microbiota imbalance; key drivers of CRC pathogenesis. Compounds such as curcumin, EGCG, resveratrol and berberine demonstrate pleiotropic effects, including chemo-sensitization, immune modulation and synergy with conventional therapies. Notably, these natural agents mitigate chemotherapy-induced toxicity while enhancing therapeutic efficacy, underscoring their potential as adjunctive or alternative treatments.

However, clinical translation faces significant hurdles and clinical efficacy from limited phase I/II trials. Low bioavailability, inconsistent clinical outcomes and heterogeneous patient responses remain critical barriers. In this regard, while curcumin exhibits dose-dependent adenoma reduction in trials, its poor absorption limits clinical utility. Similarly,

EGCG and vitamin supplementation trials revealed mixed results, emphasizing the need for optimized trial designs, standardized dosing and biomarker-driven patient stratification. Advances in nano-drug delivery systems, such as nanoparticles, liposomes and nanomicelles, offer promising solutions to enhance solubility, stability and tumor targeting. Combinatorial strategies integrating PBAs with chemotherapeutics (such as FOLFOX-curcumin) further demonstrate improved safety and efficacy, warranting expanded clinical exploration.

Future research should prioritize elucidating core mechanisms through advanced technologies such as single-cell sequencing and spatial transcriptomics, enabling precise identification of molecular targets and responsive patient subgroups. Personalized approaches, informed by CRC molecular subtypes (such as microsatellite stability, p53 status), will refine therapeutic applications. In addition, deeper investigations into gut microbiota-PBAs crosstalk and host-microbe interactions may unlock novel preventive and therapeutic avenues.

In conclusion, PBAs represent a versatile and sustainable frontier in CRC management. While challenges persist, interdisciplinary innovations in drug delivery, mechanism elucidation and precision medicine are key to unlocking their full clinical potential, ultimately bridging the gap between traditional phytotherapy and modern oncology.

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Authors' contributions

Conceptualization, investigation and writing the original draft was by DF, HF, KY, YW, BN and XL. DF, HF, KY, YW, BN and XL were responsible for writing, review and editing. DF, HF, KY, YW, BN and XL were responsible for visualization. DF, HF and XL were responsible for supervision. HF, XL and DF were responsible for project administration. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71: 209-249, 2021.
- Patel SG, Karlitz JJ, Yen T, Lieu CH and Boland CR: The rising tide of early-onset colorectal cancer: A comprehensive review of epidemiology, clinical features, biology, risk factors, prevention, and early detection. *Lancet Gastroenterol Hepatol* 7: 262-274, 2022.
- Chen EX, Jonker DJ, Loree JM, Kennecke HF, Berry SR, Couture F, Ahmad CE, Goffin JR, Kavan P, Harb M, *et al*: Effect of combined immune checkpoint inhibition vs best supportive care alone in patients with advanced colorectal cancer: The Canadian Cancer Trials Group CO.26 Study. *JAMA Oncol* 6: 831-838, 2020.
- Hudita A, Radu IC, Galateanu B, Ginghina O, Herman H, Balta C, Rosu M, Zaharia C, Costache M, Tanasa E, *et al*: Bioinspired silk fibroin nano-delivery systems protect against 5-FU induced gastrointestinal mucositis in a mouse model and display antitumor effects on HT-29 colorectal cancer cells in vitro. *Nanotoxicology* 15: 973-994, 2021.
- Georgiou A, Stewart A, Vlachogiannis G, Pickard L, Valeri N, Cunningham D, Whittaker SR and Banerji U: A phospho-proteomic study of cetuximab resistance in KRAS/NRAS/BRAF(V600) wild-type colorectal cancer. *Cell Oncol (Dordr)* 44: 1197-1206, 2021.
- Li Q, Geng S, Luo H, Wang W, Mo YQ, Luo Q, Wang L, Song GB, Sheng JP and Xu B: Signaling pathways involved in colorectal cancer: Pathogenesis and targeted therapy. *Signal Transduct Target Ther* 9: 266, 2024.
- Wang Y, Liu M, Jafari M and Tang J: A critical assessment of Traditional Chinese Medicine databases as a source for drug discovery. *Front Pharmacol* 15: 1303693, 2024.
- Sies H, Mailloux RJ and Jakob U: Fundamentals of redox regulation in biology. *Nat Rev Mol Cell Biol* 25: 701-719, 2024.
- Porter RJ, Arends MJ, Churchhouse AMD and Din S: Inflammatory bowel disease-associated colorectal cancer: Translational risks from mechanisms to medicines. *J Crohns Colitis* 15: 2131-2141, 2021.
