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Review

Applications of resveratrol in the treatment of gastrointestinal cancer

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ABSTRACT

Natural product compounds have lately attracted interest in the scientific community as a possible treatment for gastrointestinal (GI) cancer, due to their anti-inflammatory and anticancer properties. There are many preclinical, clinical, and epidemiological studies, suggesting that the consumption of polyphenol compounds, which are abundant in vegetables, grains, fruits, and pulses, may help to prevent various illnesses and disorders from developing, including several GI cancers. The development of GI malignancies follows a well-known path, in which normal gastrointestinal cells acquire abnormalities in their genetic composition, causing the cells to continuously proliferate, and metastasize to other sites, especially the brain and liver. Natural compounds with the ability to affect oncogenic pathways might be possible treatments for GI malignancies, and could easily be tested in clinical trials. Resveratrol is a non-flavonoid polyphenol and a natural stilbene, acting as a phytoestrogen with anti-cancer, cardioprotective, anti-oxidant, and anti-inflammatory properties. Resveratrol has been shown to overcome resistance mechanisms in cancer cells, and when combined with conventional anticancer drugs, could sensitize cancer cells to chemotherapy. Several new resveratrol analogs and nanostructured delivery vehicles with improved anti-GI cancer efficacy, absorption, and pharmacokinetic profiles have already been developed. This present review focuses on the in vitro and in vivo effects of resveratrol on GI cancers, as well as the underlying molecular mechanisms of action.

Abbreviation: ABCB1, ATP Binding Cassette Subfamily B Member 1; ACTA-2, Actin alpha 2; ADM, Acinar-to-ductal metaplasia; ADRB2, Adrenoceptor beta 2; AMPK, AMP-activated protein kinase; ANXA1, Annexin A1; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; BAX, Bcl-2-associated X; CDKs, Cyclin-dependent kinases; COX-2, Cyclooxygenase-2; EMT, Epithelial-mesenchymal transition; ERK, Extracellular signal-regulated kinase; EZH2, Enhancer of zeste homolog 2; FOXO1, Forkhead Box O1; GI, Gastrointestinal; GLUT1, Glucose transporter 1; GSK-3β, Glycogen synthase kinase-3β; HO-1, heme oxygenase-1; IBD, Inflammatory bowel disease; IBS, Irritable bowel syndrome; HA, Hyaluronic acid; HIF1, Hypoxia-inducible factor 1; HO-1, Heme oxygenase-1; IGF-1R, Insulin-like growth factor type 1 receptor; IL6, Interleukin 6; iNOS, Inducible nitric oxide synthase; JAK-STAT, Janus kinase-signal transducer and activator of transcription; Keap1, Kelch-like ECH-associated protein 1; MALAT1, metastasis-associated lung adenocarcinoma transcript 1, Mitogen-activated protein kinase; NF-κB, Nuclear factor kappa-B; NQO1, NAD(P)H: quinone oxidoreductase 1; Nrf2, Nuclear factor erythroid related factor 2; PC, pancreatic cancer; PD-L1, Programmed Death-Ligand 1; ROS, reactive oxygen species; SREBP1, Sterol regulatory element-binding transcription factor 1; TLR, Toll-like receptor; TNF- α, Tumor necrosis factor α; TXN, Thioredoxin; VEGF, Vascular endothelial growth factor; ZEB1, Zinc finger E-box binding homeobox 1.

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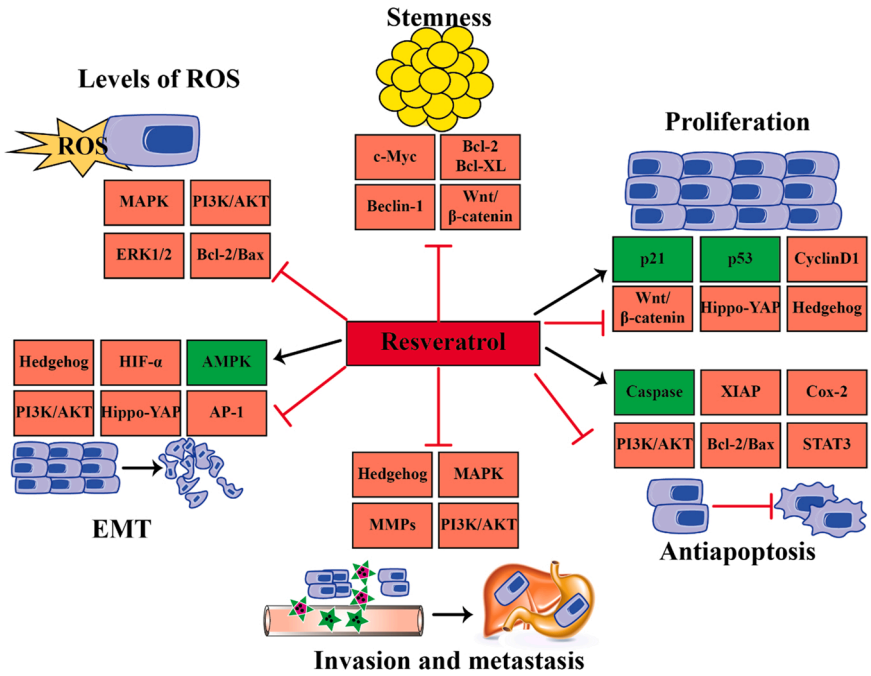

Fig. 1. Some signaling pathways involved in the suppression of biological responses of malignant cancer cells by resveratrol, including stemness, proliferation, EMT progress, migration, antiapoptosis, invasion and ROS levels [70].

1. Introduction

Gastrointestinal malignancies are frequently only discovered at a late stage, due to the absence of distinctive early symptoms. Because of the likely occurrence of metastasis in advanced disease, therapy is a complex procedure that seldom results in a complete cure. Lifestyle and nutrition are two factors that influence the initiation and progression of many cancers. Numerous studies have indicated that eating a healthy, well-balanced diet containing large amounts of vegetables and fruits is able to decrease the risk of cancer [1–3]. As a result, increased attention is being paid to naturally derived compounds that occur in the normal diet, and have been utilized in traditional medicine for centuries.

Polyphenols are organic compounds containing multiple phenolic units, primarily found as phytochemicals, and are divided into five main groups: lignans, phenolic acids, stilbenes, flavonoids, and tannins. Flavonoids are divided into seven sub-classes: flavonols, anthocyanidins, chalcones, isoflavones, flavones, flavanones, and flavan-3-ols. Polyphenols, which are secondary plant metabolites, are generally formed in response to stressful or infectious processes in plants, and act to defend plants against harm from outside [4]. Similarly, polyphenols have been shown to stimulate the natural antioxidant systems in humans by activating a variety of antioxidant pathways and efficiently scavenging free radicals. Moreover, they have the potential to act as a metal chelator in humans, thus removing toxic metals which can produce excessive free radicals and lipid peroxidation [5]. Furthermore, polyphenols have been shown to have a variety of biological benefits, in addition to their antioxidant activity, including anti-cancer, anti-inflammatory, immunomodulatory, anti-diabetic effects, and can be protective towards the GI tract, heart, and nervous system [6,7].

Resveratrol is among the most intensively investigated plant polyphenols. Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a small-molecule stilbene compound, with two aromatic rings in its structure. Resveratrol was initially isolated from the roots of white hellebore *(Veratrum grandiflorum)* in 1940. [8]. It has also been isolated from other sources, such as berries, grapes, and peanuts. [9]. Although studies on the effects of resveratrol on the pathogenesis of several diseases have produced some conflicting results, its chemopreventive properties are noteworthy [10–13]. These chemopreventive properties are linked with its antioxidant, anti-inflammatory and antiangiogenic effects [14,15]. The ability of resveratrol to inhibit cell proliferation, target several molecular pathways, and induce apoptosis in solid tumors has been shown in recent publications [14,16]. The primary goal of the current review is to discuss recent research on the pharmacological effects of resveratrol in human GI cancers.

2. Resveratrol: Potential, bioavailability and mechanisms of action in cancer therapy

Stilbenoids are natural phenolic compounds, largely acting as phytoalexins, which are synthesized in plants to preserve them from fungal infections and environmental toxins, while also inhibiting pathogen activity [17]. The most intensively researched stilbenoid, resveratrol (3,5,4′-trihydroxy-trans-stilbene; resveratrol, Fig. 1), is found in foodstuffs such as grape skin, blueberries, peanuts, and raspberries [18]. The Japanese scientist Michio Takaoka from Imperial University of Hokkaido, first isolated resveratrol from *Veratrum grandiflorum* in 1940 [19]. Its structure contains two phenolic rings attached to each other through a double styrene bond. This double bond can undergo stereoisomerization, and hence two isomeric forms (*cis* and *trans*) exist, with the *trans* isomer predominating in comparison to the *cis* isomer [20]. However, another study showed that the *cis* isomer was a better inhibitor of tumor cells [21], so there is some evidence that the isomerization of this molecule affects the bioactivity. The use of pure resveratrol as a nutraceutical is limited because of its low oral bioavailability, poor water solubility (<0.05 mg/mL), and pronounced chemical instability [22,23]. When resveratrol was consumed orally, about 75 % was eventually absorbed (25 mg oral dose) [24,25], but it is questionable if this rate would be the same at higher doses. The absorption or uptake of resveratrol by different types of cells has been reported in previous studies [26–29]. Despite its high absorption, poor bioavailability was observed [25]. We can detect resveratrol in the bloodstream 30–60 min after ingestion, showing it is rapidly absorbed from the GI tract [24,25]. Resveratrol is rapidly metabolized by sulfation and glucuronidation in the small intestine, and in the large intestine these compounds can be metabolized by the gut microbiota to generate dihydroresveratrol, lunularin, and 3,4'-dihydroxy-trans-stilbene. Furthermore, the effect of

circadian rhythms on its bioavailability has also been proposed [30], as well as the effect of the type of meal containing resveratrol [31]. With this in mind, chronopharmacokinetic studies have been proposed to identify the ideal time for taking a drug [32]. Accordingly, it has been found that resveratrol has higher bioavailability when taken in the morning [30]. Vaz-da-Silva et al. asked whether a high-fat diet consumed along with 400 mg of resveratrol may alter the bioavailability [33], and reported that the overall bioavailability was not markedly changed, although resveratrol absorption was delayed when consumed with food, in comparison with fasting.

Emerging evidence has revealed that resveratrol can be beneficial in several diseases, especially cancers, including prostate [34], colorectal [35], breast [36], and lung [37]. Moreover, it has been suggested that resveratrol could exert its antiproliferative effects via cell cycle arrest [38], apoptosis induction [39], metastasis inhibition [40], and reversing drug resistance [40].

As reported in many previous studies, resveratrol could be a suitable candidate for the prevention and treatment of various cancers, since it has shown antitumor properties in the laboratory [41,42]. Experimental research has suggested its ability to inhibit cancer at all the stages to some extent [43–45]. Many studies have found that resveratrol has chemopreventive as well as chemotherapeutic activity, attributed to its pro-apoptosis, anti-oxidant, and anti-inflammatory properties [45,46]. Additionally, resveratrol is thought to modulate various transcription factors, upstream kinases, and their regulators to affect intracellular signaling pathways, involving cell viability and death, pro-inflammatory mediators, as well as angiogenic and metastatic circuits [47]. For example, Lin Li et al. clarified the mechanism behind the anti-proliferative and pro-apoptotic effects of resveratrol on cervical cancer cell lines. The authors discovered that resveratrol was able to stimulate shrinkage and apoptosis of HeLa cells by activating caspase-3 and caspase-9, decreasing the expression of anti-apoptotic proteins (B-cell lymphoma) Bcl-XL, Bcl-2, and cyclin B, and increasing the pro-apoptotic Bcl-2-associated X (BAX) protein, p21, p27, and p53 [48]. Nrf2 is referred to as a double-edged sword, so that the activation of Nrf2 has cell protective and chemotherapeutic effects on the one hand, and inhibits apoptosis, induces proliferation and also increases cell survival on the other hand. It has been reported that oncogenes such as Myc, Kras, and Braf genes induce the transcription of Nrf2 in cells, and overexpression of Nrf2 can reduce oxidative stress [49]. Resveratrol has previously been shown to have suppressive effects on proteins and lipid oxidation and can protect the hepatocytes in oxidative stress conditions through increasing in the Nrf2 mRNA concentration and the regulation of superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase (CAT), and activation of the Sirt1/AMPK and Nrf2 pathways [50]. According to Cheng et al., Nrf2 signaling could inhibit NAF-1 expression, and induce the production of reactive oxygen species (ROS), which led to apoptosis. They found it could inhibit pancreatic cancer (PC) cell proliferation, and had anticancer effects [51]. Regarding to anti-proliferative and antioxidant activity of resveratrol, it also acts via PI3K/Akt/Nrf2 pathway and Keap1-Nrf2 pathway. Keap1, a negative Nrf2 controller, has oxidative sensors and can detect oxidative stress in the cells. The Keap1-Nrf2 signaling pathway is essential for the regulation of the anabolic pathways in the cells and reduction of oxidant [52].

