Cancers of the gastrointestinal (GI) tract are often life-threatening malignancies, which can be a severe burden to the health care system. Globally, the mortality rate from gastrointestinal tumors has been increasing due to the lack of adequate diagnostic, prognostic, and therapeutic measures to combat these tumors. Coumarin is a natural product with remarkable antitumor activity, and it is widely found in various natural plant sources. Researchers have explored coumarin and its related derivatives to investigate their antitumor activity, and the potential molecular mechanisms involved. These mechanisms include hormone antagonists, alkylating agents, inhibitors of angiogenesis, inhibitors of topoisomerase, inducers of apoptosis, agents with antimitic activity, telomerase inhibitors, inhibitors of human carbonic anhydrase, as well as other potential mechanisms. Consequently, drug design and discovery scientists and medicinal chemists have collaborated to identify new coumarin-related agents in order to produce more effective antitumor drugs against GI cancers. Herein, we summarize the therapeutic effects of coumarin and its derivatives against GI cancer.

Keywords: Coumarin – Benzimidazole, therapy, gastrointestinal cancer, natural compound, gastric cancer

INTRODUCTION

Cancer accounts for about 13% of all deaths globally (~7.9 million per year) and is considered a major cause of mortality (1). It has been projected that the cancer death toll will increase to 12 million by 2030 (2). Tumors of the gastrointestinal (GI) tract are the second most frequent cause of cancer-related mortality worldwide (3). According to studies performed in 2008, GI tumors are the fourth and fifth most frequent type of malignancy in males and females, respectively (4). The major GI cancers include tumors of the esophagus, stomach, pancreas, liver, and colon (5). Genetic heterogeneity in several genes, including tumor-promotor genes, mismatch repair genes, and anti-oncogenes, can all contribute to the tumorigenesis in the GI tract (6).

Moreover, an imbalance between cellular apoptosis and cellular proliferation can result in the development of GI tumors (7). Carcinogenesis of the GI tract is influenced by many intrinsic and...
external risk factors, including alcohol use, being overweight, genetic mutations, as well as infection with specific bacteria such as *Helicobacter pylori* (8). Most patients with GI tumors report symptoms only after the lesion has progressed, and invades into either adjacent or distant organs. Nevertheless, the most common symptoms are epigastric pain, upper abdominal bloating, and a palpable abdominal mass (9). Altogether, these tumors put a pressing load on health care providers and are considered a public health issue (8). Patients with GI tumors can have widely different prognoses, depending on the tumor type and the stage at diagnosis. The results of most patients with GI tumors can be improved with early diagnosis. Surgical resection of the tumor, chemotherapy regimens including mitomycin, cisplatin, or docetaxel, and radiotherapy alone or combined with chemotherapy are the most common treatment approaches in patients with GI cancer (10).

Phytochemicals are a group of non-nutrient bioactive compounds, widely found in many plants such as grains, vegetables, and fruits. Phytochemicals are often used to protect against the development of chronic disorders, such as cancer, neurodegenerative disorders, and cardiovascular disease (10, 11). Various studies have evaluated the chemopreventive activity of phytochemicals in GI tumors, and have shed light on their potential protective mechanisms against cancer (2).

Coumarin is a benzopyranone compound with diverse functions (12). Coumarin is usually extracted from naturally occurring sources, as well as being prepared by chemical synthesis. Coumarins are typically found in various plants, such as rhizomes, bark, leaves, plant roots, and even in marine plants (12).

Coumarins can exert a wide range of pharmaceutical functions, including activity against bacteria, viral infections, and fungal infections. It also has anti-cancer, anti-inflammatory, anticoagulant, and anti-hypertensive activity (13, 14). The benzopyrone backbone of coumarin contains many different possible substitution regions. The possible variations in the basic coumarin structure can be divided into five distinct classes: simple coumarins, isocoumarins, furanocoumarins, pyranocoumarins, and dicoumarins. Laboratory researchers have produced a wide range of more complicated coumarin–derived structures, with wider applicability and more powerful functionality. Coumarin and its derivatives have shown a variety of therapeutic benefits in cancer patients. Coumarin exerts its anticancer effects through several mechanisms of action, such as suppression of CA (carbonic anhydrase) activity, suppressing MDR (multiple drug resistance), promoting cell apoptosis, and increased activity of the PI3K/Akt/mTOR signaling pathway (15). Herein, we summarize some therapeutic effects of coumarin against GI cancer.

**PHARMACOKINETICS OF COUMARIN**

When coumarins are given orally, they are immediately absorbed through the mucosa of the GI tract and then disseminated throughout the entire body (16). Both coumarin and its derivative 7-hydroxycoumarin are water-insoluble. Nevertheless, these compounds still have a significant distribution coefficient. Coumarins can rapidly cross the lipid bilayer of the plasma membrane via passive diffusion, because they have a nonpolar structure (17). Studies in clinical pharmacokinetics have shown that coumarins are mainly metabolized in the liver via the first-pass effect, and only 2–6% of the absorbed coumarin enters the peripheral circulation (16).

Coumarin has a relatively short half-life and poor bioavailability. Pharmacokinetics studies have shown that approximately 35% of coumarin is bound to plasma proteins, whereas 47% of 7-hydroxycoumarin is bound to plasma proteins (16, 18–21). Coumarin undergoes an initial metabolic process in liver microsomes mediated by CYP2A6 (cytochrome P-450-bound mono-oxygenase enzyme), which results in the production of 7-hydroxycoumarin (22, 23). Phase-II conjugation results in the production of a glucuronide conjugate from 7-hydroxycoumarin (16, 24, 25). Coumarin and its related metabolites are readily excreted via the urine (26–29).

Hemorrhage is considered to be the main risk of coumarin administration, due to its anticoagulant effects. Administration of oral anticoagulants for prolonged periods is associated with an increased risk of bleeding (30, 31). Warfarin is a coumarin frequently used as an anticoagulant, and can cause unexpected bleeding, especially in female patients, with duration of therapy of 4 months or longer within the previous year, and those with an advanced age (31). As an anticoagulant, coumarin suppresses the metabolism of vitamin-K-dependent coagulation pathways, leading to the defective metabolism of bone minerals. This defective bone metabolism occurs mainly in older patients, and postmenopausal women who receive chronic administration of anticoagulants (30, 32). Small blood vessels such as venules and arterioles can undergo acute thrombotic events following consumption of oral anticoagulants such as coumarin; this can result complete skin necrosis, particularly in the thighs, lower extremities, and breasts. Administration of coumarin-based oral anticoagulants during pregnancy carries a higher risk of miscarriage. Consumption of warfarin between the 6th–12th weeks of gestation can lead to warfarin embryopathy, which is the most severe adverse effect of warfarin. Warfarin embryopathy includes fetal abnormalities such as narrowing of the upper respiratory tract, hypoplasia of the nasal bone, and epiphyseal stippling (30–33).

