SPANDIDOS PUBLICATIONS

Therapeutic potential of flavonoids in gastrointestinal cancer: Focus on signaling pathways and improvement strategies (Review)

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Abstract. Flavonoids are a group of polyphenolic compounds distributed in vegetables, fruits and other plants, which have considerable antioxidant, anti-tumor and anti-inflammatory activities. Several types of gastrointestinal (GI) cancer are the most common malignant tumors in the world. A large number of studies have shown that flavonoids have inhibitory effects on cancer, and they are recognized as a class of potential anti-tumor drugs. Therefore, the present review investigated the molecular mechanisms of flavonoids in the treatment of different types of GI cancer and summarized the drug delivery systems commonly used to improve their bioavailability. First, the classification of flavonoids and the therapeutic effects of various flavonoids on human diseases were briefly introduced. Then, to clarify the mechanism of action of flavonoids on different types of GI cancer in the human body, the metabolic process of flavonoids in the human body and the associated signaling pathways causing five common types of GI cancer were discussed, as well as the corresponding therapeutic targets of flavonoids. Finally, in clinical settings, flavonoids have poor water solubility, low permeability and inferior stability, which lead to low absorption efficiency *in vivo*. Therefore, the three most widely used drug delivery systems were summarized. Suggestions for improving the bioavailability of flavonoids and the focus of the next stage of research were also put forward.

Contents

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1. Introduction

There are numerous natural products in nature that have anti-cancer activity, for example, alkaloids represented by harringtonine and vincristine, terpenoids represented by artemisinin and paclitaxel, and flavonoids represented by genistein and baicalein (1). The therapeutic effects of flavonoids in various types of cancer such as breast cancer, colorectal cancer (CRC) and liver cancer have been established (2-4). Flavonoids, a class of polyphenolic compounds serving as secondary metabolites in plants, are primarily sourced from plant foods, which are distributed in vegetables, fruits, green tea and grains (5,6). Flavonoids exhibit a basic skeletal structure of diphenyl propanes (C6-C3-C6). According to the different hydroxylation and glycosylation, and other modifications of this core molecule, flavonoids are categorized into seven subclasses: Flavonols, flavones, isoflavones, anthocyanidins, flavanones, flavanols and chalcones (7-10). Flavonoids exert their anticancer effects by regulating key molecular targets such as mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) or by reducing levels of reactive oxygen species (ROS) to regulate biological processes such as DNA damage, inflammation, cell death and metastasis of cancer cells (11,12).

The various types of gastrointestinal (GI) cancer are associated with the digestive system and its accessory organs, including gastric cancer (GC), liver cancer, esophageal cancer (EC), pancreatic cancer (PC), and CRC. They represent a few of the most prevalent types of malignant tumors in the world (13). Different types of GI cancer account for a quarter of global cancer incidences and 1/3 of mortality due to cancer globally (14). According to the global cancer statistics of the

2020 Global Cancer Observatory database, the number of new mortalities of liver, stomach and rectal tumors ranked second, third and fifth among the 36 types of cancer in 185 countries respectively (15). The cause of different types of GI cancer is multifactorial, involving lifestyle, dietary habits, chemical damage and other factors (16). Types of early-stage GI cancer often lack more convenient and cost-effective screening methods beyond routine endoscopy for early detection (17). In addition, delayed surgical intervention and limited efficacy of radiotherapy and chemotherapy have led to an increase in the mortality of GI cancer year by year. Flavonoids have inhibitory effects on a variety of types of cancer and are recognized as a promising class of anti-tumor drugs, which are expected to improve the current high mortality rate caused by different types of GI cancer. Therefore, it is necessary to thoroughly investigate the molecular mechanism of its treatment, fully evaluate its safety and pharmacological properties, and propose solutions to possible difficulties, so that therapies can be applied in clinical practice as early as possible.

The present review elucidated the therapeutic effects of flavonoids on the occurrence and progression of different types of GI cancer from the perspective of signaling pathways. Various types of flavonoids exert therapeutic roles by modulating signaling pathways associated with different types of GI cancer and regulating the expression of target genes involved in these pathways (18). The present review provided a more comprehensive theoretical foundation for understanding the molecular mechanisms underlying the therapeutic potential of flavonoids in treating different types of GI cancer. In addition, the oral bioavailability of flavonoids is limited due to their poor water solubility, low permeability and inferior stability (19). To address this issue, several widely used drug delivery strategies for flavonoids are listed, the limitations and challenges of current research in this field are highlighted and key areas that require further investigation to advance future research on enhancing the efficacy of flavonoids in treating different types of GI cancer are identified.

2. Current status of different types of GI cancer treatment

Currently, the most common option for treating the different types of GI cancer is triple therapy: Surgery, chemotherapy and radiotherapy (20). For resectable localized lesions, radical surgery is the most important treatment (21). Different types of GI cancer have different surgical methods according to their anatomical characteristics. EC can be treated by transhiatal or transthoracic esophagectomy, GC can be treated by total gastrectomy and subtotal gastrectomy, PC can be treated by Whipple surgery, liver cancer can be treated with portal vein embolization and partial hepatectomy, and CRC can be treated with complete mesocolic excision with central vascular ligation (22-26). Disadvantages of surgery include large trauma, several postoperative complications, and high tolerance requirements for patients. With the development of endoscopic technology, early types of GI cancer or precancerous lesions can be detected and treated by endoscopy, thereby improving the prognosis, reducing the risk of recurrence and improving the quality of life of patients (27). Endoscopic submucosal dissection can be used to treat superficial gastrointestinal lesions. Endoscopic cholangiopancreatography has an important role in the treatment of unknown biliary strictures and malignant biliary obstructive diseases (28). The first case of laparoscopic gastrectomy for early GC was reported in 1994 and since then the advantages of laparoscopic surgery are being recognized (29). The key to the success of GC surgery is the ability to carry out an extended lymphadenectomy. Studies have found that there is no difference in the number of lymph nodes removed between laparoscopic gastrectomy and open gastrectomy, but the intraoperative blood loss and hospitalization time of laparoscopic gastrectomy are considerably decreased when compared with those of open gastrectomy (30-32). In addition, for some rare gastrointestinal tumors, such as retrorectal tumors, laparoscopic surgery has the potential advantages of being minimally invasive and is associated with reduced mortality compared with traditional surgical resection (33). However, because the organs are preserved in minimally invasive surgery, there is a risk of recurrence (34).

Perioperative chemotherapy is used in the treatment of esophagogastric adenocarcinoma (OGAC) (35,36). Compared with manual surgery, OGAC has considerably improved survival outcomes (37). Some studies have found that postoperative chemotherapy can effectively improve the overall survival of patients with OGAC treated with preoperative chemotherapy and surgery (38). During a 5-year follow-up, patients with locally advanced rectal cancer received short-term radiotherapy before total mesorectal resection, followed by six cycles of capecitabine + oxaliplatin or nine cycles of oxaliplatin + leucovorin + fluorouracil. It was found that the probability of disease-related treatment failure in the experimental group was decreased compared with that in the control group (39). Another study showed similar results, patients with operable GC, gastro-esophageal junction and lower esophageal adenocarcinoma received three cycles of epirubicin + cisplatin + 5-fluorouracil chemotherapy before and after surgery. Compared with the simple operation group, pathological evaluation of the tumor in the perioperative chemotherapy group showed a reduction in tumor volume as well as lymph node disease and patients had considerably prolonged progression-free survival (40). According to the aforementioned research conclusions, chemotherapy can effectively control the recurrence of cancer and improve the success rate of surgery, which are key for the management and treatment of cancer. However, liver cancer is not sensitive to the effect of chemotherapy, and patients with impaired liver function are usually unable to tolerate systemic chemotherapy (41). In addition, the biggest issue faced by chemotherapy in clinical practice is the emergence of drug resistance during treatment, and treatment failure for >90% of patients are caused by multidrug resistance (MDR) (42).

National Comprehensive Cancer Network guidelines recommend preoperative concurrent radio chemotherapy (nCRT) as a standard treatment for locally advanced rectal cancer (43). For resectable lesions, nCRT can reduce pathological stage and increase pathologic complete response (defined as the absence of residual cancer cells in the surgical specimen after treatment, which can be considered a sign of successful treatment and indicates that the tumor has been completely eliminated), but there is no considerable improvement in long-term survival. For unresectable lesions, nCRT can control and reduce tumor growth and spread in the treated area, improve patient local control and cancer-specific survival (44,45). Intraoperative radiation therapy can improve local control and reduce postoperative complications in patients with unresectable tumors and a high risk of local recurrence (46). The current issue in radiotherapy is effectively using the differences between tumor and host tissues for improved control of the radiation dose (47). The advantage of particle therapy (PT) is that the radiation dose can be targeted on the target tissue which avoids indirect damage to normal tissues (48). To compare the effects of charged particle therapy (CPT) and photon radiotherapy on clinical outcomes and toxicity in patients with hepatocellular carcinoma (HCC) in a systematic review and meta-analysis, patients with HCC treated with CPT were revealed to have an increased survival rate than conventional radiotherapy and decreased radiotoxicity than photon radiotherapy (49). In addition, studies are investigating the combination of PT and endoscopic techniques, such as endoscopic ultrasound (EUS), to implant radioactive particles directly into the target tissue to achieve brachytherapy (50). Direct irradiation of EUS-guided iodine-125 particles into the celiac ganglion can effectively relieve pain and the consumption of analgesics in patients with unresectable PC (51).

Cancer immunotherapy and targeted therapy have become the focus of research (52,53). Cancer immunotherapy refers to the blocking of the programmed death protein 1 (PD-1)/PD-ligand 1 (PD-L1) immune checkpoint. PD-1 inhibitors, such as pembrolizumab, nivolumab and camrelizumab, have considerable effects on patients with refractory advanced GC and advanced EC (54). In a Phase 3 clinical trial, camrelizumab + paclitaxel and cisplatin prolonged overall survival and progression-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma (55). However, the efficacy of immune checkpoint inhibitors (ICIs) in combination with chemotherapy drugs remains uncertain. In a clinical trial, pembrolizumab + cisplatin did not markedly improve the treatment effect compared with single-agent chemotherapy in patients with advanced or metastatic esophageal squamous cell carcinoma, but nivolumab + oxaliplatin markedly improved the treatment effect compared with single agent chemotherapy, it may be due to oxaliplatin being stronger in inducing immunogenic cell death than cisplatin against different types of GI cancer (56). Research has revealed that there may be a synergistic effect between radiation therapy (RT) and ICIs. For example, RT can upregulate the expression level of PD-L1 in EC (57). Adjuvant durvalumab therapy after triple therapy can markedly improve one-year recurrence-free survival in patients with esophageal and gastroesophageal junction adenocarcinoma (58). However, since tumors can become radioresistant by up-regulating PD-L1 expression, and ICIs can restore antitumor immunity by targeting similar markers, further studies are needed to select which type of ICIs to combine with RT for optimal therapeutic effects (59). Perioperative targeted therapy has a considerable therapeutic effect on patients with GC with corresponding mutation sites. Anti-HER2 and anti-vascular endothelial growth factor (VEGF) therapies are recommended as the first-line and second-line treatment for advanced GC. The median overall survival of patients with GC treated with trastuzumab plus chemotherapy (18.6 months) was increased when compared with that of patients treated with single-agent chemotherapy (11.1 months) (60). The incidence of anastomotic leakage after esophagogastric resection in patients with GC treated with bevacizumab plus chemotherapy was increased when compared with that in patients treated with chemotherapy alone group, and the 3-year overall survival was not considerably different from that in patients treated with chemotherapy alone group (48.1 vs. 50.3%) (61). Another VEGFR-2 monoclonal antibody, ramucirumab, combined with paclitaxel can markedly improve overall survival in patients with previously treated advanced GC and can be used as the standard second-line treatment for patients with advanced GC (62). Molecular targeted therapies for HCC mainly target VEGF and other angiogenic pathways. In a randomized, double-blind, placebo-controlled Phase 3 trial, injection of ramucirumab markedly improved overall survival, was well tolerated and demonstrated controllable safety in patients with HCC (63).

In conclusion, with the development of treatment technology, the effective treatment rate of different GI cancer types is increasing year by year, but it is still unable to avoid its own limitations (64). As a large group of natural drugs, flavonoids have attracted attention over the years (65-67). Flavonoids have potent anti-tumor effects and considerable preventive and therapeutic effects on numerous types of GI cancer (68-72). Studies have found that flavonoids combined with chemotherapy drugs can improve sensitivity to the chemotherapy drugs and markedly improve the occurrence of MDR (73,74). In terms of improving radiotherapy, flavonoids have good radioprotective and radio sensitizing effects, which can kill tumor cells with minimal damage to normal tissues or cells (75,76). In conclusion, flavonoids can be used not only as a single anti-tumor drug but also in combination with a variety of treatment methods to improve the success rate of existing treatment measures, positing it as a promising drug.

3. Classification of flavonoids

Phenolic compounds are metabolites derived from the secondary metabolic pathway of plants, which are mainly distributed in fruits, seeds and leaves of plants. They have an important role in regulating the growth and development of plants (77). The basic structure of phenolics comprises at least one hydroxyl group that is directly attached to the benzene ring. These can then be divided into phenolic acids, flavonoids, tannins, coumarins, lignans, quinones, stilbenes and curcuminoids, according to the complexity of the structure (78,79). Flavonoids are the largest group of natural phenolic compounds and their basic structure is a flavan nucleus, which is composed of two aromatic rings labeled as A and B in Fig. 1 connected by a dihydropyrone ring, labeled as C in Fig. 1 (80). According to different substituent groups, flavonoids can be divided into seven subclasses: Flavonols, flavones, isoflavones, anthocyanidins, flavanones, flavanols and chalcones (7,9) (Fig. 1).

The structure of flavonol, flavan-3-ols is characterized by the presence of a hydroxyl group at the 3 position of the C ring. Flavonols are primarily sourced from fruits, vegetables, tea and red wine (81). Kaempferol, quercetin, fisetin, isorhamnetin and myricetin are the five most common dietary forms (82). Flavonols are most notable for their multifaceted cardiovascular protective effects, which manifest through three primary mechanisms: Inhibition of epinephrine- and ADP-induced

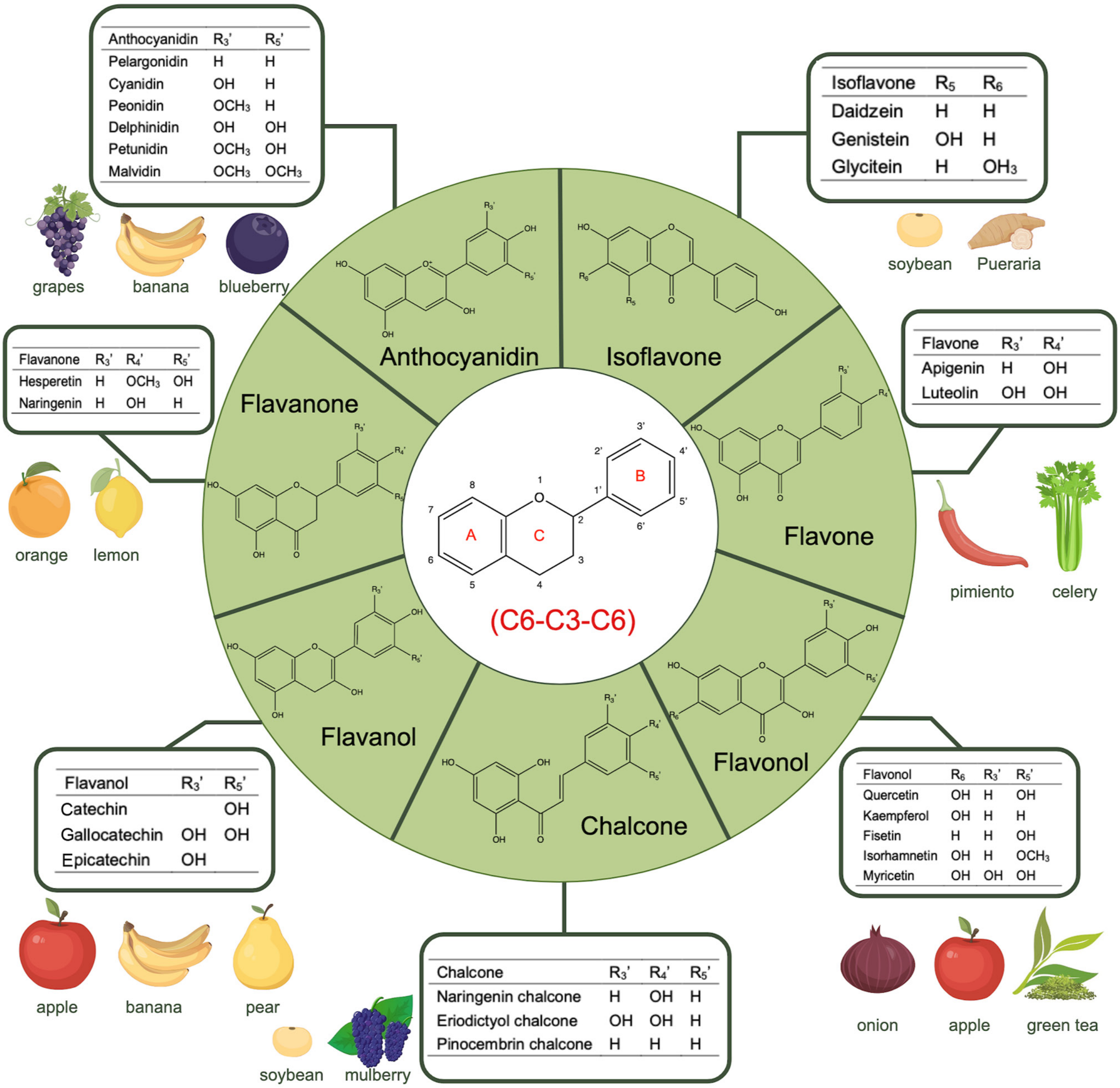


Figure 1. Schematic of the basic structure, types and food sources of flavonoids. Flavonols are primarily sourced from onions, apples and green tea, according to the different substitution groups on R_6, R_3 and R_5', the main compounds are quercetin, kaempferol, fisetin, isorhamneti and myricetin. Flavones are primarily sourced from pimientos and celery, according to its substitution groups at R_3 and R_4', the main compounds are apigenin and luteolin. Isoflavones are primarily sourced from soybeans and Puerarias, according to their substitution groups at R_5 and R_6, the major isoflavones are daidzein, genistein and glycitein. Anthocyanidins are primarily sourced from grapes, bananas and blueberries, according to the different substitution groups on R_3 and R_5', the main compounds are pelargonidin, cyanidin, peonidin, delphinidin, petunidin and malvidin. Flavanones are primarily sourced from oranges and lemons, according to the different substitution groups on R_3, R_4 and R_5', the main compounds are hesperetin and naringenin. Flavanols are primarily sourced from apples, bananas and pears, according to the different substitution groups at R_3' and R_5', the main compounds are catechin, gallocatechin and epicatechin. Chalcones are primarily sourced from soybeans and mulberries, according to its different substitution groups on R_3, R_4 and R_5', the main compounds are naringenin chalcone, eriodictyol chalcone and pinocembrin chalcone.

