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REVIEW

Flavonoids and Gastric Cancer Therapy: From Signaling Pathway to Therapeutic Significance

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Abstract: Gastric cancer (GC) is a prevalent gastrointestinal tumor characterized by high mortality and recurrence rates. Current treatments often have limitations, prompting researchers to explore novel anti-tumor substances and develop new drugs. Flavonoids, natural compounds with diverse biological activities, are gaining increasing attention in this regard. We searched from PubMed, Web of Science, SpringerLink and other databases to find the relevant literature in the last two decades. Using "gastric cancer", "stomach cancers", "flavonoid", "bioflavonoid", "2-Phenyl-Chromene" as keywords, were searched, then analyzed and summarized the mechanism of flavonoids in the treatment of GC. It was revealed that the anti-tumor mechanism of flavonoids involves inhibiting tumor growth, proliferation, invasion, and metastasis, as well as inducing cell death through various processes such as apoptosis, autophagy, ferroptosis, and pyroptosis. Additionally, combining flavonoids with other chemotherapeutic agents like 5-FU and platinum compounds can potentially reduce chemoresistance. Flavonoids have also demonstrated enhanced biological activity when used in combination with other natural products. Consequently, this review proposes innovative perspectives for the development of flavonoids as new anti-GC agents.

Keywords: flavonoid, gastric cancer, apoptosis, angiogenesis

Introduction

Gastric cancer (GC) ranks as the fifth most prevalent cancer worldwide,[1] with approximately 990,000 new cases diagnosed annually.[2] It remains one of the leading causes of cancer-related deaths globally.[3] While the overall incidence and mortality of GC have declined in most countries over the past few decades,[4–6] the disease still poses a significant burden in Asia. GC development is influenced by various common factors, such as family history, diet, alcohol consumption, smoking, *Helicobacter pylori* infection, and Epstein Barr virus (EBV) infection.[7–10] Controllable risk factors, including *H. pylori* infection, dietary habits and lifestyle, chemical radiation, or viral infections,[11,12] can be addressed to potentially prevent GC. Currently, early-stage gastric cancers (GCs) are predominantly managed through endoscopic resection, whereas surgery is employed for non-early-stage operable tumors. Advanced GCs undergo a sequential chemotherapy regimen, typically involving platinum combined with fluoropyrimidine. Nevertheless, this treatment approach is associated with severe side effects, and the median survival rate is less than one year. Notably, cisplatin, a commonly used chemotherapeutic agent, has been linked to thromboembolic disease and renal dysfunction.[13] Targeted therapies, such as trastuzumab, ramucirumab, and nivolumab or pembrolizumab, have also emerged as viable options in GC treatment. However, the diverse nature of GC among tumors, patients, and even within a single tumor poses a significant challenge to the development of effective targeted therapeutics.[14] Consequently, there is a pressing

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need for novel treatment regimens or drugs that can effectively manage GC patients while minimizing side effects and drug resistance.

Flavonoids are the most prevalent natural compounds found in plants, including *Leguminosae, Brassicaceae, Umbelliferae, Genisteinae, Lioceae*, and various plant parts. Flavonoids typically refer to a group of compounds where two benzene rings, each containing phenolic hydroxyl groups, are interconnected by three central carbon atoms to form the C6-C3-C6 unit.[15,16] They can be classified into 7 subclasses based on characteristics that include the degree of oxidation of the central three-carbon chain and the position of the B-ring attachment. Examples of these subclasses include chalcones, dihydrochalcones, flavones, and flavanols.[17–19] Because of their abundance, flavonoids are commonly present in dietary fibers and find diverse applications in food and medicine.[20] Flavonoids in the diet can influence various molecular targets and signaling pathways related to cell growth, proliferation, differentiation, migration, angiogenesis, and hormone activity.[21,22] This modulation contributes to the inhibition of different cancers, such as lung, liver, breast, and ovarian cancers.[23–26]

Recent studies have increasingly demonstrated the beneficial effects of flavonoids on inhibiting GC. Numerous studies have provided evidence that flavonoids exert a regulatory role in modulating various phenotypes of GC, encompassing tumor growth, proliferation, invasion, metastasis, angiogenesis, and cell death (Figure 1). Therefore, our review tried to find the mechanism of flavonoids in the treatment of GC and provided new ideas for researchers.

Method

We searched from PubMed (https: //pubmed.ncbi.nlm.nih.gov/), Web of Science (http://apps.webofknowledge.com/) SpringerLink (https://link.springer.com/) and other databases to search the literature in the last two decades. Using "gastric cancer", "stomach cancers", "flavonoid", "bioflavonoid", "2-Phenyl-Chromene" as keywords, were searched, then excluding literature unrelated to the topic.

The Bioactivity of Flavonoids

Extensive research has revealed that flavonoids possess diverse biological activities, including antioxidant, anti-inflammatory, and anticancer effects.[27–29] Numerous mechanisms have been investigated to understand the antioxidant effects of flavonoids. These mechanisms include direct scavenging of oxides, activation of antioxidant enzymes, metal

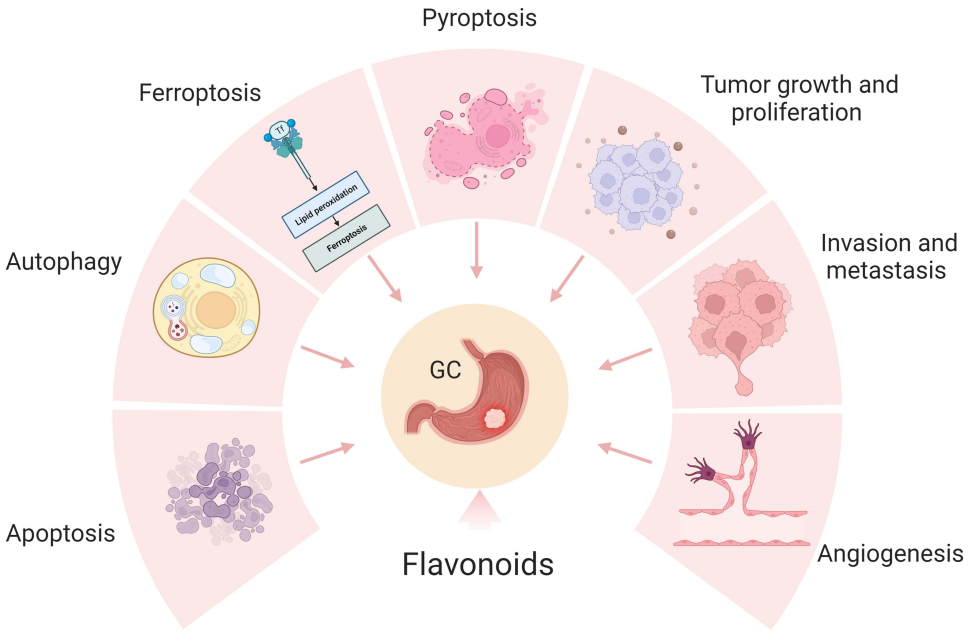

Figure 1 The potential role of flavonoids for GC therapy. Flavonoids exert a regulatory role in modulating various phenotypes of GC, encompassing tumor growth, proliferation, invasion, metastasis, angiogenesis, and cell death. Created by Biorender.com.

chelating activity, attenuation of oxidative stress, inhibition of natriuretic oxidase, enhancement of antioxidant properties of low molecular weight antioxidants, elevation of uric acid levels, and elevation of deoxygenated oxygen radicals.[30] For example, fisetin has been found to inhibit xanthine oxidase activity and reduce oxidative damage.[31] Flavonoids' anti-inflammatory effects often occur through the targeting of regulatory enzymes in signaling pathways, such as phosphatidylinositol kinase and protein kinase C.[32] Additionally, flavonoids may exert anti-inflammatory effects by inhibiting transcription factors.[29] Many flavonoids also act as potent inhibitors of arachidonic acid, cyclooxygenase, and phospholipase A2, leading to a reduction in the production of prostaglandins, leukotrienes, and nitric oxide, all of which are key inflammatory substances.[33–35] For instance, mulberry leaf flavonoids have been shown to decrease lipopolysaccharide-induced production of NO, PGE2, COX-2, and inflammatory factors in RAW 264.7 cells. Flavonoids' anticancer properties are frequently observed through their inhibitory effects on various types of cancer. Epigallocatechin and genistein, for instance, have been found to inhibit DNA methyltransferases and modify chromatin alterations in breast cancer.[25] Icaritin has been shown to enhance mitosis in hepatocellular cancer and synergistically promote immune cell death with doxorubicin.[36] Therefore, the current study suggests that flavonoids not only have diverse sources but also exhibit potent biological activities, making them attractive candidates for the development of new drugs (Figures 2 and 3).