Moreover, resveratrol by Nrf2/HO-1 pathway and STAT3/NF-κB signaling reduces TNF-α, TGF-β1, STAT3, LDH, and IL-6 and suppress the expression of P-glycoprotein, thereby reducing inflammation [53].

Resveratrol is a histone deacetylase inhibitor (epigenetic reversal agent) with antiproliferative activity, attributed to its ability to promote apoptosis, autophagy, mitotic cell death, cell cycle arrest in cancer cells, increasing ROS production and oxidative stress, and inhibiting angiogenesis [54]. The 4′-OH group in trans-conformation with the 4′-hydroxystyryl moiety is essential for inhibition of cell proliferation [55]. Enzymatic assays have shown an interaction between resveratrol and DNA polymerase enzymes leading to the inhibition of DNA synthesis [55]. Another in vitro study found that inactivation of the NF-κB protein (a transcription factor that regulates gene expression) by resveratrol could improve the effectiveness of chemotherapy. Because NF-κB can mediate resistance to cytotoxic drugs, when resveratrol inhibits this transcription factor, drugs can operate more efficiently [9,56,57]. In colon cancer cells, resveratrol was shown to inhibit the nuclear translocation, phosphorylation, and acetylation of NF-κB. Additionally in colon cancer cells, resveratrol application was associated with lower levels of iNOS, which is an enzyme producing nitric oxide in inflammatory responses. High amounts of nitric oxide can induce inflammation and cellular damage, and has been proposed to be partly responsible for colon carcinogenesis. Moreover, resveratrol administration has been associated with inhibition of the IGF-1R/Akt/Wnt signaling pathway, as well as the activation of p53, leading to anticancer activity [58]. Fig. 1 shows schematically several signaling pathways involved in the suppression of biological responses of malignant cancer cells by resveratrol.

Furthermore, the phytoestrogen resveratrol has been frequently studied as a potential chemopreventive agent against breast cancer, and as a treatment either alone or in combination with chemotherapeutic drugs [36,59]. In combination with other drugs, resveratrol can increase the sensitivity of tumor cells to drugs and consequently can overcome chemoresistance [45]. Resveratrol was also reported to be able to enhance the susceptibility of pancreatic cancer (PC) cells to gemcitabine treatment [51]. Resveratrol reduced the risk of nephrotoxicity caused by cisplatin, a chemotherapeutic drug used to treat bladder, ovarian, testicular, and many other cancers [60]. Many in vitro and animal studies have shown similar preventative activity against prostate, colon, breast, cervical, and lung cancer [45,61–66]. The antioxidant effects of resveratrol in cancer cells have also been demonstrated [67]. Furthermore, resveratrol when used as a support during cancer therapy, has favorable benefits to the patients [68–70]. Bearing in mind the molecular structure and properties of resveratol, along with experimental and clinical trial data, it has been proposed to be useful for several indications in cancer. These are: (i) as a neoadjuvant therapy before cancer surgery to reduce the tumor size, due to apoptosis and inhibition of proliferation; (ii) as an adjuvant therapy after surgery to prevent tumor invasion and metastasis; (iii) as a chemotherapy sensitizer along with chemotherapeutic drugs, such as doxorubicin, gemcitabine, docetaxel, capsaicin, and temozolomide; (iv) for individuals at high risk of developing cancer for chemoprevention; (v) as a radioprotective agent to decrease radiotherapy-related adverse such as mucositis and xerostomia.

3. Resveratrol and gastrointestinal cancer

Resvertrol is becoming recognized as an anti-cancer drug; it has powerful anti-cancer activity in various cancer cells and organs. Previous research in cell lines and animal models, has shown that resveratrol can dramatically affect numerous cell signaling pathways, and inhibit or slow tumor cell growth [64,71]. In addition to the protective role of resveratrol in the GI tract, the therapeutic effects of resveratrol in different gastrointestinal cancers are reviewed below. The main mechanisms of action are: (a) inducing apoptosis and autophagy via regulating AMPK, MAPK/ERK, PI3K/Akt, JAK/STAT, and JNK [50,71,72]; (b) regulating Smad, PI3K/AKT (PTEN), and TGF-signaling pathways to limit epithelial cell growth by affecting cell cycle proteins such cyclins and CDKs [73,74]; (c) inhibiting cell invasion, migration, and angiogenesis by modulating the MAPK and Wnt/catenin signaling pathways [75]; (d) improving DNA repair systems by upregulating TSGs such as p53 (to repair mitochondria and DNA) [50]; (e) modulating NLRP (Nod-like receptor protein), NF-kB, and Toll-like receptor (TLR) signaling pathways to modulate the secretion of various cytokines [76]; (f) modulating claudin and occludin proteins, thus improving the integrity of the GFI mucosa [71]. Moreover, resveratrol can inhibit urease synthesis by *H. pylori*, thus reducing the pH of the GI mucosal niche, contributing to the elimination of *H. pylori* bacteria [77,78]. Furthermore, it is well known that resveratrol can regulate the bacterial

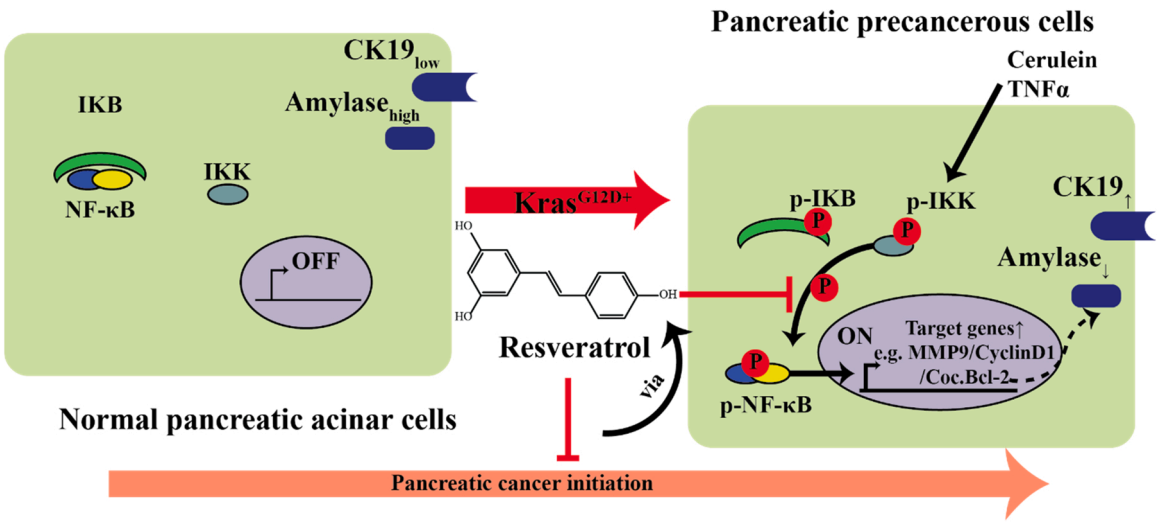

Fig. 2. Schematic of resveratrol function in prevention of NF-κB activity, slowing pancreatic cancer tumorigenesis [86].

protein synthesis of several virulence factors (e.g. CagA) that promote *H. pylori*-induced gastric cancer [79]. It could also dramatically reduce iNOS and IL-8 levels and enhance antioxidant activity in an *H. pylori*-induced gastritis model via up-regulation of the Nrf2/HO-1 (nuclear factor-E2-related factor/heme oxygenase-1) signaling pathway [80]. Resveratrol administration could increase the growth of *Lactobacillus lactis* (beneficial bacteria) while inhibiting the growth of *Enterococcus faecalis* (harmful bacteria), thereby favorably regulating host immunity, lowering inflammatory reactions, and improving gut homeostasis [81]. Moreover, resveratrol has been found to be beneficial in the treatment of irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) [82,83].

3.1. Resveratrol and pancreatic cancer

Ying Xiao et al. showed that pancreatic stem cells (PSC) could be activated by hypoxia, and then showed that resveratrol could reduce activated PSCs and intratumoral hypoxia, thus slowing the growth of pancreatic ductal adenocarcinoma [84]. Hypoxia activates PSCs via HIF-1a, and then activated PSCs release interleukin 6 (IL6), vascular endothelial growth factor (VEGF) A, and stromal cell-derived factor 1, which can enhance the epithelial-mesenchymal transition (EMT) and the invasion of PC cells, while reducing apoptosis. In a KPC (LSL-KrasG12D/+, Trp53fl/+, and Pdx1-Cre) mouse model, resveratrol reduced PC and stromal desmoplasia, inhibited hypoxia-induced PSC activation, inhibited the progression of PC cells, and suppressed the interactions between PC cells and PSCs [85].

Weikun Qian et colleagues used KC mice in a study to see if resveratrol could delay PC tumorigenesis by blocking NF-kB activation (Fig. 2) [86]. KC mice (LSL-KrasG12D/+; Pdx1-Cre) spontaneously develop pancreatic precancerous lesions, and were used as a model to identify the mechanisms behind resveratrol treatment of PC. 3-Dimensional (3D) culture of pancreatic acinar cells was used to study in vitro acinar-to-ductal metaplasia (ADM) and pancreatic intraepithelial neoplasia (PanIN). The abnormal morphology of pancreatic tissues was investigated using histopathology. Resveratrol suppressed the activation of the NF-kB signaling pathway, and delayed the growth of pancreatic precancerous lesions in pancreatic tissues from KC mice. Furthermore, experimental research has shown that resveratrol could reduce the severity of cerulein-induced pancreatitis and the development of ADM/PanINs, which may be explained by its inactivation of NF-kB. Furthermore, stimulation of the NF-kB signaling pathway enhanced the development of ADM/PanIN in mice, and this effect was inhibited by resveratrol. In conclusion, resveratrol could reduce PC tumorigenesis by decreasing NF-kB activity [86].

A study by Violetta Krajka-Kuniak et al. investigated four phytochemicals, phenethyl isothiocyanate (PEITC), indole-3-carbinol (I3C), xanthohumol (XAN), and resveratrol, as well as their mixtures, on the expression and function of NF-kB and Nrf2 in the human PC cell line PANC-1 [87]. The combination of XAN and PEITC was more effective than either compound alone, and lowered NF-kB p65 subunit binding to DNA by 47–60 %, and p65 gene expression by 28–48 %. The combination of XAN and PEITC also increased Nrf2 activation and expression, and the expression of GSTP, NQO1, and SOD genes that are all regulated by this transcription factor. The combination of XAN and PEITC was reported to inhibit PANC-1 cell growth by modulating the activity of NF-B and Nrf2. These findings suggest that a combination of XAN and PEITC might be a useful for the treatment as well as prevention of PC [87].

