Therapeutic effects of natural polyphenols on colorectal adenomas: Focus on preclinical studies (Review)

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Abstract. Colorectal adenoma (CRA) is a premalignant lesion of colorectal cancer. The current treatment is surgical resection, but CRA is prone to recurrence, and there is no safe and effective drug to prevent adenoma recurrence and canceration. Recent studies have shown that natural compounds in plants have favorable antitumor effects. According to preclinical studies, natural polyphenols can regulate different signal pathways and targets to play a role in the treatment of CRA, which is closely related to its inhibition of proliferation, induction of apoptosis, inhibition of inflammation and oxidative stress, and regulation of intestinal flora. Natural polyphenols are potential candidates for CRA therapy due to their remarkable efficacy and safety. In the present review, attention was paid to the experimental research progress of natural polyphenols extracted from numerous plants in the treatment of CRA in the last 10 years. The present review provided new guidance for the study of CRA, clarified the therapeutic role of polyphenols in CRA, and evaluated for the first time, to the best of our knowledge, the therapeutic potential of natural polyphenols to treat CRA by targeting multiple genes and signal pathways and epigenetic modification.

Contents

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1. Introduction

The incidence of colorectal adenoma (CRA) increases with age after the age of 30 and is common in young and middle-aged individuals over the age of 40, including sporadic and familial cases (1). The incidence of CRA in individuals aged >60 is as high as 40%, and the annual rate of adenoma progression to colorectal cancer (CRC) is ~0.25% (2,3). CRA is a kind of premalignant lesion. Intestinal malignant lesions usually develop from focal dysplastic polypoid precursor-adenoma, which is mainly limited to colorectal mucosa and submucosa. The occult onset of CRA may be accompanied by positive fecal occult blood, changes in stool characteristics, abdominal pain, diarrhea and other non-specific symptoms, which are usually found during enteroscopy screening. Previous studies suggested that normal mucosal epithelial cells of the intestine can grow gradually for 10-15 years before undergoing heterogeneous proliferation to carcinogenesis (4). Under the influence of multiple factors including genetic susceptibility to tumors and the immune microenvironment, adenomas further accumulate genetic mutations and invade the submucosa to become cancerous (5). Currently, according to the fifth edition of the World Health Organization classification of digestive tumors, there are two types of CRA: i) Conventional adenomas, namely tubular adenomas, villous adenomas, tubular villous adenomas, conventional serrated adenomas and ii) sessile serrated lesions (SSL; including sessile serrated adenomas/polyps). A total of ~70-90% of CRCs develop through the conventional normal epithelial-adenoma-adenocarcinoma sequence (also known as the chromosomal instability pathway), usually accompanied by mutations in the APC gene and excessive activation of the Wnt pathway (6). And tumors originating in this pathway usually occur in men and are located in the distal colon. By contrast, ~10-20% of CRC have a different pathway-serrated neoplasia pathway. The mechanism of SSLs mainly involves BRAF mutation, KRAS mutation, CpG island methylation phenotype and microsatellite instability (7). SSLs occur in the proximal colon, particularly in the cecum and ascending

colon, and grow significantly faster than tubular adenomas (8). The possible mechanisms are exhibited in Fig. 1.

Polyphenols are naturally occurring antioxidant compounds in plants, and their types and contents vary widely among fruits, vegetables, leaves and seeds. Polyphenols can reduce the oxidative damage of enzymes and DNA in cells and tissues (9), and have a variety of physiological activities, including antibacterial, antioxidant, anti-inflammatory, antiviral, antitumor and immunomodulatory functions (10-13). Numerous studies have shown that polyphenols have inhibitory effects on CRA, and polyphenols are considered an important source of natural drugs for the treatment of numerous diseases due to their remarkable efficacy and safety. In the present review, the progress of experimental studies on natural polyphenols for the treatment of CRA in the past 10 years was discussed to provide additional insight for researchers to study and develop new drugs for the treatment of CRA.

2. Current treatment and management of CRA

At present, there are few treatment options for CRA. The conventional treatment of the patient is endoscopic mucosal resection (EMR) or endoscopic mucosal dissection to remove adenomas, and the patient is given oral medication to prevent bleeding from the wound after surgery (14). There is a lack of effective drugs or treatments to prevent the recurrence and carcinogenesis of CRA in clinical treatment. Clinical studies have identified that COX-2 inhibitors including celecoxib and aspirin (ASA) may reduce the recurrence of CRA by reducing intestinal inflammation and regulating microflora (15,16). In addition, folic acid, calcium, vitamin D, eicosapentaenoic acid and antioxidants are effective in the treatment of CRA (17-19). It has been reported that traditional Chinese medicine (20,21) and natural compounds (22,23) also have favorable therapeutic effects on CRA. But the efficacy of these interventions is controversial or has certain side effects and cannot be used for a long time (24,25). Among them, those common treatment methods for CRA are exhibited in Fig. 2.

3. Classification of polyphenols and their transformation in the intestine

Polyphenols are found in plants and plant derivatives, and studies have shown that dietary polyphenols can reduce the occurrence of numerous diseases, including tumors (26). According to their chemical structure, polyphenols can be classified into flavonoids and non-flavonoids. Flavonoids are particularly abundant in fruits, vegetables, seeds, spices, vanilla, tea, cocoa and wine (27), and their chemical structure consists of 15 carbon atoms, with aromatic rings A and B linked by a three-carbon bridge to form a heterocyclic ring (ring C) (28). Depending on the functional group, the degree of oxidation of ring C and the connection between ring B and C, they can be divided into different subgroups (10), which are mainly classified into six major groups: Flavonols, flavones, anthocyanins, flavanols, flavanones and isoflavones. Flavonols are the most abundant flavonoids in plants, mainly found in tea, apples, onions and dark green vegetables, including quercetin, kaempferol and prunetin; flavones are relatively low in plants, mainly in celery, coriander and garlic, including lignan, apigenin and baicalin. Anthocyanins are also less abundant in plants, mainly found in crimson grapes, berries and red wine. However, the bioavailability of anthocyanins appears to be relatively low (29). Flavanols are mainly found in tea, nuts and grains, including (-)-epicatechin3-O-gallate (ECG) and (-)-epigallocatechin-3-O-gallate (EGCG). Oranges, lemons and other citrus fruits and their juices are rich in flavanones, including naringin and hesperidin, and isoflavones including genistein and daidzein mainly exist in soybean and soybean products. Non-flavonoids are divided into phenolic acids, lignans and stilbenes according to their different structures. Phenolic acid is divided into hydroxycinnamic acid and hydroxybenzoic acid, which mainly exists in fruits and grains. Curcumin (CUR) and caffeic acid belong to hydroxycinnamic acid, and gallic acid and vanillic acid belong to hydroxybenzoic acid (30). Lignans are phytoestrogens, similar in structure to estrogens, and they are mainly found in sesame, flaxseed, red wine and olive oil, including sesamin, allicin, magnolol and magnolol. Stilbenes are rarely found in diet and are found in berries, plums and pine nuts, such as resveratrol (RSV).

Polyphenols are usually absorbed in the intestine, combined with glucoside acid, sulfate and/or methyl and metabolized in the intestinal mucosa and liver. Polyphenols metabolized in the colon can be widely transformed by intestinal microorganisms, while polyphenols that reach the liver will undergo further-stage II metabolism (31). The main metabolite of polyphenols, phenolic acids, can enter the systemic circulation and most of them are excreted in urine and bile within 48 h (32).

4. Molecular targets of polyphenol for CRA: Preclinical studies

In vivo and *in vitro* models, natural polyphenols show significant antitumor activity, which is manifested in inhibiting proliferation, inducing apoptosis, promoting cell cycle arrest, anti-inflammatory, anti-oxidation, and regulating a variety of signal pathways to play a therapeutic role on CRA. The therapeutic effects of these polyphenols on tumors are shown in Table I, and detailed information and sources of polyphenols are shown in Table II.

Flavonoids

Flavones. Baicalein (5,6,7-trihydroxyflavone) is a flavonoid mainly derived from the root of *Scutellaria baicalensis*. Baicalein is widely used in Chinese herbal medicine for anti-inflammatory and anticancer treatment (33). Baicalein and baicalin are the traditional Chinese medicine components of *Scutellaria baicalensis*. Studies have shown that baicalin in the extract of *Scutellaria baicalensis* can be bio-transformed into baicalein after culture with intestinal microflora, and exhibits an antitumor effect in mice (34). Compared with the model group, baicalein treatment significantly reduced the number of small intestinal and CRAs, and significantly reduced the levels of inflammatory cytokines IL-1β, IL-2, IL-6, IL-10, G-CSF and GM-CSF. A recent study reported that the effect of baicalein on adenoma is partly achieved by inhibiting intestinal inflammation (35). In addition, baicalein significantly reduced the incidence of tumor and inflammation in azoxymethane (AOM)/4,4-dimethyl-4-silapentane-1-sulfonic acid (DSS) mice, which may be related to apoptosis induced