Despite flavonoids are safe, some of them also have a prooxidative effect. For example, dietary phenolic substances have been shown to act as prooxidants in systems containing redox active metals. This indicates that different flavonoids may have opposite biological activities.

Flavonoids for Fighting Against GC

Recently, numerous flavonoids have been discovered to possess varying degrees of inhibitory effects on GC, with potential antitumor properties. These flavonoids have the ability to impact tumor growth and proliferation, inhibit tumor invasion and metastasis, affect angiogenesis, and induce cell death. Examining the antitumor effects of flavonoids from these perspectives could generate novel insights for drug development (Table 1).

Inhibition of Tumor Growth and Proliferation

A hallmark of tumorigenesis is the rapid growth and extensive proliferation capacity of tumors. Malignant tumors demonstrate virtually unlimited growth and proliferation, while benign tumors display more restricted expansion. Among the most prevalent natural compounds, flavonoids frequently exert inhibitory effects on the growth and proliferation of GC cells. For instance, farrerol (Figure 2, 2), a representative natural flavanone extracted from *Rhododendron dauricum* L., serves as an illustration. Treating SGC7901 cells with farrerol demonstrated its ability to suppress cancer cell growth by inducing sustained ERK activation-mediated G0/G1 phase cell cycle arrest and significantly upregulating the p27KIP1 protein.[71] Additionally, isoliquiritigenin (Figure 2, 9), derived from licorice root, is a bioactive compound characterized by its chalcone structure.[116] It possesses the capability to modulate the tumor microenvironment and inhibit tumor stemness, effectively suppressing GC stem-like properties by down-regulating GRP78 through CREB3L-mediated pathways.[117]

Furthermore, nano-encapsulation of chrysin (Figure 2, 7) in the PLGA-PEG-chrysin complex inhibited the growth of AGS cells. This inhibition was achieved by promoting increased expression of miR-22, miR-34a, and miR-126, resulting in the suppression of GC cell growth.[63] Nano-encapsulated bryostatin exhibited more consistent antitumor activity compared to the unencapsulated form.

In addition to influencing the cell cycle through miRNAs, flavonoids affect tumor growth by targeting various pathways. One commonly targeted pathway is the PI3K signaling pathway. For instance, scutellarin (Figure 2, 3) inhibited the growth and epithelial mesenchymal transition (EMT) of GC by up-regulating PTEN to inactivate the PI3K signaling pathway.[107] Similarly, iridin (Figure 2, 4) blocked the PI3K/AKT signaling pathway in AGS cells, leading to G2/M cell cycle arrest and affecting cancer cell proliferation.[79] Galangin (Figure 3, 39), a natural flavonol found in galangal, inhibited MGC-803 cells growth through the JAK2/STAT3 pathway, increasing ROS accumulation and reversing the abnormal expression of proteins such as p-JAK2, p-STAT3, Bcl-2, cleaved PARP, and Ki67. This induced apoptosis and reduced cell proliferation in GC cells.[73] Cardamonin (Figure 2, 1), a chalcone compound with effects

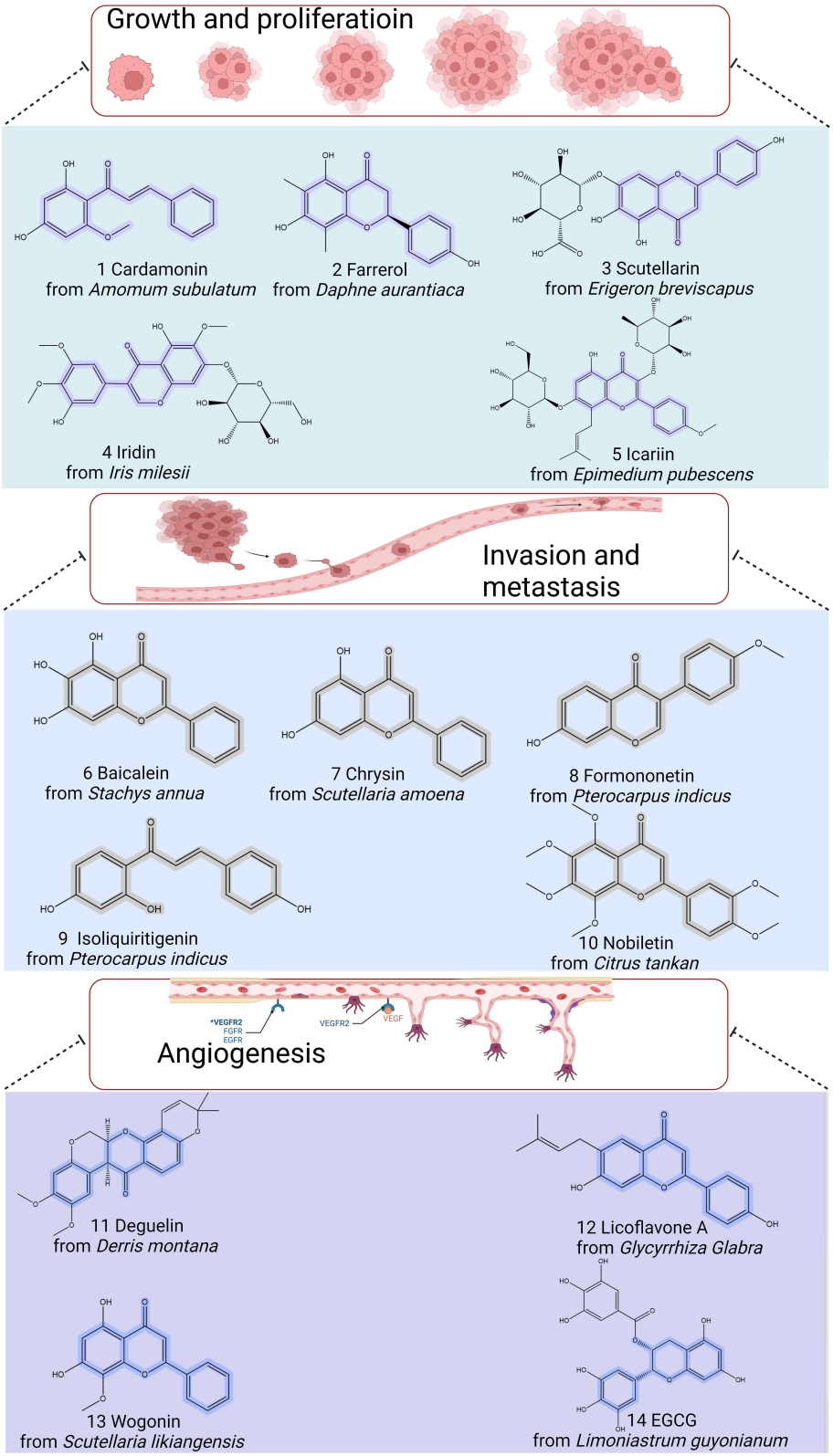

Figure 2 Chemical structures of representative flavonoids that prevent GC by modulating tumor growth, proliferation, invasion, metastasis, and angiogenesis. Created by Biorender.com.