Mustafa et al. designed a study to explore how resveratrol and quercetin could affect cell survival and EMT in PC stem cells [88]. Immunostaining for TNF-α and vimentin was greater on CD133 + cells than on CD133- cells, and further enhanced in quercetin-treated CD133 + cells, although lower levels of N-cadherin, actin alpha 2 (ACTA-2), and IL-1 were observed. Lower values of TNF-α and N-cadherin were observed in CD133 + cells treated with resveratrol. Since the decrease in ACTA-2 and N-cadherin was larger compared to the increase in vimentin immunoreactivity, resveratrol was found to be less efficient than quercetin at inhibiting the EMT in PC stem cells. Therefore, quercetin may be more beneficial than resveratrol in terms of metastasis prevention [88].

Cancan Zhou et al. found that resveratrol reduced lipid production and increased apoptosis produced by gemcitabine in PC cells, and postulated that the mechanism was the reduction of Sterol regulatory element-binding transcription factor 1 (SREBP1) expression. Furthermore, experimental research has shown that resveratrol could inhibit gemcitabine-induced stemness in PC cells [89]. Resveratrol increased gemcitabine sensitivity and inhibited lipid production through SREBP1. SREBP1 knockdown inhibited spheroid production in cell culture, and decreased the expression of CSC markers. Additionally, resveratrol-induced inhibition of SREBP1 abrogated gemcitabine-induced stemness. Similar results were found in the KPC mouse model. Their findings showed that resveratrol reversed pluripotency caused by gemcitabine, by targeting SREBP1 both in vitro and in vivo. They concluded that resveratrol may be a valuable agent for enhancing chemotherapy sensitivity of PC, and moreover SREBP1 may be a viable target for PC treatment [89].

Jiguang Ma et al. tested how resveratrol could reduce BxPC-3 human

Table 1
Effects of resveratrol in pancreatic cancer.

Dose	Targets	Results	Model (in vitro/ *in vivo*/ human)	Cell line	Ref.
0–200 μM	STAT3, NFκB	Suppressed nuclear translocation	*In vitro*	Panc-1	[92]
50,100, 200 μM	Ihh, Ptch, Smo	Inhibited proliferation and induced apoptosis of MIA & PaCa-2 PC cells	*In vitro*	MIA PaCa-2	[93]
10, 50, 100 μM	Bax, VEGF-B	Inhibited proliferation, promoted apoptosis	*In vitro*	Capan-2	[94]
12.5, 25, 50, 100, 200, 400 μM	Gli1, Ptc1, CCND1, BCL-2	Inhibited the growth of PC cells in a concentration and time-dependent manner	*In vitro*	Panc-1, AsPC-1, BxPC-3	[95]
0, 12.5, 25, 50, 100, 200 μM	CDH2, CDH1, vimentin, MMP-2, MMP-9, Akt, NF-κB	Suppressed PC migration and invasion	*In vitro*	BxPC-3, Panc-1	[96]
12.5, 25, 50 μM	uPA, MMP2, HIF-1α	Suppressed hypoxia-driven ROS-induced PC	*In vitro*	BxPC-3, Panc-1	[97]
50 μM	uPA, CDH1, Glut-1, ERK, p38, NF-κB	Suppressed hyperglycemia-driven ROS-induced migration & invasion of PC	*In vitro*	Panc-1	[98]
50 μM	SREBP1	Reversed the stemness induced by gemcitabine	*In vitro,* in vivo	MIA PaCa-2, Panc-1	[89]
10, 25, 50, 100 μM 40 mg/kg PO daily	NF-κB, Bcl-2, Bcl-xL, COX-2, cyclin D1, MMP-9, ICAM-1, survivin, Ki-67, CD31, VEGF	Suppressed markers of invasion, proliferation, angiogenesis & metastasis.	*In vitro,* in vivo	AsPC-1, MIA PaCa-2, Panc-1, Panc-28	[99]
10, 20, 30 μM 40 mg/kg	Nanog, Sox-2, c-Myc, Oct-4, ABCG2, Zeb-1, Slug, Snail, capase-3/7, Bcl-2, XIAP, cyclin D1	Inhibited pluripotency maintaining factors, Induced apoptosis, inhibited CSC's invasion, migration, and markers of EMT	*In vitro,* in vivo	Human, mice CSCs	[100]
0, 12.5, 25, 50, 100, 200 μM	miR-21	Inhibited PCC invasion & migration	*In vitro*	PSCs, Panc-1	[101]
0, 6.25, 12.5, 25, 50, 100 μM	–	Induced apoptosis	*In vitro*	Panc-1, AsPC-1	[102]
100 μM 60 mg/kg	VEGF-B, Bax, Bcl-2, β-actin, p-GSK-3β, p-Akt, cleaved-caspase3	Inhibited VEGF-B signaling pathway	*In vitro,* in vivo	Miapaca-2, Panc-1, Capan-2	[103]
0, 20, 50, 100, 200 μM	Caspase-3, p53, p21	Activated caspase-3, up-regulated p53 and p21	*In vitro*	Capan-1, colo357	[104]
0, 25, 50, 100 μM	MIC-1	Inhibited cell growth	*In vitro*	CD18, S2–013	[105]
10, 50, 100 μM	MiR-21, BCL-2	Induced apoptosis	*In vitro*	Panc-1, CFPAC-1, MIA PaCa2	[106]
0, 1, 5, 10, 25, 50 μM	BubR1, Aurora B, Cyclin B, phosphorylated histone H3	Killed and/or inhibited the growth of breast and PC cell lines	*In vitro*	Panc-1, AsPC-1, Colo-357	[107]
100 μM	MAPK, P-ERK	Antioxidant effect, induced cell proliferation	*In vitro*	AR42J	[108]
5, 10, 25, 50, 100, 150, 200 μM	Caspases, Bcl-2, Bcl-xL, XIAP, Bax	Inhibited proliferation, promoted apoptosis	*In vitro*	Panc-1, BxPC-3, AsPC-1	[109]
0–100 μM	Src and Stat3 signaling, cyclin D1, Bcl-xL, Mcl-1	Inhibited Stat3 signaling, antitumor activity	*In vitro*	Panc-1, Colo-357	[110]
0, 10, 20, 50, 100 μM	Mitochondrial cytochrome c, caspase-3, NF-κB	Inhibited PC growth, prevented metastasis by inducing mitochondrial dysfunction and apoptosis	*In vitro*	MIA PaCa-2, BSp73AS	[111]
20, 50 μM	H2.aX	Inhibited growth, promoted apoptosis	*In vitro*	Capan-2, Panc-28	[112]
1, 10, 50, 100 μM	SIRT1, β-catenin, β-actin, GSK3β, Siah1, cyclin-D1	Suppressed levels of β-catenin protein & mRNA, inhibited proliferation	*In vitro*	Panc-1	[113]
50 μg/mL	ROS	Increased apoptosis, possible intracellular drug accumulation	*In vitro*	AsPC-1	[114]
10 ppm	COX-2	Decreased total number of pancreatic lesions, including atypical hyperplasia	*In vivo*	–	[115]
25, 50, 75 and 100 μM	ADRB-2-HIF-1α axis	Inhibited proliferation of cancer cells under chronic stress	*In vitro*	BxPC-3	[90]
1, 10, 100 μM, 1 mM	c-Jun N-terminal kinase	Released Ca^{2+} from intracellular stores, reduced cell viability.	*In vitro*	AR42J	[116]
0, 25, 50, 100, 150, 200, 300 μM	RNA ribose, flavonoid luteolin	Inhibited glycogen synthesis & tumor cell proliferation	*In vitro*	MIA PaCa-2	[117]
10, 50, 100 μM	Akt, caspase	Antiproliferative & proapoptotic effects	*In vitro*	INS-1E	[118]
100 μM	P53, P21, survivin, cyclin D1, Bax, Bak, Bcl-2, Bcl-XL, CD95	Promoted apoptosis, induced cell cycle arrest associated with survivin depletion	*In vitro*	MIA PaCa2	[119]
5, 10, 20, 30 μM	LTA_4H, LTB_4, BLT_1	Suppressed proliferation & anchorage-independent growth of PC, inhibited tumor formation	*In vitro,* in vivo	MIA PaCa-2, Panc-1	[120]
20, 40, 60 mg/kg bw	LTA4H LTB4	Suppressed pancreatic tumor growth.	*In vitro,* in vivo	HCT15, H1299, LNCaP MaCa-2, Panc-1epG2, hTERT-HPNE	[121]
50 μM	caspase-3, p21, p27	Induced cell cycle arrest, apoptosis, inhibited FOXO phosphorylation & increased nuclear translocation	*In vitro*	Panc-1, Hs766T, AsPC-1	[122]
5, 10, 25, 50, 100 μM	N-cadherin, TNF-α, vimentin, N-cadherin, ACTA-2	Reduced cell proliferation, prevented EMT	*In vitro*	CD133, Panc-1	[88]
50 mg/kg/day	NAF-1, SOX2, NANOG, OCT4	Inhibited the ability of migration and invasion of PC cells	*In vitro,* in vivo	Panc-1, BxPC-3	[123]
1, 2.5, 5, 10, 15, 25, 50, 100 and 150 μM	NF-Kb, p50, p65, COX-2	Decreased the activation of NF-Kb, Reduced COX-2 expression	*In vitro*	Panc-1	[87]

(*continued on next page*)

Table 1 (*continued*)

Dose	Targets	Results	Model (in vitro/ *in vivo*/ human)	Cell line	Ref.
50 mg/kg/day	p-IKK, p-IKB, p-NFκB, MMP9, p-ERK, p-STAT3, COX2, CyclinD1, Bcl2	Pro-inflammatory, inhibited proliferation, promoted apoptosis	*In vitro,* in vivo	3D culture	[86]
50 mg/kg/day	HIF-1α, α-SMA, IL-6, SDF-1, VEGF-A, Bcl-2, caspase-3	Suppressed malignant progression of PC, increased apoptosis	*In vitro,* in vivo	Panc-1, MIA PaCa2	[85]

pancreatic cancer cell proliferation and increase apoptosis, by reducing the catecholamine neurotransmitters that are activated by the Adrenoceptor beta 2 (ADRB2)/ Hypoxia-inducible factor 1 (HIF1) axis in cancer [90]. Under prolonged cellular stress, resveratrol was able to stimulate apoptosis in malignant cells. Furthermore, the researchers discovered that resveratrol could inhibit malignant cells under chronic stress by down-regulation of the ADRB2. HIF-1 has been shown to play a vital role in cancer biology and is overexpressed in human cancers as a result of intra-tumor hypoxia and genetic changes [91]. Ma et al. indicated that resveratrol could decrease the protein expression of HIF 1 in a dose-dependent manner. Their results supported the idea that resveratrol could be useful in the treatment and prevention of PC [90].

Table 1 summarizes the effects of resveratrol in pancreatic cancer.

3.2. Resveratrol and gastric cancer

Recently, it has been demonstrated that resveratrol prevented gastric cancer (GC) metastasis and reversed the progression of EMT by targeting GC derived mesenchymal stem cells (GC–MSCs) [124]. Numerous studies revealed that Wnt/β-catenin signaling is linked to EMT process and tumor metastasis [125]. The study by Yin et al. confirmed that GC–MSCs also accelerate GC metastasis and promote EMT progression through activating Wnt/β-catenin signaling pathway [124]. They revealed that resveratrol could block these processes and prevent GC growth by regulating the GC–MSCs [124]. β-catenin, a major component of the canonical Wnt/β-catenin pathway, binds E-cadherin with α-catenin in the cytoplasm, causing E-cadherin to become anchored in the cell membrane, promoting cell adhesion and preventing cell metastasis. In resveratrol-pretreated GC cells expression of β-catenin and its downstream proteins, CD44 and Cyclin D3, decreased. Interestingly, restoration of β-catenin expression with CP21 almost completely abolished the suppressive impact of resveratrol on the progression of EMT and GC metastases. GC-MSCs express various Wnt genes, among which Wnt5a mRNA expression is the highest in these cells that can promote GC invasion [124]. Based on results, resveratrol dramatically eliminated Wnt5a mRNA and protein expression of GC–MSC, thus inactivating Wnt/β-catenin pathway of GC, inhibiting GC cell migration, and suppressing GC metastasis [124].