- Naeem A, Hu P, Yang M, Zhang J, Liu Y, Zhu W and Zheng Q: Natural products as anticancer agents: Current status and future perspectives. *Molecules* 27: 8367, 2022.
- Yang H, Yue GGL, Leung PC, Wong CK and Lau CBS: A review on the molecular mechanisms, the therapeutic treatment including the potential of herbs and natural products, and target prediction of obesity-associated colorectal cancer. *Pharmacol Res* 175: 106031, 2022.
- Bu F, Tu Y, Wan Z and Tu S: Herbal medicine and its impact on the gut microbiota in colorectal cancer. *Front Cell Infect Microbiol* 13: 1096008, 2023.
- Ding Y and Yu Y: Therapeutic potential of flavonoids in gastrointestinal cancer: Focus on signaling pathways and improvement strategies (Review). *Mol Med Rep* 31: 109, 2025.
- Janney A, Powrie F and Mann EH: Host-microbiota maladaptation in colorectal cancer. *Nature* 585: 509-517, 2020.
- Zińczuk J, Maciejczyk M, Zaręba K, Pryczynicz A, Dymicka-Piekarska V, Kamińska J, Koper-Lenkiewicz O, Matowicka-Karna J, Kędra B, Zalewska A and Guzińska-Ustymowicz K: Pro-Oxidant enzymes, redox balance and oxidative damage to proteins, lipids and DNA in colorectal cancer tissue. is oxidative stress dependent on tumour budding and inflammatory infiltration? *Cancers (Basel)* 12: 1636, 2020.
- Monticelli S and Cejka P: DNA sensing and repair systems unexpectedly team up against cancer. *Nature* 625: 457-458, 2024.
- Ajeigbe OF, Maruf OR, Anyebe DA, Opafunso IT, Ajayi BO and Farombi EO: 6-shogaol suppresses AOM/DSS-mediated colorectal adenoma through its antioxidant and anti-inflammatory effects in mice. *J Food Biochem* 46: e14422, 2022.
- Liu C, Rokavec M, Huang Z and Hermeking H: Curcumin activates a ROS/KEAP1/NRF2/miR-34a/b/c cascade to suppress colorectal cancer metastasis. *Cell Death Differ* 30: 1771-1785, 2023.

19. Sun R, Zhang Y, Zhao X, Tang T, Cao Y, Yang L, Tian Y, Zhang Z, Zhang P and Xu F: Temporal and spatial metabolic shifts revealing the transition from ulcerative colitis to colitis-associated colorectal cancer. *Adv Sci (Weinh)* 12: e2412551, 2025.
20. Bardelčíková A, Šoltys J and Mojiš J: Oxidative stress, inflammation and colorectal cancer: An overview. *Antioxidants (Basel)* 12: 901, 2023.
21. Mandal M, Mamun MAA, Rakib A, Kumar S, Park F, Hwang DJ, Li W, Miller DD and Singh UP: Modulation of occludin, NF- κ B, p-STAT3, and Th17 response by DJ-X-025 decreases inflammation and ameliorates experimental colitis. *Biomed Pharmacother* 185: 117939, 2025.
22. Li Q, Chen Y, Zhang D, Grossman J, Li L, Khurana N, Jiang H, Grierson PM, Herndon J, DeNardo DG, *et al*: IRAK4 mediates colitis-induced tumorigenesis and chemoresistance in colorectal cancer. *JCI Insight* 4: e130867, 2019.
23. Wang M, Ma Y, Yu G, Zeng B, Yang W, Huang C, Dong Y, Tang B and Wu Z: Integration of microbiome, metabolomics and transcriptome for in-depth understanding of berberine attenuates AOM/DSS-induced colitis-associated colorectal cancer. *Biomed Pharmacother* 179: 117292, 2024.
24. Burgueño JF, Fritsch J, González EE, Landau KS, Santander AM, Fernández I, Hazime H, Davies JM, Santaolalla R, Phillips MC, *et al*: Epithelial TLR4 Signaling Activates DUOX2 to induce microbiota-driven tumorigenesis. *Gastroenterology* 160: 797-808.e6, 2021.
25. Jin BR, Chung KS, Hwang S, Hwang SN, Rhee KJ, Lee M and An HJ: Rosmarinic acid represses colitis-associated colon cancer: A pivotal involvement of the TLR4-mediated NF- κ B-STAT3 axis. *Neoplasia* 23: 561-573, 2021.
26. Hernández-Rocha C, Turpin W, Borowski K, Stempak JM, Sabic K, Gettler K, Tastad C, Chasteau C, Korie U, Hanna M, *et al*: After surgically induced remission, ileal and colonic mucosa-associated microbiota predicts crohn's disease recurrence. *Clin Gastroenterol Hepatol* 23: 612-620.e10, 2025.