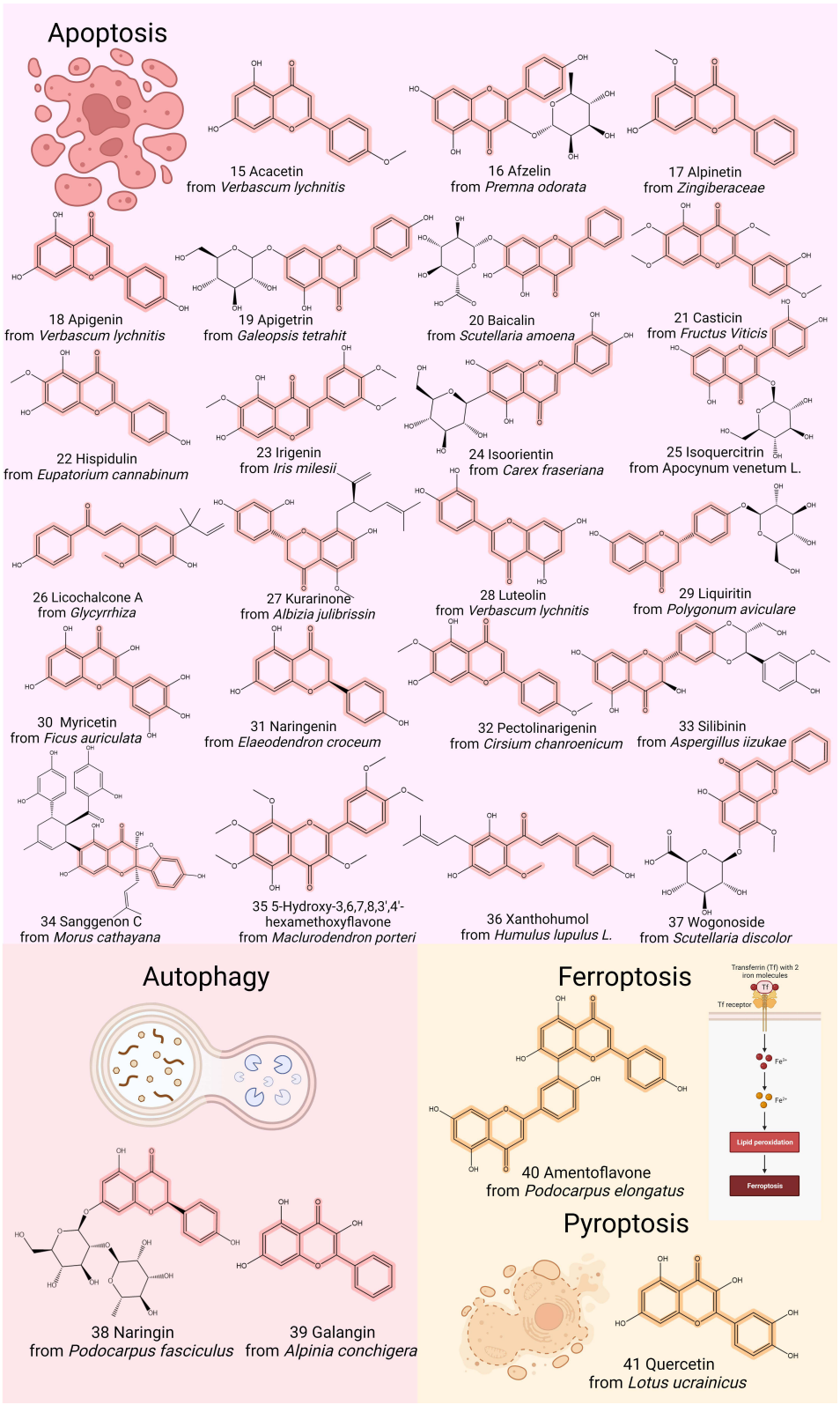

Figure 3 Chemical structures of representative flavonoids that prevent GC by modulating cell death. Created by Biorender.com.

Table 1 Profiles of Flavonoids Inhibiting GC

Flavonoid	Source	Cell Line	Targets	Reference
Acacetin	*Verbascum lychnitis (mullein)*	AGS (in vitro)	↑Bax, p53; ↓Bcl-2	[37]
		MKN-45, MGC-803 (in vitro)	↓MMP2, MMP9	[38]
Afzelin	*Premna odorata (fragrant premna)*	AGS	↑GalNAcTL5; ↓C1GalT1	[39]
Alpinetin	*Zingiberaceae*	AGS, N-87	↑Bax; ↓Bcl-2	[40]
Amentoflavone	*Podocarpus elongatus*	AGS, HGC-27 (in vivo)	↑miR-496; ↓ATF2	[41]
Apigenin	*Verbascum lychnitis (mullein)*	AGS, SNU-216, NCI-N87, SNU-638, MKN-7, MKN-74	↓p-mTOR, p62, HIF-1α, Ezh2	[42]
		HGC-27, SGC-7901	↑Caspase-3, Bax; ↓Bcl-2	[43]
		SGC-7901	Inhibits the cell proliferation	[44]
		MKN-45	↑MUC-2, IκBα; ↓NF-κB	[45]
Apigetrin	*Galeopsis tetrahit (hempnettle)*	SGC-7901, MGC-803	↑Caspase-9/-3, Bax; ↓Bcl-2	[46]
		AGS	↑Caspase-3, PARP, LC3B-II, beclin-1; ↓CDK1, cyclin B1, cdc25c proteins	[47]
Baicalein	*Stachys annua (annual hedgenettle)*	HGC-27, SGC-7901	↓FAK, PI3K, AKT, mTOR	[48]
		AGS	↓N-cadherin, vimentin, ZEB1 and ZEB2	[49]
		HGC-27, SGC-7901, MGC-803, BGC-823	↑miR-7; ↓p-FAK	[50]
		SGC-7901	↑Bax; ↓Bcl-2	[51]
		HGC-27, AGS	↓PI3K, AKT	[52]
		SGC-7901, MGC-803	↓MMP-2/-9, p38	[53]
		AGS	↑PTEN; ↓Akt, HIF-1α	[54]
Baicalin	*Scutellaria amoena (Scutellaria)*	BGC-823, MGC-803	↑Caspase-9/-3, Bax; ↓Bcl-2	[55]
		AGS (in vivo)	↓IL-1β, IL-8, IgM, IgA	[56]
		AGS, SGC-7901	↑ROS	[57]
Casticin	*Fructus Viticis*	BGC-823, SGC-7901, MGC-803	↓cFLIP, Bcl-2, XIAP, survivin	[58]
Cardamonin	*Amomum subulatum*	AGS, MGC-803, BGC-823	↑Caspase-3, Bax; ↓Bcl-2	[59]
Chrysin	*Scutellaria amoena (Scutellaria)*	AGS	↑let-7a, miR-9, miR-22, miR-34a, miR-126; ↓miR-18, miR-21, miR-221	[60]
		SGC-7901, MKN-45, BGC-823	↑p53, E-cadherin; ↓COPB2	[61]
		MKN-45	↑TET1,5hmC	[62]
		AGS	↑miR-22, miR-34a, miR-126	[63]
		AGS	↓ MMP9	[64]
		AGS	↓NF-κB, Egr-1	[65]
Deguelin	*Derris montana*	SNU-484, AGS, MKN-28	↓AKT, HIF-1α	[66]
EGCG	*Limoniastrum guyonianum (Limonium)*	MKN28, AGS	↓RON	[67]
		SGC-7901	↓VEGF	[68]
		AGS	↓STAT6, VEGF	[69]
Farrerol	*Daphne aurantiaca*	SGC-7901	↑caspase-9/-3, Bax; ↓Bcl-2	[70]
		SGC-7901 (in vitro)	↑p27KIP1, ERK1/2, p38 MAPK	[71]

(*Continued*)

Table 1 (Continued).