Mengting Ren et al. reported that resveratrol could be combined with cisplatin (DDP) for GC treatment. They tested if RES could sensitize GC cells to DDP in another investigation [126]. They discovered that the combination of resveratrol and cisplatin caused G2/M phase cell cycle arrest in AGS cells, as well as lower viability and increased apoptosis. Resveratrol was also found to increase Bax, cleaved caspase-12, cleaved poly-ADP-ribose polymerase (PARP), glucose-regulated protein 78 (GRP78), CCAAT/enhancer binding protein homologous protein (CHOP), p-eukaryotic translation initiation factor 2 (p-eIF2), and PRKR-like ER kinase (PERK) expression, when combined with cisplatin. Resveratrol and cisplatin co-treatment also increased p21Waf1/Cip1, phosphorylated cyclin-dependent kinase 1 (p-CDK1, Tyr15), and p27Kip1 proteins, while decreasing the level of Cdc25C protein. Finally, by activating caspase-12 and the PERK/eIF2/ATF4/CHOP signaling pathway, and by inhibiting the CDK1-cyclin B1 complex, resveratrol and cisplatin caused endoplasmic reticulum (ER) stress-mediated apoptosis and G2/M phase arrest, which inhibited the proliferation of the GC cell line AGS [126].

Sujin Kim et al. evaluated the effects of resveratrol on the proliferation, metastatic spread, and survival of GC cells, looking at PIM-1 (proto-oncogene serine/threonine-protein kinase 1) as a potential target [127]. The researchers discovered that resveratrol bound directly to PIM-1, limiting its catalytic activity in SNU-601 GC cells. Phosphorylation of the pro-apoptotic protein Bad (a known PIM-1 substrate) was suppressed as a result. By inactivating PIM-1, resveratrol suppressed cell anchorage-independent growth and proliferation. They used molecular docking software to investigate the molecular interactions between resveratrol and PIM-1, and discovered that resveratrol interacted directly with PIM-1 in the ATP-binding pocket. Finally, inhibition of PIM-1 kinase activity could explain the pro-apoptotic and anti-proliferative effects of resveratrol in SNU-601 cells, and could be a mechanism behind the anti-tumor and chemopreventive properties of resveratrol [127].

Yu Hu et al. attempted to improve the effectiveness of a new treatment approach in gastric carcinoma. To treat gastric cancer, they devised a novel method that combined a non-chemotherapeutic drug resveratrol with anti-miR21. Mesoporous silica nanoparticles (MSNs) coated with hyaluronic acid (HA) were employed as a delivery vehicle. Extensive in vivo research was carried out utilizing xenograft animal models [128]. Anti-miR21 and resveratrol-loaded HA-MSNs coupled with HA were investigated o improve treatment effectiveness in GC. The appearance of a greyish shell on the black MSNs clearly indicated the surface coating with HA. They found a synergistic action of the anti-miR21 and resveratrol combination. Resveratrol plus mirNP produced a substantial reduction in tumor burden. Indeed, HA/ resveratrol mirNP produced a threefold larger anti-tumor effect compared to free resveratrol, and a twofold tumor larger anti-tumor effect than resveratrol mirNP, demonstrating good anticancer activity. The proportion of TUNEL-positive cells was much higher in HA/resveratrol mirNP-treated cells than the other groups, showing that apoptosis and cell necrosis were involved in the mechanism underlying the improved anticancer activity of HA/resveratrol mir-NPs. As a result, combining resveratrol and anti-miR21 in a tailored nanocarrier could be a potential delivery strategy for GC treatment [128].

In another study, Yang et al. reported that resveratrol was able to inhibit cell viability in the human GC cell line BGC823 in a concentration-dependent fashion. They also found that resveratrol inhibited cell invasion and migration. The authors displayed that resveratrol could inhibit the expression of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), which has been postulated to be upregulated in GC cells [129]. MALAT1 is a prognostic biomarker of GC that can promote tumor growth and metastasis by inducing EMT process. MALAT1 knockdown inhibits cell viability, migration, and invasion, and promotes apoptosis of GC cells [130]. MALAT1 overexpression destabilized the phosphatase and tensin homolog (PTEN) mRNA in GC cells and impaired autophagy flux in these cells via stimulating PTEN/AKT/mTOR signaling pathway. As a consequence of autophagy inhibition, sequestosome 1 accumulation stimulates NF-κB translocation to elevate IL-6 expression, which convert fibroblasts to cancer-associated fibroblasts to promote GC progression [131]. Furthermore, binding of MALAT1 to EZH2 in GC reduces the expression of the tumor suppressor gene protocadherin-10 and enhances GC cell motility and invasion [132]. MALAT1 may also trigger GC cell growth through the overexpression of splicing factor 2/alternative splicing factor (SF2/ASF) in the nucleolus, whereas downregulation of MALAT1 or SF2/ASF prompts cell cycle arrest at the G0/G1 phase and decreases

Table 2
Effects of resveratrol in gastric cancer.

Dose	Targets	Results	Model (in vitro / *in vivo* /human)	Cell line	Ref.
0, 5, 10, 25, 50, 100, 200, 400 μM	MALAT1	Inhibited migration & invasion	*In vitro*	SGC7901, BGC823	[129]
1–100 μM	p21, p53, Fas, Fas-L	Up-regulated anti proliferative & pro-apoptotic signaling	*In vitro*	SNU-1, KATO-III	[136]
10, 20, 50, 100, 200 mg/L	PTEN	Prevented EMT by modulating PTEN/Akt signaling pathway	*In vitro,* in vivo	SGC7901, MGC803	[137]
5.7 μg/mL	p53	Modulated p53 post-translational modifications	*In vivo*	–	[138]
30, 50 μM	ABCB1, ANXA1, TXN, P-gp	Reduced cancer cell resistance by affecting the expression of several proteins & genes related to MDR	*In vitro*	EPG85–257RDB, EPG85–257RNOV	[135]
0, 50, 75, 100 μM	cyclin D, c-myc, β-catenin	Inhibited proliferation of MGC-803 cells by inhibiting the Wnt signaling pathway	*In vitro*	MGC-803	[139]
0, 10, 50, 100, 200, 400 μM	NF-κB, Bax, Bcl2, caspase-3, caspase-8	Inhibited viability, induced apoptosis	*In vitro*	SGC-7901	[140]
3.125300 μM	Gli-1, Ecadherin, Ncadherin	Inhibited EMT & Hh signaling pathway, suppressed metastasis & invasion in GC	*In vitro*	SGC7901	[141]
0, 5, 10, 25, 50, 100, 200 μM 40 mg/kg/d	cyclin D1, CDK4, CDK6, p21, p16, Sirt1	Inhibited viability & clonogenic capacity of GC cells in a Sirt1-dependent manner	*In vitro,* in vivo	AGS, BGC-823, SGC-7901	[142]
100 μM	SIRT1, STAT3, NF-κB	Inhibited viability, increased senescence	*In vitro*	AGS, MKN-45	[143]
0, 10, 50, 100 μM	P53	Increased cytotoxicity, cell cycle arrest	*In vitro*	SNU-1, SNU-668, HT-29	[144]
100 μM	caspase 3, cytochrome C oxidase	Engaged apoptotic signaling	*In vitro*	AGS, SNU-1	[145]
500, 1000, 1500 mg/kg	Bcl-2, BAX	Induced apoptosis in transplanted tumors	*In vivo*	–	[146]
0, 10, 20, 30, 40, 50, 100 μM	IL-6, Raf/MAPK pathway	Prevented IL-6 induced GC metastasis	*In vitro*	SGC7901, HSC-39	[147]
–	survivin	Inhibited proliferation, promoted apoptosis	*In vitro*	SGC7901	[148]
6.25, 12.5, 25, 50, 100, 200, 400 μM	p-GSK3β, p-PTEN, cyclin D1, p-PKB, p-PI3K	Provoked cell cycle arrest	*In vitro*	MGC803	[149]
50 mg/kg/2 days	PARP, caspase-3, pro-caspase 9, cytochrome c, Bax and Bcl-2	Induced apoptosis through mitochondrial pathway	*In vitro,* in vivo	SGC-7901	[150]
0, 25, 50, 100, 200 μM	Sirtuin1, caspase 3, γH2AX, ku70	Induced apoptosis via ROS	*In vitro*	SGC7901	[151]
10 mg/kg	–	Increased cytotoxicity & apoptosis	*In vitro,* in vivo	BGC823	[128]
1,5, 10, 25, 50, 100 μM	NOS	Induced antioxidant activity	*In vitro*	SNU-1	[152]
5, 10, 20 μg/mL	Micronuclei	Decreased the high frequency of micronuclei at 72 h	*In vitro*	–	[153]
0–100 μM	PKC, ERK1/ERK2	Inhibited proliferation	*In vitro*	KATO-III, RF-1	[154]
50 μM	LC3, β-Actin and PARP	Induced autophagy	*In vitro*	HGC-27	[155]
20 μM	TTP	Induced TTP protein expression	*In vitro*	AGS	[156]
0, 25, 50, 100 μM	PIM-1 kinase, Bad, caspase-3, PARP, Ser112	Inhibited anchorage-independent growth & proliferation, increased proportion of apoptotic cells	*In vitro*	SNU-216, SNU-601, SNU-668	[127]
0, 5, 10, 20, 30, 40, 50, 60, 70, 80 μM	Bax, PARP, GRP78, PERK, p-eIF2α, CHOP, caspase-12, Bcl-2, p-CDK1, Tyr15, p21, p27, Cdc25C	Inhibited viability, stimulated apoptosis, provoked G2/M phase cell cycle arrest in AGS cells	*In vitro*	AGS, NCI-N87, MKN-45, KATO III,	[126]
5, 10, 20, 50, 100 μM	IL-6, IL-8, VEGF, β-catenin, MCP-1, CD44, CyclinD3	Activated Wnt/β-catenin signaling, reversed the EMT	*In vitro,* in vivo	HGC-27, AGS	[124]

cell growth [133]. Resveratrol via inhibition of MALAT1-mediated EMT suppresses the invasion and migration of human GC cells [134].

Mieszala et al. investigated how resveratrol affected the expression of ANXA1, ABCB1, and TXN genes, and their related proteins, in two GC cell lines, RDB and RNOV. It is known that these genes are associated with multidrug resistance (MDR) in RNOV and RDB cells, which are resistant to mitoxantrone and daunorubicin, respectively [135]. When compared to untreated cells, resveratrol at both 30 and 50 μM concentrations had a significant effect on the expression of the aforementioned genes in RDB cells. At the protein level, TXN and P-gp showed similar results. In comparison to the control cells, resveratrol decreased TXN expression at both protein and mRNA levels in the RNOV cell line. Therefore, resveratrol may increase cancer cell chemosensitivity by influencing the expression of several MDR-related proteins and genes [135].

Table 2 illustrates the effects of resveratrol in gastric cancer.

3.3. Resveratrol and colorectal cancer

Numerous studies have reported the effects of different doses of resveratrol on colorectal cancer (Table 3). Wang et al. studied the effect of resveratrol on the toxicity of cetuximab using two colorectal cancer (CRC) cell lines, CT26 and HCT116. The goal was to see how resveratrol affected p-Akt in CRC cells, whether it affected cetuximab resistance, and how resveratrol-induced changes in Cx43 affected p-Akt [157]. Resveratrol promoted growth suppression induced by cetuximab in untreated or cetuximab-treated parental CT26 and HCT116 cells. The combination increased the expression and phosphorylation of connexin 43, improved gap junction function, and suppressed Akt and NF-κB activation both in vitro and in vivo. In cells transfected with connexin 43-shRNA, resveratrol showed no effect, suggesting that connexin 43 overexpression contributed to Akt inhibition in these cells. According to these findings, resveratrol could increase the sensitivity of CRC cells to cetuximab by overexpressing connexin 43, which also inhibited the Akt signaling pathway [157].

Another anti-cancer mechanism of resveratrol expressed in

Table 3
Effects of resveratrol in colorectal cancer.