27. Yun X, Zhang Q, Fang Y, Lv C, Chen Q, Chu Y, Zhu Y, Wei Z, Xia Y and Dai Y: Madecassic acid alleviates colitis-associated colorectal cancer by blocking the recruitment of myeloid-derived suppressor cells via the inhibition of IL-17 expression in $\gamma\delta$ T17 cells. *Biochem Pharmacol* 202: 115138, 2022.
28. Kuo IM, Lee JJ, Wang YS, Chiang HC, Huang CC, Hsieh PJ, Han W, Ke CH, Liao ATC and Lin CS: Potential enhancement of host immunity and anti-tumor efficacy of nanoscale curcumin and resveratrol in colorectal cancers by modulated electro-hyperthermia. *BMC Cancer* 20: 603, 2020.
29. Pouliquen DL, Mallocci M, Boissard A, Henry C and Guette C: Proteomes of residual tumors in curcumin-treated rats reveal changes in microenvironment/malignant cell crosstalk in a highly invasive model of mesothelioma. *Int J Mol Sci* 23: 13732, 2022.
30. Montalto FI and De Amicis F: Cyclin D1 in cancer: A molecular connection for cell cycle control, adhesion and invasion in tumor and stroma. *Cells* 9: 2648, 2020.
31. Alam M, Gulzar M, Akhtar MS, Rashid S, Zulfareen, Tanuja, Shamsi A and Hassan MI: Epigallocatechin-3-gallate therapeutic potential in human diseases: Molecular mechanisms and clinical studies. *Mol Biomed* 5: 73, 2024.
32. Ismail NI, Othman I, Abas F, H Lajis N and Naidu R: The curcumin analogue, MS13 (1,5-Bis(4-hydroxy-3-methoxyphenyl)-1,4-pentadiene-3-one), inhibits cell proliferation and induces apoptosis in primary and metastatic human colon cancer cells. *Molecules* 25: 3798, 2020.
33. Agarwal A, Kansal V, Farooqi H, Prasad R and Singh VK: Epigallocatechin gallate (EGCG), an active phenolic compound of green tea, inhibits tumor growth of head and neck cancer cells by targeting DNA hypermethylation. *Biomedicines* 11: 789, 2023.
34. Tian M, Peng S, Wang S, Li X, Li H and Shen L: Pristimerin reduces dextran sulfate sodium-induced colitis in mice by inhibiting microRNA-155. *Int Immunopharmacol* 94: 107491, 2021.
35. Liu H, Zhang L, Hao L and Fan D: Resveratrol inhibits colorectal cancer cell tumor property by activating the miR-769-5p/MSI1 pathway. *Mol Biotechnol* 67: 1893-1907, 2025.
36. Wang Z, Dan W, Zhang N, Fang J and Yang Y: Colorectal cancer and gut microbiota studies in China. *Gut Microbes* 15: 2236364, 2023.
37. Chattopadhyay I, Dhar R, Pethusamy K, Seethy A, Srivastava T, Sah R, Sharma J and Karmakar S: Exploring the role of gut microbiome in colon cancer. *Appl Biochem Biotechnol* 193: 1780-1799, 2021.
38. Liu P, Wang Y, Yang G, Zhang Q, Meng L, Xin Y and Jiang X: The role of short-chain fatty acids in intestinal barrier function, inflammation, oxidative stress, and colonic carcinogenesis. *Pharmacol Res* 165: 105420, 2021.
39. Su ACY, Ding X, Lau HCH, Kang X, Li Q, Wang X, Liu Y, Jiang L, Lu Y, Liu W, *et al*: *Lactococcus lactis* HkyuLL 10 suppresses colorectal tumorigenesis and restores gut microbiota through its generated alpha-mannosidase. *Gut* 73: 1478-1488, 2024.
40. Deng W, Xiong X, Lu M, Huang S, Luo Y, Wang Y and Ying Y: Curcumin suppresses colorectal tumorigenesis through restoring the gut microbiota and metabolites. *BMC Cancer* 24: 1141, 2024.
41. Leong W, Huang G, Liao W, Xia W, Li X, Su Z, Liu L, Wu Q, Wong VKW, Law BYK, *et al*: Traditional Patchouli essential oil modulates the host's immune responses and gut microbiota and exhibits potent anti-cancer effects in Apc(Min/+) mice. *Pharmacol Res* 176: 106082, 2022.
42. Wu Z, Huang S, Li T, Li N, Han D, Zhang B, Xu ZZ, Zhang S, Pang J, Wang S, *et al*: Gut microbiota from green tea polyphenol-dosed mice improves intestinal epithelial homeostasis and ameliorates experimental colitis. *Microbiome* 9: 184, 2021.