glycoprotein IIb/IIIa and P-Selectin expression, regulation of platelet function, and prevention of platelet adhesion (83). Additionally, they activate nitric oxide synthase, promoting nitric oxide synthesis in endothelial cells and enhancing vascular endothelial function (84). They also inhibit the oxidation of low density lipoprotein (LDL), increase paraoxonase activity and remove oxidized lipids from atherogenic lesions and lipoproteins (85). Among them, quercetin exhibits the most marked cardioprotective effect on cardiovascular diseases (CVDs) by inhibiting inflammatory responses and oxidative stress damage and improving myocardial fibrosis (86,87).

The structure of flavone is 4H-chromen-4-one, characterized by the presence of a double bond between the 2nd and 3rd positions of the C ring, and the 4th position of the C ring is replaced by a ketone group (88). Flavones usually exist in the form of 7-O-glycosides and are present in celery, tea, pimiento and oranges, representing the largest category of flavonoids (89). The two most common dietary flavones are apigenin and luteolin (90). Apigenin (4',5,7-trihydroxyflavone) is primarily derived from chamomile, parsley and onions, and is found in plants in its glycosylated form (91). It can be used as a natural anticancer, neuroprotective and antioxidant agent (92,93). Apigenin can exert its anticancer effects by regulating various cellular signaling pathways (94). Moreover, apigenin can also inhibit the production of ROS by scavenging free radicals and enhancing the activity of antioxidant enzymes, reduce the damage of brain neurons caused by oxidative stress, delay apoptosis of neuronal cells and assume a preventive and therapeutic role in the neurodegenerative diseases (95).

The basic chemical structure of isoflavones is a 3-phenylchromen-4-one backbone and is categorized as a type of phytoestrogens (96,97). In plants, isoflavones are usually modified to β-glucosides and 6-O-malonylglucosides by O-glycosidation, and stored in vacuoles (98). Isoflavones are primarily sourced from soybean or other legume derivatives, isoflavone-rich compounds include daidzein, genistein and glycitein (96). Due to their classification as phytoestrogens, isoflavones can be used in hormone replacement therapy to alleviate various symptoms and manifestations caused by estrogen reduction in menopausal women (99). Moreover, isoflavones, such as estrogen, can induce vasodilation by binding to the β-estrogen receptor in vascular endothelial cells. In terms of anticancer properties, isoflavones can competitively bind to estrogen receptors with phytoestrogens, exerting an antagonistic effect against estrogen, which is beneficial for treating estrogen-related tumors, such as breast and uterine cancer (100,101).

Anthocyanidins, which are plant pigments, exist predominantly in glycosylated forms due to their inherently unstable monomeric state (102). Anthocyanidins are responsible for the orange-red to blue-purple hues observed in plants such as fruits and flowers and primary dietary sources including grapes, bananas and some berries (103). Structurally, anthocyanidins feature glycoside attachment at the C3, C5 and C7 positions, typically comprising polyhydroxy and polymethoxy derivatives of 2-phenylbenzopyrylium or flavylium salts (104). Pelargonidin, cyanidin, peonidin, delphinidin, petunidin and malvidin are the six most prevalent anthocyanidins in the natural pelargonidin (105). The health benefits of anthocyanidins are commonly known (106,107). Anthocyanins can traverse the blood-brain barrier and blood-retinal barrier and are highly distributed in ocular tissue (108). Bilberry anthocyanins can improve night vision, and blackcurrant anthocyanins can improve adaptation of eyesight to the dark and eye fatigue in patients with open-angle glaucoma (109,110). In addition, research has demonstrated that anthocyanidins exert inhibitory effects on various malignant tumors such as CRC and breast cancer (111,112).

The chemical structure of flavanones (dihydroflavones) is characterized by the saturation of the double bond between C2 and C3 and the absence of substituents at the C3 position (113). Flavanones are mainly present in citrus fruits as glycosylated forms, and the most prevalent flavanones are hesperetin and naringenin (114). Flavanones have considerable therapeutic effects on CVDs. Epidemiological evidence indicated a substantial inverse relationship between the consumption of citrus fruit and the incidence of CVDs (115,116). Moreover, flavanones exhibit inhibitory effect on the high-risk factors of CVDs. Specifically, naringenin reduces the levels of low-density lipoprotein-cholesterol and total cholesterol, regulating blood lipid levels (117). Both naringenin and hesperetin promote the apoptosis of cancer cells, cause arrest of the cell cycle and inhibit the proliferation of cancer cells through the upregulation of apoptotic protein expression (118,119). In addition, flavanones can be combined with other anticancer chemotherapeutic drugs to enhance the efficacy of chemotherapeutic drugs (120).

The structure of flavanols (flavan-3-ols) is characterized by the substitution of a hydroxyl group at the 3 position of the C ring and the absence of a double bond between C2 and C3. Flavanols are mainly abundant in fruits such as bananas, apples and pears. Common flavanols include catechin, gallocatechin and epicatechin (121,122). Flavanols have been shown to enhance cognitive function (123). Intake of flavanol-rich foods can effectively improve blood flow in the middle cerebral artery and enhance regional cerebral perfusion of the brain (124,125). Studies have demonstrated that flavanol intake in elderly individuals with mild cognitive impairment considerably improves the verbal fluency tests core and cognitive function (126-128). Additionally, oxidative stress and ROS production are associated with neurodegenerative diseases, which may explain the improvement of cognitive-related symptoms due to the antioxidant properties of flavanols (129,130). Flavanols are also associated with the immune system. Flavanols regulate metabolic pathways and immune responses by regulating gut microbiota, exerting therapeutic effects on both metabolic and immune-related diseases (131).

Chalcones (1,3-diaryl-2-propen-1-ones) are simple chemical scaffolds found in several natural plant products and are considered precursors to flavonoids and isoflavonoids (132). Chalcones can carry up to three modified or unmodified C5-, C10-, and C15-prenyl moieties on both the A and B rings. Chalcones are primarily found in Fabaceae and Moraceae plants (133). Chalcones exhibit a variety of biological activities, such as anti-inflammatory, anticancer, antiviral and antioxidant properties, among which the most prominent is their anticancer activity (134,135). For example, Chalcone Xanthohumol, isolated from beer, can prevent the progression of prostatic hyperplasia to prostate cancer (136). Naringenin chalcone and glucoside isosalipurposide isolated from *Helichrysum* maracandicum can inhibit the formation of epidermal papilloma and the progression of skin cancer (137).

4. Absorption and metabolism of flavonoids *in vivo*

Dietary flavonoids are ingested into the human body mainly in the form of glycosides (138). An improved understanding of the metabolism of flavonoids in human body is important to comprehend the therapeutic effect of flavonoids on cancer (89). A limited number of studies have investigated the effect of saliva on the oral absorption of flavonoids. Saliva has certain catechin esterase activity, which can convert (-)-epigallocatechin-3-gallate (EGCG) to (-)-epigallocatechin (EGC) and lead to absorption of EGC by the oral mucosa (139). Procyanidin oligomers are relatively stable in the mouth and esophagus, as they cannot be decomposed or modified in saliva for up to

30 min (140). Due to the characteristics of rapid absorption, rapid decomposition and poor absorption efficiency in the stomach, the metabolic pathways of flavonoids in the stomach remain unclear. Research found that procyanidins decompose into different oligomeric units after 0.1-3.0 h incubation in simulated gastric juice (141). *In vitro* experiments reveal that flavonoid glycosides can be absorbed in the human stomach and subsequently cleaved by β-glucosidase (142). The liver is an important organ for metabolism of flavonoids. There are two key metabolic pathways: i) Oxidation reaction and ii) glucuronidation, methylation and sulfation reaction (143,144). Oxidation reaction in phase I metabolism is carried out by the cytochrome P450 enzyme system. Glucuronidation, methylation and sulfation reaction in phase II metabolism involves the addition of an endogenous substance to the polar functional groups introduced in phase I metabolism, such as glucuronidation, methylation and sulfation (145,146). Gut microbiota has an important role in the intestinal absorption of flavonoids. The oxygen-containing heterocyclic ring of flavonoids is broken under the action of glycosidases produced by gut microbiota and then recombined by uridine diphosphate UDP-glucuronosyltransferases or sulfotransferases. Products are reabsorbed into the blood and reach the liver through the hepatic portal vein completing their enterohepatic circulation (147,148). In normal conditions, the products are excreted into the urine by transporters present in the proximal renal tubular cells. In addition, the products can be reabsorbed into the kidney by organic anion transporter 4 outside of the cellular basement membrane of tubules. Flavonoids in the kidney may undergo bioconversion under the action of some enzymes (138,143). Microorganisms in the large intestine are mainly composed of various anaerobic bacteria which participate in the reduction reaction. Flavonoids are degraded into smaller phenolic acids, which will be excreted into the feces (149).

5. The role of flavonoids in different types of GI cancer

The role of flavonoids in esophageal cancer. EC is a malignant tumor originating from the esophageal mucosa, and it is the seventh leading cause of mortality due to cancer in the world (150). There are two common histological types of EC: Esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) (151). ESCC is relatively common, and it is closely associated with smoking and drinking (152). EAC is closely associated with gastroesophageal reflux disease (153). Surgical resection combined with neoadjuvant chemoradiotherapy can considerably prolong the median overall survival of patients with EC. However, prognosis for patients remains poor due to the high invasiveness of the disease (154,155).

Flavonoids have been shown to have a therapeutic effect against EC in preclinical models. A study by Liu *et al* (156) revealed that 5 and 10 μg/ml of quercetin administration effectively inhibits the invasion of the human EC cell line, Eca109. Another study reports that the expression levels of matrix metalloproteinase (MMP) 9, MMP2 and vascular endothelial growth factor A are decreased in human umbilical vein vascular endothelial cells (CLR-1730) following quercetin treatment, indicating reduced angiogenic capacity. Licochalcone A (LCA) is a flavonoid isolated from *Glycyrrhiza uralensis* (157). LCA reduces mitochondrial membrane potential, promotes apoptosis by upregulating apoptosis-related proteins, such as Caspase-3, Caspase-9 and Bax *in vitro*, and induces G_2/M cell cycle arrest in EC cells (158). It has been reported that flavonoids extracted from *Malus asiatica* Nakai leaves can effectively inhibit EC-induced visceral tissue changes by increasing the levels of interleukin-10 (IL-10) and monocyte chemotactic protein 1 and decreasing the levels of tumor necrosis factor alpha (TNF-α) and interferon-γ in 4-nitroquinoline N-oxide-induced EC mice (159).

A previous meta-analysis studied patients with EC who were given different doses and types of flavonoids. Total flavonoids, anthocyanidins, flavanones and flavones were revealed to potentially reduce the risk of developing EC (160). In a case-control study where patients with EAC (white male; n=161) and ESCC (white male; n=114; black male; n=218) along with corresponding controls were included, a negative correlation between anthocyanidin intake and cancer in white males was observed following adjustment for dietary fiber (161). Barrett's Esophagus (BE) is a precancerous lesion that can lead to EC (162). Polyphenon E (Poly E) is a mixture extracted from green tea containing catechins, including EGCG (163). A double-blinded, placebo-controlled and dose-escalated study which included 44 patients with BE assigned to receive placebo (n=11) or Poly E (n=33) revealed that EGCG considerably reduced the severity of dysplasia in BE when reaching a certain tissue concentration (164). Similarly, dietary flavonoids, anthocyanidins, were revealed to reduce the risk of developing BE in another case-control study (165). A different case-control study conducted in Urumqi and Shihezi (Xinjiang Uygur Autonomous Region; China) recruited 359 patients with EC and 380 controls and assessed the consumption of soy food data obtained through personal follow-up. Logistic regression analysis revealed that habitual consumption of soy food was associated with a reduced risk of developing EC, and isoflavone intake was inversely associated with EC risk (166).

A number of *in vitro* studies investigating the molecular mechanism of action of flavonoids in EC have revealed that flavonoids work through different signaling molecules and pathways (167-169). The c-Jun NH2-terminal kinase (JNK) is a member of the mitogen-activated protein kinase (MAPK) family that can be divided into three subtypes: JNK1, JNK2 and JNK3 (170,171). JNK is involved in regulation of apoptosis and survival by two mechanisms. JNK1 promotes cell survival and participates in the malignant transformation of cancer cells, while JNK2 facilitates apoptosis (172-174). TGF-β-activated kinase 1 (TAK1) is a core component of the JNK pathway. It can activate MAPK kinase-4 (MKK-4) and MKK7 under the stimulation of inflammatory cytokines, Toll-like receptors and ligation of antigen receptors, leading to phosphorylation and activation of the downstream JNK to regulate cell growth (175). Casticin is a type of flavonoid isolated from *Vitex* species (176). It can inhibit proliferation and promote the apoptosis of EC cells by activating the JNK signaling pathway (177) (Fig. 2A). MAPK/extracellular signal-regulated kinase (ERK) signaling pathway is a key signaling pathway involved in the regulation of a variety of cellular processes. K-RAS mutations are the most frequently mutated oncogene as it appears in ~30% of all cancer types (178). The binding of growth factors to growth-factor-receptor bound-2 (GRB2) on