Dose	Targets	Results	Model (in vitro/ *in vivo*/ human)	Cell line	Ref.
5, 10, 20, 50, 100, 250 μM	PD-L1, γH2AX, caspase 3, p38-MAPK, c-Myc, NF-κB, p65	Decreased tumor cell survival	*In vitro*	HCT116, SW480, HT29, SW620	[165]
25,50,100,200, 400 μM	vimentin, ZEB-1, E-cadherin	Induced apoptosis, invasion	*In vitro*	HCT116	[166]
0–200 μM	STAT3, pSTAT3, pAkt, Akt, CD44, slug, vimentin	Anti-telomeric & pro-apoptotic effects	*In vitro*	HCT116, DLD1	[167]
0, 5 μM	FAK, Sirt1, caspase-3, β1-Integrin, NF-κB, Ki-67, MMP-9, MMP-13, CXCR4	Anti-invasion effects	*In vitro*	HCT116, SW480	[168]
0–100 μM	p53, Bax, Bcl-XL, BCL-2, P-gp	Promoted apoptosis & enhanced intracellular uptake of DOX	*In vitro*	HCT116, HT-29	[169]
5, 10, 20, 50, 100 μM	TTP, E2F1, cIAP2, LATS2, and Lin28	Inhibited proliferation, invasion, & metastasis	*In vitro*	HCT116, SNU81	[170]
0, 50, 100, 150 mg/kg	E-cadherin, vimentin, Snail, TGF-β1/Smads signaling pathway, MMP9, MMP2, Slug, ZEB1, Twist1	Inhibited EMT, invasion & metastasis	*In vitro,* in vivo	LoVo	[171]
0, 12.5, 15, 25, 30, 50, 100, 200, 300 μM	c-Myc, MMP-7, MALAT1	Down-regulated MALAT1, inhibited invasion & metastasis	*In vitro*	LoVo, HCT116	[172]
0, 5 μM	CD133, CD44, ALDH1, TNF-β, TNF-α, caspase-3, NF-κB, MMP-9, CXCR4	Modulated TNF-β signaling pathway, induced apoptosis	*In vitro*	HCT116	[173]
51.3 μM, 47.3 μM	PMAIP1, BID, ZMAT3, CASP3, CASP7, FAS	Inhibited proliferation, induced apoptosis	*In vitro*	DLD-1, Caco-2	[174]
5, 10, 20, 40, 80, 160 μM	COX, oxidative phosphorylation (OXPHOS)	Increased fatty acid oxidation & oxygen consumption, increased mitochondrial biogenesis, induced apoptosis	*In vitro*	SW620	[175]
1, 10, 25, 50,100 μM	NADPH oxidase, histone γH2AX, sirtuin 6	Anti-tumor effect	*In vitro*	HCT116, HT-29	[176]
0, 12.5, 25, 50, 100 μM	TCF4, ERK, p38, β-catenin, c-myc, NF-κB, PARP, caspase-3	Induced apoptosis, decreased half-life of TCF4	*In vitro*	HCT116, SW480, LoVo, HT-29, CaCo-2	[177]
5, 10, 25, 50 μM	PDP1, PDP2, PDK1, PDHE1α, AMPK	Improved oxidative metabolism	*In vitro*	Caco2, MCF7, HCT 116	[178]
5 μM	TNF-β, TNF-βR, FAK, NF-κB	Induced growth, proliferation, & invasion	*In vitro*	HCT116, RKO, SW480	[179]
0.1, 1, 2, 5, 10, 20, 50 μM	NF-κB, claudin-2, E cadherin, MMP-9, caspase-3, IκBα kinase, slug, vimentin	Inhibited EMT phenotype, up-regulated intercellular junctions	*In vitro*	HCT116, SW480	[180]
0, 10, 100 μM	AKT1, IL6	Suppressed proliferation, promoted apoptosis	*In vitro*	HCT116	[181]
1, 2, 3, 5, 10, 20, 50 μM	Sirt1, Ki-67, NF-κB, MMP-9, CXCR4	Suppressed tumorigenesis	*In vitro*	HCT116, SW480	[182]
0, 12.5, 25, 50, 100, 200 μM	MDR1, NF-κB, p65, CREB, AMPK	Inhibited transcription of cAMP-responsive element (CRE)	*In vitro*	HCT116/LOHP	[183]
100 mg/kg	miR-34c, L-6, TNF-α, KITLG, p53, PI3K, IL-6, mir-28, mir34a	Suppressed tumor growth, cell viability, proliferation, invasion, & migration	*In vitro,* in vivo	HCT-116, HT-29	[184]
–	cyclin D1, cyclin E2, BCL2, BCL2 associated X, p53, AKT1, AKT2	Inhibited proliferation, induced apoptosis	*In vitro*	DLD1, HCT15	[185]
0, 10, 20, 30, 50 μM	Cox-2 and PGE2	Inhibited proliferation, induced apoptosis	*In vitro,* in vivo	HCA-17, SW480, and HT29	[186]
24, 36, 48, 64, 88 μM	COX-2	Suppressed proliferation via inhibition of COX-2 expression	*In vitro*	HCT-116	[187]
0, 12.5, 25, 30, 37.5, 50 μM	P53, BAX, Bcl2, PUMA, SET7/9, caspase-3, PARP	Increased p53 stability in colon cancer cells, activated p53-mediated apoptosis	*In vitro*	HCT116, CO115, SW48	[188]
0, 10, 20, 40, 60, 80 μM	Akt1/2/3, BMP7, PI3K	Decreased phosphorylation of PTEN	*In vitro*	HCT116	[189]
0, 0.001, 0.01, 0.1, 1, 10 μM	AMPK, p21, mTOR, NQO1, LC3-I/II, ACC, P70S6K, 4EBP1	Slowed tumor progression	*In vivo,* in vitro	Apc10.1	[190]
0, 5 μM	TNF-β, TNF-α, NF-κB, caspase-3	Inhibited inflammation & tumor cell growth	*In vitro*	HCT116	[191]
–	PTEN, Caspase-3, p53, p-AKT	Anti-proliferative effects, promoted apoptosis	in vitro	SW480 and Caco-2	[192]
0, 60 μM	Kras, miR-96, β-catenin, Kras, pBraf, LGR5, pERK, pAkt	Prevented the development and growth of colorectal tumors	*In vivo,* in vitro	HCT116, SW480	[193]
15 μg/mL	FOXOa	Anti-proliferative effect, increased apoptosis	*In vitro*	HCT116	[194]
100 mg/kg	ACC, AMPK, Caspase-3a, Cyt c	Slowed cell cycle progression, stimulated intrinsic pathway apoptosis	*In vitro,* in vivo	HCT116, RKO	[195]
0.3, 1, 3, 30 μM	VEGF, COX-2, ERK, CD31	Anti-angiogenic effects, suppressed angiogenesis	*In vitro,* in vivo	HT-29	[196]
10 μM	PDE4, cleaved caspase-3	Induced apoptosis	*In vitro*	HCT116	[197]
1–500 μM	P-gp /MDR1, MRP1, BCRP, CYP3A4, GST, caspase-3, PS, hPXR	Inhibited ABC-transporter expression & overall efflux, induced apoptosis & metabolic enzymes GST	*In vitro*	Caco-2	[198]
5 μg/mL	CCNB1, CCNB2, CDK1, p21, CDKN3, CHEK1, KPNA2, MAD2L1, SERTAD1	Inhibited cell cycle at G_0/G_1 and G2/M phases	*In vitro*	CRC cell	[199]
12.5,25,50,100 μM	p53	Potent growth-inhibitory effect.	*In vitro*	HCT-116	[200]

(*continued on next page*)

Table 3 (*continued*)

Dose	Targets	Results	Model (in vitro/ *in vivo*/ human)	Cell line	Ref.
0.5 or 1.0 g	Ki-67	Anti-carcinogenic effect	Human	CRC cell	[201]
25, 50, 100 μM	Ptch, Smo, Gli-1	Inhibited migration & viability, stimulated apoptosis, suppressed protein production	*In vitro*	HCT116	[202]
10, 50, 100, 150 μM	CDK2, CDK4, cyclin D1, P21, PCNA, caspase-7, caspase-9	Induced cell cycle arrest	*In vitro*	HCT116, Caco-2	[203]
12.5, 25, 50, 100, 200 μM	pyruvate kinase, leptin, c-Myc, VEGF, caspases 3 and 8, Bax, BCl2	Exerted cytotoxic, apoptotic, & antiangiogenic effects	*In vitro*	HCT116, Caco2	[204]
10, 25, 60 μM	IL-6, IL-1ra, IL-10, TNFα	Modulated immune recognition by peripheral blood mononuclear cells of two human CRC cell lines	*In vitro*	HT-29, RKO	[205]
0, 10, 25, 50, 100, 200 μM	Akt, mTOR, p70S6K, GRP78, GADD153, β-TrCP, cyclin D1, Sp1, caspase-3/7, PARP, AMPK	Induced dose-dependent energy reduction, suppressed glucose uptake, increased ER stress response	*In vitro*	HCT-116, Caco-2	[206]
10, 30, 50 μM	PPARγ, caspase-3	Induced apoptosis	*In vitro*	SW480, HCT116, Caco-2,	[207]
0–100 μM	cleaved caspae-3, PARP	Provoked apoptosis, inhibited growth & colony formation	*In vitro*	HCT116, HT29, Caco-2	[208]
25 μM	PARP-1, p53, γ-H2AX, TOPO II, ATM kinase	Induced DNA damage by inactivating topoisomerase II, activated ATM kinase to promote apoptosis	*In vitro*	HCT-116	[209]
50 or 150 mg/kg	PTEN, Akt1/2, β-catenin, PCNA, caspase 3, GSK-3β	Inhibited proliferation	*In vitro,* in vivo	HCT116, SW480	[210]
240 mg/kg	–	Inhibited proliferation	*In vitro,* in vivo	HCA-7, HT-29	[211]
100 μmol/l	Bak, Bax	Induced apoptosis	*In vitro*	HCT116	[212]
30, 50, 100, 200 μM	PPARγ, cytokeratin 20, p38 MAPK, PGC-1α, SIRT1, SSAT	Inhibited proliferation, activated ligand-dependent signaling, induced cytokeratin 20	*In vitro*	Caco-2, HCT-116	[213]
8 mg/kg	β-glucuronidase, β-glucosidase, β-galactosidase	Inhibited DMH-induced colon carcinogenesis	*In vivo*	–	[214]
30, 50 μM	Survivin, Bcl-2, caspase-3	Restored survivin expression at mRNA & protein levels	*In vitro*	HCT116	[215]
50, 100, 150 μM	p27, cyclin D1, IGF-1R, Akt, p53, PARP, GSK3β, β-catenin, sp1, MDM2, FKHRL1	Inhibited proliferation, induced apoptosis	*In vitro*	HT-29, SW480	[216]
12.5–200 μM	CD133, CD44, MICA/B	Inhibited proliferation, induced cell cycle arrest & apoptosis	*In vitro*	HCT116	[217]
50, 150 mg/kg	P38 MAPK, BMPR, BMP9, PCNA	Attenuated the antiproliferative effect	*In vitro,* in vivo	LoVo	[218]
10, 30, 50, 100 μM	Fas, caspase 3, 8, 9, Bax, Bak, PARP, Cyt c, Mcl-1, Bcl-2	Induced the redistribution of Fas receptor, induced apoptosis	*In vitro*	SW480, SW620, HCT116	[219]
150 mg/kg	EGFR, HER2, HER3, IGF-1R, IGF-1, IGFBP3, NF-κB	Reduced proliferation, stimulated apoptosis	*In vitro,* in vivo	HT-29, HCT-116	[220]
1 – 100 μM	UGT1A1	Inhibited viability	*In vitro*	Caco-2	[221]
200, 800 mg/kg	Bcl-2, Bax	Inhibited proliferation, induced apoptosis, reduced anti-apoptotic factors	*In vitro,* in vivo	ls174t	[222]
0–100 μM	COX-2, VEGF	Protected against nutrition-induced oxidative stress damage	*In vitro*	SW480, LT 97, HT29	[223]
0, 5, 10, 20 μM	Akt, Erk1/2, miR-34a, caspase-9, PARP-1, JNK, P38, Sirt1, C-myc	Modulated apoptosis & growth-related signaling pathways	*In vitro*	DLD-1, SW480, COLO201	[224]
50, 100, 200, 250 μM	TOPII	Induced apoptosis, negligible cytotoxicity	*In vitro*	HT29, Caco-2	[225]
10, 50, 100 μM	ATF3, Egr-1, KLF4	Induced apoptosis by increased ATF3 expression	*In vitro*	HCT-116, HT-29, Caco-2, LoVo, SW480	[226]
2 g/kg	ACF	Anti-inflammatory & antioxidant activity,	*In vivo*	–	[227]
0, 2, 4, 8, 10, 12, 16, 20, 40, 60, 80, 100 μM	Bax, caspases 3 & 9	Induced mitochondrial apoptosis	*In vitro*	HCT116	[228]
0, 10, 25, 50, 100 μM	ATF3, Id1	Induced ATF3, suppressed Id1	*In vitro*	HCT-116	[229]
5, 10, 15, 20, 30, 40, 50, 60, 80, 100 μM	POL-β, POLH, FEN1, DDB2, P21, CDC-2, PCNA, caspase-3, PTEN	Increased genotoxicity, induced apoptosis	*In vitro*	HCT-116	[230]
1, 3, 10, 30, 50, 100 μM	CD95, caspase-3 & 8, FADD, $FLIP_L$, DR5, DR4, cav-2	Induced apoptosis, redistributed death receptors into lipid rafts	*In vitro*	HT29, SW620, HCT116	[231]
0, 10, 25, 50, 100, 200 μM	$NO^{\bullet}$, Bax, Bcl-2, p53, cytochrome c, caspase 8,9,3, DR4, CD95	Induced apoptosis	*In vitro*	HCT116	[232]
1, 10, 100 μM	cathepsin D, Bax, cytochrome c, caspase 3	Cytotoxicity involving a hierarchy of proteolytic pathways	*In vitro*	DLD1, HT29	[233]
0, 10, 20 μM	PARP, BID, Bcl2, caspase-3	Induced apoptosis	*In vitro*	CT26	[234]
200 μM	caspase-6, lamin A, p53	Induced apoptosis	*In vitro*	HCT116	[235]
50,100,200,300,400 μM	PKCα, ERK	Inhibited cell growth, induced apoptosis	*In vitro*	HT-29	[236]
10, 20, 30, 40, 50 μM	iNOS, TLR-4, IκB-α		*In vitro*	Caco-2, SW480	[237]