**COUMARIN: STRUCTURE AND ANTI-CANCER ACTIVITY**

Coumarins are currently categorized into four distinct classes: pyranocoumarins, furanocoumarines, simple coumarins, and coumarins with pyrone-substituents (34). Simple coumarins include alkoxylated, alkylated, and hydroxylated–derivatives of coumarin, and associated glycosides, such as skimmnin, umbelliferone, esculetin, herniarin, limettin, esculin, daphnin, and daphnetin (34). Furanocoumarins contain a furan ring bound to the coumarin ring. Furanocoumarins can be categorized into two
groups based on the ring fusion sites: linear furanocoumarins attached at C6/C7 and angular furanocoumarins attached at C7/C8. Psoralen, imperatorin, and xanthotoxin are linear furanocoumarines, while bergapten, isobergapten, pimpinellin, isopimpinellin, and angelicin are examples of angular furanocoumarins (34–37). Pyranocoumarins have a 6-membered pyran ring attached to the benzene ring at C7–8 (angular) or C6–7 (linear). Seselin, visnadin, and xanthyletin are examples of pyranocoumarins (38, 39). Coumarins with pyrone-substituents are divided into three different groups: 3-phenylcoumarin (gravelliferone and coumestrol); 4-hydroxycoumarin (icumarol and novobiocin), and 3,4-benzocoumarin (alternariol). Plants do not contain 4-hydroxycoumarins in their natural state. Warfarin is also a synthetic compound belonging to this family (36, 40).

Coumarin compounds with multiple biological targets have been recently identified, and these could be used as new therapeutic agents to treat disorders, such as congestive heart failure and cancer. Naturally occurring drugs have become popular, since they are relatively cheap, have low toxicity, do not cause the development of resistance, as well as having significant efficacy (41, 42). Consequently, novel compounds extracted from plants and microorganisms can be combined with current chemotherapeutic drugs for cancer treatment (43). Coumarins are a large family of natural agents with diverse pharmacological properties. These compounds are currently extracted from a wide range of plants, such as Artemisia, Achillea, and Fraxinus genera, but they can also be synthesized in the laboratory using standard chemical reactions. Various techniques, including reflux, maceration, ultrasonic-mediated, and microwaves, have been used to extract and purify coumarin derivatives from plant source material. In the laboratory, organic reactions such as Von Pechmann, Perkin, Wittig, and Knovenagel have been used to synthesize coumarins (42). The shikimic acid pathway plays a pivotal role in coumarin biosynthesis in nature. The shikimic pathway consists of a series of enzymatic reactions resulting in the production of umbelliferone, chorismic acid, p-coumaric acid, and cinnamic acid. In addition, the enzyme cytochrome P450 plays a major role in converting cinnamic acid into isofraxidin, umbelliferone and scopoletin through an ortho-hydroxylation reaction (42, 44).

It is well known that many cancers can recur after being treated with conventional chemotherapy. This phenomenon is known as multidrug resistance (MDR), which is often due to up-regulation of transmembrane protein drug-efflux pumps, including p-glycoprotein (P-gp) also known as ATP-binding cassette sub-family B member 1 (ABCB1), or multidrug resistance-associated protein 2 (MRP2, ABCC2) which can actively pump many anti-cancer drugs out of the cells, a process powered by ATP hydrolysis. In this context, coumarins have the potential to decrease the activity of MRP2 and P-gp, and could overcome MDR.

Baghdadi et al. (45) isolated six coumarin derivatives, including mansorin-I, mansorin-II, mansorin-III, mansorin-A, mansorin-B, and mansorin-C, from Mansonia gagei a plant of the Sterculiaceae heartwood family. Their study showed that these agents had promising antitumor activity against hepatocellular carcinoma, breast cancer, colorectal cancer, and cervical cancer cell lines. In this context, mansorin-II and mansorin-III had the highest antitumor effect, with a half-maximal inhibitory concentration (IC50) of 3.95–35.3 μM and 0.74–36 μM, respectively. Moreover, mansorin-II was able to potentiate the antitumor effects of taxol. This effect occurred partly by inhibiting the P-gp efflux activity.

Carbonic anhydrase is a zinc-containing metalloenzyme, responsible for catalyzing the reaction between carbon dioxide and water to produce carbonic acid, bicarbonate, and hydrogen ions. This reaction maintains the balance between the intracellular and extracellular pH at stable levels, and allows the transfer of ions through the transmembrane space, and other metabolic processes to proceed (46). Sixteen different carbonic anhydrase enzymes have been identified. Of these, CA I and CA II are cytoplasmic enzymes, while CA IX and CA XII are transmembrane proteases. Because cancer cells and their surrounding microenvironment exist in a state of hypoxia, they increase their rate of glycolysis to satisfy their metabolic requirements, and therefore lactic acid accumulates in the tumor microenvironment. CA XII and CA IX are up-regulated in tumor cells due to the action of HIF (hypoxia-inducible transcription factor). Carbonic anhydrase enzyme plays a role in the growth and metastatic dissemination of primary tumors, as well as the development of resistance to chemotherapy (46, 47).

CA IX and CA XII are highly expressed in many cancer types, and may be promising targets for therapeutic intervention. Belma et al. (48) investigated a wide range of compounds for their inhibitory effect on CA XII, CA IX, CA II, and CA I enzymes in colorectal cancer cells. They found that some compounds could effectively inhibit both CA XII and CA IX. The most active was 4-(((2-(1-((3-((2-oxo-2H-chromen-7-yl)oxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)napththalen-1-yl)-methylene)amino)methyl)benzenesulfonamide, which could selectively inhibit proliferation in colorectal cancer cells, and had an inhibitory constant (Ki) of about 596.6 nM for CA XII and 45.5 nM for CA IX.

The caspase family of enzymes are involved in the induction of apoptosis. These enzymes include caspase-10, 9, 8, 7, 6, 3, and 2. Among these, caspase-10, 9, 8, and 2 are involved in the initiation of apoptosis. Caspase-2 catalyzes its own cleavage and becomes activated to trigger apoptosis under the influence of intracellular signaling. Subsequently, the process of apoptosis is executed by caspase-7, -6, and -3, which are activated by upstream promoters. These caspases cleave various functional and structural proteins, especially PARP (poly-ADP-ribose polymerase) (49). Bcl-2 (B cell lymphoma-2) is a major tumor-promoter gene that generally inhibits cellular apoptosis. The Bcl-2 family contains proteins with both anti-apoptosis and pro-apoptosis activity. PUMA, Bax, and Bad are examples of pro-apoptotic proteins which are predominantly found in the cytoplasm. After being activated by apoptosis signaling, these proteins migrate to the mitochondrial outer membrane, where they form transmembrane channels that allow the mitochondria to expel cytochrome C, thus activating caspases resulting in
apoptosis. On the other hand, the Bcl-2 family also contains proteins with anti-apoptotic properties, primarily found in the mitochondrial outer membrane, which can inhibit apoptosis by preventing loss of cytochrome C from the mitochondria (49). Coumarin-derived compounds can modulate the expression of pro-apoptotic proteins and could thus help to treat malignant tumors.

Nordin et al. (50) extracted a coumarin compound known as Pulchrin A, from a Malaysian plant called Enicosanthellum pulchrum in the Annonaceae family. They evaluated the potential of this coumarin-derived agent to produce apoptosis in ovarian tumor cells. Pulchrin A was found to reduce Bcl-2 expression and increase Bax protein expression via increasing caspase-9 and caspase-3 activity, with an IC50 level about 22 μM in ovarian cancer cells.

The phosphatidylinositol kinase PI3K is found in the intracellular compartment. PI3K can activate other protein kinases such as PKC, PKB, and PKA, and plays a pivotal role in processes, such as cell differentiation, growth, migration and apoptosis. AKT or PKB is a serine/threonine kinase, which is a downstream target for PI3K, and is significantly correlated with cellular proliferation and apoptosis. In addition, AKT activates CDK2 and CDK4 and modulates p27, and acts as a cyclin-dependent kinase inhibitor, thereby preventing cell cycle progression. AKT also has anti-apoptotic activity by acting on several pathways. Some examples of the anti-apoptotic activity of AKT include, inhibiting caspases and Bax, inhibiting GSK3 activity (which increases apoptosis through cleavage of the cytoskeleton protein β-catenin), as well as reducing the adhesion of cells. AKT can increase the activity of transcription factor NF-κB which in turn leads to increased repair of DNA damage, reducing pro-apoptotic FasL gene expression, and inhibiting the release of cytochrome C out of the mitochondria. mTOR is another threonine/serine kinase, which is a downstream target of AKT. Following its own activation, mTOR activates the ribosomal proteins p70S6K and E-BP1 (a translation inhibitor) (4). The binding of 4E-BP1 to eIF-4E becomes weaker upon phosphorylation; as a result the free eIF-4E is able to bind to other factors to initiate protein translation.