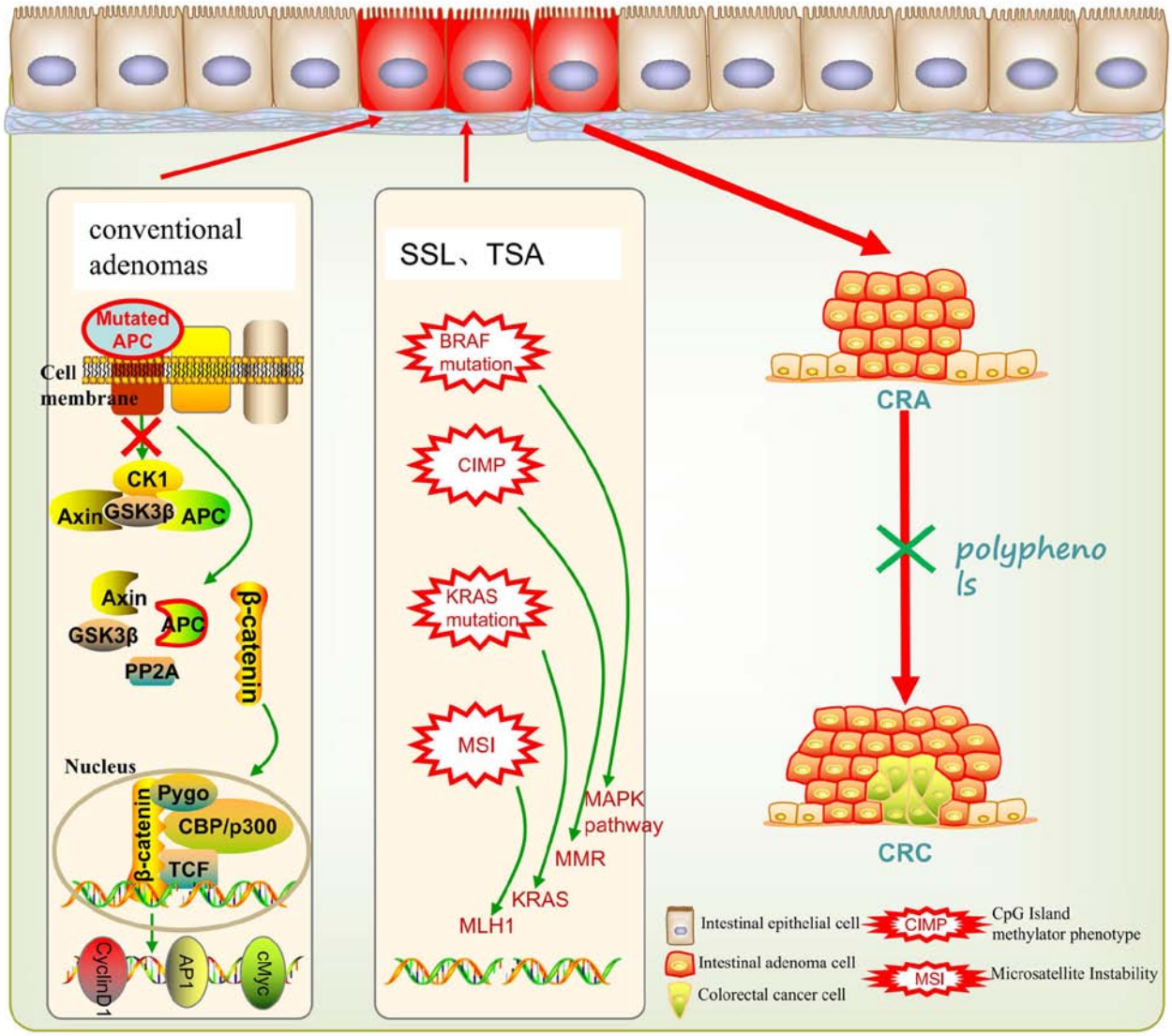


Figure 1. Relevant mechanisms of colorectal adenoma.

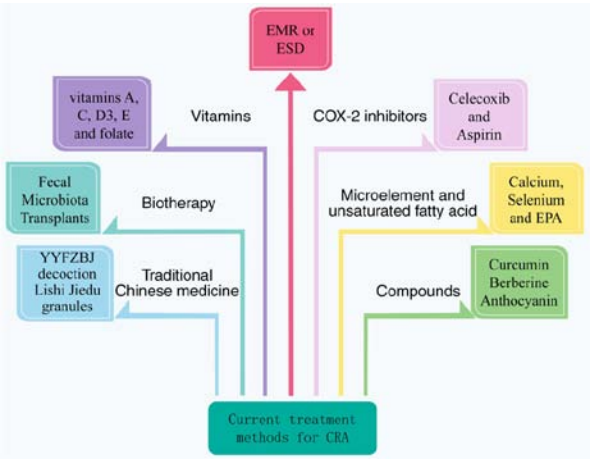


Figure 2. Current treatment methods for CRA. CRA, colorectal adenoma.

by morphological changes and cleavage of poly (ADP-ribose) polymerase and inhibition of NF-κB activation by PPARγ activation (36).

Apigenin is widely found in numerous plants, and its extensive antioxidant properties have been reported in a large number of literature (37). Apigenin can inhibit tumor by regulating multiple kinase pathways, including phosphatidylinositol 3-kinase (PI3K), protein kinase B/Akt, MAPK/ERK, casein kinase II, and arrest cell cycle in G2/M phase, reducing cyclin B1 in CRC cells (38). Previous studies have shown that apigenin can significantly reduce the number and size of polyps in $APC^{Min/+}$ mice, upregulate the expression of P21 and specifically phosphorylate p53 protein in intestinal tumor tissues of mice. *In vitro* experiments, pro-apoptotic proteins (NAG-1 and p53) and cell cycle inhibitor (p21) were induced in the presence of apigenin, PKCδ and ataxia telangiectasia mutated play an important role in activating these proteins (39). Genome integrity is maintained by blocking cell cycle progression or inducing apoptosis (40). These results indicated that apigenin affects tumor cell apoptosis in p53-dependent and p53-independent ways and reduces the occurrence of adenoma (39).

Digitoflavone as a kind of flavonoid in the diet, including broccoli, carrots, peppers and cabbage, has been used to treat

Table I. Summary of the mechanisms of anti-CRA polyphenols.

Phytochemicals	Dose, duration and testing system	Function	Molecular targets	(Refs.)
Flavones				
Baicalein	30 mg/kg/day, *In vivo*: $Apc^{Min/+}$ mice	Decreased the incidence of tumor formation with inflammation	ADP-ribose ↑PPARγ	(36)
	1, 5, 10 mg/kg for 16 weeks, *In vivo*: AOM/DSS mice	Induces apoptosis	↓NF-κB, IL-1CSF, IL-2, IL-6, IL-10, G-β and GM-CSF	
	50 μM for 24 h, *In vitro*: HCT116			
Apigenin	25, 50 mg/kg for 1 month, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation	↑NAG-1, p53, p21	(39)
	1, 10 μM for 72 h, *In vitro*: HCT116, HT-29, SW480 and LoVo	Induces apoptosis Arrests cell cycle	phosphor-p53	
Digitoflavone	50 mg/kg for 12 weeks, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation	↑Nrf2, TR, γ-GCSc, γ-GCSm, HO-1, GR, NQO-1	(42)
	1-20 μM for 8 h, *In vitro*: Caco-2, HT-29, HepG2 and HEK-293	Reduces oxidative stress	↓TNF-α, IL-1β, IL-6, ROS	
Quercetin	0. 0.2% (w/w) for 16 weeks, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation Decreases macrophage number	↓pSTAT3, IL-6	(49)
	25 mg/kg for 3 weeks, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation Attenuates the progression of cancer cachexia		(50)
Kaempferol	75, 150 mg/kg for 20 weeks, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation Inhibits cell proliferation	↑DACT2, β-catenin, ↓CTNNB1, LRP6	(53)
	(1. 25-150 μM) for 72 h, *In vitro*: HCT116, HT29 and YB5	Reduces cell migration Arrests cell cycle	At G0/G1 and S phase	
Myricetin	25 mg/kg for 13 weeks, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation Suppresses cancerization Inhibits cell proliferation Induces apoptosis Decreases inflammation	↓IL-6, PGE2, Cyclin D1, PCNA, Bcl-xL, β-catenin, p-GSK3β, IL-6, PGE 2, p-JNK, JNK, p-Erk1/2, p-p38 MAPK, p-mTOR, p-Akt, ↑TUNEL, Bax, c-Caspase-3, GSK-3β, TNF-α	(55)
	0 mg/kg for 4 weeks, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation Suppresses cancerization Decreases inflammation	TNF-α, IL-1β, IL-6, NF-κB, p-NF-κB, COX-2, PCNA, Cyclin D1	(56)
EGCG	0. 01% for 2 months, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation	↓bFGF	(71)
	1, 10, 50 μmol/l for 72 h *In vitro*: HCT-116 LoVo			
	1% (v/v) for 13 weeks, *In vivo*: AOM mice	Decreases intestinal adenoma formation Suppresses cancerization Regulates microbiota	↑*Bifidobacterium*, *Lactobacillus*	(72)
Silibinin	0. 2% (w/w) for 3 months, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation Induces apoptosis	Cdk4 ↓cyclin D1, Ki67	(87)

Table I. Continued.

Phytochemicals	Dose, duration and testing system	Function	Molecular targets	(Refs.)
		Inhibits cell proliferation Decreases intestinal adenoma formation		
Silymarin and/or lignin		Inhibits cell proliferation Induces apoptosis Suppresses migration and invasion	↑ERβ, caspase-3	(88)
Puerarin	20 h, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation Decreases inflammation Suppresses EMT Suppresses cancerization	↓TNF-α, IL-17A	(80)
Isoliquiritigenin	30, 75, 150 mg/kg for 18 weeks, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation Regulates microbiota	↓IL-6, IL-10, TNF-α, IL-1β, COX-2	(83)
Naringin	50, 100 mg/kg for 63 days, *In vivo*: AOM/DSS mice	Suppresses cancerization Decreases intestinal adenoma formation Decreases inflammation Induces autophagy	↓MDSCs, GM-CSF/M-CSF, IL-6, TNF-α, NF-κB/IL-6/STAT3 ↓GRP78, ATF6, IRE1 α, PERK, eIF-2α, ↓Complex of ATG3, ATG5, ATG7, ATG12, ATG16, ATG16L1	(75)
Isorhamnetin	85 days, *In vivo*: AOM/DSS mice 10, 20, 40 μM for 24 h *In vitro*: HT29	Decreases intestinal adenoma formation Decreases inflammation Inhibits cell proliferation	↓c-Src, β-catenin, ERK, Akt ↑CSK	(59)
Genkwanin	12. 25 mg/kg/day, *In vivo*: $Apc^{Min/+}$mice 10, 30, 60, 90, 120, μM for 48 h *In vitro*: HT-29 and SW-480	Decreases intestinal adenoma formation Suppresses cancerization Decreases inflammation Inhibits cell proliferation	↑IL-2, IL-4, IL-8, IL-12, IFN-γ, TNF-α ↓IL-10	(46)
Scutellarin	25, 50, 100 mg/kg for 11 weeks, *In vivo*: AOM/DSS mice 60, 120, 180, 240, 300, 360, 400 μM for 48 h, *In vitro*: HT-29	Suppresses cancerization Decreases inflammation	↓TNF-α, IL-6, β-catenin, Bcl-2 ↑Bax	(90)
Anthocyanins Cyanidin 3-rutinoside	5%, 7.5% lyophilized AP for 21 weeks, *In vivo*: DMH/TNBS rat 25 μM for 48 h, *In vitro*: RKO	Decreases incidence of adenoma with high-grade dysplasia Inhibits cell proliferation Decreases the total number of ACF and ACF multiplicity Decreases inflammation	↑Dlc1, Akt3, Ppara	(62)
Anthocyanin-Rich Sausages	0. 1% (w/w) for 20 weeks, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation Regulates microbiota	↓Bilophila wadsworthia ↑FRAP	(63)
Black raspberry anthocyanins	3. 5, 7 μmol/g for 12 weeks, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation Suppresses cancerization	↑SFRP2 ↓DNMT31, DNMT3B, p-STAT3	(64)

Table I. Continued.