Flavonoid	Source	Cell Line	Targets	Reference
Formononetin	*Pterocarpus indicus (Purple sandalwood)*	SGC-7901, MKN-45, MGC-803	↓SIRT1	[72]
Galangin	*Alpinia conchigera*	MGC-803	↑Caspase-3, Bax, PARP; ↓Bcl-2	[73]
		SNU-484	↑Caspase-9/-3, PARP	[74]
		MGC-803	↑LC3BII; ↓NF-κB	[75]
Hispidulin	*Eupatorium cannabinum (hemp agrimony)*	AGS	↑p21/WAF1, p16; ↓COX-2, cyclin D1/E	[76]
Icariin	*Epimedium pubescens*	BGC-823	↓Rac1, VASP	[77]
		SGC-7901, BGC-823, MKN-7, HGC-27, NUGC-3, AGS, Hs-746T, NCI-N87	↓Hsa_cir_0003159	[78]
Iridin	*Iris milesii*	AGS	↓Cdc25C, CDK1, Cyclin B1, p-PI3K, p-AKT	[79]
Irigenin	*Iris milesii*	NCI-N87	↑FADD, DR5, Bax	[80]
Isoliquiritigenin	*Pterocarpus indicus (Purple sandalwood)*	MKN-28	↑LC3II/LC3I, Beclin 1	[81]
Isoquercitrin	*Apocynum venetum L. (kender)*	AGS, HGC-27	↑HMGB1, HSP70, HSP90	[82]
Isoorientin	*Carex fraseriana*	AGS	↓p-AKT, p-GSK-3β, β-catenin	[83]
Kurarinone	*Albizia julibrissin (acacia)*	SGC-7901	↑Mcl-1, c-FLIP	[84]
Liquiritin	*Polygonum aviculare (knotgrass)*	AGS, SNU-216	↑Caspase-9/-3, PARP	[85]
Licochalcone A	*Glycyrrhiza (Licorice)*	BGC-823	↑ROS, ERK, JNK	[86]
Licoflavone A	*Glycyrrhiza Glabra (Licorice)*	SGC-7901, MKN-45, MGC-803	↓VEGFR-2, PI3K/AKT, MEK/ERK	[87]
Luteolin	*Verbascum lychnitis*	MKN-45	↑Bax, Caspase-3, cytochrome C; ↓Bcl-2, p-Akt	[88]
		Hs-746T	↓VEGF	[89]
		Hs-746T, MKN-28	↓Notch1	[90]
		BGC-823, SGC-7901	↑miR-34a; ↓Bcl-2	[91]
		CRL-1739	↓MUC1, ADAM-17	[92]
		BGC-823	↑Caspase-9/-3, Bax; ↓Bcl-2	[93]
		SGC7901/DDP, BGC-823, HGC-27	↓Mcl-1, Survivin, Bcl-xl	[94]
		MKN-45, SGC-7901	↑Caspase-3, PARP-1; ↓MMP9, cMet	[95]
		AGS, BGC-823, SGC-7901	↓HK1, miR-34a	[96]
		HGC-27, MFC, MKN-45	↑ROS	[97]
Myricetin	*Ficus auriculata*	AGS	↓PI3K/Akt/mTOR	[98]
		HGC-27, SGC-7901	↑Mad1	[99]
Naringin	*Podocarpus fasciculus*	AGS	↑Bad; ↓Bcl-xL	[100]
		MGC-803, MKN-45	↑E-cadherin; ↓Zeb1, P-AKT	[101]
		SNU-1	↑Caspase-3, Bax; ↓Bcl-2	[102]
Naringenin	*Elaeodendron croceum*	SGC-7901	↑Caspase-3, Bax; ↓Bcl-2	[103]
Nobiletin	*Citrus tankan*	SGC-7901	↑Caspase-3; ↓Bcl-2, Survivin	[104]

(*Continued*)

Table 1 (Continued).

Flavonoid	Source	Cell Line	Targets	Reference
Pectolinarigenin	*Cirsium chanroenicum*	AGS, MKN-28	↓PI3K/AKT/mTOR	[105]
Quercetin	*Lotus ucrainicus*	AGS	↑CASP3, PARP	[106]
Scutellarin	*Erigeron breviscapus*	MGC-803, AGS	↑PTEN; ↓PI3K	[107]
Sanggenon C	*Morus cathayana(voasun)*	HGC-27, AGS	↓ERK	[108]
Silibinin	*Aspergillus iizukae*	SGC-7901	↑p53, p21; ↓p34cdc2	[109]
Wogonin	*Scutellaria likiangensis*	BGC-823, MGC-803, MKN-45, HGC-27	↑Caspase-3, Bax; ↓Bcl-2	[110]
		MGC-803	↓NF-κB	[111]
		SGC-7901	↓HIF-1α, MCT-4	[112]
Wogonoside	*Scutellaria discolor*	AGS, MKN-45	↑ASK1, JNK, Caspase-3/-9	[113]
Xanthohumol	*Humulus lupulus L. (common hop)*	AGS	↑ROS; ↓NF-κB	[114]
5-Hydroxy-3,6,7,8,3',4'-hexamethoxyflavone	*Maclurodendron porteri*	BGC-7901	↑Caspase-3/-9, PARP, Bax/Bcl-2	[115]

similar to galangin (Figure 3, 39), affected GC cell (AGS, MGC-803, BGC-823) proliferation and the cell cycle by suppressing LncRNA-PVT1 expression, down-regulating p-STAT3, and inhibiting STAT3 activation.[59] Additionally, icariin (Figure 2, 5), a glycosidic flavonoid from the flavonol family, hindered the viability and growth of GC cells (SGC-7901, BGC-823, MKN-7, HGC-27, NUGC-3, AGS, Hs-746T, NCl-N87) by controlling the hsa_cir_0003159/miR-223-3p/NLRP3 axis.[78]

In summary, the available research suggests that flavonoids inhibit the growth of GC cells through multiple pathways, particularly targeting PI3K, STAT, and other signaling pathways. These mechanisms encompass regulation of the cell cycle, gene expression, protein expression, and more, resulting in significant anti-growth and anti-proliferative effects (Figure 4).

Inhibition of Invasion and Metastasis

It is widely recognized that an increase in tumor aggressiveness and metastasis indicates unfavorable disease progression. One complication following surgery or chemotherapy is tumor metastasis, making it crucial to explore avenues for reducing tumor aggressiveness and inhibiting metastasis. EMT has been identified as a key player in tumor progression, invasion, and metastasis, enabling cancer cells to acquire increased aggressiveness.[118,119] As a methoxyflavone, acacetin (Figure 3, 15) exhibited potent antitumor activity, primarily manifested in its ability to suppress tumor invasion and metastasis.[120,121] Studies have demonstrated that acacetin inhibited the PI3K/Akt/Snail signaling pathway induced by TGF-β1-mediated EMT, leading to changes in the expression of EMT-related proteins and subsequently influencing the invasion and metastasis of GC.[38] Additionally, luteolin (Figure 3, 28) derived from various plants affects Notch1 signaling and EMT, which in turn inhibited tumor progression. When the Notch receptor binds to the ligand, the activated Notch intracellular domain (NICD) forms a complex with activated β-conjugated proteins. Luteolin blocked this complex formation and inhibited cell proliferation and metastasis, thereby impeding tumor progression.[90]

Flavonoids, including baicalein (Figure 2, 6), isoliquiritigenin (Figure 2, 9), and others, not only affect EMT but also commonly inhibit the invasion and metastasis of GC cells by modulating the AKT/mTOR signaling pathway.[48,81] The suppression of tumor invasion and metastasis by chrysin has garnered significant attention among the numerous flavonoids. Chrysin (Figure 2, 7) inhibited the phosphorylation of c-Jun and c-Fos in AGS cells by inhibiting the JNK1/2 and ERK1/2 signaling pathways. Consequently, it blocked AP-1 and regulated MMP-9 production, demonstrating an anti-invasive effect.[64] Ten-eleven translocation (TET) enzymes can catalyze the production of