(*continued on next page*)

Table 3 (*continued*)

Dose	Targets	Results	Model (in vitro/ *in vivo*/ human)	Cell line	Ref.
		Reduced LPS-induced inflammation, inhibited NF-κB-dependent molecular mechanisms			
75, 150, 300 μM	AKT, S6, G6PD, TKT, PGD, PKM2	Inhibited aerobic glycolysis	*In vitro*	CACO-2, DLD-1, LoVo	[238]
0, 13, 25, 50, 100 μM	COX-2	Suppressed COX-2 promoter activity	*In vitro*	DLD-1	[239]
30, 50, 60, 100 μM	$p34^{CDC2}$, CDK7, cyclin A, cyclin B	Induced cell cycle arrest, inhibited proliferation	in vitro	HT29	[240]
1, 5, 10, 30, 50,100 μM	cyclin A, cyclin Bl, Cdkl, Cdk2	Inhibited proliferation, modulated cyclin activity	*In vitro*	SW480	[241]
50 μM	TGF-β1, p27, E-cadherin	Inhibited butyrate-induced TGF-β1 secretion	*In vitro*	Caco-2	[242]
5, 10, 25, 50, 100 μM	CYP1A1	Suggested the involvement of Ah receptor	*In vitro*	Caco-2	[243]
100 mM	p53, Bax, p21, villin, caspase-3	Triggered p53-independent apoptosis	*In vitro*	HCT116	[244]
0.3–0.4 mg/mouse/d	TTF1, cyclin D1 & D2, DP-1, YB-1, CTLA-4, LIF, TSG101, TGF-β, desmocollin 2, follistatin, MAP kinase, homeobox protein 4.2, glutamate receptor NMDA2B, thrombopoietin	Inhibited cell cycle progression & proliferation, activated immune cells, inhibited carcinogenesis & tumor growth	*In vivo*	–	[245]
10, 20, 25, 30, 50 μM	ODC	Reduced intracellular putrescine, inhibited proliferation	*In vitro*	CaCo-2	[246]
0, 20, 40, 50, 60, 80, 100 μM	CHOP, JNK, DEVDase, PARP, caspase 3, cIAP1, XIAP, Sp1	Induced apoptosis	*In vitro*	HT29	[247]
0–70 μM	12(S)-LOX	Induced apoptosis in a dose-dependent manner.	*In vitro*	SW480	[248]
100 μM	Survivin, luciferase	Induced apoptosis	*In vitro*	HCT116	[249]
50, 100, 200 μM	ODC, c-myc	Induced ceramide de novo biosynthesis, but not hydrolysis of sphingomyelin	*In vitro*	Caco-2	[250]
100 μM	Beclin1, LC3 II, class III PI3K, Lamp2b	Induced apoptosis	*In vitro*	DLD1	[251]
0, 20, 40, 50, 60, 80, 100 μM	eIF-2α, XBP1, CHOP, GRP-78, PARP, caspase 3,12,4	Induced apoptosis	*In vitro*	HT29	[252]
0, 4, 20, or 90 mg/kg	PGE2, COX-2	Decreased PGE2 levels	*In vivo*	–	[253]
50, 100, 200 μM	ODC, c-Myc, SAMDC, SSAT, c-Fos	Increased cell cycle arrest, inhibited polyamine synthesis, increased polyamine catabolism	*In vitro*	Caco-2	[254]
100 μM	P53, p21	Induced apoptosis	*In vitro*	HCT116	[255]
1,5,10,25,50,75,100 μM	AP-1–luciferase	Dose dependent increase of AP-1-luciferase activity	*In vitro*	HT-29	[256]
0.3, 3.3 and 33.3 μg/mL	NAG-1	Induced NAG-1 expression	*In vitro*	HCT116	[257]
8 mg/kg	AgNORs, TBARS	Suppressed DMH-induced colon carcinogenesis at various stages.	*In vivo*	–	[258]
10(−7), 10(−6), 10(−5), 10 (−4) M	p53	Reduced p53 content of MCF-7 breast cancer cells	*In vitro*	Colo 320 HSR (+)	[259]
0, 50, 100, 200 μM	lamin A, ribosomal protein P0, dUTPase, stathmin 1, Caspase-6, proteases	Induced apoptosis	*In vitro*	HCT116	[260]
200 μg/kg/day	Bax, $P21^{CIP}$	Induced apoptosis	*In vivo*	–	[261]
2.5, 5, 10, 20, 43 μM	β-catenin, legless (lgs), pygopusI (pygoI), SEAP	Increased proliferation, inhibited Wnt	*In vitro*	HT29, RKO	[262]
25, 50, 100, 200 μM	caspase-6, lamin A	Promoted apoptosis	*In vitro*	HCT116	[263]
3.13, 6.25, 12.5, 25, 50, 100, 200 μM	P53, Bax, Bcl-2	Inhibited proliferation, promoted apoptosis & cell cycle arrest	*In vitro*	LoVo	[264]
25, 50,100 μM	Bak, FADD	Induced apoptosis, increased FADD & Bak protein percentage ratios	*In vitro*	CaCo-2	[265]
5, 10, 20, 40 μg/mL	Telomerase	Inhibited proliferation	*In vitro*	HT-29	[266]
45 μg/kg	CYP1A1, CYP1B1, glutathione-S-transferase	Increased BaP aqueous (phase II) metabolites (detoxification).	*In vivo*	–	[164]
0 – 300 μM	ERK, JNK, Akt, FAK, Fyn, Grb2, Ras, caspase 3, SOS proteins	Activated lipid raft signaling pathways, induced apoptosis	*In vitro*	SW480, SW620, HT29	[267]
20 μM	4EBP1, Myc	Increased intracellular cAMP, decreased colony formation & proliferation	*In vitro*	HCT116, KM12C	[163]
150 mg/kg	E-cadherin, N-cadherin, phospho (p)-AKT1, p-GSK-3β, Snail	Suppressed metastasis & invasion via reversal of EMT	*In vitro*, in vivo	SW480, SW620	[162]
1 mg/ kg	Rbfox2, AMPK	Inhibited metastasis & proliferation, promoted cell cycle arrest	*In vitro*	B16-F10, HeLa	[268]
1, 2, 5, 10 μM	Sirt1, TNF-β, TGF- β3, caspase-3, p65-NF-κB, CD133, CD44, ALDH1	Promoted crosstalk between CRC & stromal cells to enhance migration & survival	*In vitro*	HCT116	[160]
100 μM	RKIP	Increased RKIP & pRKIP expression in two CRC cell lines	*In vitro*	HT-29, HCT116	[159]
1 mg/kg	connexin 43, Akt, NFκB	Inhibited proliferation, increased gap junction function	*In vitro*, *In vivo*	HCT116, CT26	[157]

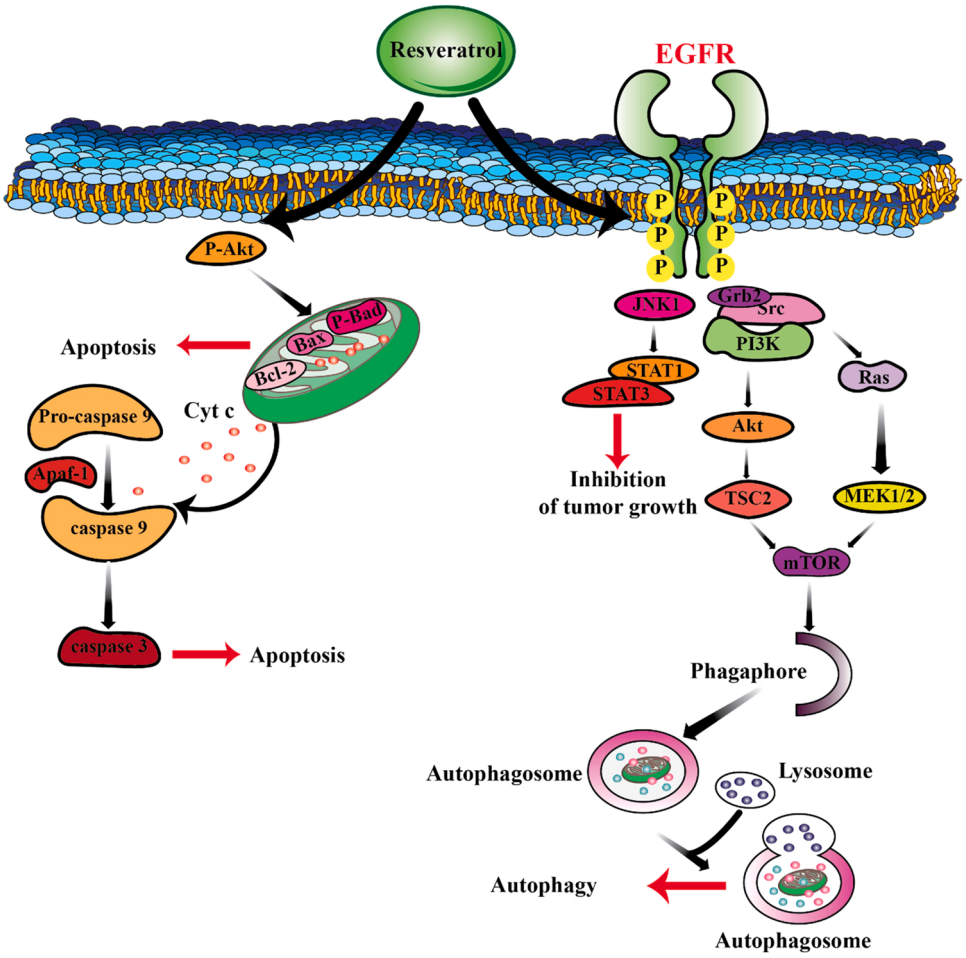

Fig. 3. Schematic of resveratrol potential to target various signaling pathways, introducing a new therapeutic approach in the colorectal cancer treatment [35].

literatures is mediated by MALAT1. Resveratrol by regulating the MALAT1 and Wnt/β-catenin signaling pathways exerts its inhibitory effect on invasion and metastasis of CRC. In detail, resveratrol inhibits Wnt/β-catenin signaling by down-regulating MALAT1, resulting in lower nuclear localization of β-catenin and c-Myc and MMP-7 expression, which inhibits CRC invasion and metastasis [158].