Phytochemicals	Dose, duration and testing system	Function	Molecular targets	(Refs.)
	25, 50, 100 μg/ml for 24 h, *In vitro*: HCT116 and LoVo	Regulates microbiota		
Anthocyanin-containing purple-fleshed potatoes	20% (w/w) for 1 week, *In vivo*: AOM mice	Decreases intestinal adenoma formation Inhibits CSCs proliferation Induces apoptosis	↓β-catenin, c-Myc, Cyclin D1, ↑Bax and cytochrome c	(65)
Anthocyanin-rich red grape extract	0. 3% oenocyanin for 16 weeks, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation	↓Ki-67, Akt, ERK	(66)
Proanthocyanidin (PA)-rich dietary fiber	1% (w/w) for 6 weeks, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation Arrests cell cycle Decreases inflammation	↓Ccnd1, Lfng, PLK3, Lck, Nfkbie, Cxcr4, H2-Ab1, Igh, Igl-V1 and Igkv1-117 ↑Gadd45a	(145)
Tart cherry anthocyanins	200, 800 mg/l anthocyanins for 16 weeks, *In vivo*: $Apc^{Min/+}$ mice	Decreases intestinal adenoma formation	↓COX enzymes	(67)
Anthocyanin-enriched Sweet Potato	10% SL222 sweet potato flesh and skin, 0. 12% ARE for 18 weeks, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation		(69)
Anthocyanin-rich extract from bilberries	1%, 10% (w/w) for 9 weeks, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation Decreases inflammation		(68)
Lonchocarpin	50, 100 mg/kg/day for 4 days, *In vivo*: AOM/DSS mice 1, 3, 5, 10, 20, 30 μM for 24 h, *In vitro*: RKO and SW480	Decreases intestinal adenoma formation Inhibits cell proliferation Reduces cell migration	↓Ki-67 and BrdU, β-catenin, dnTCF4-VP16	(84)
Neohesperidin	50, 100 mg/kg for 12 weeks, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation Regulates microbiota Induces apoptosis Suppresses angiogenesis	↑TUNEL ↓CD31	(78)
Radix Tetrastigma hemsleyani flavone (RTHF)	30, 60 mg/kg for 14 weeks, *In vivo*: AOM/DSS mice 1. 6, 3. 2, 6. 4 mg/ml for 24, 48, 72 h *In vitro*: SW620 and HT29	Suppresses cancerization Inhibits cell proliferation Arrests cell cycle	↓Lgr5, c-Myc, Cyclin D1 At G0/G1 phase	(92)
Spinosin	100, 200 mg for 13 weeks, *In vivo*: AOM/DSS mice 50, 100, 150, 200 mg/ml for 48 h *In vitro*: HCT-116, HCT-8 and HCT-8FU	Decreases intestinal adenoma formation Suppresses cancerization Decreases inflammation	↓COX-2, EMR1, Ki67	(96)
Polymethoxyflavones	0. 5, 1. 0% PMFs for 7 weeks, *In vivo*: BaP/DSS mice	Decreases intestinal adenoma formation Decreases inflammation	↓PCNA, BPDE-DNA, IL-6, IL-10, TNF-α, COX-2, MCP1, CXCL-1, calmodulin ↑HO-1, SODs 和 NQO1	(99)

Table I. Continued.

Phytochemicals	Dose, duration and testing system	Function	Molecular targets	(Refs.)
Coumestrol	0.01% coumestrol for 10 weeks, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation Inhibits cell proliferation Reduces cell migration	↓E-cadherin, beta-catenin ↑ERβ	(100)
Flavonoid-rich extract from bergamot juice	35, 70 mg/kg for 20 weeks, *In vivo*: F344/NTac-Apc^{am1137} rat	Decreases intestinal adenoma formation Decreases inflammation Induces apoptosis	↓COX-2, iNOS, IL-1β, IL-6, IL-10, Arginase1, survivin, p21 ↑p53	(106)
GEN-27	5, 15, 45 mg/kg for 16 weeks, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation Suppresses cancerization Decreases inflammation	↑APC, AXIN2, CDX2, ↓β-catenin, NF-κB/p65	(102)
Total Flavonoids from Daphne genkwa	12.5, 25 mg/kg/day, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation Immunoregulation and decreases inflammation	↓IL-1α, IL-1β, IL-6, IL-10, G-CSF, IL-2, IL-12, IFN-γ and TNF-α	(107)
Curcumin (CUR)	4.48 mg/kg for 110 days, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation Suppresses cancerization Induces apoptosis Decreases inflammation	↑caspase 3 ↓Cyclin D1,	(109)
	500 mg/kg for 9 weeks, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation Decreases inflammation	↓IL-1β, IL-6, Cox-2, β-catenin, Axin2	(114)
	8-162 mg/kg/day for 20 weeks, *In vivo*: AOM mice	Decreases intestinal adenoma formation Regulates microbiota	↑Lactobacillus	(115)
Theracurmin	500 ppm for 8 weeks, *In vivo*: $Apc^{Min/+}$mice 10-20 μM for 24 h *In vitro*: DLD-1 and HCT116 0.25% NovaSolVR for 20 weeks, *In vivo*: $MGMT^{-/-}$ AOM/DSS mice	Decreases intestinal adenoma formation Decreases inflammation Decreases intestinal adenoma formation	↓NF-κB, MCP-1, IL-6	(116)
Curcumin + aspirin	2% Curcumin or 1% Curcumin + 0.01% aspirin for 23 weeks, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation Suppresses cancerization		(117) (119)
3,3'-diindolylmethan (DIM)e + curcumin	250 ppm DIM and 2000 ppm CUR for 6.5 months, *In vivo*: F344/ NTac-Apc ^{am1137}Pirc rat	Decreases intestinal adenoma formation	↑Krt36, Tacstd2, Hoxd10, Hoxd13, Hoxd12, Klk15, Ltf, Cntn3, Krt5, Shh ↓Alb, Mfap4, B3gnt6, Alb, Gpc3, Tmigd1, Apol7e ↓Birc5	(120)
Resveratrol	150, 300 ppm for 91 days, *In vivo*: $APC^{CKO}/Kras^{mut}$ mice 60 μM for 24 h *In vitro*: HCT116 and SW480	Decreases intestinal adenoma formation Suppresses cancerization	↓Ki-67, Kras, LGR5, β-catenin, pBraf, pAkt ↑miR-96	(125)
Resveratrol + grape seed extract	0.03, 0.12% (w/w) RSV-GSE for 1 week, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation Induces apoptosis	↓CSC, β-catenin, pGSK3β, c-Myc, cyclin D1	(124)

Table I. Continued.

Phytochemicals	Dose, duration and testing system	Function	Molecular targets	(Refs.)
	9 μM RSV and 6. 25, 12. 5, 25 μg/ml GSE for 24 h, *In vitro*: HCT116		↑p53	
Caffeic Acid Phenethyl Ester	5, 15, 45 mg/kg for 16 weeks, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation Decreases inflammation	↓ROS, NLRP3, IL-1β, IL-6, TNF-α, caspase-1, ASC	(131)
Green tea polyphenols	0. 12, 0. 24% for 8 weeks, *In vivo*: AOM mice	Decreases intestinal adenoma formation Suppresses cancerization	↓β-catenin, Cyclin D1, RXRa	(137)
	0. 6% (w/v) for 8 weeks, *In vivo*: $Apc^{Min/+}$mice	Decreases intestinal adenoma formation Increases therapeutic efficacy by inducing epigenetic modification	↓RXRα, COX-2, β-catenin, cyclin D1	(139)
Oleuropein	50, 100 mg/kg for 56 days, *In vivo*: AOM/DSS mice	Decreases intestinal adenoma formation Suppresses cancerization Decreases inflammation	↓Ki-67, IL-6, IFN-γ, TNF-α, IL-17A, cyclooxygenase-2, Bax, proliferating cell nuclear antigen, p-STAT3, p-Akt	(133)
Honokiol	5 mg/kg for 24 weeks, *In vivo*: AOM/DSS mice 0-50 μM for 72 h, *In vitro*: HCT116, SW480, DLD1, RKO and HT29	Decreases intestinal adenoma formation Induces apoptosis Inhibits CSCs	↓DCLK1, LGR5, CD44, Bcl2, BclXL, YAP1, TEAD1 At G1 phase ↑caspase-3, p53, PUMA	(127)
	400 mg/kg for 10 weeks, *In vivo*: $Apc^{Min/+}$mice	Regulates Metabolic Pathways	tryptophan metabolism, citrate cycle (TCA cycle), and pentose phosphate pathway	(128)
Sesamol	500 ppm for 8 weeks, *In vivo*: $Apc^{Min/+}$mice 50, 100 μM for 48 h, *In vitro*: DLD-1/ COX-2-B2-β-gal-BSD	Decreases intestinal adenoma formation Decreases inflammation	↓COX-2, cPGES, mPGES2, EP1, EP2	(130)
Oligonol	0. 5, 5 mg/kg for 8 weeks, *In vivo*: AOM/DSS mice 0. 5, 5 mg/kg/day for 7 days, *In vivo*: DSS mice 10, 20 μM for 24 h, *In vitro*: RAW 246. 7 and CCD841CoN	Decreases intestinal adenoma formation Decreases inflammation Induces apoptosis Reduces oxidative stress	↓TUNEL, COX-2, iNOS, p-IκBα, p-p65 IL-1β, TNF-α, IL-6, COX-2 ↑IκBα, HO-1, NQO-1, TRX 1, GPx-2	(73)