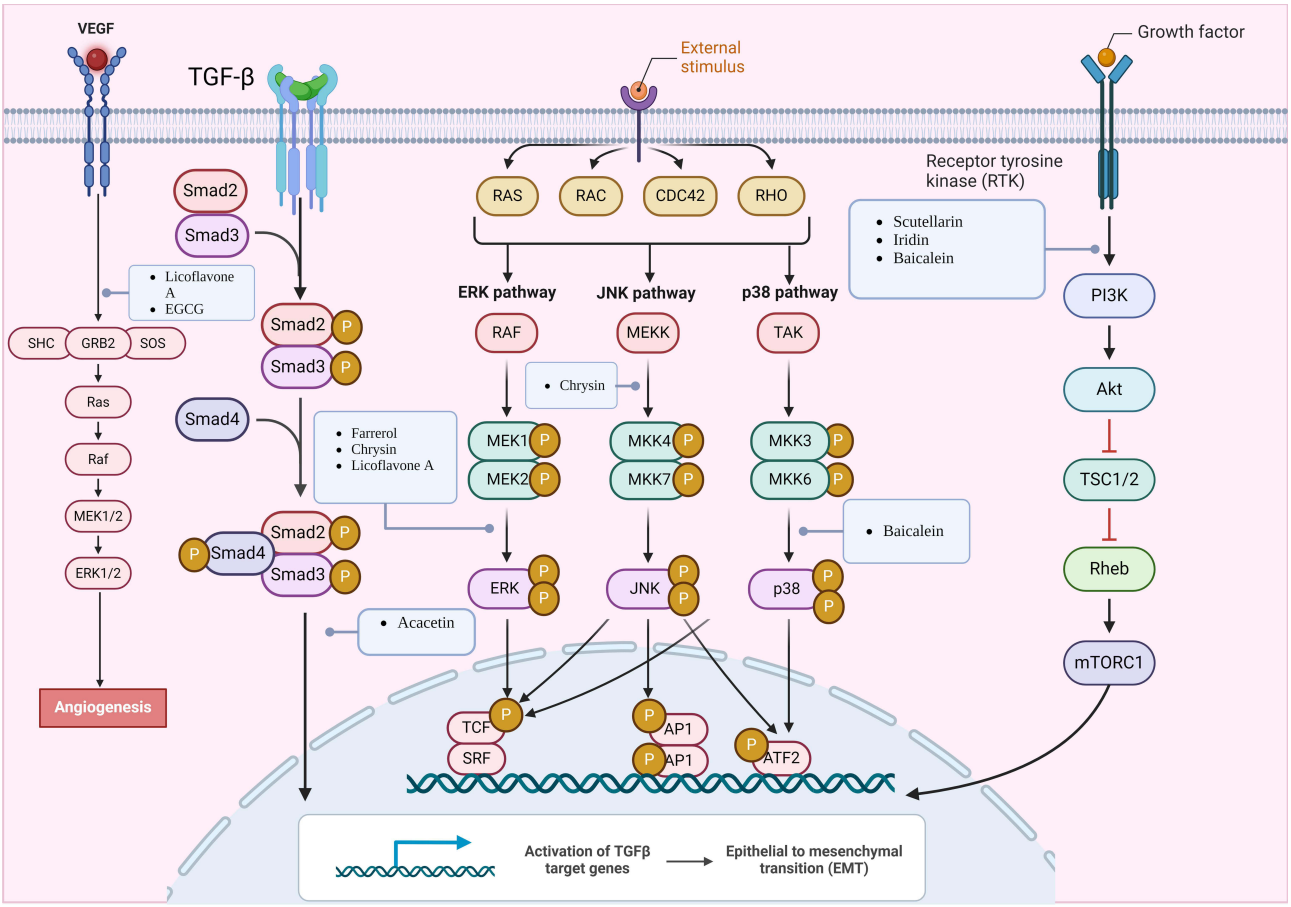

Figure 4 Mechanisms of flavonoids suppressing GC by inhibiting tumor growth and proliferation, invasive migration, and angiogenesis. Created by Biorender.com.

5-hydroxymethylcytosine (5hmC).[122] Previous studies have shown a reduction in TET3 and 5hmC expression in GC cells.[123] Researchers observed a significant increase in the expression of TET1 and 5hmC in chrysin-treated MKN-45 cells. Furthermore, the overexpression of TET1 promoted apoptosis and inhibited cell migration and invasion.[62] Recepteur d'origine Nantais (RON), a member of the c-Met family, plays an important role in the progression, invasion, and metastasis of GC. Chrysin significantly inhibited the expression of RON by suppressing the activity of Egr-1 and NF-κB transcription factors, thereby inhibiting cell invasion.[65] Consequently, based on the findings of this study, chrysin may possess an advantage in terms of drug selection for inhibiting GC invasion when compared to other flavonoids. Inhibiting EMT may serve as a promising therapeutic target for GC invasion (Figure 4).

Inhibition of Angiogenesis

Angiogenesis, an essential factor in cancer development and tumor metastasis, is associated with vascular endothelial growth factor (VEGF) and its receptor (VEGFR-2), making them important targets for treating GC. Moreover, natural compounds called flavonoids have been found to possess anti-angiogenic properties. *Scutellaria baicalensis*, a traditional Chinese medicine rich in flavonoids such as baicalein and wogonin,[124] exhibits both anticancer and antiviral properties. For instance, wogonin (Figure 2, 13) can suppress angiogenesis in SGC-7901 cells by downregulating HIF-1α and MCT-4 expression.[112] Similarly, baicalein (Figure 2, 6) inhibited angiogenesis in GC by upregulating miR-7, leading to the blockade of the FAK/PI3K/AKT pathway. As a result, angiogenesis in GC (HGC-27, SGC-7901, MGC-803, BGC-823) was suppressed.[50] In addition to the aforementioned targets, VEGF and VEGFR-2, flavonoids such as licoflavone A (Figure 2, 12), luteolin (Figure 3, 28), and deguelin (Figure 2, 11) exhibit potent antitumor effects. Licoflavone A (Figure 2, 12) affected the proliferation, cycling, apoptosis, migration, invasion, and EMT of VEGF-stimulated MKN-

45 cells by targeting VEGFR-2 and inhibiting the PI3K/AKT and MEK/ERK signaling pathways.[87] Furthermore, in AGS cells, epigallocatechin-3-gallate (EGCG) (Figure 2, 14) suppressed IL-3-induced VEGF production and angiogenesis by reducing STAT6 activity, presenting a novel approach for anti-tumor angiogenesis.[69] Although studies have consistently identified the involvement of VEGF in tumor angiogenesis, further investigations are needed to elucidate the precise pathways and mechanisms (Figure 4).

Induction of Cell Death

During tumor development, cell death is an inevitable and significant aspect of the life cycle of cancer cells. Various forms of cell death, including necrosis, apoptosis, autophagy, ferroptosis, and pyroptosis, have been identified, each with distinct biological processes and pathophysiological characteristics.[125] Initially, research on flavonoids' mechanisms against GC cells primarily focused on understanding processes like apoptosis. Consequently, most current studies investigate the apoptotic effects induced by flavonoids and their impact on signaling pathways such as PI3K/AKT, TRAIL, and MAPK. However, as research progresses, a few studies have emerged exploring the induction of GC autophagy, ferroptosis, and pyroptosis by flavonoids (Figure 5).

Induction of Apoptosis

Targeting the PI3K/Akt Signaling Pathway

PI3Ks are a family of lipoprotein kinases capable of phosphorylating the 3-OH moiety of inositol phospholipids. They are classified into three classes: I, II, and III, with class I being more relevant to cancer. Akt proteins, important downstream of PI3K, regulate processes such as cell survival, cell cycle progression, and cell growth.[126,127] In GC cells, the PI3K/AKT pathway, one of the most common pathways, is frequently studied to understand the mechanism of action of flavonoid agents.