After being activated, p70S6K can increase protein production. The PI3K/AKT/mTOR pathway plays a crucial role in the modulation of the cell cycle, cell viability, proliferation, differentiation, and metastasis (51, 52). This signaling pathway has been shown to be correlated with human carcinogenesis. Abnormal up-regulation of this signaling pathway has a role in the formation, growth, progression, and chemoresistance of cancer cells, and could be a new potential therapeutic target for cancer treatment (53, 54). 5-Methoxypsoralen is a linear furcoumarin (psoralen) extracted from plant sources (such as parsley and bergamot) by alkali treatment. In a study by Guo et al. (55), 5-methoxypsoralen was found to inhibit PI3K, mTOR, and Akt phosphorylation and expression in human glioma cells, resulting in the inhibition of the PI3K/Akt/mTOR signaling axis. Following exposure to 5-methoxypsoralen, the DNA in glioma cells was damaged by fragmentation, and abundant autophagic vacuoles were formed.

Microtubules are an important constituent of the cell cytoskeleton, and control cell cycle progression, proliferation, cell morphology, and intracellular signaling. Several anticancer drugs can cause microtubule depolymerization, or else they block microtubule aggregation, resulting in cell cycle arrest at the G2/M phase, and thus mitosis is blocked in tumor cells. Microtubules have three different binding sites for the anticancer drugs, vincristine, paclitaxel, and colchicine. Therefore paclitaxel, vincristine, and colchicine are often used to inhibit microtubules. Moreover, these drugs are substrates of efflux systems mediated by P-gp pumps, resulting in multidrug resistance in cancer cells. A study by Dahong evaluated the effects of the coumarin derivative, Ferulin C on proliferation in breast cancer in vitro and in vivo. Ferulin C is a coumarin isolated from the roots of Ferula ferulaceoides, which can also bind to colchicine binding sites on β-tubulin, thus preventing its aggregation. Ferulin C can inhibit the polymerization of tubulin (IC50 = 9.2 μM) compared to colchicine (IC50 = 1.8 μM) used as the reference. Ferulin C was found to specifically alter the microtubule structure without affecting tubulin expression. Ferulin C destabilized microtubules, and increased the activity of p21, while it suppressed PAK1. Higher levels of PAK1 are correlated with unfavorable outcomes, while higher levels of p21 are correlated with favorable outcomes in patients with breast cancer.

Ferulin C caused cell cycle arrest at the G1/S phase by activating the p21Cip1/Waf1-CDK2 signaling axis. A xenograft model of breast tumor was used in an in vivo study by Dahong, where they assessed the anti-cancer effects of Ferulin C (low dose, 25 mg/kg; median dose, 50 mg/kg; high dose, 100 mg/kg). Their study showed that Ferulin C could block breast tumor cell proliferation in the xenograft model, and this anti-cancer activity correlated with the in vitro results (56).

COUMARINS AND GASTRIC CANCER

Gastric cancer (GC) is among the most prevalent GI tumors globally. Approximately 1 million patients are newly diagnosed with gastric carcinoma each year. Because of its aggressiveness, gastric cancer is the third cause of cancer-related death (57). However, the conventional drugs are limited by unwanted toxicity and adverse side effects due to their poor selectivity for cancer cells compared to normal mammalian cells (58). Consequently, identifying novel therapeutic agents with lower toxicity is needed for more successful management of patients with gastric cancer.

Molecular hybridization is a novel concept in drug development and discovery. It is based on combining two or more biologically active molecules by attaching them together using appropriate covalent bonds. Compared to their individual elements, the hybridized structures show superior or novel biological functions (59).

Nucleotides are nitrogen-containing heterocyclic structures that are basic components of RNA and DNA (60, 61). Because nucleobases play major roles in various cellular processes, nucleotides are often utilized as pharmacophores, especially in
antitumor drugs (62–64). Interestingly, nucleobases can show in vitro cytotoxicity in a variety of human tumor cell lines (64) caused by several mechanisms. The click reaction is an easy synthetic approach to prepare the triazole scaffold (a nitrogen containing heterocyclic compound) frequently used as a linker in pharmaceutical research (65). Furthermore, the use of 1,2,3-triazole is associated with increased solubility (66), improved strength of binding to other biological compounds, and can show synergistic effects on biological functions (67). Considering their specific rigid structure and binding to particular hormone receptors, steroids are a major family of biological compounds, widely used in drug design (68). Modification of the C-16 atom in steroids can be used to attach other moieties, in order to produce tumor-targeted cytotoxic agents (69–73).

Using the molecular hybridization technique, Zhao et al. prepared a group of analogues of the 1,4-disubstituted 1,2,3-triazole-nucleobase, including additional moieties such as steroids, coumarins, or quinolines (74). In their study, a number of these compounds were shown to suppress the cellular proliferation of tumor cells. In this context, compound 20c showed an anti-proliferative activity in SGC-7901 cells (IC50 = 2.28 μM) and MGC-803 cells (IC50 = 1.48 μM) and did not affect healthy non-cancerous cells. Compound 20c may inhibit TGF β1 expression in gastric cancer cell lines, and suppress cellular invasion and migration. Compound 20c could be used as a novel skeleton for therapeutic agents against GC with minimal side effects (74).

ISOIM (isoimperatorin) is a member of the 6,7-furanocoumarin family and is isolated from plants in the umbelliferae family, including Heracleum maximum, Angelica dahurica, Peucedanum ostruthium. Chinese angelica has been frequently utilized in ancient Chinese medicine (75). Isoimperatorin is a secondary plant metabolite with numerous pharmacological properties, such as anti-hypertensive, analgesic, anti-inflammatory, antitumor, antiviral, and antibacterial activity (76–80). In addition, ISOIM can inhibit proliferation in several cancer cell lines, including skin cancer SK-MEL-2, ovarian cancer SK-OV-3, lung cancer A549, breast cancer MCF-7, glioblastoma XF498, and colon cancer HCT-15 (76–81). ISOIM was found to suppress the proliferation of SGC-7901 gastric cancer cells and modify the expression of several anti- and pro-apoptotic proteins (82).

In a study by Yang et al., the pro-apoptotic and anti-proliferation properties of ISOIM in BGC-823 gastric cancer cells were evaluated, along with the potential biological mechanisms (83). The MTT assay measured cellular proliferation, while hematoxylin and eosin staining, acridine orange/ethidium bromide staining, and Hoechst 33258 were employed to assess cell morphology. Flow cytometry assays measured apoptosis and cell cycle status, and the expression level of pro-apoptotic proteins was evaluated using Western blotting. It was found that ISOIM could suppress proliferation through inducing cell cycle arrest at the G2/M stage. Moreover, ISOIM induced apoptosis through increased expression of Bax (Bcl-2-associated X) and reduced expression of Bcl-2, thus reducing the Bcl-2/Bax ratio compared to the control cells.

Furthermore, the administration of ISOIM led to cytochrome c release from the mitochondria into the cytosol, along with activation of caspase-3, indicating that apoptosis was stimulated by the mitochondrial pathway in BGC-823 cells (83).