43. Urošević M, Nikolić L, Gajić I, Nikolić V, Dinić A and Miljković V: Curcumin: biological activities and modern pharmaceutical forms. *Antibiotics (Basel)* 11: 135, 2022.
44. Weng W and Goel A: Curcumin and colorectal cancer: An update and current perspective on this natural medicine. *Semin Cancer Biol* 80: 73-86, 2022.
45. López-Gómez L and Uranga JA: Polyphenols in the prevention and treatment of colorectal cancer: A systematic review of clinical evidence. *Nutrients* 16: 2735, 2024.
46. Neira M, Mena C, Torres K and Simón L: The potential benefits of curcumin-enriched diets for adults with colorectal cancer: A systematic review. *Antioxidants (Basel)* 14: 388, 2025.
47. Khan S, Karmokar A, Howells L, Britton RG, Parrott E, Palacios-Gallego R, Tufarelli C, Cai H, Higgins J, Sylvius N, *et al*: An old spice with new tricks: Curcumin targets adenoma and colorectal cancer stem-like cells associated with poor survival outcomes. *Cancer Lett* 629: 217885, 2025.
48. Ming T, Lei J, Peng Y, Wang M, Liang Y, Tang S, Tao Q, Wang M, Tang X, He Z, *et al*: Curcumin suppresses colorectal cancer by induction of ferroptosis via regulation of p53 and solute carrier family 7 member 11/glutathione/glutathione peroxidase 4 signaling axis. *Phytother Res* 38: 3954-3972, 2024.
49. Chuang HY, Chan HW and Shih KC: Suppression of colorectal cancer growth: Interplay between curcumin and metformin through DMT1 downregulation and ROS-mediated pathways. *Biofactors* 51: e2137, 2025.
50. Li D, Cao D, Cui Y, Sun Y, Jiang J and Cao X: The potential of epigallocatechin gallate in the chemoprevention and therapy of hepatocellular carcinoma. *Front Pharmacol* 14: 1201085, 2023.
51. Zhu W and Oteiza PI: NADPH oxidase 1: A target in the capacity of dimeric ECG and EGCG procyanidins to inhibit colorectal cancer cell invasion. *Redox Biol* 65: 102827, 2023.
52. Dong J, Zheng Z, Zhou M, Wang Y, Chen J, Cen J, Cao T, Yang T, Xu Y, Shu G, *et al*: EGCG-LYS Fibrils-Mediated CircMAP2K2 silencing decreases the proliferation and metastasis ability of gastric cancer cells in vitro and in vivo. *Adv Sci (Weinh)* 10: e2304075, 2023.
53. Guan Y, Wu Q, Li M, Chen D, Su J, Zuo L, Zhu B and Li Y: Epigallocatechin-3-gallate Induced HepG2 Cells Apoptosis through ROS-mediated AKT/JNK and p53 signaling pathway. *Curr Cancer Drug Targets* 23: 447-460, 2023.
54. Suetsugu F, Tadokoro T, Fujita K, Fujihara S, Sasaki K, Omayu E, Nakatani K, Koyama Y, Kozuka K, Matsui T, *et al*: Antitumor effects of epigallocatechin-3-gallate on colorectal cancer: An in vitro and in vivo study. *Anticancer Res* 45: 2937-2947, 2025.
55. Wang Z, Wang M, Huang J, Lin M and Wei P: Dichotomic role of low-concentration EGCG in the oxaliplatin sensitivity of colorectal cancer cells. *Dokl Biochem Biophys* 515: 29-35, 2024.
56. Yi J, Ye Z, Xu H, Zhang H, Cao H, Li X, Wang T, Dong C, Du Y, Dong S and Zhou W: EGCG targeting STAT3 transcriptionally represses PLXNC1 to inhibit M2 polarization mediated by gastric cancer cell-derived exosomal miR-92b-5p. *Phytomedicine* 135: 156137, 2024.
57. Wu SX, Xiong RG, Huang SY, Zhou DD, Saimaiti A, Zhao CN, Shang A, Zhang YJ, Gan RY and Li HB: Effects and mechanisms of resveratrol for prevention and management of cancers: An updated review. *Crit Rev Food Sci Nutr* 63: 12422-12440, 2023.

58. Brockmueller A, Shayan P and Shakibaei M: Evidence that β 1-integrin is required for the anti-viability and anti-proliferative effect of resveratrol in CRC cells. *Int J Mol Sci* 23: 4714, 2022.
59. Brockmueller A, Buhrmann C, Shayan P and Shakibaei M: Resveratrol induces apoptosis by modulating the reciprocal crosstalk between p53 and Sirt-1 in the CRC tumor microenvironment. *Front Immunol* 14: 1225530, 2023.