ACF, aberrant crypt foci; AOM, azoxymethane; APC, adenomatous polyposis coli; ATF, activating transcription factor; ATG, autophagy-related protein; ATM, ataxia telangiectasia-mutated gene; Bax, B-cell lymphoma 2 associated X protein; Bcl-2, B-cell lymphoma; Braf, B rapidly accelerated fibrosarcoma; CDK, cyclin-dependent kinase; CIN, chromosomal instability; CIMP, CpG island methylator phenotype; COX-2, cyclooxygenase 2; CRA, colorectal adenoma; CRC, colorectal cancer; CSC, cancer stem cell; CSF, Colony Stimulating Factor; CTNNB1, Catenin Beta 1; CXCR4, C-X-C chemokine receptor type 4; DMH, 1, 2-dimethylhydrazine; DNMT, DNA methyltransferase; DSS, 4, 4-dimethyl-4-silapentane-1-sulfonic acid; EGCG, epigallocatechin-3-gallate; EMT, epithelial-mesenchymal transition; Erk1/2, extra-cellular-signal-regulated kinase 1/2; GPx, glutathione peroxidase; GSK-3β, glycogen synthase kinase 3-β; Ifn-γ, interferon γ; IL, interleukin; iNOS, inducible nitric oxide synthase; IPP, isopentenyl diphosphate; IRE-1, inositol requiring kinase-1; JNK, Jun N-terminal kinase; Klf4, Kruppel Like Factor 4; Kras, Kirsten rat sarcoma virus oncogene homolog; MAPK, mitogen-activated protein kinase; MMP-2, matrix metalloproteinase 2; MMP, mitochondrial membrane potential; MSI, micro-satellite instability; c-MYC, Myc proto-oncogene; NSAID, Non-steroidal anti-inflammatory drug activated gene; NF-κB, nuclear factor kappa B; Nrf2, nuclear related factor 2; PARP, poly (ADP-ribose) polymerase; PAS, Periodic Acid-Schiff; PCNA, proliferating cell nuclear antigen; PERK, protein kinase-like ER kinase; PGE2, prostaglandin E2; PI3K, phosphatidylinositol 3-kinase; PIK3CA, Phosphatidylinositol-4, 5-Bisphosphate 3-Kinase Catalytic Subunit Alpha; PKCδ, Protein kinase C delta; PPAR, Peroxisome Proliferator Activated Receptor; Rb, retinoblastoma; ROS, reactive oxygen species; RXRα, retinoid X receptor alpha; SMAD4, Recombinant Mothers Against Decapentaplegic Homolog 4; SOD, superoxide dismutase; Sox2, SRY-Box Transcription Factor 2; SSLs, sessile serrated lesions; STAT, signal transducer and activator of transcription; TCF, Transcription Factor; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor alpha; TP53, Tumor Protein P53; Wnt, wingless-type.

hypertension, inflammatory diseases and cancer (41). Previous studies have shown that digitoflavone inhibits tumorigenesis. Yang *et al* (42) found that digitoflavone significantly reduced the incidence, number, and size of adenomas in AOM/DSS mice, and upregulated Nrf2, TR, γ-GCSc, γ-GCSm, and HO-1 protein expression levels, as well as GR, TR, HO-1, γ-GCSc, γ-GCSm and NQO-1 mRNA levels. It was proved that the beneficial effect of digitoflavone on adenoma progression was attributed to the activation of Nrf2 pathway.

Genkwanin (GKA) is a typical bioactive non-glycosylated flavonoid isolated from *Daphne genkwa* and has significant anti-inflammatory, antibacterial and immunomodulatory activities (43,44). GKA has favorable anti-inflammatory activity in lipopolysaccharide (LPS)-activated macrophages by regulating miR-101/MKP-1/MAPK pathway (45). Wang *et al* (46) found that after oral administration of 12.5-25 mg/kg/day GKA, abnormal adenomas in $APC^{Min/+}$ mice were significantly improved, particularly for large adenomas, and tumor diversity was reduced. GKA upregulated IL-2, IL-4, IL-12, IFN-γ, and TNF-α levels and downregulation of IL-10 levels. The studies showed that GKA's antitumor activity was partly through enhancing host immunity and reducing inflammatory cytokines. In another study, the researchers developed a GKA-loaded self-nanoemulsifying drug delivery system (GKA-SNEDDS) to improve the solubility of GKA, intestinal permeability and oral bioavailability. A recent study revealed that GKA-SNEdDS can induce intestinal tumor cell apoptosis in AOM/DSS mice to inhibit adenoma carcinogenesis, significantly improve weight loss and disease activity index (DAI), and lower the histological score of inflammatory cytokines (47).

Flavonols. Quercetin, a common flavonoid in plants, can induce G2 cell cycle arrest, inhibit angiogenesis and downregulate NF-κB expression due to its strong antioxidant and free radical scavenging properties (48). Quercetin-rich plants have been used to treat inflammatory diseases, tumors and hypertension (41). Previous studies showed that quercetin significantly reduced the number of intestinal adenomas (>2 mm 69%, 1-2 mm 79%) in $APC^{Min/+}$ mice (49). Velazquez *et al* (50) showed that quercetin may reduce the adenoma load of $APC^{Min/+}$ mice by inducing phosphorylation of plasma IL-6 and muscle signal transduction and transcriptional activator 3. In addition, quercetin significantly improved the decline of body function and metabolism in mice.

Kaempferol is found in a variety of plants and has been proven to have anti-inflammatory, antioxidant, antibacterial and antitumor activities (51). Kaempferol is associated with reduced incidence of various types of cancer, including skin, liver and gastric cancer (52). Kaempferol significantly reduces adenomatosis and tumor load in AOM/DSS mice and increases DACT2 gene expression in tumor tissues. β-catenin, CTNNB1 and LRP6 gene expression levels in CRC tissues were significantly inhibited by kaempferol-induced DACT2 repair. Similarly, kaempferol significantly increased gene expression of DACT2 in HCT116, HT29 and YB5, significantly decreased methylation of DACT2, and increased unmethylated DACT2 by 13.72 times. Further studies showed that the proliferation and migration of CRC cells are limited, and kaempferol could inhibit nuclear β-catenin and inactivates the Wnt/β-catenin pathway by directly binding DNA methyltransferase (DNMT) 1 (53).

Myricetin, as a natural dietary flavonoid compound, has the potential of enhancing immune regulation, inhibiting cytokine storm and antiviral, and has therapeutic effects on different types of tumors, inflammatory diseases, atherosclerosis, thrombosis and diabetes (54). Previous studies have shown that myricetin can reduce the number of adenomas in $APC^{Min/+}$ mice and reduce the number and degree of dysplasia in adenomas without any side effects. Myricetin selectively inhibits cell proliferation by downregulating Cyclin D1 and PCNA expression, and induces apoptosis of adenoma cells by downregulating Bax, c-Caspase-3, which may be related to the regulation of GSK-3β and Wnt/β-catenin pathways. Myricetin reduces the concentration of IL-6 and PGE2 in the blood. These results suggested that the mechanism of myricetin in treating adenoma may be the downregulation of phosphorylated p38MAPK/Akt/mTOR signaling pathway (55). Another study showed that myricetin significantly reduces the size and degree of small CRAs in AOM/DSS mice. In addition, myricetin significantly reduces the expression of inflammation factor TNF-α, IL-1β, NF-κB, p-NF-κB and COX-2 (56).

Isorhamnetin is one of the most important active components in *Ginkgo biloba* leaves, with antitumor, antibacterial, anti-inflammatory and antioxidant effects (57). Clinical studies have shown that intake of a diet rich in isorhamnetin is associated with a reduced risk of advanced adenoma recurrence (58), but the mechanism is unclear. A recent study reported that supplementation with an isorhamnetin diet significantly reduced the incidence of CRA, tumor number and load in AOM/DSS mice. Further studies demonstrated that isorhamnetin reduced DSS-induced inflammatory response, inhibited C-SRC activation and β-catenin nuclear translocation, and promoted the expression of c-terminal Src kinase (CSK), a negative regulator of the Src family of tyrosine kinases, which was also verified *in vitro*. In conclusion, the chemoprotective effects of isorhamnetin in adenomas are associated with anti-inflammatory activity, inhibition of carcinogenic Src activity, and loss of nuclear β-catenin (CSK-dependent activity) (59).

Anthocyanins. Anthocyanins are water-soluble flavonoids, whose stability is affected by pH, light, temperature and other factors (60). Studies have shown that anthocyanins can treat a variety of diseases, including neurodegenerative, cardiovascular and metabolic diseases and cancer, and regulate oxidative stress and intestinal microbiota (61). Freeze-dried Acai berry pulp (AP) is rich in cyanidin 3-rutinoside (C3R). In 1, 2-dimethylhydrazine and 2, 4, 6-trinitrobenzoic acid-induced male Wistar rats, intake of freeze-dried AP reduced adenoma proliferation, the incidence of high-grade intraepithelial adenoma, the total number of aberrant crypt foci (ACF) and ACF multiplicity. In addition, C3R (25 μM) has the potential to decrease RKO cell motility *in vitro*, and AP increases gene expression of negative cell proliferation regulators including Dlc1 and Akt3 (62). Fernandez *et al* (63) found that anthocyanins from a mixture of dehydrated blackberries and strawberries significantly reduced the number of CRAs in AOM/DSS mice and increased the total antioxidant activity of FRAP (plasma iron reduction capacity). Differences in colon microbiota before and after intervention were examined by 16S rRNA, which showed that anthocyanins could reduce

Table II. List of polyphenols isolated from natural sources.