Numerous flavonoids have been reported to induce apoptosis in GC cells through the PI3K/AKT signaling pathway. For instance, overexpression of the B-cell translocation gene 3 (BTG3) suppresses PI3K/AKT/mTOR pathway

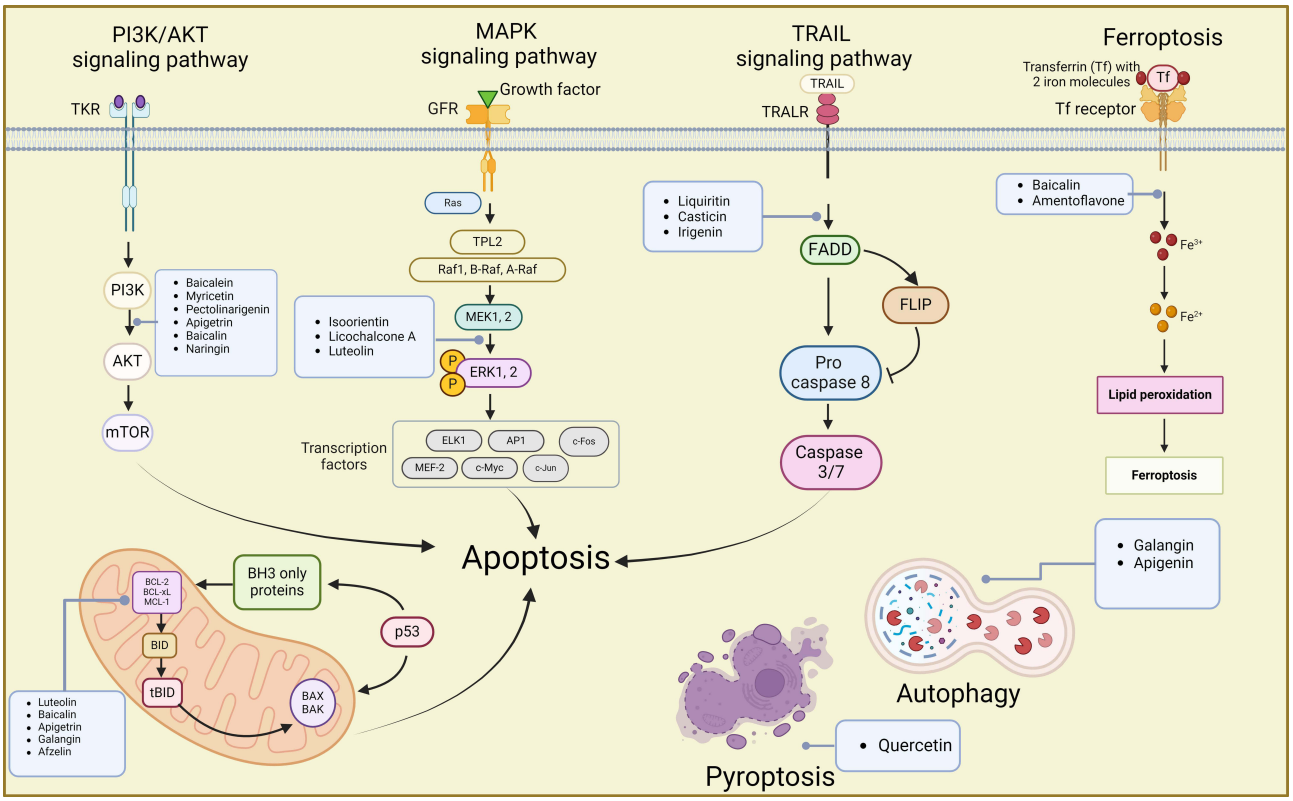

Figure 5 Mechanisms of flavonoids suppressing GC by inducing cell death inducing apoptosis, autophagy, ferroptosis, and pyroptosis. Created by Biorender.com.

activation, thereby regulating GC cell proliferation, migration, and apoptosis.[128,129] Baicalein (Figure 2, 6) inhibited the PI3K/AKT pathway by activating BTG3, resulting in endoplasmic reticulum stress (ERS) and apoptosis.[52] Myricetin (Figure 3, 30), found in various natural plants including bayberry, induced apoptosis by inhibiting the PI3K/Akt/mTOR pathway, thereby reducing the expression of related proteins and affecting the viability of AGS cells.[98] Similarly, pectolinarigenin (Figure 3, 32), present in *Cirsium chanroenicum*, led to autophagy and apoptosis in AGS and MKN-28 cells by downregulating the PI3K/AKT/mTOR pathway.[105] Whereas apigetrin (Figure 3, 19)-treated AGS cells inhibited cancer progression by enhancing exogenous apoptosis and autophagic cell death via the PI3K/AKT/mTOR pathway.[47] Naringin (Figure 3, 38), isolated from citrus fruits, stimulated the expression of apoptosis-associated proteins Bax, decreased the expression of Bcl-2, and affected the apoptosis of SNU-1 cells by blocking the PI3K/AKT pathway.[102] In another study, naringin (Figure 3, 38) was found to block the cell cycle, induced apoptosis, and inhibited the EMT process by inhibiting the PI3K-AKT/Zeb1 pathway in GC cells.[101] These findings suggest that naringin has multiple targets on the PI3K/AKT signaling pathway, contributing to its multifaceted anti-tumor activities. In conclusion, various flavonoids can induce cell death by acting on the PI3K/AKT signaling pathway, indicating their potential against GC.

Targeting TRAIL Signaling Pathway

TRAIL is a pro-apoptotic protein that initiates apoptosis by binding to death receptors (DR).[130,131] However, GC cells exhibit reduced sensitivity to TRAIL-induced apoptosis. Therefore, several scientific studies have focused on targeting TRAIL-induced apoptosis in GC cells using natural products like flavonoids. Liquiritin (Figure 3, 29) is a flavanone glycoside present in licorice,[132] while irigenin (Figure 3, 23) is an isoflavonoid isolated from the roots of Belamcanda chinensis.[133] Both of them could induce apoptosis by sensitizing TRAIL, which in turn promoted the enhancement of pro-apoptotic proteins and the generation of ROS.[80,85] Furthermore, casticin (Figure 3, 21), isolated from *Fructus Viticis*, enhanced TRAIL-induced apoptosis by down-regulating cell survival proteins and up-regulating the DR5 receptor via the ROS-ER stress-CHOP pathway.[58] Although there are limited studies on flavonoid-targeted TRAIL-induced apoptosis in GC, the current study presents a novel approach for GC treatment.

Targeting Bcl-2 Family

The Bcl-2 family plays a crucial role in apoptosis. Bcl-2, a pro-survival protein, regulates apoptosis by inhibiting the release of pro-apoptotic factors and the subsequent activation of the caspase cascade.[134] Flavonoids such as baicalin (Figure 3, 20), apigetrin (Figure 3, 19) and afzelin (Figure 3, 16) can interact with this protein.[39,46,55] For instance, baicalin (Figure 3, 20) has been shown to induce apoptosis in BGC-823 and MGC-803 cells. This effect is achieved by up-regulating Bcl-2-associated X (Bax) protein, down-regulating Bcl-2, and activating caspase-3 and caspase-9 at both protein and mRNA levels.[55] Apigetrin (Figure 3, 19) acted as an apoptosis inducer by reducing Bcl-2 and enhancing Bax, caspase-9/-3, and PARP cleavage in SGC-7901, MGC-803.[46] In another study, afzelin (Figure 3, 16) was found to stimulate the apoptotic response by increasing the expression of Bax and caspase-8/-9/-3 mRNA, while simultaneously decreasing the expression of the extracellular structural domain of MUC1 (a transmembrane glycoprotein) and the extracellular expression of galectin-3 (a galactose-binding protein).[39] Therefore, targeting the Bcl-2 family is a potential pathway for flavonoids to combat GC.

Targeting MAPK Signaling Pathway

The mitogen-activated protein kinase (MAPK) signaling pathway is an evolutionarily conserved pathway that plays a vital role in carcinogenesis. It consists of five cascades: ERK1/2, SAPK/JNK, p38 MAPK, ERK5, and ERK3/4.[135] The MAPK pathway has been implicated in various cellular processes such as proliferation, differentiation, migration, senescence, and apoptosis.[136] Therefore, researchers have investigated the interplay between flavonoids' anticancer properties and the MAPK signaling pathway.