Perumalsamy et al. performed an in silico and in vitro study to investigate whether SSBC (styrene substituted biscoumarin) could induce apoptosis and inhibit proliferation of tumor cells (84). The MTT assay was used to measure proliferation in gastric cancer (AGS) cell lines in addition to healthy lung cell lines (MRC-5 and L-132). Molecular docking was used to examine the binding between SSBC and Bcl2. Moreover, PASS (spectrum prediction analysis) was used to evaluate the biological effects, and ADME was used to measure pharmacological properties and drug likeness. DAPI/PI staining, Hoechst staining, and FACS were employed to evaluate SSBC-induced apoptosis in AGS cells. Western blotting and Quantitative Real-Time Reverse Transcription (qRT-PCR) were used to investigate the mechanisms of apoptosis induction. The IC50 values of SSBC for MRC-5 and L-132 cells were 285 and 268 μg/mL, respectively, while for AGS cells the IC50 was 4.56 μg/mL. In silico analysis predicted that SSBC could bind to the BH3 domain of anti-apoptotic proteins, which could then activate apoptosis and cell death. Using ADME predicted that SSBC had a high binding affinity (~99.08%) and a high absorption rate (~95.57%) in the small intestine. The PASS software suggested that SSBC could affect the expression level of several proteins involved in apoptosis. Western blotting, FACS, DAPI/PI staining, qRT-PCR, and Hoechst staining confirmed apoptosis in AGS cells. SSBC may be particularly effective to trigger apoptosis mediated by the intrinsic pathway, and thus in vivo studies and human clinical trials for GC may be justified (84).

Farnesiferol C (FC) is a member of the coumarin family, belonging to the sesquiterpene group, which is routinely extracted from Ferula szovitziana DC roots (85). Apioiaceae (genus Ferula) are plants that are widely distributed in Northern Africa, Central Asia, and the Mediterranean region (86), and these plants are a rich source of natural compounds, including coumarins and sesquiterpenes (87). FC has a variety of biological functions, including anti-tumor activity in vitro and in vivo, reducing the formation of new blood vessels, and also shows activity against Leishmania infection (88). Nevertheless, FC has poor solubility, and relatively low bioavailability both in vivo and in vitro, which hinders its potential therapeutic applications (89). However, recent studies have shown that FC solubility and antiproliferative effects against cancer cells may be improved by incorporation into dendrosome nanoparticles. Dendrosomes are spherical, covalently linked, degradable, neutral, and self-assembled nanoparticles which have become popular for their ability to deliver herbal agents and genes into various cell lines (89–93).

Aas et al. performed a study to determine the potential antitumor effects on AGS cells of DFC (dendrosomal farnesiferol C) (94). RT-PCR was used to assess the Bax/Bcl-2 ratio in order to determine apoptosis. MTT assay was used to evaluate the antiproliferative effects of DFC. DFC inhibited AGS proliferation in a time- and dose-dependent manner, compared
to free FC. DFC increased the Bcl-2/Bax expression ratio in AGS cells. Taken together, the nano-formulated farnesiferol C may be useful in tumor-targeted therapy (94).

Table 1 lists some studies describing the anti-gastric cancer effects of coumarins.

COUMARINS AND COLON CANCER

Colon cancer is a leading cause of morbidity and mortality throughout the world (106). It has the second highest incidence and cause of cancer-associated death. More than 1.8 million new cases and 881,000 deaths occurred in 2018 globally (57). The mortality of colon cancer has fallen over recent decades due to advances in both treatment and early detection; however, the five-year survival rates remain low at advanced or metastatic stages (106). At an early stage, the 5-year survival rate is nearly 90%, but the survival rate falls to near 10% when the disease is advanced. Therefore, better understanding of the molecular pathway of colon cancer progression is a serious need (107).

HMGA2 (high mobility group AT-hook 2) belongs to the high mobility group family of proteins. It is a non-histone chromatin protein with three AT-hook domains capable of binding in the minor groove of AT-rich DNA sequences (108). HMGA2 acts as an architectural transcription factor due to its ability to assemble the nucleoprotein structure leading either to transcription enhancement or repression (109). The expression of HMGA2 is higher during embryogenesis, whereas in adult tissues its expression is zero or very low (110). HMGA2 has an important function in metastasis and regulates the epithelial-mesenchymal transition (EMT) (107). The EMT is where epithelial cells transform into mesenchymal cells, and is essential for both tumor progression and embryonic development. The EMT results in elevated invasion, migration, or unrestricted proliferation (111, 112). Besides, HMGA2 is commonly upregulated in many types of cancer, and was correlated with poor prognosis and lower survival rates in colon cancer (113).

Oxidative stress modulates many cellular processes, and provides a favorable environment for cancer cells to progress and survive. Many studies have shown the importance of oxidative stress or oxidative damage in cancer initiation and progression (114). Furthermore, oxidative stress-resistance is a critical adaptive response that allows cancer cells to develop resistance to chemotherapy drugs, resulting in chemoresistance and cancer recurrence (115, 116). On the other hand, several anti-cancer treatments are based on the production of excessive reactive oxygen species (ROS) or the abrogation of antioxidant pathways to kill cancer cells (117–120).

Chen et al. studied the involvement of HMGA2 in the modulation of oxidative stress using luciferase reporter assays (121). In addition, they studied dicoumarol (DIC), a coumarin derivative involved in redox modulation that has some anti-cancer effects. It was found that DIC could trigger apoptosis and inhibit the migration of colon cancer cells that over-expressed HMGA2. DIC could also promote the anti-cancer effect of 5-FU in colony formation assays. Overall, their findings provided a novel understanding of the molecular function of HMGA2, and suggested a possible therapeutic application of DIC to prevent progression in colon cancer cells that over-express HMGA2 (121).

| Coumarin compound | Dose | Mechanisms | Model | Cell line | Ref |
|-------------------|------|------------|-------|-----------|-----|
| Steroid/coumarin/quinoline mixtures | 1.48 µM, 2.28 µM | Reduced expression of TGF β1, inhibited invasion and migration | In vitro | SGC-7901, MGC-803 | (74) |
| Styrene substituted biscoumarin (SSBC) | 4-64 µg/mL | Induced apoptosis through intrinsic pathway | In vitro | AGS | (84) |
| Isocoumarin (3,4,7) Esculetin | 0.05-2 mM | Anti-proliferative and pro-apoptotic effects | In vitro | BGC-823 | (83) |
| 2′-Z auraptene A | 1, 2, 4 µM | Anti-proliferative and pro-apoptotic effects | In vitro | MGC-803 | (95) |
| Esculetin | 850 µM | Inhibited proliferation, induced apoptosis through IGF-1/PI3K/Akt mitochondrial pathway | In vitro | MGC-803 | (96) |
| Isocoumarin 3,4,7 | 12.5, 25, 50 µM | Apoptosis via cyclophilin D-induced mitochondrial permeability transition pore, increased ROS | In vitro | MGC80 | (97) |
| Dendrosomal farnesiferol C (DFC) | 80 µM | Inhibited proliferation, increased Bax/Bcl-2 ratio | In vitro | MGC-803, BGC-82 | (98) |
| 3-Bromoacetyl coumarin | IC50 = 29 nM | Significant cytotoxicity | In vitro | NUGC | (99) |
| 7-Diethylamino-3(20-benzoxazolyl)-coumarin (DBC) | 30, 100, 1000, 3000 nM | Induced caspase-dependent apoptosis, reduced expression of anti-apoptotic genes | In vitro | SNU-620, SNU-620-5FU | (100) |
| Novel coumarin (compound 3d) | 2.69 ± 0.60 µg/mL | Acted as telomerase inhibitor, bound to telomerase active site | In vitro | SGC-7901 | (101) |
| Xanthoxyletin | 200, 400 µM | Increased ROS | In vitro | SGC-7901 | (102) |
| 6,7-Dihydroxy derivative | 100, 400 µM | Antiproliferative activity | In vitro | TGBc11TKB | (103) |
| Coumarin | — — — — — | Quenched organic hydroperoxides and hydrogen peroxide | In vitro | — | (104) |
| Coumarin (C), 7-hydroxycoumarin (7-OH-C) | IC50 = 1.59-3.57 mM for C, 0.88-2.69 mM for 7-OH-C | Inhibited cell proliferation | In vitro | — | (105) |
Sulfonamides act as inhibitors of carbonic anhydrase (CA) enzymes, and show antitumor, antiepileptic, antiglaucoma, and diuretic properties (122–127). In addition, coumarin sulfonamides, and their derivatives act as selective inhibitors for two carbonic anhydrase isoforms, including CA XII and CA IX (128–132).