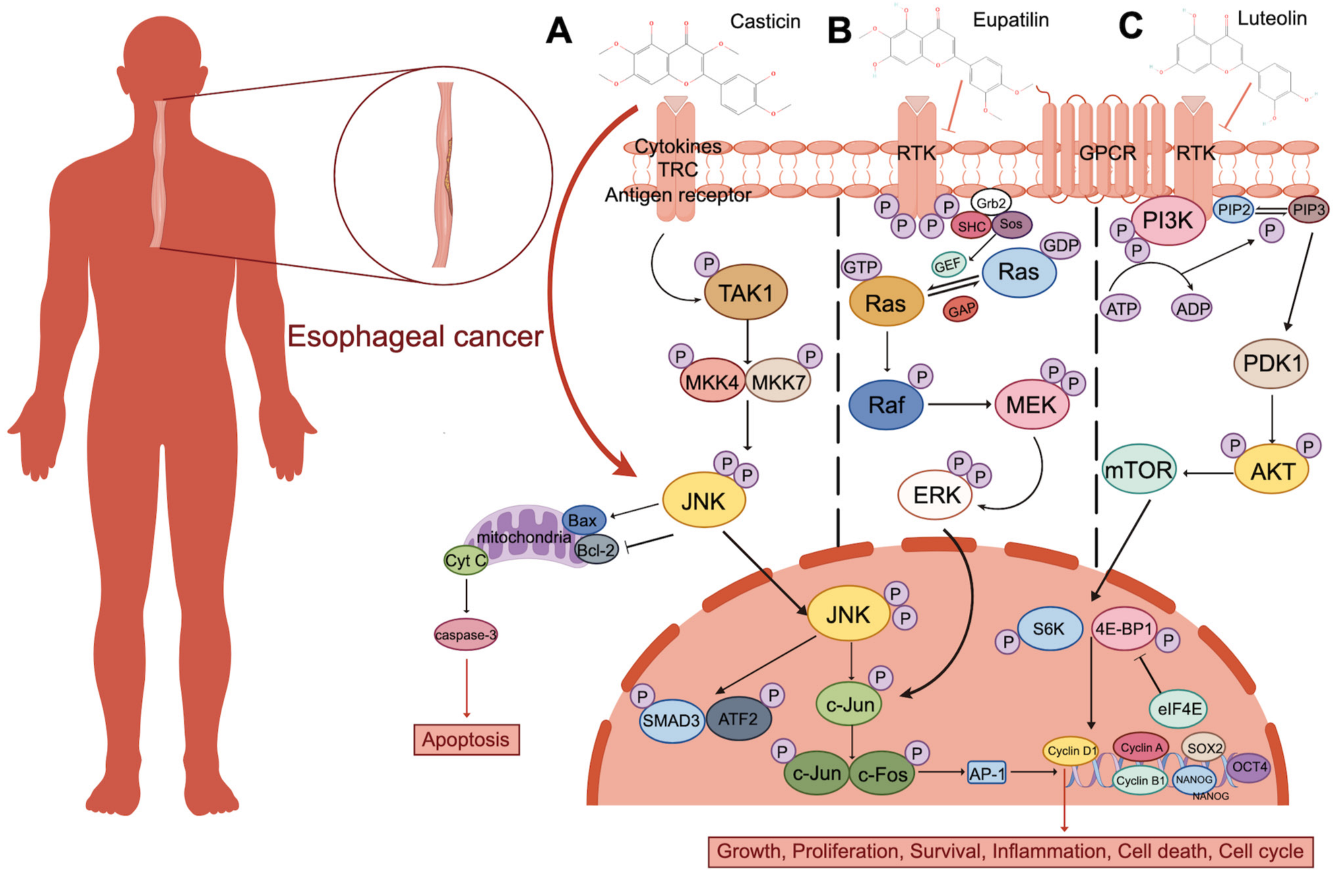
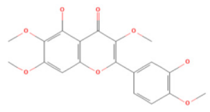
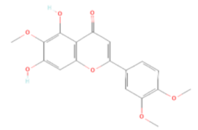
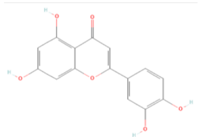
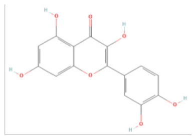


Figure 2. Role of flavonoids in esophageal cancer. (A) Casticin exerts its anti-EC effect by activating the JNK pathway. Activating TAK1, then phosphorylates MKK4 and MKK7. The downstream JNK is activated by phosphorylation to activate the transcriptional activity of c-Jun. Phosphorylated c-Jun can promote the formation of the c-Jun/c-Fos heterodimer. It binds to its binding site in the AP-1 promoter region to regulate the transcription of associated genes. In addition, JNK activation can also phosphorylate SMAD3 and ATF2, which Scutellarin involved in the occurrence of inflammation and fibrosis. Activated JNK can also regulate apoptosis through the mitochondria-mediated apoptosis pathway. (B) Eupatilin exerts its anti-EC effect by inhibiting the MAPK/ERK pathway. When the corresponding ligand binds to RTKs, it phosphorylates the tyrosine residues at their tails. It recruits GRB2/Shc/SOS to the cell membrane to convert GDP-bound Ras to active GTP-bound Ras. Upon Ras activation, the serine/threonine kinase, Raf, is recruited to the cell membrane and activated by phosphorylation. Direct regulation of MEK ultimately leads to the phosphorylation of downstream ERK. Phosphorylated ERK enters the nucleus and activates the key transcription factors c-Jun and c-Fos to bind to the binding site in the AP-1 promoter region and regulate the transcription of associated genes. (C) Luteolin exerts its anti-EC effect by inhibiting the PI3K/Akt pathway. Receptor binding to ligand results in the activation of GPCR and RTK, which activate PI3K. Activated PI3K phosphorylates PIP2 to PIP3, PIP3 further activates PDK1, phosphorylates downstream AKT and activates mTOR. Finally, mTOR acts on substrates S6K and 4E-BP1, eIF4E binds to 4E-BP1 to inhibit its transcription, and p-4E-BP1 loses its binding ability to eIF4E. It promotes S6K and 4E-BP1 transcription to regulate cell growth and development. JNK, c-Jun NH2-terminal kinase; TAK1, TGF-β-activated kinase 1; MAPK, mitogen-activated protein kinase; MKK4, MAPK kinase 4; MKK7, MAPK kinase 7; AP-1, activator protein 1; ATF2, activate transcription factor 2; EC, esophageal cancer; ERK, extracellular signal-regulated kinase; GRB2, growth-factor-receptor bound-2; SOS, son of sevenless; GDP, guanosine diphosphate; GTP, guanosine triphosphate; Ras, Rat sarcoma; Raf, Raf protein kinase; PI3K, phosphatidylinositol 3-kinase; AKT, serine/threonine kinase B; GPCR, G protein-coupled receptor; RTK, receptor tyrosine kinases; PIP2, phosphatidylinositol-4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PDK1, phosphoinositide-dependent protein kinase-1; mTOR, mammalian target of rapamycin; S6K, S6 kinase 1; 4E-BP1, 4E binding protein.

the cell membrane initiates the RAS-RAF-Mitogen-activated protein kinase (MEK) cascade, leading to ERK activation. Phosphorylated ERK regulates transcription factor activity and gene expression from the cytoplasm into the nucleus (179). Clinical research revealed that eupatilin could inhibit the proliferation of the human EC cell line, TE-1, by regulating the protein kinase B (AKT)/GSK-3β and MAPK/ERK signaling pathways (180) (Fig. 2B). The phosphoinositide 3-kinase (PI3K)/AKT signaling pathway is abnormally activated in numerous types of cancer (181,182). The mutation in the PI3KCA gene, encoding the p110α catalytic subunit of PI3K, is the most common (183). Activated PI3K can activate and phosphorylate the downstream kinase AKT, thereby regulating cell biological behaviors, such as growth, differentiation and metabolism. This process is often accompanied by the inactivation of tumor suppressor phosphatase and tensin homolog deleted on chromosome 10 (184). Luteolin can reduce the levels of phosphorylated (p-)AKT and UBR5 expression by inhibiting the PI3K/AKT pathway, and it can weaken the stem-like properties of paclitaxel (PTX) resistant cells by downregulating the expression of the SOX2 protein. In addition, luteolin can block epithelial-mesenchymal transition to inhibit the migration and invasion of PTX-resistant EC cells (185). Quercetin can inhibit the invasion and proliferation of EC cells and promote apoptosis through the miR-1-3p/TAGLN2 axis (186) (Table I).

The role of flavonoids in gastric cancer. GC is a malignancy originating from the gastric mucosa, and it is the fifth most common cancer and the third most common cause of cancer-associated mortality in the world (187). According to the

Table I. Role of flavonoids in esophageal cancer.

First author/s, year	Flavonoids	Chemical structure	Model	Target	Effect	(Refs.)
Qiao, 2019	Casticin		*In vitro, in vivo*	Bcl-2, Bax, Caspase-3, Caspase-9, PARP, cytochrome C, p-JNK	Promotes apoptosis of EC cells *in vitro* by downregulating the expression of Bcl-2 and upregulating the expression of Bax, Caspase-3 and Caspase-9. Decreases mitochondrial membrane potential and promotes cytochrome *c* release. JNK is involved in the anti-proliferative and pro-apoptotic effects of Casticin. Downregulation of Bcl-2 expression and upregulation of p-JNK, Bax, Caspase-3 and Caspase-9 protein expression results in the reduction of tumor volume and weight in an *in vivo* xenograft model.	(177)
Wang, 2018	Eupatilin		*In vitro, in vivo*	Akt/GSK 3β, MAPK/ERK	Inhibition of EC cell proliferation and colony formation *in vitro*. Inhibition of Akt/GSK 3β and MAPK/ERK signaling pathways inhibits cell proliferation. The levels of p-Akt and p-ERK in tumor tissues are decreased, and the tumor volume and weight are decreased in an *in vivo* xenograft mouse model.	(180)
Zhao, 2021	Luteolin		*In vitro*	SOX2, OCT4, NANOG, UBR5, PI3K/Akt	Downregulation of SOX2 expression attenuates the stem cell properties of PTX-resistant cancer cells. Inhibition of PI3K/Akt pathway reduces the expression of p-AKT and UBR5. Inhibition of migration and invasion of PTX-resistant cancer cells by blocking epithelial-mesenchymal transition.	(185)
Wang, 2022	Quercetin		*In vitro*	miR-1-3p/TAGLN2	Inhibits colony formation, migration and invasion of EC cells and promotes apoptosis. Inhibition of TAGLN2 expression by inducing miR-1-3p expression. The inhibitory effect on EC cells is blocked by miR-1-3p inhibitors. Inhibition of EC cells by inducing miR-1-3p.	(186)

EC, esophageal cancer; Bcl-2, B-cell lymphoma-2; Bax, BCL2-associated X; PARP, poly(ADP-ribose) polymerase; p-JNK, phosphorylated c-Jun NH2-terminal kinase; Akt, serine/threonine kinase B; GSK 3β, glycogen synthase kinase 3β; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; SOX2, sex determining region (SRY)-box 2; OCT4, octamer-binding transcription factor 4; NANOG, Nanog homeobox; UBR5, ubiquitin protein ligase 5; PI3K, phosphatidylinositol 3-kinase; TAGLN2, transgelin 2.

World Health Organization classification, GC can be divided into the following subtypes: Adenocarcinoma, adenosquamous carcinoma, squamous cell carcinoma, undifferentiated carcinoma and unclassified carcinoma, among which adenocarcinoma accounts for the highest proportion, accounting for 55-74% of diagnoses (188). *Helicobacter pylori*, one of the few bacteria directly associated with cancer, is closely associated with the occurrence and development of GC (189). *Helicobacter pylori* carry a variety of pathogenic genes such as CagA, VacA and BabA, which can cause damage to the gastric mucosa and accelerate the progress from gastritis to GC (190). Endoscopic resection is currently an optimal treatment for early GC. Perioperative or neoadjuvant chemotherapy can improve the survival rate of patients with advanced GC (191).

The therapeutic effect of flavonoids against GC has been demonstrated in various preclinical models. For instance, the effect of luterolin on the GC cell line SGC-7901 was previously assessed on cell proliferation, apoptosis and G_0/G_1 cell cycle arrest. Analysis revealed that the combination of luteolin and oxaliplatin was superior to single drug, suggesting that combined treatment produced improved synergistic anti-tumor effect. Additionally, the combined treatment could also enhance the sensitivity of GC cells to oxaliplatin (192). Hesperetin, a common citrus flavanone, has been shown to have an inhibitory effect on GC in both *in vitro* and *in vivo* models (193). Hesperetin decreases the migration, invasion and damage of telomeric silencing-1-like expression levels in GC cells. Additionally, hesperetin inhibits the methylation of histone H3 at lysine residue 79 in tumor tissues of mice, and it considerably reduces lung metastasis in immunodeficient mice (194). Calycosin is a key active ingredient in *Astragalus membranaceus*, which is mainly used in the treatment of cancer and liver disease (195,196). Calycosin can improve intestinal metaplasia and dysplasia of gastric mucosal cells, and improve microvascular abnormalities and parietal cell morphology in rats with precancerous lesions. These findings indicate that calycosin protects the gastric mucosa in GC (197).

A Korean case-control study reports a negative relationship between dietary flavonoids and risk of developing GC (198). In a multi-center population-based study in the United States, flavanone intake was associated with 34% lower risk for death in patients with gastric adenocarcinoma compared with controls (199). In a cohort study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a negative relationship between total dietary intake of flavonoids and GC risk was reported in females. However, no meaningful association was found in males (200). In a case-control study where 230 patients with histologically confirmed GC and 547 controls without a history of cancer completed a food frequency questionnaire (FFQ), dietary flavonoids were inversely associated with GC risk (201). Furthermore, other studies have revealed that flavonoids could prevent GC by inhibiting urease, damaging genetic material, inhibiting protein synthesis and promoting host cell adhesion against *Helicobacter pylori* (202-204). Collectively, flavonoids are a potential drug candidate for the treatment of GC.

PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathway has an important role in the pathogenesis of GC, and it serves as a regulator of apoptosis and autophagy (205). Activated and p-AKT activates serval downstream apoptosis-related genes such as Bcl-2 associated X (BAX) and forkhead box protein O1, revealing a role in the GC pathway. Autophagy is mainly regulated by a set of autophagy-related genes involved in mTOR signaling pathway (206,207). Studies have revealed that the PI3K/AKT/mTOR signaling pathway is engaged in the mechanism of action of various flavonoids in GC (208-210). For example, procyanidin B2 can promote the apoptosis of GC cells and induce autophagy by inhibiting the AKT/mTOR signaling pathway (208). Similar effects are also observed in numerous other flavonoids, such as acacetin and isoliquiritigenin (ISL) (209,210) (Fig. 3A). Mitochondrial ROS participates in stress signaling in normal cells *in vivo*, but it can also lead to cancer development and expansion of tumor cell phenotypes (211). In response to pathological changes, such as tumor, ischemia/reperfusion or traumatic brain injury, ROS accumulates in cells and affects cell homeostasis and function, leading to oxidative stress and mitochondrial damage. This process is accompanied by autophagy induction (212,213). Autophagy deficiency will elevate the expression of hypoxia inducible factor (HIF)-1α through the ROS-NF-κB-HIF-1α pathway and affect cell metabolism, in turn promoting glycolysis, growth and metastasis of GC cells *in vivo* (214). Jaceosidin (JAC) is a natural flavonoid that can induce apoptosis in GC cells through the ROS-mediated MAPK/STAT3/NF-κB signaling pathway. Additionally, JAC can induce cell cycle arrest in the G_0/G_1 phase by inhibiting the AKT pathway, and it can also inhibit cell migration by influencing the Wnt/GSK3β/β-catenin pathway (215) (Fig. 3B; Table II).

The role of flavonoids in pancreatic cancer. PC, a highly malignant tumor originating from the pancreatic ductal epithelium and acinar cells, is the seventh leading cause of cancer-associated mortality worldwide (216). The pancreas performs both endocrine and exocrine functions. PC can be sub-divided into two categories based on the origin of the tumor cells: Endocrine tumors and exocrine tumors. The common malignant exocrine pancreatic tumors mainly include pancreatic ductal adenocarcinomas (PDAC) and acinar cell carcinomas. PDAC is more common that accounts for ~90% of all diagnosed PCs (217,218). Surgical resection remains the most effective treatment for PC (219). However, it is not applicable in 80-85% of patients who are at an advanced stage at initial diagnosis, and PC is not sensitive to most chemotherapeutic drugs (220). These factors lead to poor survival rates in patients with PC.