Isoorientin (Figure 3, 24), a C-glucosyl flavone naturally occurring in various foods and beverages, has been found to inhibit the p-ERK, p-STAT3, and NF-κB signaling pathways through ROS-mediated MAPK/STAT3/NF-κB signaling. This resulted in increased expression levels of STAT3 and NF-κB and induced apoptosis in AGS cells.[83,137] Likewise,

licochalcone A (Figure 3, 26) isolated from *Glycyrrhiza glabra* suppressed the MAPK signaling cascade, induced ROS generation and oxidative stress in BGC cells, leading to cell death.[86] In addition, luteolin (Figure 3, 28) inhibited the MAPK and PI16K signaling pathways at the mRNA level by up-regulating specific dual-specificity phosphatases and down-regulating chemokine (C-X-C motif) ligand 3, leading to apoptosis.[93] Therefore, these flavonoids have shown the potential to induce apoptosis and exhibit antitumor effects in GC cells through the modulation of the MAPK signaling pathway.

Induction of Autophagy

Autophagy is a process of programmed cell death whereby dead cells trigger the formation of autophagosomes, followed by degradation.[138,139] There is increasing evidence supporting the role of flavonoids in inducing autophagy in GC cells. Notably, the citrus flavonoid naringin (Figure 3, 38) was found to induce autophagic cell death by promoting ROS production. This, in turn, activated the ERK1/2-p38 MAPK pathway and caused LMP-mediated lysosomal damage, ultimately leading to autophagy.[100] Similarly, treatment of AGS cells with apigenin (Figure 3, 18) resulted in increased autophagic cell death. This was evidenced by the upregulation of LC3B-II and beclin-1, the formation of autophagic vesicles and acidic vesicular organelles, as well as the elevated expression of the autophagic flux marker protein p62, all of which were induced by ERS.[47] Mechanistically, it has been reported that apigenin induced autophagic cell death in GC cells through the mTOR/AMPK/ULK1 pathway, leading to the down-regulation of p-mTOR, while increasing AMPK and ULK1 phosphorylation. Furthermore, under both normoxic and hypoxic conditions, apigenin induced ERS and autophagic cell death by inhibiting HIF-1α and Ezh2.[42] Conversely, in a tumor tissue model using nude mice, galangin (Figure 3, 39) reduced the phosphorylation level of proteins related to the NF-κB signaling pathway, down-regulated the expression of the autophagy marker protein LC3B-I, up-regulated LC3B-II, and induced autophagy in MGC803 tumor tissues.[75]

Induction of Ferroptosis and Pyroptosis

Ferroptosis is an iron-dependent, non-apoptotic form of cell death characterized by an accumulation of iron and ROS.[125,140] Substances that induce ferroptosis can directly or indirectly modulate glutathione peroxidase, leading to a reduction in antioxidant capacity, an increase in ROS, and ultimately oxidative cell death.[141] A limited number of studies have investigated the potential anti-GC activity of flavonoids through ferroptosis. For instance, baicalin (Figure 3, 20) promoted ROS-associated ferroptosis in AGS and SGC-7901 cells.[57] Amentoflavone (Figure 3, 40), a naturally occurring multifunctional biflavonoid, was found to inhibit activating transcription factor 2 (ATF2) by up-regulating miR-496 and subsequently malondialdehyde (MDA), ROS, and glutathione down-regulation. As a result, amentoflavone inhibited GC cell proliferation and induced ferroptosis.[41]

In contrast to ferroptosis, pyroptosis is an inflammatory vesicle-triggered, lysogenic programmed cell death characterized by cell swelling, lysis, and the release of various pro-inflammatory factors such as IL-1β, IL-18, ATP, and HMGB1.[142,143] In one study, quercetin (Figure 3, 41), a dietary flavonol, exerted its pyroptosis effect on AGS cells by activating the core pyroptosis gene and significantly upregulating the expression levels of pyroptosis makers (GSDMD, GSDME, Cleaved CASP1, NLRP3).[106] Although there are fewer studies investigating the impact of flavonoids on these two pathways, further research can explore additional flavonoids' effects on GC cell activity through ferroptosis and pyroptosis.

Combination with Other Drugs

In current treatments for GC, 5-FU and platinum compounds are frequently selected as chemotherapeutic agents. Consequently, combinations of these agents with flavonoids have emerged as a common approach to investigate their synergistic antitumor effects (Table 2).

Combination with 5-FU

5-FU, a uracil analog, functions by inhibiting thymidylate synthase, thus reducing DNA synthesis. It is widely employed as a chemotherapeutic drug in the treatment of GC.[164] However, the emergence of resistance poses a significant challenge

Table 2 Profiles of Flavonoids Combined Other Drugs Inhibiting GC

Flavonoid	Combination of Drugs	Cell Line	Targets	Reference
Baicalein	Baicalin, berberine chloride	AGS	↓IL-8, COX-2, iNOS	[144]
	Cisplatin	MGC-803, HGC-27, SGC-7901, SGC-7901/DDP	↑Nrf2; ↓Keap1, MDR1	[145]
	5-FU	AGS	↑PTEN; ↓HIF-1α	[54]
Cardamonin	5-FU	BGC-823	↓P-glycoprotein, β-catenin, TCF4	[146]
Catechin	5-FU	SNU-620, SNU-620/5FU	↑Caspase-3, Bax; ↓Bcl-2	[147]
Chrysin	5-FU	AGS, AGS/FR	↓MDR1	[148]
Isoliquiritigenin	5-FU	MKN-45	↓GRP78	[117]
Licochalcone A	5-FU	SGC-7901, MKN-45	↑Caspase-3, Bax; ↓Bcl-2	[149]
Troxerutin	5-FU	SGC-7901	↓STAT3/NF-κB, Bcl-2	[150]
Kaempferol	Cisplatin/paclitaxel	AGS, SNU-216, NCI-N87, SNU-638	↑LC3-II; ↓G9a, p62	[151]
Liquiritin	Cisplatin	SGC7901/DDP (in vivo)	↑p53, p21; ↓cyclin D1, cyclin A, CDK4	[152]
Luteolin	Cisplatin	AGS	↑p21/cip1;↓Cdc2,Cyclin B1, Cdc25C	[153]
	Oxaliplatin	SGC-7901	Inhibit cell proliferation	[154]
	Oxaliplatin	MFC	↑Bad; ↓Bcl-xL	[155]
Naringenin	ABT-737	SGC-7901	↑p53; ↓Akt	[156]
Nobiletin	Cisplatin	TMK-1, MKN-45, MKN-74, KATO-III	Inhibit cell proliferation	[157]
Quercetin	Irinotecan	AGS (in vivo)	↓VEGF	[158]
Rutin	Cisplatin, isoquercetin	AGS	Increase cytotoxicity	[159]
	Oxaliplatin	SGC-7901	↑p38/Caspase	[160]
	Lobetyolin, calycosin-7-glucoside	MGC-803, SGC-7901, BGC-823	↑HIF-1α	[161]
	Quercetin, d-chiro-inositol	MGC-803	Inhibit cell proliferation	[162]
Wogonin	Oxaliplatin	BGC-823	↑JNK	[163]

in chemotherapy. Catechin, an antioxidant flavonoid predominantly found in woody plants as (+)-catechin and (-)-epicatechin[165], was found to effectively inhibit lactic acid production and lactate dehydrogenase A (LDHA) activity. It specifically targeted lactate dehydrogenase A to enhance the susceptibility of SNU620 GC cells to 5-FU.[147] This suggests that combining catechin with 5-FU enhances the cytotoxic effect on GC cells. Furthermore, similar resistance-reversing effects of flavonoids and 5-FU combinations were observed in other types of GC cells, such as AGS and MGS cells. For instance, the combination of chrysin (figure 2, 7) and 5-FU resulted in enhanced chemotherapeutic effects by blocking the G2/M phase in 5-FU-resistant AGS cells.[148] Under hypoxic conditions, baicalein (Figure 2, 6) inhibited glycolysis by modulating the PTEN/Akt/HIF-1α signaling pathway and increased the sensitivity of AGS cells to 5-FU. It also reversed the resistance of cancer cells to 5-FU under hypoxic conditions.[54] In the case of MGC-803 cells, wogonin (Figure 2, 13) modulated metabolizing enzymes of 5-FU, prolonging catabolism and sensitizing MGC-803 cells to 5-FU-induced apoptosis by inhibiting NF-κB nuclear translocation.[111] Additional studies on flavonoids combined with 5-FU in GC are listed in Table 2.[117,146,149,150]