Begum Dariya et al. used a combinatorial *in silico* approach with several computational tools to assess the effects of resveratrol on Raf kinase inhibitory protein (RKIP) and RKIP-phosphorylation [159]. They discovered that resveratrol increased RKIP protein expression. Computational analysis was used to evaluate resveratrol binding affinity and ligand efficiency against RKIP, in order to fully understand the fundamental nature of the interaction. This study suggested that RKIP could decrease metastasis in CRC, and its structural configuration changed during resveratrol-target interaction [159].

Constanze Buhrmann et al. studied if resveratrol could alter paracrine signaling mechanisms in CRC cells undergoing a multicellular TME [160]. The investigators found that multicellular-TME, similar to TNF-α-induced TME, increased CRC proliferation, invasion, colony formation, and CSC activation. The malignancy of multicellular-TME was reversed by co-treatment with resveratrol. In 3D-alginate cultures of HCT116 cells with either multicellular-TME or TNF-α-induced TME, but not Sirt-1, resveratrol inhibited the NF-κB activation, protein secretion, and nuclear translocation induced by T-lymphocytes or fibroblasts. They found significant associations between the expression of NF-κB biomarkers and CSC invasion, proliferation, and survival. Their findings suggested that multicellular-TME improved the contact between stromal cells and CRC cells, increasing HCT116 migration and survival, and that the resveratrol/Sirt1 axis reduced this loop activity via altering NF-κB activation and paracrine agent secretion. It is possible that resveratrol could target fibroblasts and T-lymphocytes to prevent CRC metastasis [160].

EMT plays an important role in the progression of cancer metastasis [161]. PI3K/Akt, JAK/Stat3, TGF-β/Smad, and Wnt/β-catenin signaling cascades have all been implicated in the regulation of the EMT process. Furthermore, the Akt/GSK-3β /Snail signaling pathway promotes tumor invasion and metastasis. In this route, Akt activation decreases GSK-3β activity, which in turn suppresses Snail phosphorylation, resulting in Snail protein stability and nucleus localization, ultimately triggering EMT.After AKT1 knockdown, the inhibitory effects of resveratrol on CRC invasion and metastasis, along with its likely mechanism of action, were investigated in vitro and in vivo [162]. In their study, Yuan et al. observed that following AKT1 knockdown, the anti-cancer effects of resveratrol were attenuated or even nullified. As a result, they propose that resveratrol may regulate EMT in colon cancer cells and limit colon cancer invasion and metastasis via the AKT1/GSK-3β /Snail signaling pathway [162].

Kim et al. investigated the physiological activity of PDE4B, a member of the PDE4 gene family, in CRC as well as the underlying mechanism [163]. PDE4B was found to be a key controller of intracellular cyclic AMP (cAMP) levels in CRC cells, as shown by the fact that forskolin, an adenylyl cyclase (AC) inducer, raised cAMP levels in PDE4B-low cells but not in PDE4B-high cells. cAMP altered AKT and AMPK activity in a PDE4B-dependent manner, which resulted in a considerable reduction in mTOR-Myc signaling and oncogenic characteristics of CRC cells, such as anchorage-independent growth and colony formation. They

Table 4
Effects of resveratrol in esophageal cancer.

Dose	Target (s)	Results	Model (in vitro / *in vivo* /human)	Cell line	Ref.
0, 50, 100, 200, 400 μM	ADAM9	Inhibited migration & viability	*In vitro*	CE48T, CE81T, CE146T	[269]
0, 20, 40, 80 μM	cyclin D1, cleaved PARP/cleaved caspase-3, EGFR	Caused cell cycle arrest & cell death	*In vitro*	KYSE15, KYSE51, Eca109	[270]
0, 10, 50, 100, 150 μM	Caspase-3, Bcl-2, Bax, Beclin-1, ATG-5, LC3I, LC3II, LKB-1, AMPK	Inhibited proliferation	*In vitro*	EC109, EC9706, K562	[271]
0.1, 1, 10, 100 mM	Bcl-2, Bax	Induced apoptosis	*In vitro*	EC-9706	[275]
7 mg/kg	Catalase, PCNA	Decreased esophagitis, lowered incidence of metaplasia & EAC	*In vivo*	–	[272]
1, 2 mg/kg	COX-1, COX-2, PGE2	Inhibited DMBA induced esophageal carcinogenesis in F344 rats	*In vivo*	–	[276]

discovered that the Myc proto-oncogene was a significant downstream target of the AKT/mTOR and AMPK/mTOR pathways, resulting in an anti-tumor effect of cAMP. Resveratrol, which has been proven to inhibit PDE4, also inhibited the mTOR-Myc axis, which has anti-cancer properties. They found that Myc served as a transcriptional activator of PDE4B in CRC cells, which contain low levels of intracellular cAMP and promoted cell longevity. These results suggested that cAMP/PDE4B signaling helps to control the malignant phenotype of CRC cells [163].

Ashley C Huderson et al. sought to gain a molecular understanding of how resveratrol could inhibit benzo (a) pyrene (BaP)-induced colon polyp growth in mice, by modifying cytochrome P450-mediated metabolic pathways [164]. Higher expression of CYP1A1 in the liver and colon, as well as CYP1B1 in the liver, was found in mice treated with BaP, whereas resveratrol reduced the activity of CYP1A1 enzymes in the corresponding samples. There was an increase in the expression of GST in the colon of BaP-treated mice when resveratrol was given before or concurrently with BaP. There was no difference in GST expression in the liver between the BaP and resveratrol groups. Higher values of BaP aqueous (phase II) metabolites were detected compared to BaP organic (phase I) intermediates, suggesting that although resveratrol inhibited BaP phase I metabolism (activation), it promoted phase II metabolism (detoxification). Besides that, the level of BaP-DNA adducts in the colon and liver of BaP plus resveratrol-treated mice were lower in comparison to BaP alone. Altogether, their findings showed that resveratrol reduced BaP-induced colon carcinogenesis via affecting metabolism and DNA adduct production, and thus may have anti-carcinogenic potential [164]. The resveratrol exerts its anti-tumorigenic performance in colorectal cancer cells by modulating various signaling pathways, as seen in Fig. 3.

3.4. Resveratrol and esophageal cancer

Yu-Sen Lin et al. studied the effects of resveratrol on cell migration in lung cancer and esophageal squamous cell carcinoma (ESCC) cells, along with the biochemical pathways involved [269]. They discovered that resveratrol reduced cancer cell migration and survival in lung and esophageal cancer cells by regulating ADAM9. Resveratrol reduced the levels of ADAM9 protein in cancer cells via ubiquitin-proteasome degradation. Furthermore, when combined with clinical chemotherapeutic drugs, resveratrol showed synergistic anticancer effects. Their findings revealed that resveratrol may slow the growth of human lung cancer and ESCC by reducing ADAM9 expression, offering a possible explanation for its anticancer activity [269].

The anti-tumor activity of resveratrol in human ESCC cells, the role of EGFR in resveratrol activity, and the factors underlying the inhibition of EGFR by resveratrol were assessed in a study by Zixuan Jin et al. [270]. According to their findings, resveratrol or an analog, could be effective in the treatment of human ESCC. The authors showed that resveratrol inhibited proliferation of human ESCC, which was attributed to its capability to cause cell death and cell cycle arrest at G0/G1 phase, and was associated with lower cyclin D1 and higher expression of cleaved PARP and cleaved caspase-3, respectively. Downregulation of epidermal growth factor receptor (EGFR) signaling was proposed to be responsible for the anticancer activity of resveratrol in this model. It was also reported that resveratrol treatment was associated with inhibition of EGF-induced EGFR activation, as well as the reduction of total protein values of EGFR, and its membrane/nuclear localization in ESCC cells [270].

Qishan Tang et al. dissected the effects of resveratrol in ESCC cells, looking at autophagy, apoptosis, cell growth, and the cell cycle [271]. They found that resveratrol caused cell cycle arrest at sub-G1 phase and induced apoptosis in a concentration-dependent manner. Autophagy was induced by resveratrol in ESCC cells, but was not mediated by the AMPK/mTOR pathway. Because both genetic and small molecule inhibition of autophagy increased resveratrol-induced cytotoxicity in ESCC cells, this could be a new strategy for increasing the effects of resveratrol (and other chemotherapeutic drugs) in the treatment of ESCC [271].

Using an established rat surgical model, Charles E Woodall et al. investigated how resveratrol affected the progressive development of reflux esophagitis into Barrett's metaplasia, and then to dysplasia and finally to esophageal adenocarcinoma (EAC) [272]. Thirty-one animals in the 5-month resveratrol group showed less severe esophagitis, a lower incidence of intestinal metaplasia and carcinoma, than the saline control group. Histopathology revealed that the resveratrol group had morphological characteristics consistent with less esophagitis, as well as lower rates of metaplasia and EAC. Resveratrol inhibited carcinogenesis and metaplasia advancement in reflux esophagitis, and human studies could be useful to investigate the clinical potential in this common condition [272].

The anti-cancer activity of resveratrol in ESCC cells might be related to induce their apoptosis. Bax and Bcl-2 proteins are essential regulators of the mitochondrial-dependent apoptotic pathway. Bax that positively regulates apoptosis promotes mitochondrial damage, whereas Bcl-2 that negatively regulates apoptosis stimulates cell survival [273]. As an apoptosis index, the Bax/Bcl2 ratio determines the fate of the cell in the direction of cell death or apoptosis. Based on evidence, the impact of Bcl2 gene downregulation on apoptosis process is more significant than the impact of upregulation of Bax gene. It is demonstrated that resveratrol leads to the downregulation of Bcl2 in HCT-116 colon cancer cells through downregulation of miR-21 and the PTEN/AKT axis [274]. The increased ratio of Bax/Bcl-2 by resveratrol has been also reported in treated liver cancer cells. Hai-Bo Zhou et al. investigated resveratrol-induced apoptosis in esophageal cancer cells, as well as the link between apoptosis and the expression of Bax and Bcl-2 [275]. They reported that resveratrol inhibited the proliferation of EC-9706 esophageal cancer cells in a time and dose-dependent manner. Additionally, TUNEL assay showed that after the treatment of EC-9706 cells with resveratrol, expression of Bcl-2 and Bax genes decreased and increased, respectively. Therefore, increasing the Bax/Bcl-2 ratio leading to induction of apoptosis may be one of the inhibitory effects of resveratrol in

esophageal cancer [275].

The effects of resveratrol in esophageal cancer summarized in Table 4.

3.5. Resveratrol and oral cancer

In oral cancer cells (SSC-25 and OEC-M1) Chia-Cheng Lin et al. investigated how thyroxine (T4) affected the expression of checkpoint genes PD-L1 and BTLA, as well as the proliferation gene CCND1. In SSC-25 and OEC-M1 cells, T4 suppressed pro-apoptotic BAD expression while enhancing proliferative CCND1 expression. It boosted PD-L1 and BTLA expression in both cell lines. Resveratrol inhibited the growth-promoting effects of T4. T4 inhibited the expression of pro-apoptotic genes, but resveratrol co-treatment reversed BAD expression. Furthermore, resveratrol inhibited the increase of PD-L1 in the nucleus caused by T4. These data suggest that T4 increases the expression of other checkpoint genes in addition to PD-L1, allowing cancer to evade the immune response. Resveratrol, on the other hand, could inhibit the effects of pro-thyroid hormones [277].