Various preclinical models have confirmed the therapeutic effect of flavonoids against PC. Silibinin has an inhibitory effect on PC both *in vivo* and *in vitro* (221,222). Silibinin can inhibit proliferation of PC cells, promote their apoptosis, induce cell cycle arrest in G_1 phase, inhibit tumor growth in a xenograft nude mouse model, and lead to the reduction of tumor volume and weight (223). Research reveals that myricetin can inhibit the proliferation of PC cells and induce their apoptosis, but has no significant effect on normal pancreatic ductal cells, and it can significantly reduce the tumor volume in a PC mouse model (224). Quercetin is a flavonoid compound that can be used in combination with chemotherapy for the treatment of PC. An animal experiment found increased quercetin

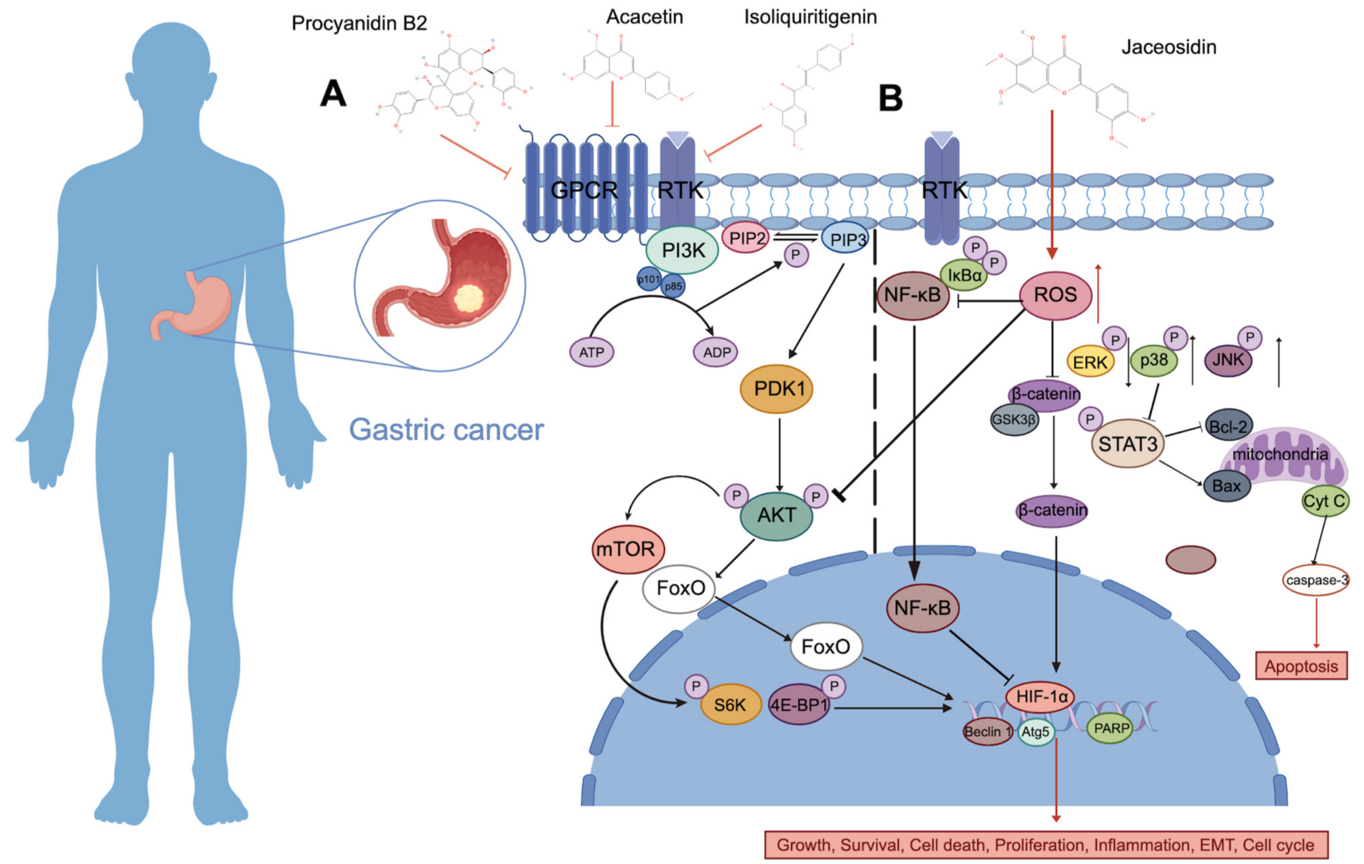


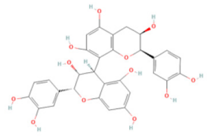
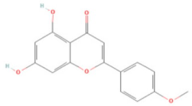
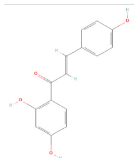
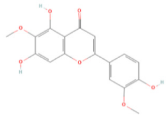
Figure 3. Role of flavonoids in gastric cancer. (A) Procyanidin B2, acacetin and isoliquiritigenin exerts anti-GC effects by inhibiting the PI3K/Akt/mTOR pathway. When ligands bind to GPCR and RTKs to activate PI3K, activated PI3K phosphorylates PIP2 to PIP3, which in turn activates PDK1, phosphorylates downstream AKT, which in turn activates FoxO and mTOR. It regulates the transcription of associated genes. (B) Jaceosidin activates multiple signaling pathways by aggregation of ROS. ROS regulates ERK, p38 and JNK, thereby activating STAT3 to regulate the mitochondria-dependent apoptotic pathway. ROS is also involved in the NF-κB pathway, which is inhibited by IκBα and downregulation of NF-κB (p50 and p65). NF-κB enters the nucleus, inhibits the transcription of HIF-1α and regulates the occurrence of inflammation. ROS could also reduce the stability and transcriptional activity of HIF-1α by inhibiting the MAPK/p38 and MAPK/ERK pathways. ROS also inhibits AKT and Wnt/GSK 3β/β-catenin pathways, downregulates p-AKT and β-catenin, arrests the cell cycle and inhibits cell migration. FoxO, forkhead box protein O; STAT3, signaling transducer and activator of the transcription 3; ROS, reactive oxygen species; NF-κB, nuclear factor-κB; IκBα, inhibitors of NF-κB α; Wnt, wingless/integrated; GSK-3β, glycogen synthase kinase 3β; HIF-1α, hypoxia-inducible factor-1α; p-AKT, phosphorylated AKT.

accumulation in PC tissue of nude mice and gemcitabine cotreatment with quercetin reduced the absorption of quercetin in the mouse circulatory system and liver (225).

In a cohort study including 326 patients with PC and 652 healthy controls, FFQ analysis showed a negative relationship between the intake of flavonoids including proanthocyanidins and risk of developing PC. Additionally, a study revealed eating fruits rich in proanthocyanidins reduces the risk of developing PC by ~25% (226). Similarly, Australian native fruits containing flavonoids are also reported to have therapeutic effect against the development of PC (227). A multi-ethnic cohort study evaluated the role of quercetin, kaempferol and myricetin in PC incidence, and revealed that all three flavonols could reduce the risk of developing PC, especially in smokers (228). A similar finding was also reported in a Finnish investigation (229).

Flavonoids mainly exert their therapeutic effect in PC through different signaling pathways. The RAS gene family includes KRAS, HRAS and NRAS and they are under the regulation of guanine nucleotide-exchange factors and GTPase-activating proteins (GAPs). Under pathological conditions, the interaction between RAS and GAP decreases, and the rate of GAP-stimulated GTP hydrolysis decreases. In the meantime, the interaction between guanine nucleotide exchange factor and RAS improves, resulting in continuous activation of RAS (230,231). In the RAS family, KRAS mutation has an important role in the occurrence and development of PC and it occurs in nearly 90% of patients with PDAC (232). Research reveals that epicatechin has no obvious effect on normal pancreatic ductal epithelial (PDE) cells, but it reduces the proliferation and transcriptional activity of precancerous and malignant KRAS-activated PDE cells (233) (Fig. 4A). Cancer stem cells (CSCs) are known to cause treatment resistance and early PDAC progression. It has been established that EGCG, epicatechin gallate and catechin gallate have anti-CSCs activity. Flavonoids can induce apoptosis and inhibit cell migration and levels of the MMPs, MMP9 and MMP2 by downregulating the level of KRAS (234,235). The PI3K/AKT/mTOR signaling pathway also participates in the growth, survival, proliferation and metabolism of PC cells (236). Grape seed proanthocyanidin extract can induce apoptosis and cell cycle arrest in G_2/M phase in PC cells *in vitro*, and inhibit the growth of transplanted tumors in nude mice. The levels of PI3K and p-AKT were also considerably

Table II. Role of flavonoids in gastric cancer.

First author/s, year	Flavonoid	Chemical structure	Model	Target	Effect	(Refs.)
Li, 2021	Procyanidin B2		*In vitro*	Caspase-3, Caspase-9, LC3, Beclin1, Atg5, Akt/mTOR	Induces apoptosis of GC cells and promotes the activities of Caspase-3 and Caspase-9. Induces autophagy in GC cells by increasing the expression of LC3, Beclin1 and Atg5. 3-MA can reduce the effect of PB2 on EC cells by inhibiting autophagy. Procyanidin B2 can considerably reduce the expression of p-Akt and p-mTOR proteins in EC cells and induce apoptosis and autophagy.	(208)
Zhang, 2022	Acacetin		*In vitro, in vivo*	PI3K/Akt/Snail, MMP2, MMP9, TGF-β1, E-cadherin, N-cadherin, Vimentin	Inhibits the proliferation, invasion and migration of GC cells by inhibiting the expression of EMT-associated proteins. Reverses the morphological changes of cells in the TGF-β1-induced EMT model and inhibits the invasion and migration of GC cells by regulating EMT. Inhibition of PI3K/Akt pathway activation in GC cells. Delays the peritoneal metastasis of gastric cancer in nude mice.	(209)
Zhang, 2018	Isoliquiritigenin		*In vitro*	LC3I, LC3II, Beclin1, p62, PI3K/Akt/mTOR	Inhibits the proliferation, migration and invasion of GC cells and promotes apoptosis. Induces autophagy in GC cells by upregulating the expression of autophagy-related proteins. Influences apoptosis of GC cells and autophagy by regulating the PI3K/Akt/mTOR pathway.	(210)
Liu, 2024	Jaceosidin (JAC)		*In vitro*	p-JNK, p-p38, IκB-α, p-ERK, p-STAT3, NF-κB, p21, p27, p-Akt, CDK2, CDK4, CDK6, Cyclin D1, Cyclin E, Wnt-3a, p-GSK 3β, N-cadherin, β-catenin, E-cadherin	JAC activity was associated with ROS, AKT and MAPK pathways. Upregulates p21 and p27 protein expression and downregulates of p-AKT, CDK 2, CDK 4, CDK 6, Cyclin D1 and Cyclin E protein expression by ROS accumulation resulting in cell arrest at the G_0/G_1 phase. The expression of Wnt-3a, p-GSK-3β, N-cadherin and β-catenin proteins is downregulated, E-cadherin protein expression is upregulated and cell migration is inhibited by ROS accumulation.	(215)

LC3, microtubule-associated protein 1 light chain 3; Atg5, autophagy related gene 5; Akt, serine/threonine kinase B; mTOR, mammalian target of rapamycin; MMP2, matrix metalloproteinase 2; MMP9, matrix metalloproteinase 9 ; TGF-β1, transforming growth factor-β1; p62, sequestosome-1; PI3K, phosphatidylinositol 3-kinase; p-JNK, phosphorylated JNK; p-p38, phosphorylated p38 MAPK; IκB-α, inhibitors of NF-κB α; p-ERK, phosphorylated ERK; STAT3, signaling transducer and activator of the transcription 3; NF-κB, nuclear factor-κB; p21, cyclin dependent kinase inhibitor p21; p27, cyclin dependent kinase inhibitor p27; p-Akt, phosphorylated Akt; CDK2, cyclin dependent kinase 2; CDK4, cyclin dependent kinase 4; CDK6, cyclin dependent kinase 6; Wnt-3a, wingless/integrated-3a; p-GSK 3β, phosphorylated GSK 3β.

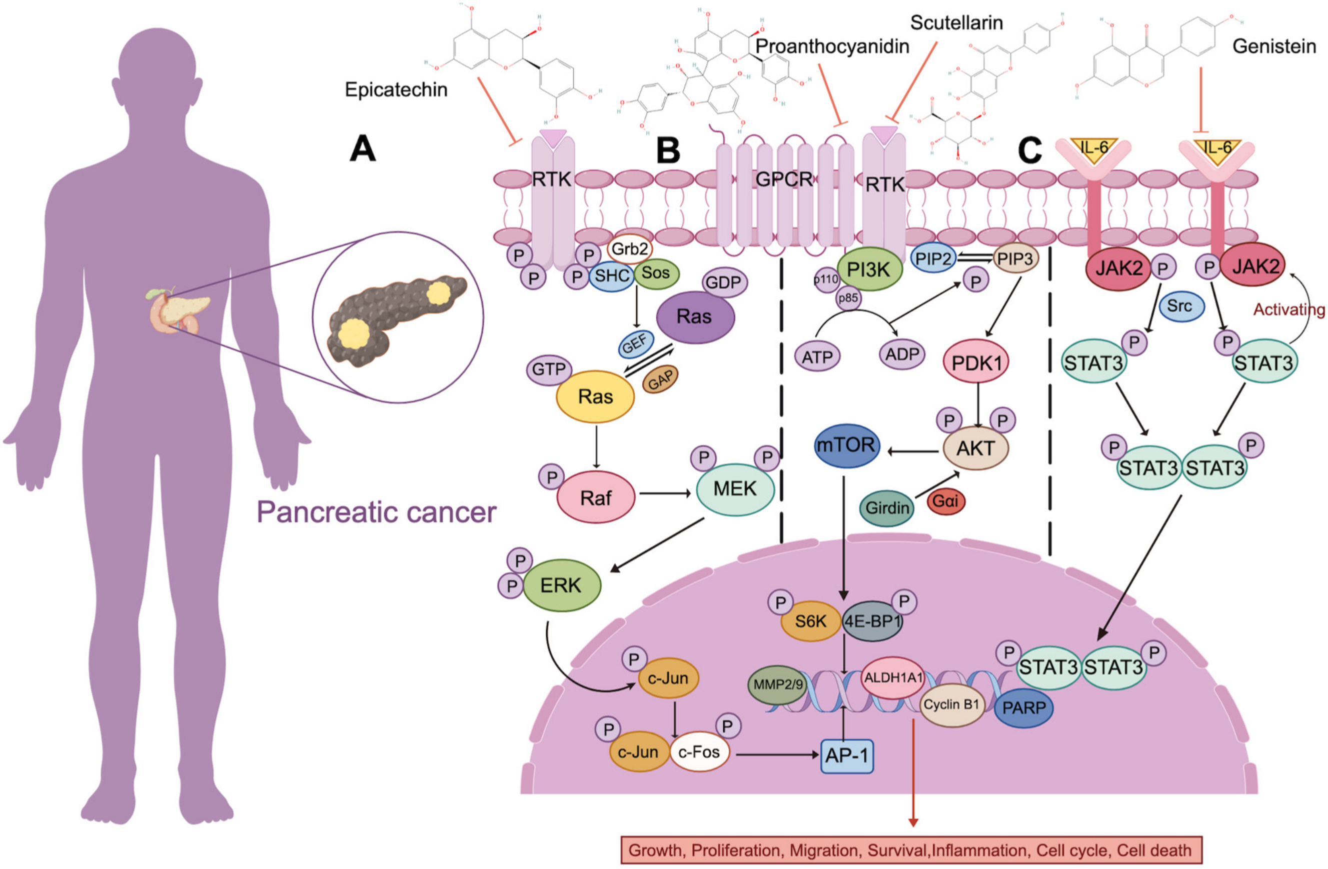


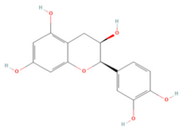
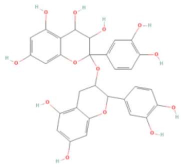
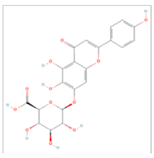
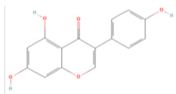
Figure 4. Role of flavonoids in pancreatic cancer. (A) Epicatechin exerts its anti-PC effect by inhibiting the MAPK/ERK pathway. When the ligands bind to RTKs, the tyrosine residues at their tails are phosphorylated, recruiting GRB2/Shc/SOS to the cell membrane, and converting GDP-bound Ras to active GTP-bound Ras. Upon Ras activation, Raf is recruited to the cell membrane and phosphorylated. It directly regulates MEK and ultimately leads to downstream ERK phosphorylation. Phosphorylated ERK enters the nucleus and activates the key transcription factors c-Jun and c-Fos to bind to the binding site in the AP-1 promoter region and regulate the transcription of associated genes. (B) Proanthocyanidin and Scutellarin exert their anti-PC effects by inhibiting the PI3K/Akt/mTOR pathway. When ligands bind to GPCR and RTKs to activate PI3K, activated PI3K phosphorylates PIP2 to PIP3, which further activates PDK1 and phosphorylates downstream AKT. Girdin, as a substrate of AKT, can mediate AKT activation, and this process is regulated by Gαi. Activated AKT in turn activates downstream mTOR, which phosphorylates substrates S6K and 4E-BP1 to regulate transcription of associated genes. (C) Epicatechin exerts its anti-PC effect by inhibiting the IL-6/JAK2/STAT3 pathway. When IL-6 binds to its receptor and activates JAK2, it recruits SRC to bind to the SH2 domain-containing STAT3 to activate downstream STAT3. The two activated STAT3 monomers form a dimer that enters the nucleus and binds to specific DNA response elements on target genes to induce gene transcription. Over-activation of STAT3 also induces IL-6 production, forming positive feedback that reinforces activation of the pathway. PC, pancreatic cancer; IL-6, interleukin-6; JAK2, Janus kinase 2; SRC, SRC proto-oncogene.

decreased in both PC cells *in vitro* and transplanted tumor tissue following treatment. These findings demonstrate that grape seed proanthocyanidin extract can inhibit PC progression through the PI3K/AKT pathway (237). Girdin, an AKT substrate, has been found to prolong AKT activation and DNA replication and have a role in cell migration and invasion (238). Flavonoid Scutellarin can considerably reduce the angiogenic ability of PC cells by inhibiting Girdin signaling (239) (Fig. 4B). Interleukin (IL)6 is an important inflammatory cytokine in the human body that has a role in the development of PDAC. In comparison with healthy individuals and patients with chronic pancreatitis, patients with PC have increased levels of serum IL-6 (240,241). IL-6 activates the downstream Janus kinase 2/STAT3 signaling pathway by binding to membrane receptors. Overactivation of STAT3 also induces IL-6 production, forming a positive feedback loop and in turn promoting PC cell proliferation and tumor formation *in vivo* (242). The flavonoid genistein has a therapeutic effect against PC by inhibiting the STAT3 signaling pathway (243) (Fig. 4C; Table III).