60. Dariya B, Girish BP, Merchant N, Srilatha M and Nagaraju GP: Resveratrol: Biology, metabolism, and detrimental role on the tumor microenvironment of colorectal cancer. *Nutr Rev* 82: 1420-1436, 2024.
61. Chen S, Tamaki N, Kudo Y, Tsunematsu T, Miki K, Ishimaru N and Ito HO: Protective effects of resveratrol against 5-fluorouracil-induced oxidative stress and inflammatory responses in human keratinocytes. *J Clin Biochem Nutr* 69: 238-246, 2021.
62. Choi CY, Lim SC, Lee TB and Han SI: Molecular basis of resveratrol-induced resensitization of acquired drug-resistant cancer cells. *Nutrients* 14: 699, 2022.
63. Recalde MD, Miguel CA, Noya-Riobó MV, González SL, Villar MJ and Coronel MF: Resveratrol exerts anti-oxidant and anti-inflammatory actions and prevents oxaliplatin-induced mechanical and thermal allodynia. *Brain Res* 1748: 147079, 2020.
64. Motawea MH, Abd Elmaksoud HA, Elharrif MG, Desoky AAE and Ibrahim A: Evaluation of anti-inflammatory and antioxidant profile of oleuropein in experimentally induced ulcerative colitis. *Int J Mol Cell Med* 9: 224-233, 2020.
65. Sokal-Dembowska A, Jarmakiewicz-Czaja S and Filip R: Flavonoids and their role in preventing the development and progression of MAFLD by modifying the microbiota. *Int J Mol Sci* 25: 11187, 2024.
66. Yang B, Bai H, Sa Y, Zhu P and Liu P: Inhibiting EMT, stemness and cell cycle involved in baicalin-induced growth inhibition and apoptosis in colorectal cancer cells. *J Cancer* 11: 2303-2317, 2020.
67. Zhang J, Lei H, Hu X and Dong W: Hesperetin ameliorates DSS-induced colitis by maintaining the epithelial barrier via blocking RIPK3/MLKL necroptosis signaling. *Eur J Pharmacol* 873: 172992, 2020.
68. Vukelić I, Detel D, Batičić L, Potočnjak I and Domitrović R: Luteolin ameliorates experimental colitis in mice through ERK-mediated suppression of inflammation, apoptosis and autophagy. *Food Chem Toxicol* 145: 111680, 2020.
69. Panda SK, Peng V, Sudan R, Ulezko Antonova A, Di Luccia B, Ohara TE, Fachi JL, Grajales-Reyes GE, Jaeger N, Trsan T, *et al*: Repression of the aryl-hydrocarbon receptor prevents oxidative stress and ferroptosis of intestinal intraepithelial lymphocytes. *Immunity* 56: 797-812.e4, 2023.
70. Wu Q, Luo Y, Lu H, Xie T, Hu Z, Chu Z and Luo F: The potential role of vitamin E and the mechanism in the prevention and treatment of inflammatory bowel disease. *Foods* 13: 898, 2024.
71. Tao S, Ren Z, Yang Z, Duan S, Wan Z, Huang J, Liu C and Wei G: Effects of different molecular weight polysaccharides from dendrobium officinale kimura & migo on human colorectal cancer and transcriptome analysis of differentially expressed genes. *Front Pharmacol* 12: 704486, 2021.
72. Cao Q, Zhou R, Guo S, Meng K, Yang X, Liu M, Ma B, Su C and Duan X: PLGA-Astragalus polysaccharide nanovaccines exert therapeutic effect in colorectal cancer. *Int J Nanomedicine* 19: 9437-9458, 2024.
73. Li Q, Zhang C, Xu G, Shang X, Nan X, Li Y, Liu J, Hong Y, Wang Q and Peng G: Astragalus polysaccharide ameliorates CD8(+) T cell dysfunction through STAT3/Gal-3/LAG3 pathway in inflammation-induced colorectal cancer. *Biomed Pharmacother* 171: 116172, 2024.
74. Cheng H, Liu J, Zhang D, Wang J, Tan Y, Feng W and Peng C: Ginsenoside Rg1 alleviates acute ulcerative colitis by modulating gut microbiota and microbial tryptophan metabolism. *Front Immunol* 13: 817600, 2022.
75. Yang R, Gao W, Wang Z, Jian H, Peng L, Yu X, Xue P, Peng W, Li K and Zeng P: Polyphyllin I induced ferroptosis to suppress the progression of hepatocellular carcinoma through activation of the mitochondrial dysfunction via Nrf2/HO-1/GPX4 axis. *Phytomedicine* 122: 155135, 2024.