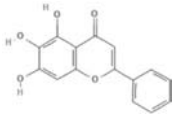
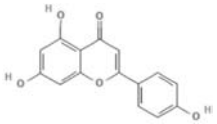
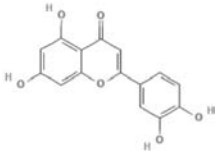
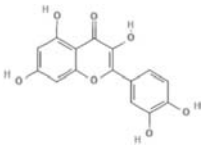
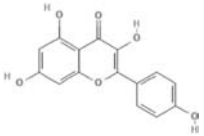
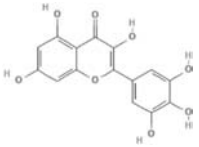
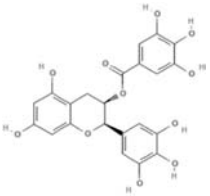
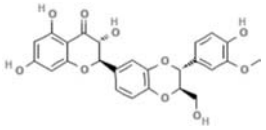
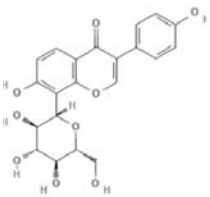
Phytochemicals	Chemical structures and Molecular formula	Molecular weight (g/mol)	Primary sources	(Refs.)
Baicalein	$C_{15}H_{10}O_5$ 	270.24	*Scutellariae Radix* *Arum Ternatum Thunb* *Scutellariae Barbatae Herba* *Plantaginis Herba* *Carthami Flos*	(36)
Apigenin	$C_{15}H_{10}O_5$ 	270.24	*Herba Patriniae* *Isatidis Radix* *Lobeliae Chinensis Herba* *Menthae Herba*	(39)
Digitoflavone	$C_{15}H_{10}O_6$ 	286.24	*Herba Patriniae* *Anisi Stellati Fructus* *Menthae Herba* *Ajugae Decumbentis Herba*	
Quercetin	$C_{21}H_{20}O_{11}$ 	302.23	*Herba Patriniae* *Hedyotis Diffusae Herba* *Folium Artemisiae Argyi* *Anisi Stellati Fructus*	(50)
Kaempferol	$C_{15}H_{10}O_6$ 	286.24	*Herba Patriniae* *Paeoniae Radix Alba* *Anisi Stellati Fructus* *Ardisiae Japonicae Herba*	(53)
Myricetin	$C_{15}H_{10}O_8$ 	318.23	*Carthami Flos* *Sedum Aizoon L.* *Choerospondiatis Fructus* *Folium Nelumbinis*	(55)
EGCG	$C_{22}H_{18}O_{11}$ 	458.4	*Green tea* *Ginkgo Semen* *Eriobotryae Folium* *Phyllanthi Fructus*	(71)
Silibinin	$C_{25}H_{22}O_{10}$ 	482.4	*Silybum Marianum*	(87)
Puerarin	$C_{21}H_{20}O_9$ 	416.4	*Radix Bupleuri* *Cyathulae Radix* *Radix Puerariae* *Puerariae Flos* *Hemerocallis Radix*	(80)
Isoliquiritigenin	$C_{15}H_{12}O_4$	256.25	*Licorice*	(83)

Table II. Continued.

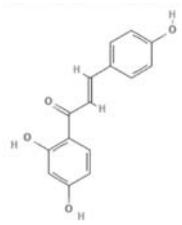
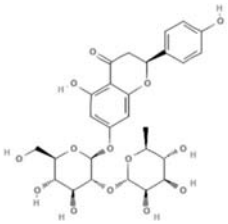
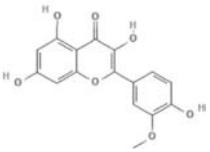
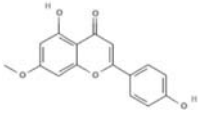
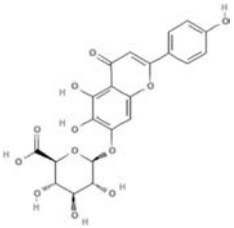
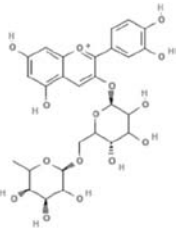
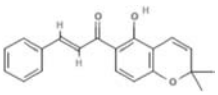
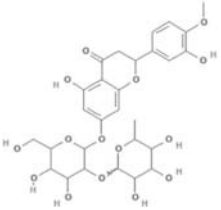
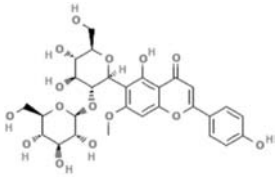
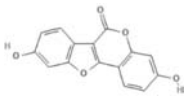
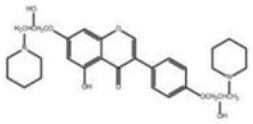
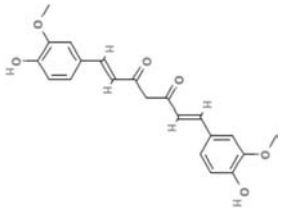
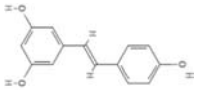
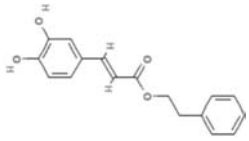
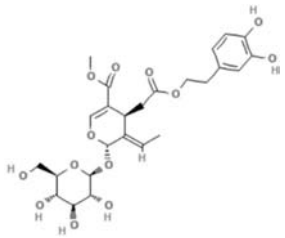
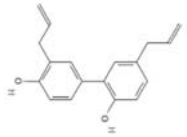
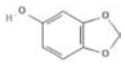
Phytochemicals	Chemical structures and Molecular formula	Molecular weight (g/mol)	Primary sources	(Refs.)
			*Radix Bupleuri* *Isatidis Radix* *Amygdalus Communis Vas* *Myristicae Semen* *Epimrdii Herba*	
Naringin	$C_{27}H_{32}O_{14}$ 	580.5	*Citrus Reticulata* *Citri Exocarpium Rubrum* *Aurantii Fructus Immaturus* *Licorice* *Hedysari Radix* *Canarii Fructus*	(75)
Isorhamnetin	$C_{16}H_{12}O_{7}$ 	316.26	*Ginkgo Semen* *Pulsatilliae Radix* *Licorice* *Folium Nelumbinis* *Radix Bupleuri*	(59)
Genkwanin	$C_{16}H_{12}O_{5}$ 	284.26	*Flos Genkwa* *Ephedra Herba* *Ginkgo Folium* *Artemisiae Scopariae Herba*	(46)
Scutellarin	$C_{21}H_{18}O_{12}$ 	462.4	*Scutellariae Radix* *Scutellariae Barbatae Herba* *Oroxyli Semen* *Perilla Frutescens*	(90)
Cyanidin 3-rutinoside	$C_{27}H_{31}O_{15}$ 	595.5	*açaí pulp*	(62)
Lonchocarpin	$C_{20}H_{18}O_{3}$ 	306.4	*Lonchocarpus sericeus*	(84)
Neohesperidin	$C_{28}H_{34}O_{15}$ 	610.6	*Aurantii Fructus*	(78)

Table II. Continued.

Phytochemicals	Chemical structures and Molecular formula	Molecular weight (g/mol)	Primary sources	(Refs.)
Spinosin	$C_{28}H_{32}O_{15}$ 	608.5	*Ziziphi Spinosae Semen* *Jujubae Fructus*	(96)
Coumestrol	$C_{15}H_8O_5$ 	268.22	*Jujubae Fructus* *Puerariae Flos*	(100)
GEN-27	$C_{31}H_{40}N_2O_7$ 	552		(102)
Curcumin	$C_{21}H_{20}O_6$ 	368.4	*Alpiniae Officinarum Rhizome* *Momordicae Fructus* *Curcumae Radix*	(109)
Resveratrol	$C_{14}H_{12}O_3$ 	228.24	*Polygoni Cuspidati Rhizoma Et Radix* *Mori Cortex* *Smilacis Glabrae Rhixoma*	(124)
Caffeic Acid Phenethyl Ester	$C_{17}H_{16}O_4$ 	284.31	*propolis*	(131)
Oleuropein	$C_{25}H_{32}O_{13}$ 	540.5	*Olea europaea* *Fructus Ligustri Lucidi*	(133)
Honokiol	$C_{18}H_{18}O_2$ 	266.3	*Magnolia Officinalis Rehd Et Wils* *Anisi Stellati Fructus*	(127)
Sesamol	$C_7H_6O_3$ 	138.12	*Sesami Nigrum Semen* *Asari Radix Et Rhizoma* *Piperis Longi Fructus*	(130)

the occurrence of adenomas by reducing the abundance of pro-inflammatory *Bilophila wadsworthia* population.

Freeze-dried black raspberry (BRB) powder reduced the rate of adenoma canceration in AOM/DSS mice. The

number of pathogenic bacteria, including *Desulfovibrio* and *Enterococcus*, was significantly increased, while probiotics such as *Eubacterium rectale*, *Faecalibacterium prausnitzii* and *Lactobacillus* were significantly decreased in AOM/DSS mice, but BRB anthocyanin supplementation reversed this imbalance in the gut microbiome. BRB anthocyanins also cause demethylation of the SFRP2 gene promoter, resulting in increased SFRP2 expression at mRNA and protein levels. In addition, BRB anthocyanins downregulated the expression of DNMT31 and DNMT3B as well as P-STAT3. These results suggested that BRB anthocyanins may play a role in reducing the carcinogenesis rate of adenomas by regulating the composition of intestinal microbiota, changes in inflammation and methylation status of SFRP2 gene (64).

Another study showed that anthocyanin-containing purple-fleshed potatoes reduced the number of cells containing nuclear β-catenin (an indicator of colon CSC) by inducing mitochondria-mediated apoptosis and reduced adenoma incidence similar to sulindac in AOM/DSS mice. Further research showed that anthocyanin-containing baked purple-fleshed potato extracts inhibited proliferation and promoted apoptosis in colon CSCs in a p53-independent manner. It also inhibited the levels of Wnt pathway effector β-catenin (a key regulator of CSC proliferation) and its downstream proteins (c-myc and cyclin D1) and increased the levels of Bax and cytochrome C (proteins that mediate mitochondrial apoptosis) (65).

Anthocyanins from red grape pomace significantly reduced the adenoma load and the number of adenomas in $APC^{Min/+}$ mice, downregulated the expression levels of Ki-67, Akt and ERK proteins, and upregulated the expression of pERK, suggesting that Akt and pERK may be suitable biomarkers for the efficacy of anthocyanin target organs (66).

Kang *et al* (67) found that anthocyanins from red grape pomace may reduce the cecal adenoma load in $APC^{Min/+}$ mice by inhibiting cyclooxygenase, and its inhibitory effect is more significant than sulindac. In addition, anthocyanins in cherry diet also significantly inhibited the proliferation of HT29 and HCT116, indicating that anthocyanins have favorable antitumor effects.