The role of flavonoids in liver cancer. Liver cancer is a common malignant tumor and is usually the terminal state of chronic liver disease (244). Of all cases of liver cancer, ~82% are in developing countries with 55% being in China alone (154). HCC is the most common primary malignant tumor of the liver. Hepatitis B virus (HBV) and aflatoxin are considered to be the main causes of liver cancer (245). Current treatment approaches for early-stage HCC include surgical resection and liver transplantation, while radical resection often results in a high recurrence rate (246). As understanding of disease pathogenesis increases, multiple therapies, including molecular targeted therapy, immuno-oncology monotherapy and combination therapy, have achieved encouraging results in patients who are diagnosed with advanced disease stages and cannot receive radical treatment (247).

The therapeutic effect of flavonoids against HCC has been reported in several preclinical models. Hesperidin was reported to have a protective effect in rats with diethylnitrosamine-induced HCC. Analysis revealed that hesperidin considerably reduced the levels of liver function enzymes,

Table III. Role of flavonoids in pancreatic cancer.

First author/s, year	Flavonoid	Chemical structure	Model	Target	Effect	(Refs.)
Siddique, 2012	Epicatechin		*In vitro, in vivo*	Ras, Bcl-2, Bax, Caspase-3, Caspase-8, PARP116, NF-κB, p-IκB-α, p-p38	No induction of NF-κB in normal PDE cells, but the transcriptional activity of Nf-κB is reduced in Kras activated PDE cells. Promotes apoptosis by upregulating the expression of Caspase-3, Caspase-8, and Bax, and downregulating the expression of Bcl-2 and PARP116. Inhibits the activation of p-p38 and MAPK to exert pro-apoptotic and anti-proliferative effects. Inhibits of Kras-PDE cell-derived tumor growth in xenograft mice.	(233)
Prasad, 2012	Proanthocyanidin		*In vitro, in vivo*	PI3K/Akt, Bax, Bcl-xl, Bcl-2, Caspase-3, Cyclin B1, Cdc25B, Cdc25C	Apoptosis is induced by downregulating Bcl-2 and Bcl-xl and upregulating Bax and Caspase-3 levels. The expression levels of Cyclin B1 and cell cycle regulatory proteins Cdc25B and Cdc25C are decreased and the cells are arrested in the G_2/M phase. Regulates pancreatic cancer cells (Miapaca-2, PANC-1 and AsPC-1) by inhibiting the PI3K/Akt pathway. Inhibits tumor volume and number in a xenograft mouse model.	(237)
Hayashi, 2023	Scutellarin		*In vitro*	Girdin	Inhibits Girdin phosphorylation, inhibits the invasion and migration of pancreatic cancer cells. Activation of Girdin has no effect on the expression of VEGF-A.	(239)
Bi, 2018	Genistein		*In vitro*	Caspase-3, Caspase-9, MMP2, MMP9, Cyclin D1, ALDH1A1, surviving, p-STAT3	Exerts anti-proliferative and pro-apoptotic effects by upregulating the expression of cytochrome *c*, Bax, Caspase-3 and Caspase-9 and down-regulating the expression of Bcl-2. Inhibits STAT3 phosphorylation and downregulates Cyclin D1, ALDH1A1 and survivin which causes cell cycle arrest at G0/G1 phase. Downregulation of MMP2 and MMP9 inhibits the migration of pancreatic cancer cells. Induces apoptosis by producing large amounts of ROS and reducing mitochondrial membrane potential.	(243)

Ras, Rat sarcoma; Bcl-2, B-cell lymphoma-2; Bax, BCL2-associated X; PARP116, poly(ADP-ribose) polymerase 116; NF-κB, nuclear factor-κB; p-IκB-α, phosphorylated inhibitors of NF-κB-α; p-p38, phosphorylated p38 MAPK; PI3K, phosphatidylinositol 3-kinase; Akt, serine/threonine kinase B; Bcl-xl, B-cell lymphoma-extra large; Cdc25B, cell division cyclin 25B; MMP2, matrix metalloproteinase 2; ALDH1A1, aldehyde dehydrogenase 1 family member A1; STAT3, signaling transducer and activator of the transcription 3.

serum α-fetoprotein and markers of oxidative stress (248). γ-glutamyl transpeptidase (GGT) is a tumor marker that can be detected in liver lesions induced by carcinogens (249). Carrasco-Torres *et al* (250) found that quercetin was able to prevent and even reverse precancerous lesions in rat liver, and the number and area of GGT-positive lesions were decreased considerably after quercetin administration, indicating that quercetin could prevent precancerous lesions. Insulin-like growth factor 1 (IGF-1) is an indicator of liver functional status. A study reports that IGF-1 levels is markedly restored following quercetin treatment. Another study reveals that both baicalein or silymarin alone and their combination effectively inhibit the proliferation of HCC cells. Notably, the cumulative effect exerted by their combination could be observed at 24 h and the synergistic effect could be observed at 48 h, inducing apoptosis and G_0/G_1 cell cycle arrest to a greater extent, but almost no effect was observed in non-tumor Chang liver cells (251).

A case-control study conducted in Greece found that patients with HCC with or without hepatitis B or C virus infection inversely correlated to the intake of flavonoids (252). In a clinical study that investigated the relationship between dietary and urinary isoflavonoids contents and the risk of liver cancer in a Shanghai cohort of women, urinary genistein content was revealed to be negatively associated with the risk of developing liver cancer (253). 8-hydroxydeoxyguanosine (8-OHdG), a biomarker of oxidative DNA damage, in a population at high risk of developing HCC (254). A randomized, double-blinded, placebo-controlled phase IIa trial evaluated the regulatory effect of green tea polyphenols (GTPs) on 8-OHdG, and significantly lower levels of 8-OHdG excreted into the urine was observed in patients treated with GTPs compared with those given placebo treatment (255). This implies that GTPs can effectively reduce oxidative DNA damage and prevent the occurrence of HCC in high-risk populations. A cohort study nested within the European prospective investigation into cancer and nutrition study reported a negative relationship between flavanols and HCC risk. This finding indicates that a higher intake of flavanols is associated with a reduced risk of HCC (256).

p53 is a tumor suppressor gene that has an important role in the occurrence of HCC. Mutation of p53 can lead to loss of normal p53 function (anti-tumor effect) and gain of mutant function of p53 (carcinogenic effect) (257). Mouse double minute (MDM)2 and MDM4 are negative regulators of p53 (258). MDM2 is an E3 ubiquitin ligase that can degrade p53 by ubiquitination (259). MDM4 can negatively regulate the inhibitory effect of p53 on tumors by binding to the transcriptional activation domain of p53 (260). Resveratrol, a flavonoid isolated from the roots of white hellebore, can induce autophagy in hepatoma cells by activating p53 and inhibiting the PI3K/AKT signaling pathway, thereby inhibiting cell proliferation, invasion and migration (261) (Fig. 5A). Studies have revealed that p53 can form a complex with Bcl-xl and Bcl-2, which can alter mitochondrial outer membrane permeability and then induce the release of cytochrome *c*. As a consequence, apoptosis is directly initiated (262-264). p53 is also a positive transcriptional activator of the pro-apoptotic protein Bax and a negative transcriptional activator of the anti-apoptotic protein Bcl-2 (265). Activated normal p53 can downregulate β-catenin, leading to ubiquitination or proteasomal degradation of β-catenin. The activity of GSK-3β, a core component of β-catenin, is subsequently reduced, resulting in loss of function (266). Silymarin is a mixture of the following four isomeric flavonoids: Silibinin, isosilibinin, silydianin and silychristin. Silymarin increases the level of p53 protein in hepatoma cells with increasing drug concentration. Additionally, silymarin can induce cell cycle arrest in G_0/G_1 phase by downregulating the expression of β-catenin, cyclin D1, c-Myc and proliferating cell nuclear antigen. It is also found that silymarin could induce mitochondrial membrane depolarization and cytochrome *c* release into the cytoplasm, regulate the expression of apoptosis-related proteins and promote the apoptosis of HepG2 cells (267). Doxorubicin (DOX) is commonly used as a routine chemotherapeutic drug for the treatment of liver cancer (268). However, its clinical application is limited due to the liver, kidney and heart toxicity that is dose-dependent (269,270). Certain studies reported that flavonoids selectively enhance the toxic effect of DOX on liver cancer cells and the combined use of flavonoids and DOX produces an improved therapeutic effect (271,272). For example, quercetin increases the activity of Caspase 3/9 by upregulating the expression of p53 and downregulating the expression of Bcl-xl, thereby promoting the DOX-induced apoptosis in liver cancer cells (273) (Fig. 5B; Table IV).

The role of flavonoids in colorectal cancer. CRC is a general term for malignant tumors occurring in the colon and rectum. It is the third most common malignancy and the fourth leading cause of cancer-associated mortality in the world (274). Endoscopic resection is feasible for early CRC, but 50% of patients experience local recurrence or distant metastasis of different degrees within 2 years after resection (275). The liver is the most common metastatic site of CRC (276). Radiofrequency ablation, local radiotherapy, preoperative radiotherapy and chemotherapy can reduce the risk of local recurrence (277). Molecular targeted drugs have been used for the treatments of CRC, such as the anti-VEGF drug bevacizumab and anti-epidermal growth factor receptor drug cetuximab. These drugs have achieved good efficacy in the management of metastatic CRC (278).

A number of studies using preclinical models have identified the therapeutic effect of flavonoids against CRC. Naringin has a preventive effect against precancerous lesions in rats with CRC induced by chemical carcinogens. Analysis reveals that administration of 200 mg/kg naringin effectively reduces the number of aberrant crypt foci, argyrophilic nucleolar organizing regions/nucleus and mitosis in rats with 1,2-dimethylhydrazine-induced CRC. Additionally, naringin also reduces cell proliferation and levels of iron in tissues and promotes the recovery of the antioxidant minerals such as copper, magnesium and zinc (279). Apigenin has been revealed as a promising flavonoid that can inhibit the growth of CRC cells (280). Apigenin reduces the number of intestinal polyps in APC mice with multiple intestinal neoplasia. A clinical study reported that apigenin increases the expression of p53 and non-steroidal anti-inflammatory drug activated gene-1 (NAG-1) proteins in human colon cancer cells, facilitating apoptosis. Apigenin also increases p21 protein expression levels and induces cell cycle arrest (281). ISL exerts an

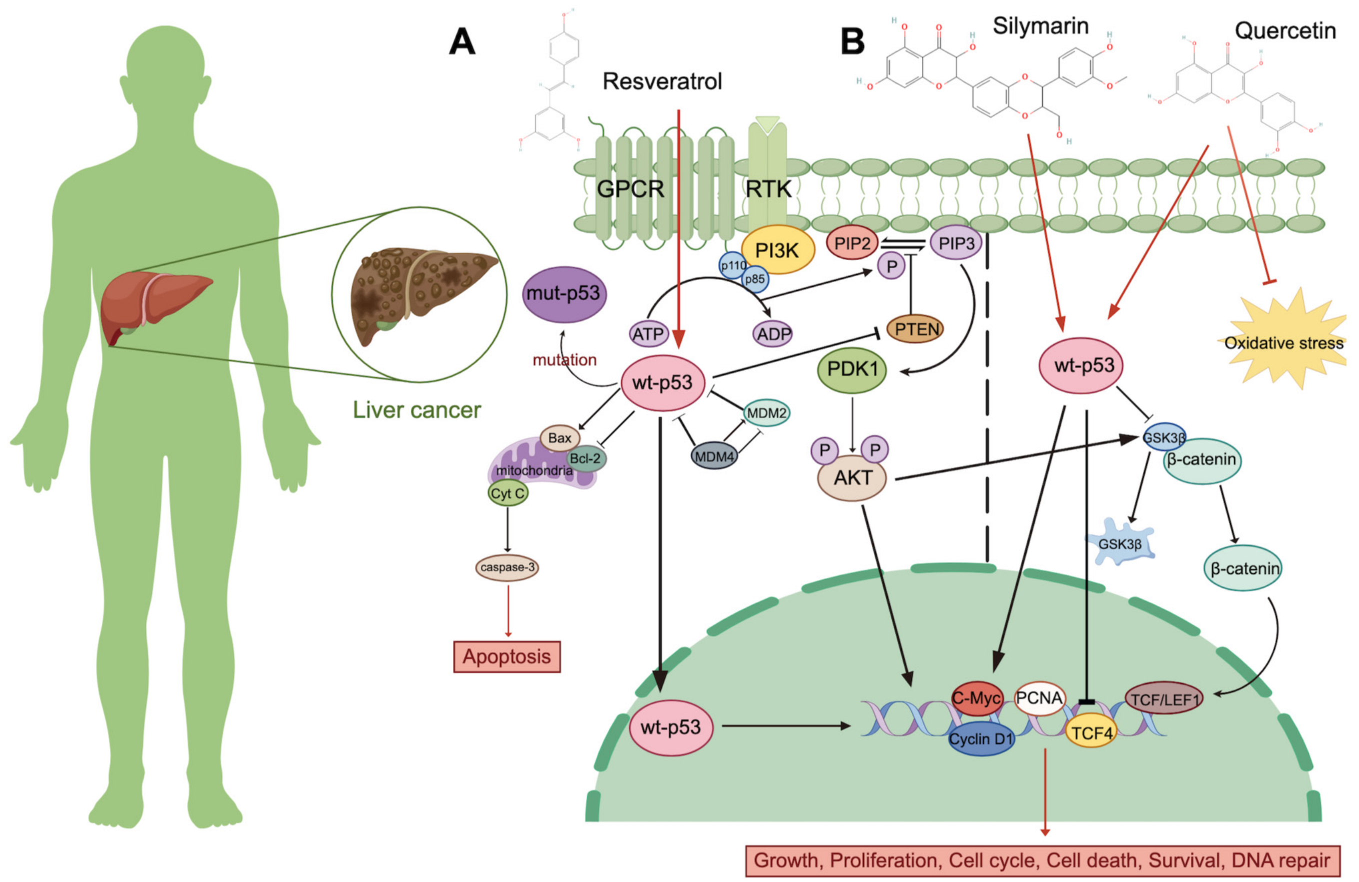


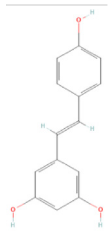
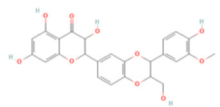
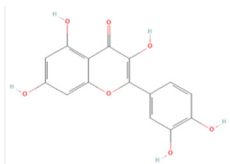
Figure 5. Role of flavonoids in liver cancer. (A) Resveratrol exerts its anti-HCC effects by activating p53 and inhibiting the PI3K/Akt pathway. Wt-p53 can inhibit the activation of the PI3K/Akt pathway by inhibiting phosphatase and tensin homologue deleted on PTEN. Phosphorylated AKT can also indirectly inhibit wt-p53 through activation of MDM2. (B) Silymarin can activate wt-p53 and downregulate β-catenin simultaneously. β-catenin undergoes ubiquitination and proteasome degradation, dissociates from GSK-3β, and enters the nucleus to regulate the transcription of downstream TCF4, C-Myc, PCNA and Cyclin D1, and regulates the cell growth, proliferation and cell cycle. At the same time, p53 can also directly repress TCF4 transcription. In addition, p53 can also induce mitochondria-mediated apoptosis pathway by inhibiting the expression of Bcl-2 and promoting the expression of Bax, regulating the permeability of the mitochondrial outer membrane, promoting the release of cytochrome *c*, and then activating caspase-3 to induce apoptosis of liver cancer cells. Quercetin increases the expression of p53 induced by DOX in HCC cells. Moreover, DOX-induced oxidative stress is reduced to increase the survival of normal hepatocytes. p53, tumor protein 53; TCF4, T-cell factor 4; PCNA, proliferating cell nuclear antigen; Bcl-2, B-cell lymphoma-2; Bax, BCL2-associated X; DOX, doxorubicin; HCC, hepatocellular carcinoma.

anticancer effect in mice with colitis-associated cancer (CAC), which is associated with the gut microbiota. ISL intervention reduces the abundance of opportunistic pathogens in the gut of CAC-induced mice, increases the levels of probiotics and alters gut microbiota composition (282).