76. Li JK, Sun HT, Jiang XL, Chen YF, Zhang Z, Wang Y, Chen WQ, Zhang Z, Sze SCW, Zhu PL and Yung KKL: Polyphyllin II induces protective autophagy and apoptosis via Inhibiting PI3K/AKT/mTOR and STAT3 signaling in colorectal cancer cells. *Int J Mol Sci* 23: 11890, 2022.
77. Li Z, Wang Y, Xu Q, Ma J, Li X, Yan J, Tian Y, Wen Y and Chen T: Berberine and health outcomes: An umbrella review. *Phytother Res* 37: 2051-2066, 2023.
78. Yan S, Chang J, Hao X, Liu J, Tan X, Geng Z and Wang Z: Berberine regulates short-chain fatty acid metabolism and alleviates the colitis-associated colorectal tumorigenesis through remodeling intestinal flora. *Phytomedicine* 102: 154217, 2022.
79. Wu X, Chen X, Liu H, He ZW, Wang Z, Wei LJ, Wang WY, Zhong S, He Q, Zhang Z, *et al*: Rescuing Dicer expression in inflamed colon tissues alleviates colitis and prevents colitis-associated tumorigenesis. *Theranostics* 10: 5749-5762, 2020.
80. Wang Q, Zhao X, Jiang Y, Jin B and Wang L: Functions of representative terpenoids and their biosynthesis mechanisms in medicinal plants. *Biomolecules* 13: 1725, 2023.
81. Lima DAN, Pelegrini BB, Uechi FAA, Varago RC, Pimenta BB, Kaneshima AMS, Kaneshima EN, Souza PDC, Pedrosa RB, Silveira TGV and Becker TCA: Evaluation of antineoplastic activity of zingiber officinale essential oil in the colorectal region of wistar rats. *Asian Pac J Cancer Prev* 21: 2141-2147, 2020.
82. Chen H, Tang X, Liu T, Jing L and Wu J: Zingiberene inhibits in vitro and in vivo human colon cancer cell growth via autophagy induction, suppression of PI3K/AKT/mTOR Pathway and caspase 2 deactivation. *J Buon* 24: 1470-1475, 2019.
83. Qi H, Zhang X, Liu H, Han M, Tang X, Qu S, Wang X and Yang Y: Shikonin induced apoptosis mediated by endoplasmic reticulum stress in colorectal cancer cells. *J Cancer* 13: 243-252, 2022.
84. Zhang Y, Pu W, Bousquenaud M, Cattin S, Zaric J, Sun LK and Rüegg C: Emodin inhibits inflammation, carcinogenesis, and cancer progression in the AOM/DSS model of colitis-associated intestinal tumorigenesis. *Front Oncol* 10: 564674, 2021.
85. Carroll RE, Benya RV, Turgeon DK, Vareed S, Neuman M, Rodriguez L, Kakarala M, Carpenter PM, McLaren C, Meyskens FL Jr and Brenner DE: Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. *Cancer Prev Res (Phila)* 4: 354-364, 2011.
86. Cruz-Correa M, Shoskes DA, Sanchez P, Zhao R, Hyland LM, Wexner SD and Giardiello FM: Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 4: 1035-1038, 2006.
87. Cruz-Correa M, Hyland LM, Marrero JH, Zahurak ML, Murray-Stewart T, Casero RA Jr, Montgomery EA, Iacobuzio-Donahue C, Brosens LA, Offerhaus GJ, *et al*: Efficacy and safety of curcumin in treatment of intestinal adenomas in patients with familial adenomatous polyposis. *Gastroenterology* 155: 668-673, 2018.
88. Panahi Y, Saberi-Karimian M, Valizadeh O, Behnam B, Saadat A, Jamialahmadi T, Majeed M and Sahebkar A: Effects of curcuminoids on systemic inflammation and quality of life in patients with colorectal cancer undergoing chemotherapy: A randomized controlled trial. *Adv Exp Med Biol* 1328: 1-9, 2021.
89. Patel KR, Brown VA, Jones DJ, Britton RG, Hemingway D, Miller AS, West KP, Booth TD, Perloff M, Crowell JA, *et al*: Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. *Cancer Res* 70: 7392-7399, 2010.
90. Seufferlein T, Ettrich TJ, Menzler S, Messmann H, Kleber G, Zipprich A, Frank-Gleich S, Algül H, Metter K, Odemar F, *et al*: Green tea extract to prevent colorectal adenomas, results of a randomized, placebo-controlled clinical trial. *Am J Gastroenterol* 117: 884-894, 2022.