A previous study demonstrated that anthocyanin-rich bilberry extract reduces the occurrence of adenomas in AOM/DSS mice, and decreases inflammatory response and intestinal length reduction caused by inflammation (68). In addition, it has been revealed that anthocyanin-enriched Sweet Potatoes significantly reduced the number of adenomas in $APC^{Min/+}$ mice (69).

Flavanol. EGCG is the main catechin in green tea and has been shown to have a variety of pharmacological effects, including antioxidant, antitumor, anti-inflammatory, anti-microbial, anti-angiogenic, and cholesterol-lowering effects (70). EGCG was found to inhibit adenoma formation and reduce adenoma load in $APC^{Min/+}$ mice. BFGF protein degrades rapidly in the presence of EGCG, but this degradation is inhibited by proteasome inhibitors, while EGCG increases ubiquitin of bFGF and trypsin-like activity of 20S proteasome, leading to bFGF protein degradation. These results indicated that EGCG inhibition of adenoma is related to the decrease of bFGF expression (71). Similarly, Wang *et al* (72) showed that EGCG can reduce the adenoma load of AOM/DSS mice and reduce the number of ACF to delay the histological progression, and the intestinal microbiota structure is relatively stable during EGCG intervention, which may be the potential mechanism of EGCG inhibiting tumor.

Oligonol is a catechin oligomer extracted from litchi fruit, consisting of 17.6% of catechin-type monomers and 18.6% of proanthocyanidin dimers and trimers derived from grape seeds or lychee fruit with antioxidative and anti-inflammatory properties. A previous study showed that oligonol significantly inhibited the incidence and diversity of CRAs in AOM/DSS mice, and inhibited the activation of NF-κB and STAT3, as well as the expression of COX-2, iNOS and cyclin D1 in DSS-induced mice.

In addition, oligonol prevents oxidative stress-induced apoptosis of colon epithelial cells by attenuating lipid peroxidation (malondialdehyde) and protein oxidation (4-hydroxy-2-nonenal). Further studies showed that oligonol reduced the expression of IL-1β, TNF-α, IL-6, COX-2 and inosine in LPS-induced RAW264.7 cells. In another study, Ho-1, NQO-1, TRX 1 and GPX-2 antioxidant genes were upregulated by oligonol in intestinal epithelial CCD841CoN cells (73).

Flavanones. Naringin, a natural flavonoid, is rich in citrus fruits and has a wide range of pharmacological activities, including anti-inflammatory, anticancer, oxidative stress and genetic damage (74). A study evaluating the inhibitory effect of naringin on AOM/DSS mice found that naringin reduced the severity of CRAs by inhibiting myeloid-derived suppressor cells, pro-inflammatory mediators GM-CSF/M-CSF, IL-6 and NF-κB/IL-6/ST pathway in CRAs. Moreover, naringin can prevent ulcerative colitis and canceration induced by AOM/DSS without obvious side effects. Naringin-treated mice showed normal colorectal tissue structure and electron microscopic analysis showed that endoplasmic reticulum (ER) stress-induced autophagy was inhibited. Naringin inhibits the secretion of ER transmembrane proteins including GRP78 ATF6, IRE1, and activated PERK-phosphorylated EIF-2, as well as the autophagosome complexes ATG3, ATG5, ATG7, ATG12, ATG16 and ATG16L1 in intestinal mucosal cells. In conclusion, naringin prevents adenoma occurrence and progression by inhibiting ER stress-induced autophagy of mucosal cells in CRC (75).

Neohesperidin (NHP) is widely found in citrus fruits regulating intestinal microbiota (76) and regulating immunity (77). A recent study reported that NHP inhibits adenomatosis in $APC^{Min/+}$ mice, induces apoptosis and blocks angiogenesis *in vivo*. In the presence of NHP, the relative abundance of *Bacteroidetes* decreased, while the relative abundance of *Firmicutes* and *Proteobacteria* increased. In addition, fecal microbiota transplantation experiments further demonstrated that intestinal adenoma was significantly inhibited by feeding with NHP-treated fecal extract of mice, suggesting that changes in intestinal microbiota are the cause of NHP-mediated prevention of colorectal tumor (78).

Isoflavones. Puerarin, a natural isoflavone extracted from *Pueraria lobata*, has potential antitumor, antioxidant and anti-inflammatory activities (79), but it has low solubility and low bioavailability. In a recent study, puerarin-loaded alginate microspheres (plams) were prepared by emulsion/internal gel method for the treatment of adenomas. Plams not only significantly reduced the inflammatory response by downregulating

the expression of tumor-promoting cytokines TNF-α and IL-17A but reduced the occurrence of adenoma and carcinogenesis by inhibiting AOM/DSS-induced EMT in mice (80).

Chalcones. Isoliquiritigenin (ISL), a flavonoid with chalcone structure extracted from *Glycyrrhiza uralensis*, can activate the antioxidant system mediated by nuclear factor erythroid-2 related factor 2 (Nrf2) and negatively regulate nuclear factors-κB(NF-κB) and nod-like receptor thermal protein domain associated protein 3 (NLRP3) (81) and has significant antitumor effect (82). A previous study has shown that ISL can significantly reduce the incidence of intestinal adenomas and regulate the intestinal microbiota in AOM/DSS mice. 16S rRNA detection revealed that the structure of intestinal microbial community in AOM/DSS mice changed significantly, the level of *Bacteroidetes* decreased, and *Firmicutes* increased. High dose ISL (150 mg/kg) reversed the imbalance at phylum level and changed the diversity composition of the intestinal microbiota, in which the abundance of *Helicobacter* increased, while the abundance of *Lachnospiraceae* and *Rikenellacea*e decreased. At the genus level, ISL reduced the abundance of opportunistic pathogens (*E. coli* and *Enterococcus*) and increased the level of probiotics, particularly butyrate-producing bacteria (*Coccidioides butyricus*, *Clostridium* and *Ruminococcus*). In addition, ISL decreased IL-6, IL-10, TNF-α, IL-1 β and COX-2 expression, suggesting that ISL may have a synergistic effect with intestinal microbiota in protecting AOM/DSS mice (83).

Lonchocarpin is a Wnt/β-catenin pathway inhibitor isolated from *Lonchocarpus sericeus*, which is cytotoxic to neuroblastoma and leukemia cell lines (79). A recent study demonstrated that lonchocarpin could reduce the proliferation of adenoma cells in AOM/DSS mice and significantly reduce the proportion of Ki-67 and BrdU positive cells in the tumors of mice without any toxicity (84). Further studies showed that lonchocarpin inhibited nuclear localization of β-catenin and constitutive active form of TCF4-dnTCF4-VP16. Embryological analysis of *Xenopus laevis* showed that lonchocarpin plays a role at the transcriptional level. In addition, lonchocarpin inhibited cell migration and proliferation in HCT116, SW480 and DLD-1 CRC cell lines, without any detectable effect on the non-tumorigenic intestinal cell line IEC-6 (84).

Other flavonoids. Milk thistle, a flavonoid antioxidant compound mainly composed of silibinin, is a key regulator of CDK4 cell cycle. When CDK4 becomes active by binding to cyclin D1, it allows cells to enter the G1 phase of the cell cycle, and enters the S phase by phosphorylating retinoblastoma protein. APC mutation, which functions by activating CDK4 pathway, plays a key role in the early stage of intestinal tumorigenesis (85). A previous study demonstrated that silibinin inhibits cell proliferation *in vivo* and *in vitro* and leads to G1 arrest of cell cycle (regulated by CDK4 pathway) (86). It was also identified that silibinin could significantly reduce the size and number of adenomas in $APC^{Min/+}$ mice, and significantly reduce the expression of CDK4 and Ki67 pathway components in the epithelium (87). In the study of Barone *et al* (88), the role of silybin has been confirmed. Silybin is the main component of silymarin (SIL). Estrogen receptor beta (ERβ) is considered to be gradually decreased in human adenoma-cancer sequence, and ERβ deficiency increases small intestinal tumorigenesis in rodents.

ERβ selective agonists SIL and/or lignin (LIG) were added to $APC^{Min/+}$ mice, and even a specific combination of SIL and LIG significantly counteracted the occurrence of intestinal adenomas and increased ERβ mRNA and protein levels. Cell proliferation and apoptosis were rebalanced and cell migration was accelerated, which was similar to that of wild-type mice (88).

Scutellarin is a flavonoid isolated from *Scutellaria baicalensis*, which has the effects of anti-inflammation, antioxidation and regulating immunity (89). A recent study has shown that scutellarin inhibits adenoma carcinogenesis and alleviates pathological symptoms in AOM/DSS mice. Scutellarin decreased the concentration of serum TNF-α and IL-6, increased the expression of Bax and decreased the level of Bcl-2 in adenoma by downregulating the cascade of Wnt/β-catenin signal, which was verified *in vitro*. It was suggested that scutellarin can prevent the carcinogenesis of adenoma by reducing the cascade of Wnt/β-catenin signal (90).

Radix *Tetrastigma hemsleyani* flavone (RTHF) is the main component of the root of *Radix Astragali*, which has been shown to have anti-inflammatory, analgesic, antiviral and immunomodulatory effects (91). Wu *et al* (92) found that RTHF can reduce the number and size of intestinal adenomas and prevent adenoma carcinogenesis in AOM/DSS mice, and RTHF can reduce cell proliferation, induce cell cycle arrest in G0/G1 phase and inhibit epithelial-mesenchymal transition in a dose-dependent manner. In addition, RTHF inhibits the expression of Lgr5, c-Myc and Cyclin D1 in tumor tissues. In conclusion, the inhibition of CRA by RTHF is related to the decrease of the activity of Wnt/β-catenin pathway and the downregulation of target gene expression (92).

Spinosin exists widely in *Ziziphi Spinosae* semen (ZSSP), which has the effects of anti-inflammation and antioxidant stress, and has a favorable curative effect on colitis, anxiety and sleep disorder (93,94). The water-soluble polyphenols extracted from ZSSP have significant anti-colorectal tumor activity, including inhibiting cell proliferation and promoting cell apoptosis (95). In AOM/DSS mice, ZSSP reduced the number and volume of adenomas in a dose-dependent manner, inhibited the carcinogenesis of adenomas and reduced AOM/DSS-induced organ damage in mice. Immunohistochemical analysis demonstrated that ZSSP could downregulate the expression of COX-2, EMR1 and Ki67. Further studies showed that spinosin was identified as an antitumor component of ZSSP by the macroporous resin of SP207 and RP-HPLC-MS/MS (96).