An FFQ was applied in a multi-center case-control study from Italy and reported that increased intake of isoflavones, anthocyanidins, flavones and flavonols considerably reduced the risk of CRC (283). Similarly, questionnaire data from a Korean case-control study showed that a high intake of soy products, which contain high levels of isoflavones, is associated with a reduced risk of CRC development, especially distal and rectal types of cancer (284). In a study where CSCs derived from patients with colorectal liver metastases were sampled to evaluate whether curcumin can provide additional benefits over fluorouracil and folinic acid, fluorouracil and oxaliplatin (FOLFOX); the combination of curcumin and FOLFOX chemotherapy outperforms chemotherapy alone (285). A clinical study showed that curcuminoid complex improves erythrocyte sedimentation rate and serum C-reactive protein (CRP) levels, reduces systemic inflammatory response and improves quality of life for patients with CRC (286). Flavonoids are also used to reduce the risk of recurrence following CRC resection. A clinical study investigated the efficacy of apigenin combined with EGCG in patients with CRC receiving surgical resection and adenoma polypectomy and performed colonoscopy surveillance and questionnaire survey after a follow-up period of 3-4 years. The tumor recurrence rate was 7% in patients treated with flavonoids following surgical resection and 47% in untreated control patients. This result suggests that long-term treatment with flavonoids can considerably reduce tumor recurrence in patients with CRC receiving surgical resection (287). Moreover, colonoscopy at the end of the fourth year showed that dietary flavonol supplementation decreased the risk of recurrence in patients with CRC (288). Another two cohort studies revealed that an increased intake of flavonol resulted in a decreased rate of mortality in patients with CRC during follow-up (289).

Nuclear factor-κB (NF-κB) is a B-cell specific transcription factor (290). It has considerably high levels of expression in a variety of tumor tissues and is associated with tumor metastasis and disease prognosis (291,292). The p50-p65

Table IV. Role of flavonoids in liver cancer.

First author/s, year	Flavonoid	Chemical structure	Model	Target	Effect	(Refs.)
Zhang, 2018	Resveratrol		*In vitro*	Beclin1, p62, LC3 I/II, p53, PI3K/Akt	Upregulates the expression of autophagy-related proteins Beclin1 and LC3 I/II and downregulates the expression of p62 to promote autophagy in liver cancer cells. Autophagy inhibitor 3-MA counteracts the inhibitory effects of Resveratrol on the proliferation, invasion and migration of HCC cells. The expression of p53 protein is upregulated and the ratio of p-Akt/Akt was decreased. Activation of p53 and inhibition of PI3K/Akt pathway induces autophagy to inhibit the proliferation, invasion and migration of HCC.	(261)
Ramakrishnan, 2009	Silymarin		*In Vitro*	Cytochrome C, p53, Bax, Bcl-2, APAF-1, Caspase-3, survivin, β-catenin, Cyclin D1, c-Myc, PCNA	Up-regulating the expression of pro-apoptotic proteins (p53, Bax, APAF-1 and Caspase-3) and down-regulating the expression of anti-apoptotic proteins (Bcl-2 and survivin) promotes the apoptosis of liver cancer cells. Decrease the expression of proliferation-related proteins (β-catenin, Cyclin D1, c-Myc, PCNA) and inhibit the proliferation of liver cancer cells. Silymarin decreases the mitochondrial transmembrane potential, thereby increasing the level of cytochrome C.	(267)
Wang, 2012	Quercetin (Que)		*In Vitro* *In Vivo*	P53, Bcl-xl, Bcl-2, Caspase-3, Caspase-8, Caspase-9, PARP, Bax, Bid	Increased adriamycin-mediated apoptosis in HCC cells is p53-dependent and occurs through downregulation of Bcl-xl expression. Z-VAD inhibitor (caspase inhibitor), pifithrin-a (p53 inhibitor), or overexpression of Bcl-xl reduced the effect of quercetin on DOX-mediated apoptosis. Co-treatment with DOX significantly reduced the growth of HCC xenografts in mice. Decreased serum levels of alanine aminotransferase and aspartate aminotransferase increased. Reverse the pathological changes of the liver induced by adriamycin in mice.	(273)

p62, sequestosome-1; LC3 I, microtubule-associated protein 1 light chain 3 I; LC3 II, microtubule-associated protein 1 light chain 3 II; p53, tumor protein 53; PI3K, phosphatidylinositol 3-kinase; Akt, serine/threonine kinase B; Bax, BCL2-associated X; Bcl-2, B-cell lymphoma-2; APAF-1, apoptotic protease activating factor-1; PCNA, proliferating cell nuclear antigen; Bcl-xl, B-cell lymphoma-extra large; PARP, poly(ADP-ribose) polymerase; Bid, BH3-interaction domain death agonist.

heterodimer is the most common form of NF-κB, and it can bind to inhibitors of NF-κB (IκB) in the cytoplasm (293). IκB is mainly regulated by IκB kinase (IKK). IKK is activated through trans-autophosphorylation by the catalytic domains of IKKα and IKKβ, leading to phosphorylation and ubiquitin-mediated degradation of IκB. NF-κB is then released into the nucleus, resulting in the transcription, translation and expression of NF-κB related genes (292,294,295). Chronic inflammation is one of the main risks of CRC and patients with inflammatory bowel disease have an increased risk of colitis-associated CRC. Chronic intestinal inflammation leads to tissue hyperplasia and affects key cytokine-mediated signaling pathways (296-298). A study has reported that activated NF-κB in intestinal epithelial cells is an important factor leading to the occurrence of colon cancer in colitis-induced mice (299). NF-κB is a key regulator of the inflammatory response and overactivation of NF-κB can aggravate the occurrence of chronic inflammation (300). Baicalin has an anti-CRC role by promoting apoptosis and regulating the tumor immune microenvironment through the TLR4/NF-κB signaling pathway (301). Silibinin has been reported to inhibit the growth and progression of colon cancer by promoting TNF-α-induced NF-κB activity (302) (Fig. 6A). The Wnt/β-catenin signaling pathway is also involved in the occurrence of CRC. In normal conditions, Wnt binds to Frizzled/low-density lipoprotein-related protein 5/6 to maintain the stability of β-catenin in the cytoplasm. APC is a component of the β-catenin degradation complex and it is also the most commonly mutated gene that leads to inactivation in CRC (303). Under pathological conditions, the β-catenin degradation complex is inactivated. p-β-catenin is recognized and ubiquitinated by β-transducing repeats-containing proteins, leading to proteasome degradation. When the β-catenin degradation complex is inactivated, a large amount of accumulated β-catenin enters the nucleus and binds to the transcription factor T cell factor/lymph enhancer factor 1, initiating the expression of downstream target genes (304-306). A large number of studies have shown that the occurrence of CRC is associated with the activation of the Wnt/β-catenin signaling pathway (307,308). Proanthocyanidins can enhance the sensitivity of colon cancer cells to oxaliplatin through the Wnt/β-catenin signaling pathway, and they can inhibit CSCs in CRC and tumorigenesis (309). EGCG can inhibit colorectal CSCs by downregulating the Wnt/β-catenin signaling pathway (310). In addition, scutellarin and apigenin can improve CRC by weakening the Wnt/β-catenin signaling pathway (311,312) (Fig. 6B; Table V).

6. Regimens to enhance the efficacy of flavonoids in preclinical models

Poor water solubility, low permeability and inferior stability of most flavonoids result in their low bioavailability and limit their clinical use (19). Based on relevant preclinical experiments, the following four main ways improve the efficacy of flavonoids in preclinical models: Changing the drug dosage form and preparation technology, improving the extraction and separation methods of flavonoids, combining with other drugs or components and studying the biotransformation of flavonoids by intestinal bacteria.

The bioavailability and efficacy of flavonoids can be improved by changing their pharmaceutical dosage forms and preparation techniques. For example, the study by Guo *et al* (313) prepared myricetin microemulsion (MYR-ME), and the optimized MYR-ME showed a 1,225-fold increase in solubility compared with myricetin. In the cell model, the anti-proliferative activity of MYR-ME was revealed to be stronger than that of myricetin on the human hepatoma cell line HepG2, while it had little effect on the normal liver cell line LO2. MYR-ME also considerably enhanced the antioxidant activity of myricetin. In the same study, oral administration of MYR-ME to Sprague-Dawley rats revealed oral availability of MYR-ME to be 14.43 times greater than myricetin suspension. Encapsulation of tangeretin in whey protein-stabled emulsions considerably improved the low solubility and oral bioavailability of tangeretin. *In vivo*, pharmacokinetics showed that the emulsion increased the plasma concentration of tangeretin from 4-fold to 20-fold and prolonged the release time of tangeretin to 22 h in rats (314).

The purity and activity of flavonoids can be improved by optimizing extraction and separation methods (315). Ultrasound-assisted extraction produces mechanical and thermal effects on plant cells by ultrasonic energy, causing cell wall rupture and releasing bioactive components into the solvent medium (316). Parameters such as extraction temperature and ultrasonic power required for ultrasound-assisted extraction can promote the solubility of flavonoids, resulting in the acquisition of plant active compounds with high extraction rates and increased bioaccessibility of oral compounds (317). The study by Lin *et al* (318) extracted total flavonoids by ultrasound-assisted extraction, which effectively increased the total flavonoid content and antioxidant activity. Supercritical fluid extraction has been commonly used in the pharmaceutical industry, with its excellent performance in extracting ginkgolides and flavonoid compounds in *Ginkgo biloba* (319). Supercritical carbon dioxide (SC-CO_2) is the most commonly used solvent as it is non-toxic, safe, readily available and easy to remove. The study by He *et al* (320) extracted flavonoid compounds from pomelo [*Citrus grandis* (L.) Osbeck] peels with SC-CO_2 and found an increased flavonoid yield and antioxidant activity than flavonoids obtained from conventional extraction solvents.

The efficacy of flavonoids can be enhanced by combining them with other drugs or components. For example, the study by Wang *et al* (321) prepared a phospholipid complex by binding total flavones of *Hippophae rhamnoides* L. (TFH) to phospholipids (TFH-PC). The solubility of isorhamnetin, kaempferol and quercetin in TFH-PC was increased 22.0-26.8-fold compared with TFH alone. After oral administration of TFH-PC to rats, the bioavailability of the three flavonoid classes was considerably increased. Flavonoids can combine with certain metal ions to form flavonoid-metal ion complexes. Most of the classified flavonoid-metal ion complexes exhibit affinity for DNA. It can interact with the DNA by binding either to the major or minor grooves or by intercalation (322). Lanthanum, in combination with the active ingredients found in certain plants, showed a more potent cytotoxic effect than when administered alone (323). The combination of quercetin with lanthanum resulted in the formation of quercetin/lanthanum complex, which exhibited

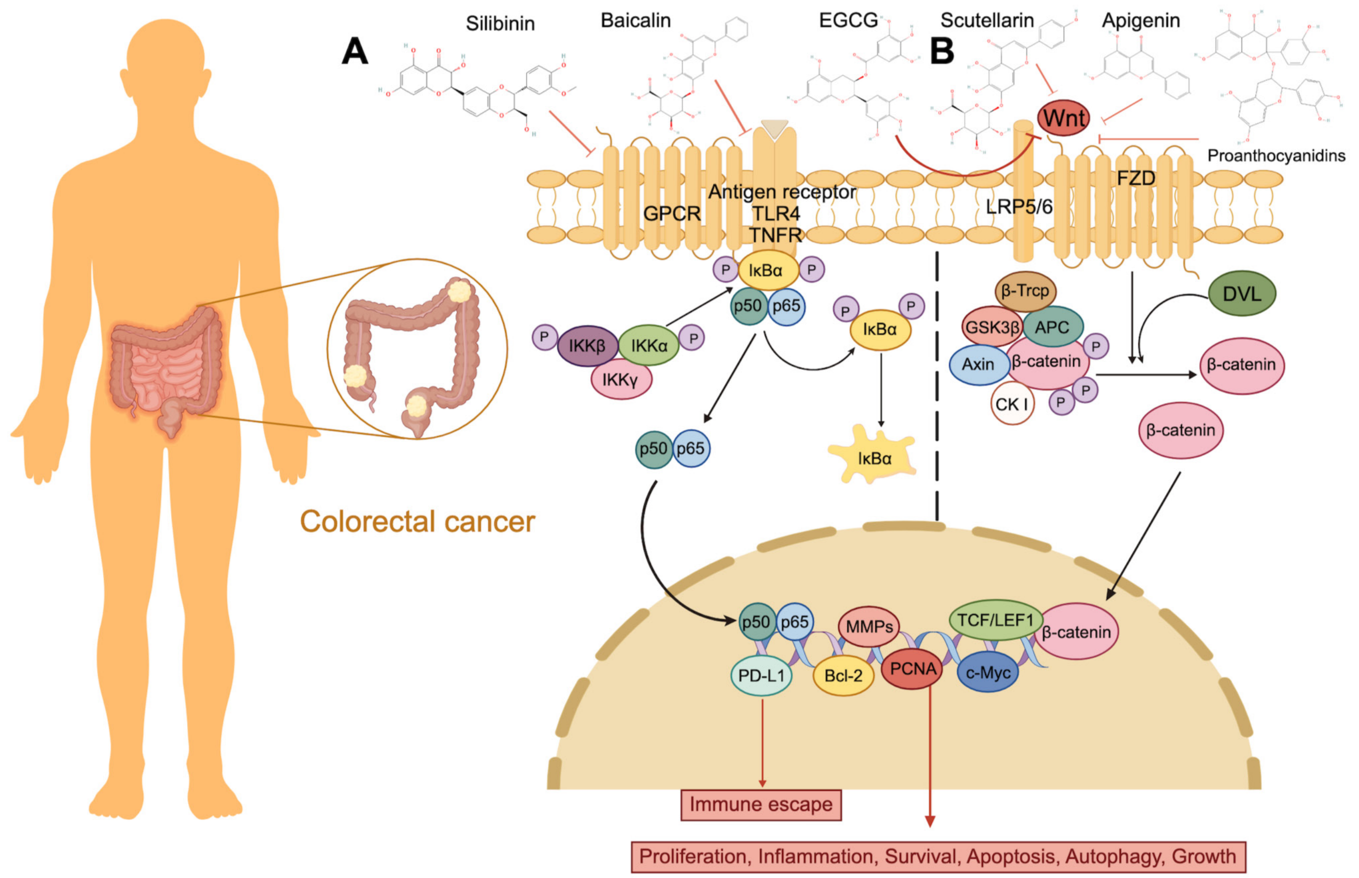


Figure 6. Role of flavonoids in colorectal cancer. (A) Baicalin and silibinin exert their anti-CRC effects by inhibiting the NF-κB pathway. The NF-κB pathway is activated by TLR, antigen receptor and TNFR binding to their corresponding ligands. The activation of IKK leads to the degradation of IκBα and the release of NF-κB (p50 and p65) into the nucleus, which induces inflammation, cell proliferation and survival. NF-κB can also directly promote PD-L1, transcription and trigger immune escape of tumor cells. (B) Proanthocyanidins, EGCG, Scutellari and apigenin exert their anti-CRC effects by inhibiting the Wnt/β-catenin pathway. In the absence of ligands for the Wnt receptor, β-catenin is phosphorylated by the Axin/GSK 3β/APC degradation complex and degraded by ubiquitination of β-Trcp. When Wnt receptors bind to their ligands, they inhibit β-catenin degradation by recruiting DVL proteins in the cytoplasm and destroying the degradation complex, resulting in a large accumulation of β-catenin in the cytoplasm and into the nucleus. It binds to transcription factor TCF/LEF1 and initiates the expression of downstream Wnt target genes to regulate cell growth and development and other characteristics. CRC, colorectal cancer; TLR, toll-like receptor; TNFR, tumor necrosis factor receptor; PD-L1, programmed cell death ligand-l; EGCG, (-)-epigallocatechin-3-gallate; APC, adenomatous polyposis coli; β-Trcp, F-box/WD repeat-containing protein 1A; DVL, drosophila dishevelled homolog; TCF, T-cell factor; LEF1, lymph enhancer factor 1.

cytotoxic effects on human cervical cancer cells and also induced dose-dependent pro-oxidation and DNA single-and double-strand breaks (324).

Studies on the biotransformation of flavonoids by intestinal bacteria *in vitro* and *in vivo* could optimize their metabolic pathways *in vivo* and thus improve their efficacy. Fecal incubation and digestive tract contents incubation are commonly used for *in vitro* experiments (325,326). *In vivo*, experiments are often used to assess the biotransformation of flavonoids by comparing oral or non-oral administration and comparing metabolites of common animals and germ-free or pseudo-germ-free animals (327). Rutin can be hydrolyzed by intestinal bacteria to quercetin, which is then converted to 3, 4-dihydroxyphenylacetic acid and finally absorbed into the blood circulation, and its antiplatelet activity is greater than that of rutin and quercetin (328). Therefore, in the preparation of rutin as the main active ingredient, in addition to the choice of dosage form, it is also necessary to consider appropriately increasing the residence time of rutin in the intestine to enhance the metabolism and biotransformation of intestinal flora, to enhance the efficacy of rutin.

7. Strategies to improve therapeutic efficacy and bioavailability of flavonoids

In daily life, individuals mainly consume flavonoid extract or flavonoid-rich foods to supplement the flavonoids needed by the body (329). The oral bioavailability of flavonoids is low due to their poor water solubility, low permeability and inferior stability (19). For example, the double bond between position 2 and 3 in flavones and flavonols makes it easy to form a planar structure, resulting in tight molecular arrangement and difficulty for solvent molecules to penetrate into its molecular structures (330,331). To solve these problems, a variety of new drug delivery strategies have been identified.