Combination with Platinum Compounds

Platinum compounds, being dominant and critical metalloids, find extensive application in the treatment of solid malignant tumors. They are commonly used in clinical practice as anticancer drugs for both monotherapy and combination therapy.[166,167] However, flavonoids obtained from natural products often combine with platinum compounds to produce specific antitumor effects. For instance, when liquiritin (Figure 3, 29) and cisplatin were combined, they effectively induced apoptosis and autophagy both in vitro and in vivo in a GC cell model using nude mice. This combination enhanced the cleavage of caspase8/-9/-3 and PARP, as well as the expression of LC3B and Beclin 1.[152]

Luteolin (Figure 3, 28) impaired the cellular mitochondrial membrane potential and hindered the growth and proliferation of GC cells when MFC cells were treated with low-dose oxaliplatin.[155] Additionally, wogonin (Figure 2, 13) enhanced not only the cytotoxic effect of 5-FU but also the cytotoxicity of oxaliplatin. Wogonin further aggravated the damage to the mitochondrial membrane potential induced by oxaliplatin in BGC-823 cells. Furthermore, when used in combination, wogonin allowed for a reduction in the dosage of oxaliplatin, thereby reducing the side effects of chemotherapeutic agents.[163] More flavonoids in conjunction with platinum chemicals for GC are listed in Table 2.[145,151,153,154,157,159,160]

Combination with Other Natural Products

In addition to these two commonly used chemotherapeutic agents, flavonoids can be combined with other natural products to combat GC. For example, Hwanglyeonhaedok-tang, a traditional medicine, contains baicalein (Figure 2, 6) along with small amounts of alkaloids. This compound has been shown to inhibit *H. pylori* adhesion, as well as the increase of IL-8 and COX-2 in AGS cells [144] Another example is Modified Spleen and Nutritional Soup, which contains mangostensin and rutin. These compounds have been found to inhibit GC progression by regulating tumor-associated macrophages and decreasing aerobic glycolysis in GC cells.[161]

Overall, these findings indicate that flavonoids alone possess certain antitumor effects on GC cells. However, when combined with chemotherapeutic drugs, they can help reduce drug resistance. Additionally, when combined with natural products, they can enhance their cytotoxic effects.

Discussion

GC, as a tumor with high morbidity and mortality, often faces major challenges in its treatment. We reviewed the mechanisms of action of flavonoids against gastric cancer from different pathways, such as inhibition of tumor growth and proliferation, invasion and metastasis, neovascularization, and induction of cell death. Several studies have found that flavonoids act on a variety of different biological pathways to inhibit GC, especially inducing cell death in gastric cancer. Flavonoids target pathways such as PI3K/Akt, TRAIL, MAPK, and the Bcl-2 family. In addition, it is worth our attention that flavonoids also act on common gastric cancer targets HER2, cMet, and VEGF. However, only some of the flavonoids have been found to inhibit these common gastric cancer targets, but the strength of the inhibitory effect needs to be verified by other experiments, and it remains to be explored whether other flavonoids also act on these targets. Moreover, compared with the studies that are associated with the signaling pathway, the research about flavonoids inhibiting HER2, Met, and PD-1 targets seems less, and even studies of flavonoids on Claudin 18.2 targets are lacking.

Flavonoids are mostly extracted from plants and often have multi-target effects. In addition to the common signaling pathways such as PI3K/Akt, there are some other targets that deserve our attention, one of which is short-chain ribonucleic acid. miR-7 and miR-496 are the two flavonoid drug targets that have been discovered so far, but their specific effects and strengths of action have not yet been explored. In addition, other solid tumor targets may be of interest. MUC1, a glycosylated type I transmembrane protein, is a potential drug target. Direct methods, including biotin labeling technology, click chemistry, and photocrosslinking reaction labeling technology, and indirect methods, including proteomics, metabolomics, and computer-aided drug design, are used for validation. Currently, there are many drug targets for gastric cancer, and the most common ones are HER2 and VEGF, which are mentioned above, but they are far from being sufficient for the treatment of tumors, so it is necessary to seek more new drug targets.

In addition to their antitumor effects through targeting, flavonoids may act in combination with other drugs. Most gastric cancers are insensitive to immune checkpoint inhibitor monotherapy, so patients with gastric cancer may need combination therapy to improve the response to immune checkpoint inhibitors. ADC drugs are a class of targeted biopharmaceuticals consisting of antibodies, linkers, and cytotoxic drugs, which can be used in tandem with small-molecule drugs to exert antitumor effects. Flavonoids are mostly natural small molecules, and more monomers have inhibitory effects on certain targets. Whether it is possible to develop flavonoids as new ADC drugs for gastric cancer treatment in the future, alone or in combination with PD-1 inhibitor K drugs, requires more research to explore.

However, even though there are more studies demonstrating the anticancer activity of flavonoids, their clinical aspects of research still need to be further deepened. In addition, age, gender, and genotype affect the absorption, distribution, metabolism, and elimination of flavonoids, resulting in low absorption, extensive metabolism, and rapid elimination,

which affects the bioavailability and bioactivity of flavonoids, among others. Moreover, flavonoids are categorized into different subgroups, including isoflavonols, flavanones, flavones, flavonols, anthocyanins, chalcones and so on. One of the representative compounds of flavonols is quercetin (Figure 3, 41), which may be detrimental to athletes, the elderly, or people with enzyme problems. Therefore, researchers should explore how to maximize the retention of flavonoids' bioactivity while reducing their side effects and maximizing the use of the drug in the future.

In conclusion, flavonoids have a wide range of biological effects, with particularly prominent anti-cancer effects. Due to the advantages of flavonoids' wide source, safety, and certain anticancer effects, in the future, flavonoids can be used in tumor therapy as drug formulations alone or in combination with existing antitumor drugs for multi-targeted or directed-targeted therapies. Therefore, flavonoids can be a good research direction for exploring GC therapeutic options and providing new possibilities for GC treatment.

Abbreviations

5hmC, 5-hydroxymethylcytosine; ASK1, apoptosis signal-regulating kinase 1; ATF2, activating transcription factor 2; ATF2, activating transcription factor 2; Bax, Bcl-2-associated X; BTG3, B-cell translocation gene 3; CDK1, cyclin-dependent kinase 1; cFLIP, cellular FLICE-like inhibitory protein; DR, death receptors; EBV, Epstein Barr virus; EGCG, epigallocatechin-3-gallate; EMT, epithelial mesenchymal transition; ERK, extracellular signal-regulated kinase; ERS, endoplasmic reticulum stress; EZH2, The enhancer of zeste homolog 2; FADD, Fas-associated protein with death domain; FAK, focal adhesion kinase; GC, gastric cancer; GCs, gastric cancers; H. pylori, Helicobacter pylori; HIF-1alpha, hypoxia-inducible factor-1alpha; LDHA, lactate dehydrogenase A; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MMP-9, matrix metalloproteinase 9; MUC, mucin; NICD, Notch intracellular domain; PARP, polymerase; PI3K, phosphatidylinositol 3 kinase; PTEN, phosphatase and tensin homolog; RON, Recepteur d'origine Nantais; SIRT1, silent information regulator 1; TET, ten-eleven translocation; VEGF, vascular endothelial growth factor.

Consent for Publication

All authors read and approved the final manuscript.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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