91. Sinicrope FA, Viggiano TR, Buttar NS, Song LMWK, Schroeder KW, Kraichely RE, Larson MV, Sedlack RE, Kiesel JB, Gostout CJ, *et al*: Randomized phase II trial of polyphenon e versus placebo in patients at high risk of recurrent colonic neoplasia. *Cancer Prev Res (Phila)* 14: 573-580, 2021.
92. Bonelli L, Puntoni M, Gatteschi B, Massa P, Missale G, Munizzi F, Turbino L, Villanacci V, De Censi A and Bruzzi P: Antioxidant supplement and long-term reduction of recurrent adenomas of the large bowel. A double-blind randomized trial. *J Gastroenterol* 48: 698-705, 2013.
93. Oliai Araghi S, Kieffe-de Jong JC, van Dijk SC, Swart KMA, van Laarhoven HW, van Schoor NM, de Groot LCPGM, Lemmens V, Stricker BH, Uitterlinden AG and van der Velde N: Folic acid and vitamin B12 supplementation and the risk of cancer: Long-term Follow-up of the B vitamins for the prevention of osteoporotic fractures (B-PROOF) trial. *Cancer Epidemiol Biomarkers Prev* 28: 275-282, 2019.

94. Greenberg ER, Baron JA, Tosteson TD, Freeman DH Jr, Beck GJ, Bond JH, Colacchio TA, Collier JA, Frankl HD, Haile RW, *et al*: A clinical trial of antioxidant vitamins to prevent colorectal adenoma. Polyp Prevention Study Group. *N Engl J Med* 331: 141-147, 1994.
95. Gaziano JM, Glynn RJ, Christen WG, Kurth T, Belanger C, MacFadyen J, Bubes V, Manson JE, Sesso HD and Buring JE: Vitamins E and C in the prevention of prostate and total cancer in men: The physicians' health study II randomized controlled trial. *JAMA* 301: 52-62, 2009.
96. Wang Z, Joshi AM, Ohnaka K, Morita M, Toyomura K, Kono S, Ueki T, Tanaka M, Kakeji Y, Maehara Y, *et al*: Dietary intakes of retinol, carotenes, vitamin C, and vitamin E and colorectal cancer risk: The Fukuoka colorectal cancer study. *Nutr Cancer* 64: 798-805, 2012.
97. Ng K, Nimeiri HS, McCleary NJ, Abrams TA, Yurgelun MB, Cleary JM, Rubinson DA, Schrag D, Miksad R, Bullock AJ, *et al*: Effect of high-dose vs standard-dose vitamin D3 supplementation on progression-free survival among patients with advanced or metastatic colorectal cancer: The SUNSHINE randomized clinical trial. *JAMA* 321: 1370-1379, 2019.
98. Chen YX, Gao QY, Zou TH, Wang BM, Liu SD, Sheng JQ, Ren JL, Zou XP, Liu ZJ, Song YY, *et al*: Berberine versus placebo for the prevention of recurrence of colorectal adenoma: A multicentre, double-blinded, randomised controlled study. *Lancet Gastroenterol Hepatol* 5: 267-275, 2020.
99. Mao Q, Min J, Zeng R, Liu H, Li H, Zhang C, Zheng A, Lin J, Liu X and Wu M: Self-assembled traditional Chinese nanomedicine modulating tumor immunosuppressive microenvironment for colorectal cancer immunotherapy. *Theranostics* 12: 6088-6105, 2022.
100. Ali ES, Sharker SM, Islam MT, Khan IN, Shaw S, Rahman MA, Uddin SJ, Shill MC, Rehman S, Das N, *et al*: Targeting cancer cells with nanotherapeutics and nanodiagnostics: Current status and future perspectives. *Semin Cancer Biol* 69: 52-68, 2021.
101. Cheng Z, Li M, Dey R and Chen Y: Nanomaterials for cancer therapy: Current progress and perspectives. *J Hematol Oncol* 14: 85, 2021.
102. Zhang Z, Ji Y, Hu N, Yu Q, Zhang X, Li J, Wu F, Xu H, Tang Q and Li X: Ferroptosis-induced anticancer effect of resveratrol with a biomimetic nano-delivery system in colorectal cancer treatment. *Asian J Pharm Sci* 17: 751-766, 2022.
103. Sun D, Zou Y, Song L, Han S, Yang H, Chu D, Dai Y, Ma J, O'Driscoll CM, Yu Z and Guo J: A cyclodextrin-based nanof ormulation achieves co-delivery of ginsenoside Rg3 and quercetin for chemo-immunotherapy in colorectal cancer. *Acta Pharm Sin B* 12: 378-393, 2022.
104. Tawfik SM, Azizov S, Elmasry MR, Sharipov M and Lee YI: Recent advances in nanomicelles delivery systems. *Nanomaterials (Basel)* 11: 70, 2020.