Absorption enhancers. Absorption enhancers are a group of components that can increase the intestinal absorption rate of active drug components, usually referring to reagents that promote absorption by enhancing membrane penetration rather than increasing solubility (332). Absorption enhancers are effective ways to improve drug bioavailability, increase

Table V. Role of flavonoids in colorectal cancer.

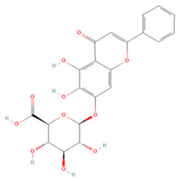
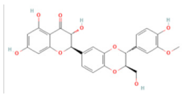
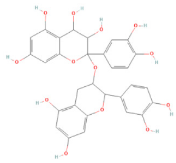
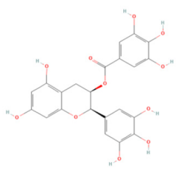
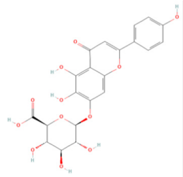
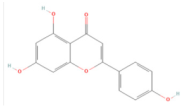
First author/s, year	Flavonoid	Chemical structure	Model	Target	Effect	(Refs.)
Song, 2022	Baicalin		*In vitro, in vivo*	TLR4, MMP2, MMP9, Bcl-2, NF-κB, IκBα, PD-L1, CD4, CD8, Caspase-3, Bax	Induces apoptosis by altering mitochondrial membrane potential and increasing ROS levels. Inhibition of the TLR4/NF-κB pathway inhibits cancer cell migration and invasion. Delays tumor growth in the xenograft mouse model. Downregulates the expression of PD-L1 and the proportion of myeloid-derived suppressor cells, upregulates the percentage of $CD4^+$ and $CD8^+$ T cells, improving the tumor immune microenvironment and enhancing tumor immunity.	(301)
Raina, 2013	Silibinin		*In vitro, in vivo*	TNF-α, NF-κB, p-IκBα, Bcl-2, COX-2, iNOS, VEGF, MMPs	Inhibits TNF-α-induced NF-κB activation and reduction of nuclear levels of p65 and p50 subunits in human colorectal cancer cells. Increases the level of IκBα and decreases the phosphorylation of IκBα. Inhibition of NF-κB activation in xenograft mouse tumors. Decreases the protein expression levels of various NF-κB regulatory factors, such as Bcl-2, COX-2, iNOS, VEGF and MMPs.	(302)
Chen, 2023	Proanthocyanidin		*In vitro, in vivo*	Wnt/β-catenin, DVL 1, DVL 2, DVL 3, OCT-4, CD44, CD133, NANOG, P-GSK 3β	Inhibits the proliferation of CRC cells and improves the sensitivity of colorectal cancer cells to oxaliplatin. Inhibits the tumor growth in nude mice. Downregulates the expression of tumor stem cell surface molecules and stem cell transcription factors. Inhibits tumor sphere and cell colony formation in CRC cells.	(309)
Chen, 2017	(-)-Epigallocatechin-3-Gallate (EGCG)		*In vitro*	Wnt/β-catenin, CD133, CD44, ALDHA1, NANOG, OCT-4, P-GSK 3β, c-Myc, PCNA, Bax, Bcl-2, Caspase-3, Caspase-9, Caspase-8	Inhibits the spheroid formation capability of CRC cells and the expression of colorectal CSC markers. Inhibits CRC cell proliferation and induction of apoptosis. Inhibition of colorectal CSCs is exerted by downregulating the Wnt/β-catenin pathway.	(310)

Table V. Continued.

First author/s, year	Flavonoid	Chemical structure	Model	Target	Effect	(Refs.)
Zeng, 2021	Scutellarin		*In vitro, in vivo*	Wnt/β-catenin, TNF-α, IL-6, Bax, Bcl-2, Cyclin D1, TCF4, c-Myc, P-GSK 3β	Reduces serum levels of TNF-α and IL-6 in CAC mice. Inhibits the proliferation and migration of colon cancer cells. Upregulates the expression of Bax and downregulates the expression of Bcl-2 to induce the apoptosis of colon cancer cells. Improves CAC by attenuating the Wnt/β-catenin pathway.	(311)
Xu, 2016	Apigenin		*In vitro*	Wnt/β-catenin, c-Myc, Cyclin D1, Axin2, Ephb2, Ephb3	Inhibits the proliferation, migration and invasion of colon cancer cells in a dose-dependent manner. Inhibits activation of β-catenin/T-cell factor/lymphoid enhancer factor signaling.	(312)

TLR4, toll-like receptor 4; MMP2, matrix metalloproteinase 2; Bcl-2, B-cell lymphoma-2; NF-κB, nuclear factor-κB; IκBα, inhibitors of NF-κB α; PD-L1, programmed cell death ligand-l; CD4, cluster of differentiation 4; Bax, BCL2-associated X; TNF-α, tumor necrosis factor-α; p-IκBα, phosphorylated IκBα; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; VEGF, vascular endothelial growth factor; Wnt, wingless/integrated; DVL1, drosophila dishevelled homolog 1; OCT-4, octamer binding transcription factor 4; NANOG, Nanog homeobox; GSK3β, glycogen synthase 3β; ALDHA1, aldehyde dehydrogenase 1 family member A1; PCNA, proliferating cell nuclear antigen; IL-6, interleukin-6; TCF4, T-cell factor 4; Ephb2, Eph receptor B2.

the plasma concentration of the drug rapidly and reversibly and are easy to formulate with the active pharmaceutical ingredient (333).

Numerous types of absorption enhancers, such as fatty acids, surfactants and chitosan have been used in clinics to improve the oral availability of drugs (334,335). Cremophor EL is a non-ionic surfactant, which can inhibit the efflux transport of scutellarin by multidrug resistance-associated protein (MRP)2 and breast cancer resistance protein (336). Promoting scutellarin transport by MRP3 increases the drug from cells into blood circulation and can considerably improve the rate of scutellarin oral absorption in rats (337). It has been shown that phytic acid, as a safe and effective absorption enhancer, can improve the water solubility and permeability of isorhamnetin, kaempferol and quercetin in total flavones of TFH in rats and increase its oral bioavailability without obvious intestinal irritation and cytotoxicity (338). Chitosan is a biocompatible, biodegradable and non-toxic biopolymer (339). Quercetin-loaded nanoparticles (QCG-NPs) are prepared by ion gelation between chitosan and gum Arabic. QCG-NPs can increase the adhesion rate to tissues or cells through electrostatic interaction with the mucin layer. This results in an increase in the surface area and residence time of QCG-NPs at the absorption site. QCG-NPs were found to effectively improve the absorption of quercetin in enterocyte models and rats, resulting in a considerable increase in its antioxidant activity (340). N-trimethyl chitosan chloride (TMC) is used as an absorption enhancer in a variety of peptides and macromolecular substance delivery systems (341). It has been found that oral bioavailability of puerarin TMC-modified microemulsions in rats is 6.8-fold higher than that of control puerarin suspension (342).

However, while the absorption enhancers destroy the tight junctions of cells, they may also cause potentially toxic molecules to enter the blood circulation, which may lead to immune response and systemic inflammatory response syndrome (343). To reduce the adverse reactions of absorption enhancers and improve the bioavailability of flavonoids, non-toxic and effective absorption enhancers should be selected, and the concentration and exposure time of absorption enhancers in intestinal epithelial cells should be reduced.

Structural modification. Structural modification is another method that can change the physicochemical properties of a compound. Depending on the chemical groups attached to the flavonoid molecules, they can be divided into acylation, glycosylation, de-glycosylation, O-methylation, hydroxylation, halogenation and sulfation (Fig. 7).

Acylation refers to the attachment of one or more acyl groups to the hydroxyl group of flavonoids; acylation usually occurs at the 3, 4, 5, 3, and 7'hydroxyl groups on the ring of flavonoid compounds and at the 3' or 6' hydroxyl group on the glycosyl moiety of flavonoid glycosides (344,345). Acylated flavonoids can be prepared by chemical, enzymatic and microbial methods. The chemical method is simple and inexpensive, but its preparation requires highly toxic catalysts and may

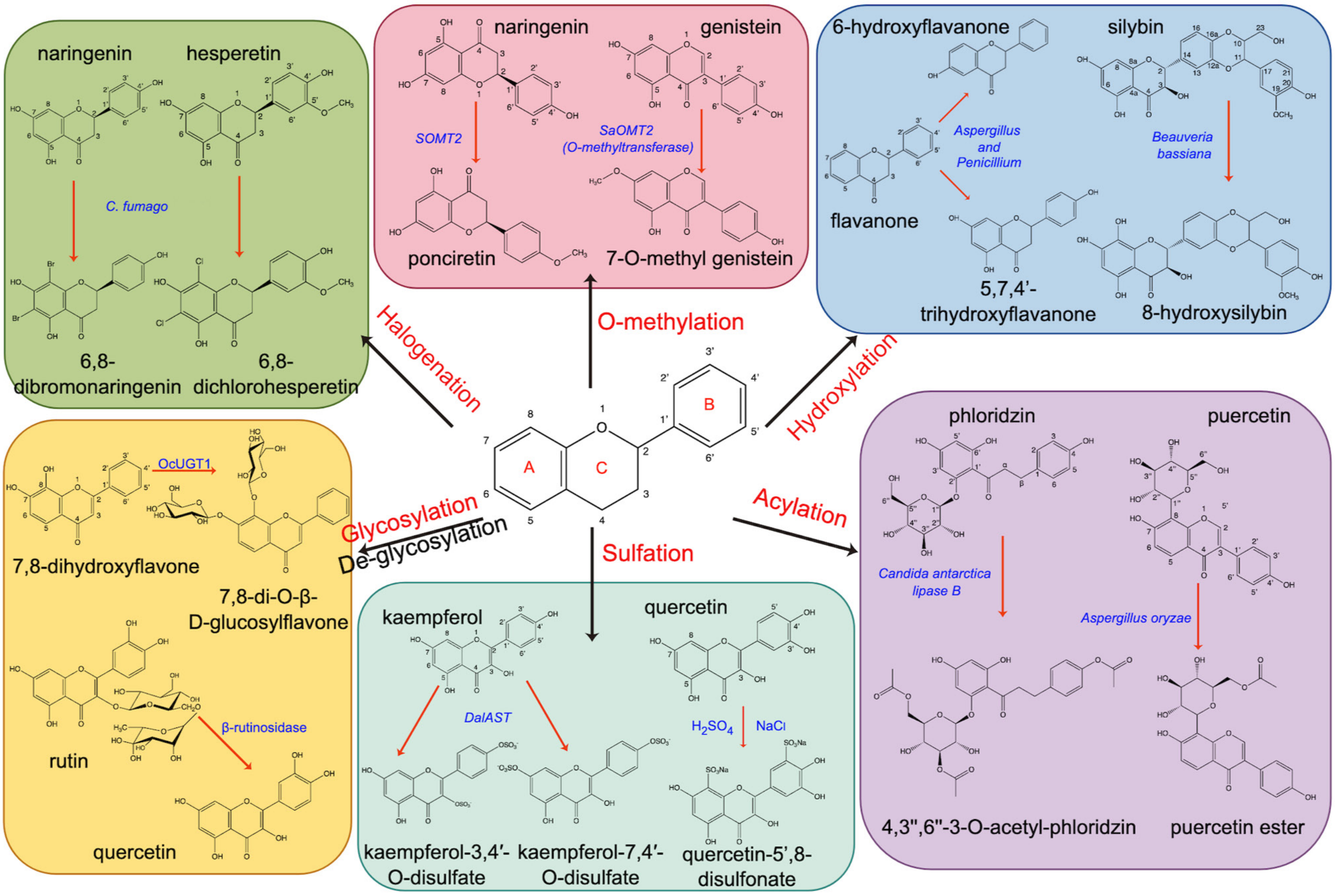


Figure 7. Different structural modifications of flavonoids. *Aspergillus oryzae* selectively acylated puerarin at the 6'-hydroxyl group to form puerarin ester and CALB selectively acylated phloridzin at the 4,3',6'-hydroxyl group to form 4,3',6'-3-O-acetyl-phloridzin. OcUGT1 selectively glycosylated the C-8 of 7,8-dihydroxyflavone on the 7,8-hydroxyl group, yielding two monoglycosides and one dihydroxyflavone, yielding two monoglycosides and one diglycoside. Rutin undergoes de-glycosylation in response to β-rutinosidase to generate quercetin. SaOMT2 can selectively methylate genistein at the 7-hydroxyl group to produce ponciretin. SOMT2 can selectively methylate naringenin at the 4'-hydroxyl group to produce 7-O-methyl genistein. *Aspergillus* and *Penicillium* selectively hydroxylate flavanone at positions 6, 5, 7 and 4' to form 6-hydroxyflavanone and 5,7,4'-trihydroxyflavanone, and *Beauveria bassiana* selectively produces 8-hydroxysilybin by hydroxylation at position 8 of silybin. Naringenin and hesperetin, catalyzed by a peroxidase from CPO, are replaced at positions 6 and 8 by Br and Cl halogen elements, and 6,8-dibromonaringenin and 6,8-dichlorohesperetin were generated. *Dal*AST sulfates kaempferol at positions 4', 3 and 7, yielding kaempferol-3,4'-O-disulfate and kaempferol-7,4'-O-disulfate. Quercetin undergoes sulfation at positions 5' and 8 under the catalysis of NaCl and H_2SO_4 to form quercetin-5',8-disulfonate. CALB, *Candida antarctica* lipase B; OcUGT1, *O. caundatum*-uridine diphosphate glucuronosyl-transferase 1; SOMT2, soybean *O*-methyltransferase 2; SaOMT2, *S. avermitilis*-originated *O*-methyltransferase 2; CPO, *Caldariomyces fumago*; *Dal*AST, *Desulfofalx alkaliphile*-aryl sulfotransferase.

produce toxic reaction products, leading to safety and pollution problems (346). Compared with chemical methods, enzymatic methods have milder reaction conditions and less toxic catalysts and have become one of the most commonly used acylation methods (345). To date, proteases, acyltransferases and lipases have been used for acylation modification (344). Microbial methods refer to the specific enzymes that can release the acylation reaction by some microorganisms and the reactants are incubated with specific microorganisms to make the acylation of flavonoids. *Aspergillus oryzae* can selectively acylate puerarin on the 6-hydroxyl group, improving its lipid solubility and making it easier to absorb (347). *Rhizopus oryzae* lipase can acylate ferulic and quercetin to form synthesized quercetin ferulate and its antioxidant activity is considerably increased compared with that of either monomer, making it easier to absorb (348). The anti-tumor activity of acylated flavonoids was increased; for example, palmitoyl group (EGCG-C16) modified EGCG synthesized by lipase catalyzed transesterification method is more stable than EGCG and does not produce H_2O_2, which can effectively inhibit the growth of CRC in mice (349). Acetylation of phloridzin was catalyzed by *Candida antarctica* lipase B. The generated 4,3',6'-3-O-acetyl-phloridzin shows increased antiproliferative activity against the human hepatoma cell line HepG2 when compared with phloridzin (345).

Glycosylation modification has an important role in the regulation of multiple pharmacokinetics of flavonoids (350). Glycosylation is usually the last step in the synthesis of flavonoids, through which the solubility and stability of flavonoids aglycones can be improved or enhanced (351). Glycosylation refers to the attachment of glycosyls to the hydroxyl groups or carbon atoms of flavonoids to form O-glycosides or C-glycosides of which O-glycosylation is more common in nature (352). O-glycosylation sites were commonly found at positions 3, 7, 4 and 5' (353). There are three methods for the chemical synthesis of flavonoid O-glucosides: Koening-Knorr, glycosyl trichloroacetimidate and phase transfer catalysis methods. The first two methods have been used infrequently due to their low yield, but the phase transfer catalysis method is currently the preferred method for glycosylation of flavan-3-ols (354). A study by Yao *et al* (355) synthesized flavone-glycoside aciculatin by regio- and stereoselective glycosylation-Fries-type O-to-C rearrangement and Baker-Venkataraman rearrangement, but the yield was only 8.3%. By contrast, de-glycosylation is accomplished by a simple acid hydrolysis process (356). The enzymatic glycosylation process is mainly realized by glycosyltransferase (GT). OcUGT1 catalyzes the C-8 position of 7,8-dihydroxyflavone to generate two monoglycosides and one diglycoside (357). De-glycosylation is mainly accomplished by glycosidases hydrolysis of the glycosidic bonds. De-glycosylation is commonly used in the food industry, such as debittering citrus juice or aroma enhancement in wine (358). The microbial method mainly introduces recombinant gene plasmids into strains and then expresses the corresponding products (359). Studies have shown that the cloning of GT genes into strains can be used to produce enzymes for glycosylation reactions (360). The study by Lyu *et al* (361) introduced UDP-rhamnose synthase and 3-O-GTs plasmids into yeast strains, and the obtained GTs could catalyze the glycosylation reaction at the C-3 position of flavonoids. However, the conversion rate of the microbial method is decreased compared with that of the enzymatic method (362). The anticancer activity of glycosylated flavonoids tends to be reduced compared with that of their precursors. For example, the inhibitory effect of apigenin7-O-glucoside on tumor cells is weaker than that of apigenin (363). This may be associated with the increased hydrophilicity and steric hindrance of the flavonoid glycoside, preventing it from crossing the cell membrane to the cytoplasm (364). Certain studies revealed that the effect of O-glycosylation on antioxidant activity is the opposite to that of C-glycosylation. For instance, the free radical scavenging energy of kaempferol 3-O-glycosides was decreased compared with that of kaempferol (365). However, luteolin 6-O-glycoside revealed stronger scavenging of ROS than luteolin (366).