Polymethoxyflavones (PMF), a family of natural compounds containing nobiletin, hesperidin, heptamethoxyflavonoids and tetramethoxyflavonoids, are found almost exclusively in citrus plants (97). PMF is higher in pericarp than in other edible parts of fruit and has a wide range of biological activities, including antioxidant, antitumor and anti-inflammatory (98). A previous study reported that PMF significantly inhibits the formation of BaP/DSS-induced CRAs by regulating BaP metabolism and reducing BaP mutagenic metabolites and DNA adducts, and downregulates the expression levels of IL-6, IL-10, TNF-α, COX-2, MCP1 and CXCL-1 to alleviate inflammation. The results of RNA-sequencing (RNA-seq) showed that PMFs improved the abnormal molecular mechanism induced by BaP/DSS, including activating inflammation, downregulating antioxidant targets and inducing transfer genes. Autophagy

defects caused by BaP/DSS-induced tumorigenesis were improved by PMF. In addition, PMFs also changed the composition of intestinal microbiota, increased butyrate-producing probiotics and reduced tumor-related bacteria (99).

Coumestrol is a kind of phytoestrogen and belongs to flavonoids. Previous studies have shown that ovariectomy increased the number of intestinal adenomas in $APC^{Min/+}$ mice by 77%. Replacing estradiol (E2) in ovariectomized $APC^{Min/+}$ mice reduced the number of adenomas to baseline levels and upregulated the expression of estrogen receptor beta (ERβ). A previous study revealed that coumestrol significantly inhibited the volume of intestinal adenomas in ovariectomized $APC^{Min/+}$ mice. Moreover, coumestrol improved the damage of E-cadherin and β-catenin and upregulated the protein expression of ERβ (100).

Genistein, an isoflavone found in soybean, can inhibit inflammation, promote apoptosis and regulate steroid hormone receptors (101). It has been found that genistein reduces the number of adenomas at the same level as non-ovariectomized mice (100). Genistein 27 (GEN-27), a derivative of genistein, protects mice from adenoma carcinogenesis induced by AOM/DSS, reduces the number and volume of adenomas and reduces the mortality of mice. Furthermore, GEN-27 increased the expression of APC and AXIN2 and decreased the nuclear localization of β-catenin, which was due to the inhibition of nuclear localization of NF-κB/p65 and upregulation of CDX2. Moreover, GEN-27 decreased the binding of p65 to CDX2 silent region and increased the binding of CDX2 to APC and AXIN2 promoter regions, thus inhibiting the activation of β-catenin induced by TNF-α. In addition, GEN-27 significantly decreased the secretion of proinflammatory cytokines and macrophage infiltration. The results showed that the anti-proliferation effect of GEN-27 is mediated by p65-CDX2-β-catenin pathway through the inhibition of β-catenin target gene (102).

Bergamot is a typical plant produced in Italy, and its fruit is mainly used to extract essential oil. It was previously identified that flavonoid-rich extract from bergamot juice (BJe) has antitumor effects (103), which is related to the fact that BJe can interfere with intracellular signaling pathways related to tumor initiation, promotion and progression (104). It has been found that Bje has antioxidant and anti-inflammatory activities *in vitro* and *in vivo* (105). BJe (35-70 mg/kg) significantly reduced the number of colonic and small intestinal adenomas in Apc mutant rats, and the mucin depletion foci of colon premalignant lesions showed a significant dose-related decrease.

It should be noted that BJe of 70 mg/kg significantly downregulated inflammation-related genes (COX-2, iNOS, IL-1 β, IL-6, IL-10 and Arginase1), induced apoptosis, significantly upregulated p53 and survivin, and downregulated p21 gene expression in rat colon tumors. It is suggested that the inhibitory effect of Bje on adenoma is partly due to its pro-apoptotic and anti-inflammatory effects (106).

Daphne genkwa Sieb. et Zucc. is a famous medicinal plant, and total flavonoids of *Daphne genkwa* (TFDG) are the active ingredient. In $Apc^{Min/+}$mice, the number and diversity of colonic adenomas decreased significantly after TFDG treatment, and the life span of mice was significantly prolonged. TFDG significantly downregulated the expression of IL-1α, IL-1β, IL-6, IL-10 and G-CSF in intestinal tissue and serum, and downregulated the expression of IL-2, IL-12, IFN-γ and TNF-α in serum. These results suggested that the effect of TFDG may be related to its ability to regulate immunity and inhibit the production of inflammatory cytokines (107).

Phenolic acids. CUR is a bioactive component derived from the rhizome of turmeric. It has been shown to exert anti-inflammatory and antitumor properties by interacting with several molecular targets, including transcription factors, enzymes, cyclins, cytokines, receptors and adhesion molecules (108). Girardi *et al* (109) showed that a diet rich in CUR could reduce the total number and average size of adenomas in $APC^{Min/+}$ mice. In the high CUR diet group, the number of atypical hyperplasia and CRC decreased significantly, and CUR significantly upregulated caspase3 and downregulated the level of Cyclin D1 (109). COX2 is one of the most important molecules involved in tumorigenesis. High expression of COX-2 can be detected in adenomas (110,111). CUR can reduce the size and number of adenomas by significantly inhibiting the mRNA and protein expression of COX2, but does not inhibit the expression of COX1 (112,113). In addition, CUR may play a role in the treatment of adenoma by inhibiting the expression of pro-inflammatory cytokines IL-1 β, IL-6 and Cox-2 and downregulating Axin2 in Wnt/β-catenin signal pathway (114). McFadden *et al* (115) showed that CUR increased the abundance of intestinal bacteria in AOM mice, prevented the decrease of age-related alpha diversity, increased the relative abundance of *Lactobacillus*, and reduced or eliminated the load of CRAs, indicating that the beneficial effect of CUR on tumorigenesis is related to the maintenance of more diverse intestinal microecology. CUR has the disadvantage of being insoluble in water due to its high hydrophobicity. Adachi *et al* (116) used surface control technology to form submicron particles of CUR, which significantly improved its water solubility, and this derivative was named Theracurmin. Treatment with 500 ppm Theracurmin for 8 weeks inhibited the development of intestinal adenoma and did not change the transcriptional activity of NF-κB promoter, but inhibited the expression of MCP-1 and IL-6 mRNA, the downstream target of NF-κB (116). Seiwert *et al* (117) also confirmed the therapeutic effect of CUR on adenomas. Compared with the control group, the number of adenomas in mice treated with micellar CUR (mCUR) decreased significantly. No side effects were observed in animals that received mCur daily for at least three months (117).

Turmerone (TUR) is another compound of turmeric, which is composed of five structure-related sesquiterpenes including ar-TUR. A study of combination therapy showed that both TUR and CUR could inhibit the expression of iNOS and COX-2 in AOM/DSS mice induced by LPS. Tracing experiments with actinomycin D showed that CUR accelerated the decay of iNOS and COX-2 mRNA and prevented LPS-induced HuR translocation, which indicated that there was a post-transcriptional mechanism. In AOM/DSS mice, TUR significantly inhibited the diversity of adenomas, the combination of CUR and TUR eliminated tumor formation, and oral TUR significantly inhibited colorectal shortening by 52-58% (118).

Another study on the treatment of AOM/DSS mice with CUR combined with ASA showed that CUR significantly

inhibited the occurrence and development of adenoma in a dose-dependent manner compared with ASA. RNA-seq revealed that compared with the single treatment, the low-dose combination of CUR and ASA could downregulate the protein expression of Alb and Mfap4, and upregulate the mRNA expression of Krt36, Tacstd2, Hoxd10 and Hoxd13. These differentially expressed genes are located in several classical pathways in adenomatous inflammatory carcinogenesis and liver metastasis of CRC (119). Another study of 3,3-diindolylmethane (DIM) combined with CUR in the treatment of tumors in F344/NTac-Apc^{am1137} Pirc rats showed that DIM and CUR significantly decreased the number and severity of CRAs and increased apoptosis in mucosa. In addition, a slight decrease in Survivin-Birc5 expression was observed in all treatments compared with the control group (120). Lev-Ari *et al* (121) have shown that physiological dose of celecoxib (5 μmol/l) inhibits cell proliferation and promotes apoptosis through COX-2-dependent and independent pathways in the presence of 10-15 μmol CUR, thus inhibiting the growth of CRAs.

Stilbenes. RSV (3,4,5-Trihydroxy-trans-stilbene) is a kind of natural polyphenol with antioxidant, anti-inflammatory and anticancer properties, which is well absorbed *in vivo* and metabolized rapidly and widely (122). Studies have shown that RSV significantly reduces the number of adenomas in AOM/DSS mice (123). RSV combined with grape seed extract (RSV-GSE) significantly inhibited the occurrence of intestinal adenoma in AOM/DSS mice without any gastrointestinal toxicity. RSV-GSE reduced the number of crypts containing nuclear β-catenin by inducing apoptosis. *In vitro*, RSV-GSE inhibited Wnt/β-catenin pathway, c-Myc and cyclin D1 protein levels, but sulindac did not. RSV-GSE also induces mitochondrial-mediated apoptosis in colonic CSC, which is characterized by p53, increased Bax/Bcl-2 ratio and PARP cleavage. In addition, short hairpin RNA-mediated knockdown of p53 (a tumor suppressor gene) in colonic CSC did not change the efficacy of RSV-GSE (124). Saud *et al* (125) constructed APC^{CKO}/Kras^{mut} mice to study the antitumor effect of RSV. They found that adding 150 or 300 ppm RSV to mice inhibits 60% of tumorigenesis. In 40% of the mice with tumors, the expression of Kras was lost and the expression of miR-96 was increased. MiR-96 is a miRNA previously shown to regulate Kras translation. The results showed that RSV could prevent the formation and growth of colorectal tumors by downregulating the expression of Kras.