105. Ran P, Wang W, An Z, Gao N, He Y and Wu Z: Preparation and in vitro biological studies of photothermal response ginsenoside CK-carboxymethyl chitosan-based prodrug nanomicelles for synergistic therapy. *Int J Biol Macromol* 316: 144747, 2025.
106. Zhu C, Gong S, Ding J, Yu M, Ahmad E, Feng Y and Gan Y: Supersaturated polymeric micelles for oral silybin delivery: The role of the Soluplus-PVPVA complex. *Acta Pharm Sin B* 9: 107-117, 2019.
107. Li M, Du C, Guo N, Teng Y, Meng X, Sun H, Li S, Yu P and Galons H: Composition design and medical application of liposomes. *Eur J Med Chem* 164: 640-653, 2019.
108. Rahman S, Cao S, Steadman KJ, Wei M and Parekh HS: Native and β -cyclodextrin-enclosed curcumin: Entrapment within liposomes and their in vitro cytotoxicity in lung and colon cancer. *Drug Deliv* 19: 346-353, 2012.
109. Zhang Y, Li Z, Huang Y, Xu Y and Zou B: Nanotechnology and curcumin: A novel and promising approach in digestive cancer therapy. *Nanomedicine (Lond)* 18: 2081-2099, 2023.
110. Bhattacharjya D and Sivalingam N: Mechanism of 5-fluorouracil induced resistance and role of piperine and curcumin as chemo-sensitizers in colon cancer. *Naunyn Schmiedebergs Arch Pharmacol* 397: 8445-8475, 2024.
111. Brockmueller A, Samuel SM, Mazurakova A, Busselberg D, Kubatka P and Shakibaei M: Curcumin, calebin A and chemo-sensitization: How are they linked to colorectal cancer? *Life Sci* 318: 121504, 2023.
112. Suman I, Jezidzic A, Dobric D and Domitrovic R: Differential effects of rutin and its aglycone quercetin on cytotoxicity and chemosensitization of HCT 116 colon cancer cells to anticancer drugs 5-fluorouracil and doxorubicin. *Biology (Basel)* 14: 527, 2025.
113. Lee J, Jang CH, Kim Y, Oh J and Kim JS: Quercetin-induced glutathione depletion sensitizes colorectal cancer cells to oxaliplatin. *Foods* 12: 1733, 2023.
114. Deng H, Wei F, Han W, Li Y, Xu X, Zhang L and Zhang Y: Synergistic chemotherapy and immunomodulatory effects of Quercetin in cancer: A review. *Front Immunol* 16: 1547992, 2025.
115. Wu W, Li J, Yin Y, Zhou Y, Huang X, Cao Y, Chen X, Zhou Y, Du J, Xu Z, *et al*: Rutin attenuates ensartinib-induced hepatotoxicity by non-transcriptional regulation of TXNIP. *Cell Biol Toxicol* 40: 38, 2024.
116. Howells LM, Iwuji COO, Irving GRB, Barber S, Walter H, Sidat Z, Griffin-Teall N, Singh R, Foreman N, Patel SR, *et al*: Curcumin combined with FOLFOX chemotherapy is safe and tolerable in patients with metastatic colorectal cancer in a randomized phase IIa trial. *J Nutr* 149: 1133-1139, 2019.
117. Sen K, Banerjee S and Mandal M: Dual drug loaded liposome bearing apigenin and 5-Fluorouracil for synergistic therapeutic efficacy in colorectal cancer. *Colloids Surf B Biointerfaces* 180: 9-22, 2019.
118. Liu Y, Zhang H, Cui H, Zhang F, Zhao L, Liu Y and Meng Q: Combined and targeted drugs delivery system for colorectal cancer treatment: Conatumumab decorated, reactive oxygen species sensitive irinotecan prodrug and quercetin co-loaded nanostructured lipid carriers. *Drug Deliv* 29: 342-350, 2022.
119. Vandereyken K, Sifrim A, Thienpont B and Voet T: Methods and applications for single-cell and spatial multi-omics. *Nat Rev Genet* 24: 494-515, 2023.
120. Lu L, Przybylla R, Shang Y, Dai M, Krohn M, Krämer OH, Mullins CS and Linnebacher M: Microsatellite Status and I κ B α expression levels predict sensitivity to pharmaceutical curcumin in colorectal cancer cells. *Cancers (Basel)* 14: 1032, 2022.
121. Kadosh E, Snir-Alkalay I, Venkatachalam A, May S, Lasry A, Elyada E, Zinger A, Shaham M, Vaalani G, Mernberger M, *et al*: The gut microbiome switches mutant p53 from tumour-suppressive to oncogenic. *Nature* 586: 133-138, 2020.



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