O-methylation refers to the substitution of a methyl group for specific hydrogen atoms on flavonoids, which usually occurs at sites 3, 5, 4 and 7' on the ring of flavonoids (364). In chemistry, phenolic compounds are usually treated with diazomethane, dimethyl sulfate, methyl iodide and other highly toxic reagents to carry out the reaction. Previously, dimethyl carbonate, as a safe and non-toxic alternative reagent, has been used to promote methylation reactions under mild and practical conditions (367). In the enzymatic method, S-adenosyl-l-methionone is a methyl donor, which is attached to hydroxyl groups of flavonoids by O-methyltransferases (OMTs). A variety of OMTs have been identified and isolated from different bacteria, fungi and plants that can transfer methyl groups to specific hydroxyl groups of flavonoids (368). For example, a new OMT isolated from 3-methoxylation of pinosylvin, can be used for the methylation of pinosylvin (369). However, the experimental requirements and cost of isolating OMTs are not suitable for large-scale commercial use. In the microbial method, OMTs can be obtained by introducing the OMT gene into *Escherichia coli* (*E. coli*) by fermentation. An OMT gene isolated from methylated catechins was introduced into *E. coli* for expression to obtain OMT, which can methylate flavonoids at specific sites (370). At present, the synthesis of flavonoids by the microbial method still faces the problem of having a low conversion rate preventing its use in large-scale production. Studies have revealed that methylation can increase the anticancer activity of flavonoids. For example, by comparing the anticancer activities of six flavonoids from *Pulicaria jaubertii*, it was found that among them, the methylated flavonoids had increased anticancer activities with compared with unmethylated flavonoids, and their ability to inhibit the proliferation and promote apoptosis of colon cancer cells was improved compared with unmethylated flavonoids (371). The anticancer activity is also affected by structural differences in flavonoids. For example, by methylating genistein and daidzein, the anti-proliferative ability of 7-O-methyl genistein and 7-O-methyl daidzein was also changed, reducing the anti-proliferative activity of 7-O-methyl genistein, but increasing the anti-proliferative activity of 7-O-methyl daidzein (372).

Hydroxylation refers to one or more hydroxyl groups substituted with hydrogen atoms on flavonoids, and the common hydroxylation sites for flavonoids occur at position 8 on flavonols and position 5, 6, and 4' on flavanone (373). The microbial method is the main method for the synthesis of hydroxyl flavonoids. The phase I metabolite produced by *Beauveria bassiana* can hydroxylate silybin to 8-hydroxysilybin, resulting in increased antioxidant activity (374). Flavanone was catalyzed by *Aspergillus* and *Penicillium* to produce 6-hydroxyflavanone and 5,7,4'-trihydroxyflavanone with increased antioxidant activity (375). Alternatively, some enzymes can be used to hydroxylated flavonoids. For example, the cytochrome P450 family and monooxygenases utilize either dioxygen or H_2O_2 as oxygen donors to introduce oxygen atoms into aromatic molecules (376). A study by Zhang *et al* (377) successfully established and optimized a multienzyme synthesis system to achieve a high conversion rate of naringenin to kaempferol through the key enzymes Atf3h and Atfls1. If large-scale commercial applications are to be realized, the fermentation conditions of microorganisms need to be continuously optimized. A study suggests that the anticancer activity of flavonoids increases after the introduction of Catechol moiety (378). The sites and numbers of hydroxylation of flavonoids have a considerable influence on their biological activity. Compared with the 5, 6 and 7 hydroxyl groups in the A ring, the hydroxyl groups in the B ring, especially the 3',4'-dihydroxyphenol structure, are most important for scavenging ROS (379,380).

Halogenation refers to the introduction of one or more halogen atoms into flavonoid molecules, usually at the 3, 6, 8, 4 and 3' sites (381). Halogenated flavonoids are mainly produced by chemical methods. For example, a variety of halogen chalcones have been prepared by simple condensation reaction of 4-bromoacetophenone with different substituted halogen benzaldehydes under the catalysis of sodium hydroxide (382). Naringenin and hesperetin can be catalyzed by a peroxidase from *Caldariomyces fumago* (CPO) and replaced at positions 6 and 8 by halogenated elements such as Br or Cl to generate different halogenated flavonoids (383). A large number of studies have proved that halogenation can change the anticancer and antibacterial activities of flavonoids. The chlorination reaction of genistein can considerably enhance its antioxidant and anticancer activities. Antitumor activities of 3',8-dichlorogenistein and 8-chlorogenistein are 2.6 and 7.7 times higher compared with genistein, respectively (384). Brominated chalcone derivatives can induce apoptosis of GC cells *in vitro* and inhibit tumor growth in a nude mouse xenograft model without toxic effects (385). It has been shown that the antiproliferative activity of flavonoid halogenated derivatives increases with substituents from F to Cl and Br, and the 3-position halogen can enhance the anticancer activity of chalcone, while 4-position halogen can enhance the activity of flavonol derivatives (386).

Sulfation refers to the introduction of sulfate groups into flavonoids. The common sulfation sites are 3, 7, 4 and 3'. A study by Zhang *et al* (387) synthesized sulfated flavonoids by chemical methods, and quercetin reacted with concentrated sulfuric acid to obtain quercetin-5',8-disulfonate. A study showed that quercetin-5',8-disulfonate had an improved inhibitory effect on colon and breast cancer cells than quercetin. Sulfotransferase (ST) is an enzyme that catalyzes the transfer of sulfo groups from donors to recipients, ST-catalyzed donors are generally 3'-phosphoadenosine 5'-phosphosulfate (PAPS), and the sulfation of a variety of flavonoid compounds can be achieved by ST (388). P-nitrophenylsulfate has been used as a donor to synthesize a series of sulfated flavonoid derivatives catalyzed by arylsulfotransferase (389). However, the enzymatic reaction is complicated and its commercial use is limited. For this purpose, the microbial method was developed to sulfate flavonoids. Flavonoids can be enzymatically synthesized by PAPS-independent bacterial aryl sulfotransferases *in vitro*. AST from *Desulfofalx alkaliphile* (*Dal*AST) and *Campylobacter fetus* showed very high efficiency in the sulfation of flavonoids, kaempferol and luteolin were the best switching receptors, and *Dal*AST could be sulfated at positions 4, 3 and 7' of kaempferol (390). After the sulfation of flavonoids, the increase of water solubility and negative charge can effectively improve their bioavailability and have considerable improvements in anticancer, anticoagulation, and antioxidant activities. A study showed that quercetin-5',8-disulfonate has potent antitumor activity against human colon and breast cancer cells (387). The anticoagulant properties of a variety of flavonoid compounds such as hesperetin and rutin have been demonstrated, and polysulfated flavonosides can be used as safe and effective anticoagulant therapy drugs (391).

Pharmaceutical technologies. Development of pharmaceutical technologies also provides new ideas for drug delivery. Carrier complexation is a new technology that complexes drug molecules with different carriers to improve the absorption rate and bioavailability of drugs (392). At present, the most used carriers are cyclodextrins (CDs) and phospholipids, which can improve drug solubility and protect active molecules from the influence of temperature, pH and other conditions (393). Studies revealed that the complexation of several types of flavonoids with carriers can greatly improve their oral bioavailability and reduce side effects. For instance, the solubility and *in vitro* release of quercetin, fisetin and chrysin prepared by CDs were increased and even their original biological activity was enhanced (394-396). Oral administration of silybin-phosphatidylcholine complex considerably increased systemic absorption in 130 subjects (397).

Nanotechnology is a modification of chemical compounds at the nanoscale and has been used in the treatment of cancer. Due to the low specificity of drugs to tissues, the conventional drug administration regimens lead to non-target tissue, which often causes serious toxic side effects and drug resistance (398). New nanodevices can deliver anti-tumor drugs to specific tumor sites and target cells, reducing side effects and improving therapeutic efficacy. Moreover, the release rate of drugs can be changed by changing the size and surface tunable properties of nanoparticles to provide continuous blood circulation (399,400). Nanotechnology-based drug delivery systems are applied to improve the bioavailability of poor water-soluble flavonoids. At present, nanotechnology-based drug delivery systems are mainly developed with the following three considerations: i) Reducing the particle size of drugs, such as nanocrystals, ii) nanometer-scale emulsion droplet encapsulated systems, such as nanoemulsions and nanosuspensions and iii) carrier-based nanoparticle delivery systems, such as lipid nanoparticles and nanogels (330). Apigenin nanocrystals were prepared by the supercritical antisolvent process to study their absorption efficiency in rats. The results show that the plasma concentration of apigenin following oral administration of apigenin nanocrystals was considerably increased when compared with that of apigenin powder and the dissolution degree *in vitro* showed that apigenin nanocrystals were faster and more complete (401). This may be because the decreased particle size and increased surface area can increase the adhesion of apigenin to the mucosa and prolong the residence time in the gastrointestinal tract, resulting in increased bioavailability (402). It has been found that MYR-ME formed by combining myricetin with nanoemulsions can considerably improve the solubility and oral availability of myricetin in rats. Compared with myricetin suspension, it increased by 14.43 times (313). Due to the poor stability of EGCG at physiological pH, encapsulation of EGCG in solid lipid nanoparticles (SLN) can enhance its stability and anticancer activity. The cytotoxicity of EGCG-SLN to prostate and breast cancer cells is considerably increased and it shows high stability in serum and phosphate buffer saline (403). The poor water solubility and low bioavailability of flavonoids can be effectively improved by nanotechnology. However, the side effects, toxicity to normal tissues and organs, and the absorption of surfactants and emulsifying agents have limited their clinical application. To solve these problems, the study by Yao *et al* (350) developed myricetin-loaded nanogel/gel, which exhibited high oral availability and low cytotoxicity.

8. Limitations and potential consequences

Although flavonoids have revealed a range of anticancer effects on a variety of GI cancer types and have fewer side effects than conventional anticancer drugs, flavonoids still have some limitations in the treatment of different types of GI cancer and may cause potential consequences.

Bioavailability of flavonoids. Although flavonoids have shown anticancer potential *in vitro*, their bioavailability in humans is low (19). Absorption of flavonoids in the gastrointestinal tract is limited and they are often rapidly metabolized in the gut to other forms, so their anticancer effects may be less pronounced than expected compared with *in vitro* studies (404). The low bioavailability of flavonoids may limit their practical use as a treatment for different types of GI cancer. Although bioavailability may be increased through nanotechnology, drug loading systems and other ways to improve dosage forms, these technologies are still in the research and development stage and are expensive.

Effect of flavonoids on different types of GI cancer is variable. Therapeutic effects of flavonoids on different types of GI cancer are not similar for different types of cancer. Different types of cancer cells may differ considerably in their molecular mechanisms, signaling pathways and sensitivity to drugs. Flavonoids may be effective in some types of cancer and less effective in others. Therefore, the application of flavonoids may require individualized adjustment for specific cancer types, which increases the complexity of the treatment regimen.

Complexity and diversity of signaling pathways. Anticancer effects of flavonoids is often achieved by regulating a variety of signaling pathways, such as the PI3K/Akt pathway, NF-κB pathway and MAPK pathway as aforementioned. However, the occurrence and development of different types of GI cancer are the result of the interaction of complex gene mutations, epigenetic changes and microenvironment (405). A single action of flavonoids may not effectively regulate all key pathways. If flavonoids are relied on alone to regulate certain signaling pathways, cancer cell proliferation and metastasis may not be comprehensively inhibited, and it is easy to produce drug resistance during treatment (406). Therefore, it may be necessary to combine other therapeutic strategies such as chemotherapy, immunotherapy and targeted therapy, amongst others to enhance its therapeutic effect.

Side effects and toxicity of flavonoids. Although flavonoids are generally considered natural substances and have low toxicity, some side effects such as indigestion, allergic reactions and liver or kidney burden may still occur at high doses or with long-term use (407,408). In addition, the interaction of flavonoids with other drugs may also influence the therapeutic effect. If the side effects of flavonoids are not adequately evaluated or managed, the therapeutic effect in patients may be affected. Therefore, in-depth studies on long-term safety and potential toxicity are needed before clinical use.

Individualized treatment of flavonoids. Therapeutic effects of flavonoids may vary between individuals. Factors such as genetic differences, immune system status and differences in gut microbiota can affect the metabolic processes and anticancer effects of flavonoids (409). If individual differences are not fully considered, the generalized use of flavonoids may not produce the desired effect, and may even lead to adverse consequences due to different individual reactions. Future studies should focus on how to tailor the use of flavonoids to the specific conditions of patients.

Challenges of combination therapy. As an adjuvant therapy, flavonoids may need to be used in combination with other treatment methods, such as chemotherapy, targeted therapy and immunotherapy, amongst others (410,411). However, the interaction of flavonoids with other drugs is not fully understood, which may lead to drug interference or side effects. If combination therapy is not adequate, it may affect treatment effectiveness or aggravate the side effects. Therefore, the combination of flavonoids needs to be carefully designed and validated in clinical practice.

In conclusion, the potential of flavonoids in the treatment of different types of GI cancer is considerable, especially exhibiting beneficial effects in anti-inflammation, antioxidation and inhibition of cancer cell proliferation. However, its practical application faces challenges, including issues such as low bioavailability, variable therapeutic efficacy according to cancer type and individual differences, insufficient clinical research, side effects and toxicity. More basic research, clinical trials and optimization and improvement of treatment strategies are still needed to fully realize the therapeutic potential of flavonoids.

9. Conclusion and prospects

In the present review, the mechanisms of flavonoids in the treatment of different types of GI cancer by influencing signaling pathways and the research progress of flavonoids in preclinical experiments and clinical trials have been summarized. Several commonly used drug delivery systems to improve the bioavailability of flavonoids have been introduced and the advantages and possible limitations of each method have been discussed. Flavonoid drugs have potential and prospects for drug delivery research in anti-tumor treatment efforts. However, there are still several challenges in the current drug delivery strategy: Instability of the carrier and low drug loading (the amount of drug carried per unit weight or per unit volume of a carrier) may be caused by the complexity of the preparation process and a large number of adjuvants. Possible side effects of structural modifications, as well as incomplete degradation of the carrier. Therefore, future research should address the following aspects: i) Investigate new delivery materials and improve existing delivery systems, using natural materials or carriers that are inexpensive, easy to prepare and safe. In addition, the evaluation of the safety of other delivery materials such as absorption enhancers, carrier complexation and nanoparticles should be investigated in detail to determine whether they can be completely degraded in the human body, whether the degradation products produce side effects or toxicity to the human body and whether the degradation products can be completely excreted. ii) Control the release efficiency of the drug in the human body and prolong the time of the active components of the drug in the blood circulation. This can not only achieve adequate therapeutic effects, but also reduce a series of side effects caused by excessive drug intake, and greatly improve the convenience and compliance of patients taking drugs. iii) Most of the current clinical trials are case-control studies, which evaluate the efficacy of flavonoids by investigating consumption of foods rich in flavonoids by patients, but there is no regulation of the content of flavonoids in foods making it difficult to determine the optimal dose for the development of new flavonoid drugs.

Therefore, attention should be paid to the effect of flavonoid dosage on the disease in subsequent clinical studies. iv) At present, there are relatively few clinical studies on flavonoids in the treatment of different types of GI cancer and the vast majority of studies focus on animal experiments and *in vitro* experiments. Although these findings have certain reference values, the clinical effects of flavonoids have not been fully verified due to the differences in metabolism and immune response between humans and experimental animals. Clinical studies are needed to evaluate the safety and efficacy of flavonoid delivery systems. For example, as a very popular drug delivery material, nanoparticles are commonly used in the development of drugs for the targeted therapy against tumors. However, most drug preparations that are effective in mice are not completely effective in humans, and seemingly effective nanoparticle delivery systems have not achieved the expected therapeutic effect on xenograft tumors (412). Therefore, in future research, it is necessary to focus on improving the loading efficiency of the carriers, using safe and cheap carriers, simplifying the production steps, comprehensively analyzing the differences between the effects of drugs in animals and humans, systematically studying the therapeutic effect of drugs on humans, and further solving the issue of animal-to-human transition. By overcoming these difficulties and with continued research, flavonoids have potential in the treatment of different types of GI cancer.

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Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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