Zengin Kurt and his colleagues synthesized and characterized 27 novel compounds divided into three series: (1) sulfonamide-based imines (6a-6i); (2) coumarin-based aldehydes (7a-7i); and (3) coumarin-sulfonamide hybrid molecules (8a-8i), which were characterized by IR, NMR, etc. (48). These compounds were tested on different CA isoforms, including CA (I, II, IX, XII), to measure the degree of inhibition. 4-(((2-((1-(3-(2-oxo-2H-chromen-7-yl)oxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)naphthalen-1-yl)methylene)aminomethyl)benzensulfonamide (8i) was the best CA IX inhibitor with a Ki of 45.5 nM. Furthermore, 8i could also selectively inhibit colon cancer cell (HT-29) proliferation by directly targeting CA XII and CA IX (48).

Cancer treatment is affected by genetic mutations occurring in the tumor, and the survival rate in advanced or metastatic stages remains poor. For instance, one of the clinical challenges for EGFR targeted therapies is the KRAS gene mutation, so alternative approaches are needed to reduce failure in colon cancer therapy. One of these approaches may involve coumarin or its derivatives (biological or synthetic). Lin et al. synthesized five coumarin derivatives; nitro-substituted, dimethoxy-substituted, and trifluoromethyl-substituted at various locations (133). According to their findings, one nitro-coumarin derivative, 5,7-dimethoxy-4-methyl-6-nitro-chromen-2-one, had the highest cytotoxicity against colon cancer cells and triggered apoptosis. This compound could also inhibit long-term and short-term proliferation, and reduced colon cancer cell migration. It was effective against colon cancer cells with either mutant or wild-type KRAS genes (133).

Table 2 lists some studies on the anti-colon cancer effects of coumarins.

Coumarins and Pancreatic Cancer

More than 300,000 patients die from pancreatic cancer every year (159, 160). Pancreatic ductal adenocarcinoma (PDAC) is the most lethal and aggressive type of pancreatic cancer with less than 5% of patients surviving for five years (161). The CMGC kinome group includes tyrosine-(Y)-phosphorylation-regulated kinases (DYRKs), which carry out serine/threonine phosphorylation and tyrosine phosphorylation (162). Due to kinases (DYRKs), which carry out serine/threonine phosphorylation and tyrosine phosphorylation (162). Due to its location on human chromosome 21q22.2, which covers the Down syndrome critical region (DSCR), DYRK1A has received much interest amongst other DYRKs (163, 164). DYRK1A has been described as a double-edged kinase, because it can either act as a tumor suppressor or as an oncogene depending on the substrates and cellular environment (163). DYRK1A over-expression leads to cell cycle disturbance, cancer progression, and increased aggressiveness, so that DYRK1A could be an appealing drug target in chemotherapy. Over-expression of DYRK1A disrupts the cell cycle by phosphorylating components of the cell cycle machinery, as well as increasing the expression of Bcl-XL (anti-apoptotic protein) and phosphorylating caspase 9 at threonine residue 125 (165–167). A recent study revealed that DYRKY1A kinase could play an oncogenic role in NSCLC (non-small-cell lung cancer) (113), glioma, and myeloid leukemia (108). Reducing the activity of DYRK1A in cancer cells might be a new way to attack cancers that have developed an innate resistance to pro-apoptotic stimuli (165). For some time, the involvement of DYRK1A in PDAC was not understood (168). Recently, it was discovered that DYRK1A is elevated in PDAC and has a pro-tumorigenic effect. Moreover, the expression of DYRK1A at protein and gene levels in human pancreatic tumors are both significantly increased (168). Upregulation of c-MET is another frequent alteration in PDAC. Moreover, Sprouty2 (SPRY2) is a DYRK1A substrate, which upregulates c-MET, and might increase oncogenesis (168).

Eight different isopentenyl-substituted compounds were isolated from Glycyrrhiza uralensis Fisch. These were, four coumarins, three flavonoids, and one benzofuran (169). Licocoumarone (LC), one of the isolated compounds, inhibited DYRK1A with an IC50 value of 12.56 μM. According to molecular docking studies, LC filled the DYRK1A pocket and generated hydrophobic contacts and hydrogen bonds with the DYRK1A amino acids. The binding of LC to DYRK1A was confirmed using drug affinity responsive target stability (DARTS) and microscale thermophoresis (MST) approaches. LC showed cytotoxicity against BxPC-3 cells that over-expressed DYRK1A with an IC50 of 50.77 μM. LC also lowered the quantity of c-MET protein, and could play a role in new pancreatic cancer treatments (169).

Fu et al. prepared paclitaxel PEG-PLGA nanoparticles emulsified in d-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS) called PTX-PEG-PLGA-NP, and evaluated its effects on apoptosis in pancreatic cancer cell line (MIAPACA-2) (170). PTX-PEG-PLGA-NP was prepared in a single step utilizing TPGS as an emulsifier, and had a high drug loading. The physical and chemical properties, such as in vitro release and stability, were assessed, and the drug loading and particle size were used to optimize the formulation. The cellular uptake of fluorescein coumarin 6 (C6) loaded PEG-PLGA-NP by MIAPACA-2 cells was visualized using fluorescence microscopy, and flow cytometry. The MTT assay was used to measure proliferation and apoptosis of MIAPACA-2 cells following exposure to PTX-PEG-PLGA-NP. The nanoparticles had a 90.26% PTX entrapment efficiency, a 10.13% PTX loading, an average particle size of 92.33 nm, and a zeta potential of +10.48 mV. The nano preparation showed 25.9% drug release in 4 hours compared to 98.5% for Taxol for injection, thus showing a sustained-release effect. Cell uptake tests revealed that MIAPACA-2 cells steadily took up C6-PEG-PLGA-NP over time. The inhibition of MIAPACA-2 cell proliferation was not significantly different in the PTX-PEG-PLGA-NP group compared to the PTX group, according to MTT data. Flow cytometry revealed that PTX-PEG-PLGA-NP caused more apoptosis in MIAPACA-2 cells compared to PTX. The TPGS emulsification process is simple to use and environmentally friendly. The nanoparticles might be employed for pancreatic cancer treatment in the future.
**TABLE 2 |** Anti-colon cancer effects of coumarins.