Lignans. Honokiol (HNK) is a lignan that inhibits the proliferation, invasion and survival of numerous human cancer cell lines. HNK exerts its antitumor effect by regulating the main checkpoints, including NF-κB, STAT3, m-TOR and EGFR (126). A recent study showed that HNK decreased the number and volume of adenomas in AOM/DSS mice, and significantly decreased the expression of YAP1, TEAD1 and stem cell marker proteins. *In vitro* experiments revealed that HNK could inhibit the proliferation and colony formation of tumor cells and induce apoptosis. In addition, HNK inhibited the activity of DCLK1 kinase and the expression of LGR5, CD44, and inhibited Ser127 phosphorylation in YAP1 (127). Another study demonstrated that the therapeutic effect of HNK on APC$^{Min/+}$ mice is highly related to citric acid cycle, pentose phosphate pathway, pyrimidine, tyrosine, arginine, proline and glutathione metabolism (128).

Sesamol is a common lignan in sesame, which can mediate anti-inflammatory effects by downregulating the transcription of inflammatory markers including cytokines, redox status, protein kinases and pro-inflammatory enzymes. Sesamol also induces apoptosis and activates caspase cascades through mitochondria and receptors (129). Shimizu *et al* (130) found that sesamol could reduce the number of polyps in the middle small intestine of APC$^{Min/+}$ mice, and sesamol downregulated the expression levels of COX-2, cPGES, mPGES2, EP1 and EP2 genes in polyps. In addition, sesamol did not inhibit the expression levels of COX-1 and EP4 mRNA in non-polyps and intestinal polyps. In the aforementioned study, *in vitro* experiments demonstrated that the basal cyclooxygenase-2 transcriptional activity decreased by 50% under 100 μM sesamol through the β-galactosidase reporter gene system, suggesting that sesamol may play an antitumor role as a cyclooxygenase-2 inhibitor (130).

Catechols. Caffeic acid phenethyl ester (CAPE) is a phenolic antioxidant extracted from propolis (bee resin) and a kind of catechol. It has been reported that CAPE has strong anti-inflammatory activity, which can significantly reduce the size, number and load of adenomas in AOM/DSS mice, alleviate intestinal atrophy and increase the length of colon in a dose-dependent manner. CAPE decreased the activation of NLRP3 inflammatory bodies in BMDMs and THP-1 cells. Further studies have shown that CAPE regulates NLRP3 at the post-transcriptional level by inhibiting the production of ROS. However, CAPE does not affect the transcription of NLRP3 or IL-1β, but enhances the binding of NLRP3 to ubiquitin molecules and promotes the ubiquitin of NLRP3. Notably, CAPE suppressed the interaction between NLRP3 and CSN5, but enhanced the interaction between NLRP3 and Cullin1 (131).

Oleuropein, the main phenolic active ingredient of *Olea europaea* (*Oleaceae*), belongs to catechins. It has been proven to have the effects of anti-oxidation, antitumor, anti-inflammation, neuroprotection and liver protection. Oleuropein can effectively inhibit the progression of esophageal, gastric, lung and liver cancer (132).

A previous study has shown that oleuropein can inhibit the occurrence and diversity of CRA, improve adverse symptoms, and DAI score, downregulate the expression of IL-6, IFN-γ, TNF-α and IL-17A, and reduce the expression of COX-2 and PCNA. In addition, oleuropein significantly downregulated NF-κ B, Wnt/β-catenin, P3IK/Akt and STAT3, and decreased the expression of CD4 (+) Roγ t (+) IL-17 (+) IFN-γ (+) T cell subsets and IL-17A and IFN-γ in lamina propria (133).

Other polyphenols

Tea polyphenols (TPs). TPs are the main components isolated from tea and are known to have antioxidant, anti-inflammatory and antitumor activities (134). Previous studies have identified that TPs can play an important role in the treatment of most cancers by causing cell cycle arrest in G0/G1 phase and inhibiting angiogenesis, and has fewer side effects than traditional drugs (135,136). A previous study has shown that TPs can inhibit the development of adenoma induced by AOM in male Fischer rats and F344 rats, reduce

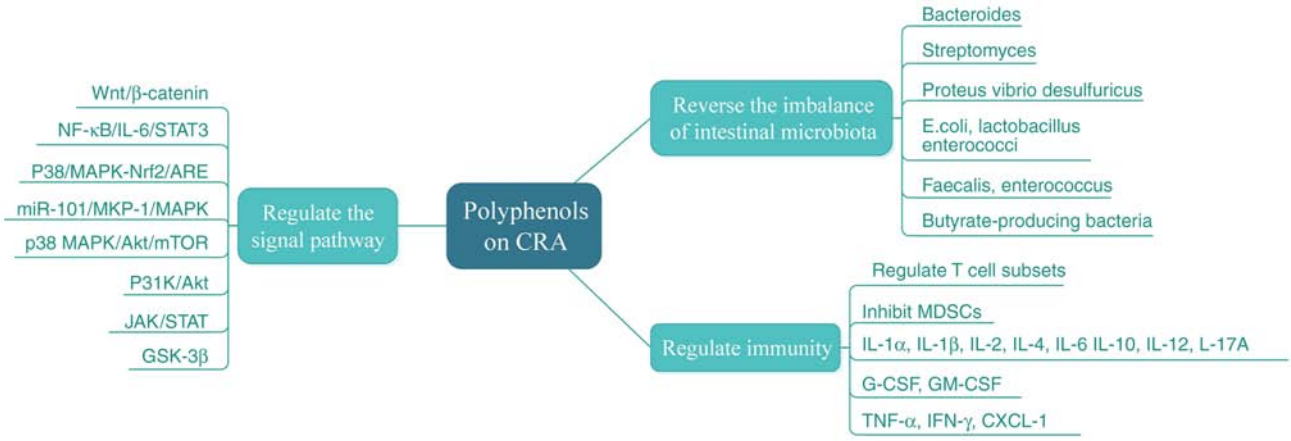


Figure 3. Therapeutic mechanism of polyphenols on CRA. CRA, colorectal adenoma.

the incidence and average number of adenomas in rats, and reduce the occurrence of ACF, but there is no dose-dependent relationship in male Fischer rats (137). In addition, TPs can regulate MAPK, PI3K/Akt, Wnt/β-catenin, NF-κB, JAK/STAT and 67 kDa-laminin receptor pathway (137,138). In another study, green tea rich in TPs significantly reduced the number of small adenomas (diameters ≤1 mm) in $Apc^{Min/+}$ mice, downregulated the levels of β-catenin and its downstream target cyclin D1, and increased Retinoid X receptor α (RXR α) mRNA and protein expression. Colonic DNA was treated with bisulfite, and then 24 CpG sites in the promoter region of RXR α gene were sequenced with pyrophosphate. The results revealed that CpG methylation decreased significantly. It has been suggested that low concentration of TPs is sufficient to desilence RXR α and inhibit intestinal tumorigenesis in $Apc^{Min/+}$ mice (139).

Bioactive components of polyphenol-rich cranberry extracts. Cranberry contains a variety of ingredients related to human health. Studies have shown that cranberry polyphenol extract significantly decreased the incidence of adenoma and canceration rate induced by AOM/DSS, reduced the size of adenoma and downregulated the expression of IL-1β and IL-6, TNF-α in mice (140). Walnut phenolic extract significantly reduced the development of adenoma induced by AOM/DSS, reduced IκB phosphorylation/degradation and NF-κB DNA binding activity induced by TNF-α, and decreased NF-κB signal transduction in colon (141). Polyphenols extracted from *Annurca* significantly reduced the number of adenomas in colon and small intestine, slowed down weight loss and severe rectal bleeding in $Apc^{Min/+}$ mice, increased antioxidant activity and upregulated DNA methylation in mice (142).

5. Discussion

This is the first review devoted to the study of the therapeutic effect of natural polyphenols on CRA. Although natural polyphenols are considered as possible tumor inhibitors, their potential effects, mechanisms and safety remain to be solved. As a highly malignant tumor, the current treatment of CRC is limited, thus the prevention of CRC is particularly important. It has been reported that the 10-year cumulative canceration rates of tubular adenoma, tubular villous adenoma and villous adenoma are 2.7, 5.1 and 8.6% respectively, while serrated polyps are 2.5% (143). As a premalignant lesion of CRC, early intervention of CRA is very important to reduce the morbidity and mortality of CRC (144).

Natural polyphenols have unique advantages in the treatment of CRA due to their multi-targets and high safety, and certain polyphenols have been proven to play a potential role in preventing the occurrence and development of adenomas. The results showed that natural polyphenols significantly reduced adenoma and carcinogenesis in animal models by inhibiting intestinal cell proliferation, inducing apoptosis, inhibiting inflammation and oxidative stress, regulating intestinal microbiota and inducing intestinal barrier function recovery. These beneficial effects are mainly related to the inhibition of activation of multiple signal pathways, including Wnt/β-catenin, NF-κB, GSK-3β, MAPK, STAT3 and PI3K/Akt/mTOR. In addition, numerous studies suggested that the bioavailability of natural polyphenols is low, and it is suggested that the metabolites generated in the intestine by the resident microbiota may contribute to the cancer prevention properties (145). All of the aforementioned evidence suggests that these natural polyphenols are effective and promising candidates for the treatment of adenomas. However, the potential molecular mechanism or toxicological tests of most natural polyphenols need to be further studied. At present, the actual efficacy of a few polyphenols in patients with CRA has been confirmed in clinical studies, including CUR, RSV and anthocyanins. Most polyphenols have not been confirmed in clinical trials. Therefore, their molecular mechanism, long-term efficacy and safety should be further clarified in clinical trials.

6. Conclusion and prospects

The present study reviewed the protective effect of natural polyphenols on CRA and shows its potential antitumor mechanism (Fig. 3). Natural polyphenols have great potential in the treatment of colorectal tumors. In future research, the role of natural substances in preventing colorectal tumors is significant. Research should focus on the molecular targets of natural polyphenols and their in-depth mechanistic studies, metabolism and toxicology *in vivo* to determine the safe dose

for human studies. Given the low bioavailability of natural polyphenols and the critical role of intestinal microbiota in tumor development, the synergistic interaction of drugs, the development of phytochemical derivatives, synthetic analogs or nanoparticles, the metabolism of compounds by intestinal microflora cannot be ignored, to promote these polyphenols to play a greater role in the treatment of tumors in the future.

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Authors' contributions

FQM and YHL participated in the writing of the manuscript. ZHN contributed to the editing of the manuscript. XBW and TC served as scientific advisors. All authors have 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.

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