| Coumarin compound | Dose | Mechanisms | Model | Cell line | Ref |
|-------------------|------|------------|-------|-----------|-----|
| Furancoumarin     | 100 µM | Anti cancer effects | *in vitro* | HCT116 | (134) |
| Dicoumarol (DIC)  | 10 µM | Inhibited proliferation in HMGA2 overexpressing cells | *in vitro* | DLD-1 | (121) |
| Butyrate/GC combination | 10 µM GC + 2mM butyrate | Increased apoptosis | *in vitro* | HCT116 | (135) |
| Coumarin 8a       | —— | Inhibited proliferation by targeting CA XII and CA IX | *in vitro*, *in vivo* | HT-29 | (48) |
| Coumarin derivatives | —— | Inhibited proliferation | *in vitro* | LoVo | (136) |
| Copper-redox cycling by coumarin-di(2-picolyl)amine hybrid molecule | 50 µM | Pro-oxidant, inhibited proliferation. | *in vitro* | HCT116 | (137) |
| Nitro-coumarin derivative, 5,7-dimethoxy-4-methyl-6-nitro-chromen-2-one Poly(DGU-BDT) nanoparticles | 100 µg/mL | Activated apoptosis pathways | *in vitro* | HeLa | (133) |
| Coumarin derivatives (6, 11, 13, 19, 21, 25, 39) | 30, 100, 300 µM | Inhibited CA IX and XII in hypoxia, another unidentified target in normoxia | *in vitro* | HT-29 | (139) |
| Coumarin | —— | Cytotoxicity, high cellular uptake | *in vitro* | HeLa | (138) |
| Coumarin-6-sulfonamide derivatives (4a, b, 8a−d, 11a−d, 13a, b, and 15a−c) | 8a (IC50 ¼ 8.5 3 ± 0.72), 11a (IC50 ¼ 10.12 ± 0.90), 8d 16.02 ± 1.32, 11d 16.06 ± 1.28 | Activated apoptosis pathways | *in vitro* | HCT116 | (140) |
| Coumarin-6 (TK-MS/DOX) | IC50 = 1.6 ± 0.48 mg/mL | Cytotoxicity | *in vitro* | HCT116 | (142) |
| Columbianadin (CBN) | 25, 50 µM | Induced apoptosis and necroptosis | *in vitro* | Caco-2 | (141) |
| coumarin Compounds 2, 3−15, 17−18, and 20−23 | 50 µM | Cytotoxicity | *in vitro* | HCT116 | (143) |
| Coumarin compound 7a | IC50 = 4.8 ± 0.18 µg.mL-1 | Cytotoxicity | *in vitro* | HCT116 | (144) |
| Coumarins (clausarin, dentatin, nordentatin, xanthoxyletin) | —— | Cytotoxicity | *in vitro* | HCT116 | (145) |
| Coumarins (mammeisin, mammein) | OCOLO205 (9.7-10.7 µM), KM12 (10.9-12.0 µM), IC50 = 532 nM | Inhibited proliferation | *in vitro* | COLO205, KM12 | (147) |
| Fused tricyclic coumarin sulfonate derivatives | 40, 80 µM | Inhibited cyclooxygenase-2 (COX-2) enzyme | *in vitro* | HT-29 | (148) |
| Coumarin compounds | IC50 = 0.01− 2.8 µM | Cytotoxicity | *in vitro* | HCT116 | (150) |
| Coumarin compounds | —— | Cytotoxicity | *in vitro* | HT-29 | (151) |
| Esculetin | IC50 = 55 µg/mL | Induced apoptosis, activated mitogen-activated protein kinases; specific inhibitors of these kinases protected cells | *in vitro* | HT-29 | (152) |
| 3-(1H-benzo[d]imidazol-2-yl)-7-(substituted amino)-2H-chromen-2-one (Compound 8) | 10 µM | Anticancer activity | *in vitro* | HCT-116, HCT-15 | (153) |
| Aesculetin | 20,40,80 µM | Inhibited proliferation | *in vitro* | HCT116, HCT15, HCT15, DLD1 | (154) |
| SN38-P-II, SN38-P-IV | 40 mg/kg, IC50 = 15 to 90 ng/mL | Anti-tumor activity | *in vivo* | HT-29, HCT116 | (155) |
| Furo[3,2-c]coumarin derivatives | IC50 = 9 µM, 8 µM | Inhibited proliferation | *in vitro* | HCT-15 | (156) |
| Esculetin | —— | Induced apoptosis (ER stress response) | *in vitro* | HT-29 | (157) |
| (3E)-3-(4-Methylbenzylidene)-3,4-di hydro-2H-chromen-2-one (MBDC) | IC50 = 15.6 µg/ml | Cytotoxicity | *in vitro* | HT-29 | (158) |
**Table 3** lists some studies on the anti-pancreatic cancer effects of coumarins.

**Coumarins and Hepatocellular Carcinoma**

Over 900,000 new cases of hepatocellular carcinoma (HCC) are diagnosed annually worldwide, and it is the third main cause of cancer-associated death (186, 187). The stage of HCC at diagnosis is strongly associated with prognosis (187). Traditional chemotherapy agents for advanced-stage HCC are often ineffective. The development of new surgical approaches for HCC have improved the 5-year survival rate (188). If HCC is resistant to chemo-radiotherapy, it can spread to the lungs, brain, adrenal glands, and lymph nodes (188). Researchers are trying to understand more about the origin and progression of HCC, and the relevant molecular mechanisms (189–191), but more studies are needed to discover new agents for improved HCC treatment. Misfolded proteins and damaged organelles are destroyed within the cell by autophagy and lysosomal cleavage (192). Autophagy is essential for cell survival (193, 194). Many natural compounds have been found to have anti-cancer effects by promoting autophagy (195, 196). Cui et al. studied HepG2 and MHCC97 (two human HCC cell lines) treated with hydroxypyridinone-coumarin (HPC) *in vitro* (197). The MTT cytotoxicity test assessed proliferation and viability with and without HPC treatment. Cell autophagosomes were tagged with GFP-LC3 and visualized with confocal fluorescence microscopy, and Western blotting measured protein expression. HPC treatment reduced HepG2 cell proliferation by 29% and MHCC97 proliferation by 36%. HPC treatment increased expression of Atg-3, Atg5, LC3-II (LC3-phosphatidylethanolamine conjugate), and beclin-1, but decreased protein expression of Akt and p62. HPC treatment increased autophagy in MHCC97 and HepG2 cells as shown by GFP-LC3B fluorescence labeling. HPC also induced phosphorylation of ERK1/2 and led to Akt pathway down-regulation (197).

The hydrazide-hydrazine molecular structure is a new scaffold in medicinal chemistry that can inhibit both α- and β-glucosidase enzymes and potentially show anti-cancer activity (184, 198–206). The potential mechanisms of this are fourfold. Firstly, the hydrazide-hydrazine moiety is a metal chelator that can remove the catalytic zinc ion from metalloenzymes (207, 208); Secondly, it can form stable hydrogen bonds to its targets. Thirdly, its molecular structure includes an amino group, which can serve as a stand-in for aza-substituted amino acids. Fourthly the keto-enol tautomerization (E- and Z-forms) may orient and fix the conjugated hydrophobic substituent into the protein binding pocket via the best fit configuration (209). The formation of molecular hybrids between coumarins and hydrazide-hydrazone moieties might lead to novel anti-cancer compounds. Nasr and colleagues evaluated a new series of coumarin hydrazide-hydrazone derivatives, for their activity against leukemia (CCRF), resistant pancreatic carcinoma (Panc-1), and hepatocellular carcinoma (HepG2) cancer cells *in vitro* (175). One of the novel coumarin hydrazide-hydrazone hybrids, bromocoumarin hydrazide-hydrazone derivative (BCHHD) 11b, demonstrated outstanding anti-cancer activity against cancer cells. Furthermore, BCHHD 11b triggered apoptosis by activating caspases 3/7, and led to inhibition of cell metabolism. Inhibition of CYP3A4 and GST led to cell death in a 11b dose-dependent manner. Furthermore, microarray evaluation revealed up-regulation and down-regulation of genes associated with tumor growth, cell cycle, and apoptosis. Moreover, BCHHD 11b could be not only useful in chemotherapy, but also could be used as a transporter for radioactive Tc in vivo, as a radiopharmaceutical imaging agent for cancer treatment (170, 175).

**Table 4** lists some studies on anti-HCC cancer effects of coumarins.

**Coumarin and Esophageal Cancer**

The most prevalent type of esophageal cancer is esophageal squamous cell carcinoma (ESCC). The rate of ESCC incidence varies by country, but the highest rates are seen in regions within the esophageal cancer belt, which runs from North of Iran to North and Central China (225). The early stages of ESCC show only vague symptoms leading to delayed diagnosis, and the presence of drug-resistant cells has a detrimental effect on the results of standard chemotheray regimens (226, 227). Recently, there has been a focus on cancer stem cells (CSCs) as a target for more effective cancer therapy, because it has been found that CSCs are largely responsible for recurrence, therapy resistance, and metastasis in several human cancer types (228). Various molecular markers are used to identify CSCs in different human malignancies. For instance, CSCs are positive for CD15, CD44, CD90, CXCR4, and CD133 antigens in ESCC (229–231).

Auraptene (AUR), or 7-geranylxycooumarin, is a naturally occurring prenyloxycoumarin found in plants within the *Apiaceae* and *Rutaceae* families. AUR has been found to have different biological benefits such as, antioxidant, anti-inflammatory, anti-protozoal, anti-fungal, antibacterial, and immune system boosting activities (232). AUR supplements have been tested in animal cancer models, and it was shown that they had chemopreventive effects in GI, liver, skin, prostate, and breast cancer (233–242). The mechanisms of AUR chemoprevention include inhibition of lipid peroxidation, induction of glutathione S transferase activity, regulation of inflammation, and inhibition of superoxide generation (233, 235, 236, 242). Furthermore, researchers have shown that AUR has anti-cancer effects in *vitro*, and can inhibit the proliferation of breast and renal cancer cell lines, and can induce apoptosis in gastric, colon cancer, and leukemia cells. Some studies have shown the anti-cancer activity of AUR against colon CSCs, and AUR could inhibit the recurrence of colon tumors (243–248).

Saboor-Maleki and his colleagues investigated the anti-cancer activity of AUR on ESCC cells and CSCs looking at specific markers (249). They used the KYSE30 ESCC cell line to examine the effects of AUR and combinations with 5-fluorouracil, cisplatin, and paclitaxel. Furthermore, they used qRT-PCR to evaluate the expression of p21 and p53 (two tumor suppressor genes), BMI-1 (B cell-specific Moloney murine leukemia virus integration site 1), and CD44 (cluster of differentiation 44). Their findings revealed that AUR...
TABLE 3 | Anti-pancreatic cancer effects of coumarins.

| Coumarin compound | Dose | Mechanisms | Model | Cell line | Ref |
|-------------------|------|------------|-------|-----------|-----|
| Licocoumarone      | 25 µM, 50 µM | Inhibited DYRK1A and cell proliferation, induced apoptosis | in vitro | Human PDAC cell line BxPC-3 | (169) |
| Scopoletin (SPL)   | Animals: 1 mg/kg bw/day | Decreased activating transcription factor 6 (ATF6) and protein kinase RNA-like endoplasmic reticulum kinase (PERK) in β-cells; reduced expression of eukaryotic initiation factor2α, X-box binding protein 1, C/EBP homologous protein, ATF4 | in vitro | Rat insulinoma 5f (RIN5f) cells, Sprague Dawley rats | (171) |
| Coumarin−triazole  | | | in vitro | Porcine pancreatic lipase (PPL) | (172) |
| Furocoumarin (psoralen) | | Selective cytotoxicity attributed to inhibition of mtkV1.3 | in vitro | B16F10 cells | (173) |
| Isoprenylated coumarins | 25 µM | Compound 6 showed highest cytotoxicity with an LC50 of 4 µM, induced apoptosis following a 24-h incubation | in vitro | Panc1 | (174) |
| Bromocoumarin hydrazide-hydrazone derivative (BCHHD) | 50 µM | Induced apoptosis by caspase 3/7 activation, inhibited CYP3A4 and GST in a dose-dependent manner, induced cytotoxicity | in vitro | Panc1 | (175) |
| Daphnetin (7, 8-dihydroxycoumarin) | 1, 10, 20, 40 µM | Pre-treatment with daphnetin increased glucose stimulated insulin secretion, decreased lipid peroxidation markers, increased antioxidant enzymes in STZ-induced INS-1 cells, inhibited apoptosis by increasing Bcl-2 protein, down-regulated Bax and NF-κB protein levels | in vitro | INS-1 | (176) |
| Derivatives of 9-amlycoumarin (6a-f and 7a-f) Flourescein coumarin 6 (C6) | (0–100 µM)CC-50 | Inhibited proliferation, induced apoptosis | in vitro | (BxPC3) | (177) |
| Geranylgeranyl ether coumarin derivative 9 | 6.25 µM | Induced apoptosis and morphological changes within 24 h | in vitro | Panc-1 | (178) |
| Esculetin | 100 µM | Inhibited proliferation, induced apoptosis | in vitro | Panc-1 | (179) |
| FurancoumarinBergamottin | Bergamottin 25 µM. | Inhibited membrane blebbing, cell shrinkage, organelle disintegration in Panc-1 cells. | in vitro | Panc-1 | (180) |
| 4-Methylumbelliferone (MU) | 0–100 µM | 7-Hydroxy group was critical for inhibition of HA synthesis, two hydroxyl groups, 5, 7 or 6, 7 positions, were more effective | in vitro | KP1-NL | (181) |
| 17 synthetic coumarins | 100 µM | Six compounds were shown to have poor activity against Panc-1. Two trifluoromethylphenyl compounds 33 and 34 were effective against three cancer cell lines. The position of the trifluoromethyl substituent on the phenyl ring (meta vs. para) was associated with selective activity against MIA and PaCa-2 cells | in vitro | Panc-1, MIA PaCa-2, Capan-1 | (182) |
| 7-Hydroxy-2-oxo-2H-chromene-3-carboxylic acid (3-phenylpropylamide 2c) Derivatives of 6-brominated coumarin hydrazide-hydrazone (BCHHDs) | PC50 = 0.44 µM | Inhibited Panc-1 colony formation and migration in a concentration-dependent manner, compound 2c was lead structure against pancreatic cancer. | in vitro | Panc-1 | (183) |
| | IC50: 3.60-6.50 µM | Activated caspase 3/7, induced apoptosis in resistant Panc-1 cells. Microarray analysis showed that BCHHD 7c induced apoptosis and cell cycle arrest (G2/M), and up-regulated CDKN1A, DDIT4, GDF-15 genes, and down-regulated CDC2, CDC20, CDK2 genes | in vitro | Panc-1 | (184) |
| Daphnetin | 4 mg/kg body weight IP 30 min before the injection of sodium taurocholate. | Daphnetin decreased serum alanine transaminase and creatinine (CR) levels, increased superoxide dismutase (SCD) activity, lowered apoptosis and neutrophil infiltration of pancreatic tissues in rats. Daphnetin reduced pro-inflammatory cytokines and increased anti-inflammatory cytokines in rat SAP. Decreased expression of TLR4 and suppressed NF-κB signaling pathway. | in vivo | rat severe acute pancreatitis (SAP) model | (185) |

increased the cytotoxicity of 5-fluorouracil, paclitaxel, and cisplatin in KYSE30 cells, and the maximal effect was seen after 72 hours of AUR treatment, which induced apoptosis. In addition, qRT-PCR revealed that p53 and p21 were up-regulated, but BMI-1 and CD44 were down-regulated after AUR treatment. AUR inhibited esophageal cancer stem-like cells by increasing the effects of chemotheraphy, and down-regulating BMI-1 and CD44 (249).
TABLE 4 | Anti-hepatocellular cancer effects of coumarins.

| Coumarin compound                  | Dose       | Mechanisms                                                                 | Model   | Cell line | Ref |
|------------------------------------|------------|----------------------------------------------------------------------------|---------|-----------|-----|
| Hydroxypropyridinone-coumarin      | 2 µM       | Induced autophagy, inhibited proliferation, activated ERK1/2, down-regulated the Akt pathway | In vitro | MHCC97    |     |
| Furancoumarin                      | 100 µM     | Anti cancer effect                                                          | In vitro | HepG2     |     |
| Coumarin-3-carboxylic acid         | 0–1000 µM  | Inhibited DNA synthesis not by intercalation. Ames tests showed that all the tested agents or phase I metabolites were non-mutagenic | In vitro | CHANG     |     |
| Esculetin                          | 2.24 mM    | Triggered mitochondrial caspase-dependent apoptosis                        | In vivo  | Hepa1-6   |     |
| Osthole                            | 161.4 mM   | Inhibited HCC growth in vivo and in vitro, induced apoptosis by repressing NF-κB, increased expression of apoptosis-related genes. | In vivo  | Hepa1-6   |     |
| 4-Hydroxy-3-nitro-coumarin         | 0, 20, 40, 80 µM for 4 h or 24 h | Inhibited proliferation                                                   | In vitro | Hepa2     |     |
| Ligand silver + 4-oxy-3-nitro-coumarin-bis (phenanthonine) | IC50 at 4 h = 80 µM and at 24 h | [Cu(cdoa)(phen)2] inhibited proliferation more than the parent ligand [CdoaH2], phen, or the simple salt. | In vitro | Hepa2     |     |
| Coumarin-dioxy-acetic acid (cdoa) copper-coumarin-dioxyacetic acetate-phenanthonine [Cu(cdoa) (phen)2] | Novel synthetic coumarins | Inhibited expression of NF-κB targeted genes | In vitro | Hep2G2 |     |
| Natural coumarin                   | 4.9 µM     | Increased necrosis                                                          | In vitro | Hep2G2    |     |
| Clausarin, dentatin, nortalentin, xantoxyltin | IC50 (µM) | Coumarin had the highest selective cytotoxicity. Xantoxyltin caused apoptosis and lowest necrosis in HepG2 cells after 24 h | In vitro | Hep2G2    |     |
| Coumarin-triazole hybrid           | IC50 = 0.80 µM | Inhibited proliferation                                                      | In vitro | Hep2G2   |     |
| Thiazolopyrazolyl coumarin derivatives | IC50 = 5.4–10.7 µM | Anticancer activity                                                          | In vitro | Hep2G2    |     |
| Coumarin hybids                    | IC50 = 0.49-3.96 µM | Inhibited proliferation                                                      | In vitro | Hep2G2   |     |
| 7,8-Dihydroxy-3-(4-nitrophenyl) coumarin 7-Hydroxy-6,8-dimethoxy-2H-1-benzyopyran-2-one (isofraxidin) | IC50 = 17.65 µM | Cell cycle arrest at S phase, loss of mitochondrial membrane potential, mediated ROS-independent cell death | In vitro | Hep2G2 |     |
| Jugalanside C extracted from bark of Juglans mandshurica | IC50 = 70.9 μM | Inhibited invasion without influencing proliferation or attachment. Inhibited TPA-induced matrix metalloproteinase-7 (MMP-7) at both protein and mRNA levels. More effective at low cell density than at high density. Inhibited phosphorylation of ERK1/2, without affecting NF-κB nuclear translocation, activator protein-1 (AP-1) DNA binding activity, or degradation of IkB. | In vitro | Huh-7, Hep2G2 |     |
| 7-OH-4-Methylcoumarin              | IC50 = 356 µM | Inhibited proliferation in a dose-dependent manner. Reversed malignant phenotype and caused re-differentiation. | In vitro | SMCC-7721 |     |

Osthole (7-methoxy-8-(3-methyl-2-butenyl)-2H-1-benzyopyran-2-one) has the chemical formula C15H16O3, and is a biologically active coumarin compound isolated from Fructus cnidii, a herb used in traditional Chinese medicine to manage rheumatic pain, lumbar pain, and impotence (250, 251). Earlier studies have shown that osthole has various medical properties, including vasodilation, anti-osteoporosis, anti-inflammation, anti-allergy, and anti-seizure activity (252–257). In addition, osthole can trigger cellular apoptosis and suppress proliferation and metastasis in tumor cells, and may inhibit tumorigenesis (258–260).

In a study by Zhu et al., the proliferation of ESCC cells was suppressed by osthole in a time – and dose-dependent manner (261). Additionally, osthole caused cell cycle arrest at G2/M phase and triggered apoptosis. Moreover, cleaved caspase 9, cleaved PARP1, cleaved caspase3, and BAX were up-regulated, while the expression level of survivin, cyclin B1, PARP1, Bcl-2, and Cdc2, were decreased Osthole increased PTEN expression and decreased p-AKT (phosphorylated AKT) and PI3K, thereby modulating the PTEN-PI3K/AKT signaling pathway. Consequently, osthole may have a role in managing patients suffering from ESCC (261).
CONCLUSIONS

Coumarin compounds have a broad range of biological activity, and consequently for decades many scientists have investigated these compounds, and some have devised new related structures to potentially treat cancer, as well as a plethora of other diseases. Coumarins play a crucial role in numerous biological processes such as antioxidant systems, regulation of cell growth, and chemoprevention from various disorders. Coumarin compounds have anti-cancer activity by regulating cell differentiation, growth, and the immune system responses. Therefore, coumarins can be combined with conventional drugs, to produce novel antitumor treatments with higher efficacy and fewer adverse effects.

Various synthetic methods such as the Knoevenagel, Pechmann, Perkin, Wittig, and Claisen reactions have been used to prepare coumarins as well as a diverse range of derivatives. Thanks to these new molecular manipulation techniques, analogs with more potent activity and a higher therapeutic index have been discovered, even though coumarin itself and some of its natural compounds may show hepatotoxicity, which may limit their clinical use. Recent studies have shown that the antitumor effects of coumarins may be increased by the addition of various substituents to specific areas of the coumarin structure. As a result, this approach has led to the identification of some novel antitumor compounds.

Moreover, both synthetic and natural coumarins have been found to modulate specific signaling pathways, providing mechanistic explanations for their antitumor activity. Coumarin and its derivatives have promising antitumor properties and may result in novel antitumor drug regimens, however further laboratory studies are required before large scale clinical trials can be undertaken.

AUTHOR CONTRIBUTIONS

HM involved to conception, design, statistical analysis and drafting of the manuscript. ZB, SMM, FD, MRM, KM, FA, MA, AR, MC, MT and MRH contributed to data collection and manuscript drafting. All authors contributed to the article and approved the submitted version.

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