Yi-Ru Chen et al. investigated how T4 could interfere with the anti-proliferative effect of resveratrol in oral cancer cells [278]. T4 reversed resveratrol-induced anti-proliferation by promoting pro-inflammatory gene expression (IL-1 or TGF-1) and PD-L1 protein expression in two oral cancer cell lines. The resveratrol-induced increase in nuclear COX-2 was reduced by co-incubation with T4, and COX-2 was retained in the cytoplasm. S31–201, a selective inhibitor of signal transducer and activator of transcription 3 (STAT3), blocked the effects of T4, while restoring resveratrol-induced nuclear COX-2 accumulation. This showed that STAT3 signaling inhibited the expression of proinflammatory genes and PD-L1, but this could be reduced by T4. Therefore, resveratrol could restore COX-2/p53-dependent gene expression and inhibit cell proliferation by blocking the T4-activated STAT3 signal transduction axis [278].

Yih Ho et al. investigated the mechanisms behind the anti-proliferative effects of NDAT (nano-diamino-tetrac, a tetraiodothyroxine deaminated nano-particulate analog) and resveratrol in human oral cancer cells. The expression of proinflammatory cytokines IL-1 and TNF-α were decreased by both resveratrol and NDAT. These compounds also lowered the expression of PD-L1and CCND1. In OEC-M1 and SCC-25 cells, both NDAT and resveratrol stimulated BAD expression, however only resveratrol stimulated COX-2 expression. The combined treatment lowered gene expression in both cancer cell lines when compared to resveratrol treatment alone. Resveratrol decreased nuclear PD-L1 accumulation, which was increased by S31–201, a STAT3 inhibitor, or NDAT, showing that NDAT can inhibit PD-L1 expression by inactivating STAT3. In the presence of T4, NDAT boosted the anti-proliferative effects of resveratrol in both cell lines. These findings suggest the ability of NDAT to inhibit the pro-inflammatory effects of T4, which reduce the anticancer activity of resveratrol [279].

DNTTIP1 (deoxynucleotidyltransferase terminal interacting protein 1) has been shown to be overexpressed in oral squamous cell carcinoma (OSCC) cell lines and primary OSCCs. Yuki Sawai and colleagues evaluated the clinical significance of DNTTIP1 in cancer, using a knockdown model and resveratrol as an HDAC inhibitor [280]. They found that the interaction between DNTTIP1 and HDAC could promote tumor growth by deacetylating p53, and that DNTTIP1 could be a key target for OSCC treatment by resvertrol [280].

According to Hayashi et al., TRIML2 (tripartite motif family like 2) up-regulation has been observed in human OSCC cells and primary OSCCs [281]. TRIML2 knockdown in OSCC cells was associated with reduced proliferation, caused by cell cycle arrest at G1 phase and decreased expression of cyclin D1, CDK4, and CDK6, along with overexpression of p27Kip1 and p21Cip1. Resveratrol was found to reduce TRIML2 expression, and also produced cell-cycle arrest in the G1 phase. They suggested that TRIML2 could be critical for tumor growth, and resveratrol could disrupt TRIML2 function as a potential treatment for

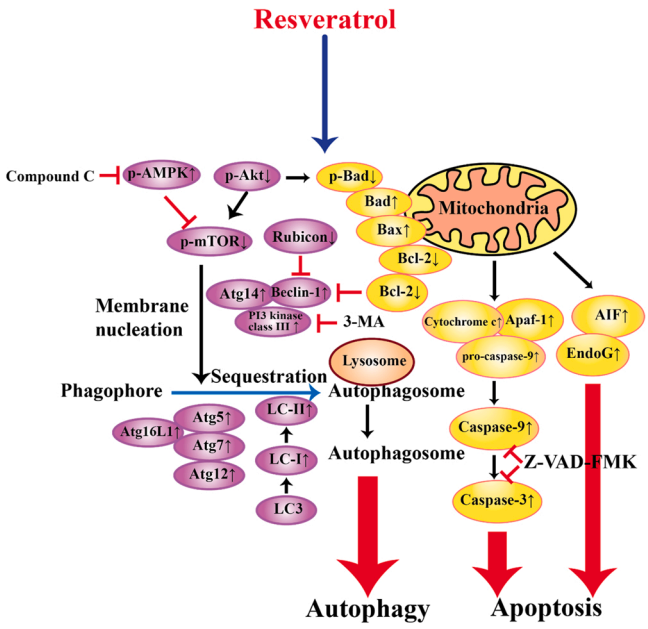

Fig. 4. Schematic of molecular mechanism employed by resveratrol-induced apoptosis and autophagy in human cisplatin-resistant oral cancer CAR cell line [282].

OSCC [281].

Resveratrol is known to be an effective chemopreventive agent against multiple cancers. However, increasing drug resistance can lead to treatment failure in oral cavity cancer. Chang et al. [282] investigated the antitumor activity of resveratrol and its mechanism in cisplatin-resistant human oral cancer CAR cells. They found that resveratrol had low toxicity in normal oral cells, but provoked autophagic cell death in CAR cells. This was shown by the formation of acidic vesicular organelles (AVOs) and autophagic vacuoles stained by acridine orange (AO) and monodansylcadaverine (MDC). Resveratrol also enhanced phosphorylation of AMPK and regulated autophagy and pro-apoptotic signals in resveratrol-treated CAR cells. Importantly, resveratrol also increased the mRNA expression of autophagy-related genes, including Atg5, Atg12, Beclin-1 and LC3-II in CAR cells. Overall, they suggested that resveratrol could induce autophagic and apoptotic death in drug-resistant oral cancer cells (Fig. 4) and might be a new approach for oral cancer treatment in the near future.

Resveratrol is a known chemo-preventive phytochemical agent in the control of various tumor cells. However, a serious challenge in the treatment of oral cancer is the growing emergence of drug resistance. In a study by Chang et al. [282], the resveratrol was examined for its oral antitumor potential and relevant pathways in human cisplatin-resistant oral cancer cell line (CAR). According to their findings, the resveratrol was found in normal oral cells with ultra-low toxicity and triggered an autophagic cell death, thereby generating acidic vesicular organelles (AVOs) as well as autophagic vacuoles in CAR cells, using monodansylcadaverine (MDC) and acridine orange (AO) staining protocols. The CAR cells exposed to resveratrol exhibited an increase in the AMPK phosphorylation and a regulation in autophagy-related and proapoptotic signals. It should be noted that the resveratrol-treated CAR cells experienced an elevation in the expression level of autophagic mRNA genes, such as Beclin-1, LC3-II, Atg5 and Atg12. Their findings revealed that the apoptotic and autophagic cell death may be induced by the resveratrol in drug-resistant oral cancer cells (Fig. 4), suggesting a novel therapeutic strategy for oral cancers in the future. Table 5 summarizes the effects of resveratrol in oral cancer.

Table 5
Effects of resveratrol in oral cancer.

Dose	Targets	Results	Model (in vitro/ *in vivo*/ human)	Cell line	Ref.
1, 10, 100 μM	–	Inhibited proliferation & DNA synthesis	*In vitro*	SCC-25	[283]
40 μM	PD-L1, BTLA, CCND1, BAD	Increased expression of pro-apoptotic genes	*In vitro*	OEC-M1, SCC-25	[277]
25, 50, 75, 100, 200 μM	LC3-II, PI3K class III,	Stimulated apoptosis & autophagic death in drug-resistant oral cancer	*In vitro*	CAR cells	[284]
25, 50, 100 μM	ZEB1, miR-200c, EZH2, H3K27me3, ACTA2, COL1A1, S100A4, α-SMA	Inhibited EB1 expression to suppress the myofibroblast activity of fBMFs	*In vitro*	fBMF1, fBMF2, fBMF3	[285]
25, 50, 75, 100 μM	MMP-9, JNK 1/2, ERK 1/2	Inhibited gene expression & proliferation	*In vitro*	SCC-9	[286]
10, 40 μM	CCND1, PD-L1, COX-2, BAD, ERK1/2	Inhibited proliferation gene expression	*In vitro*	OEC-M1, SCC-25	[278]
10 μM	IL-1β, TNF-α, CCND1, PD-L1, COX-2, BAD	Inhibited gene expression	*In vitro*	OEC-M1, SCC-25	[279]
0.5, 0.7,1.0 μg/mL	Phosphorylated-cdc2 (Tyr 15), cyclin B1, cyclin A2	Inhibited proliferation	*In vitro*	SCC-VII, SCC-25, YD-38	[287]
50 μM	DNTTIP1, HDAC	Promoted tumor growth	*In vitro*, in vivo	HSC-2, HSC-4	[280]
50 μM	TRIML2	Affected tumor growth	*In vitro*	Sa3, SAS	[288]
6.25, 12.5, 25, 50, 100 μM	–	Boosted doxorubicin cytotoxicity	*In vitro*	HSC-2	[289]
20–100 μM	Tetrazolium-1, fura-2 fluorescence	Caused Ca2 + -independent apoptosis.	*In vitro*	OC2	[290]
10–500 μM	Bak, Bax, Bcl-2, Bcl-xl, Apaf-1, PARP, ICAD, E-cadherin	Increased apoptotic cell ratio, inhibited invasion & migration	*In vitro*	CAL-27, SCC15, SCC25	[291]
5, 10, 25, 50, 100 μM	–	Increased cytotoxicity, reduced migration	*In vitro*	PE/CA-PJ15	[292]
0.25 % Res (w/w)	phospho-AMPK (Thr172), p62	Prevented 4NQO-induced oral tumorigenesis, inhibited proliferation, induced apoptosis & autophagy	*In vivo*	4NQO	[293]
25, 50, 100 μM	–	Inhibited adhesion, migration, & invasion	*In vitro*	KB	[294]
20 μM 100 mg/kg	uPAR, pERK1/2, integrin β1	Reversed cetuximab resistance in OSCC.	*In vitro*, in vivo	SAS, Sa3, HSC-3	[295]
5, 10, 50, 100 μM	HIF-1α, VEGF, Erk1/2, PI-3 K/Akt, p42/p44 MAPK	Chemopreventive effects	*In vitro*	SCC-9	[296]
5, 10, 15, 20, 30, 45, 70, 100 μM	–	Inhibited DMBA carcinogenesis in hamster cheek pouch	*In vivo*	HCPC I	[297]

3.6. Resveratrol and hepatocellular cancer

Gene therapy with suicide genes is an appealing therapeutic option for hepatocellular carcinoma (HCC), and thymidine kinase (TK), obtained from the herpes simplex virus (HSV), is a suicide gene that has received much research [298]. A clinical trial has already shown that HSV-TK/GCV therapy for HCC treatment is feasible and safe [299]. Evidence proves that cytotoxicity of multiple drugs is augmented via bystander effect, which is partly mediated by cell-cell communication mediated by gap junction [300]. Unfortunately, HCC cells have poor cell-to-cell communication due to a lack of gap junctions; also, HCC cells prefer to suppress connexin (Cx) expression.

Jianyong Xiao et al. theorized that the killing effect of the HSV-TK suicide gene on HCC cells is boosted by resveratrol via elevation of the bystander effect [301]. The researchers also looked at Cx expression in HCC cells following resveratrol treatment, because of the strong relationship between resveratrol and GJIC (gap junctional intercellular communication) [301]. Their findings showed that resveratrol could enhancement the bystander effect of the HSV-TK/GCV (gancyclovir) suicide gene system via improving Cx-mediated gap junctional communication. In murine hepatoma cells (CBRH7919), they discovered that resveratrol increased expression of both essential elements of gap junctions, Cx43 and Cx26. Theoretically, resveratrol-induced gap junction upregulation could improve the HSV-TK/GCV bystander effect in hepatoma cells. Resveratrol could increase intercellular communication at gap junctions allowing GCV to kill the CBRH7919-TK cells. The long-term inhibitor of gap junctions, alpha-glycyrrhetinic acid reduced the cytotoxicity of HSV-TK/GCV gene therapy. Furthermore, co-treatment of tumor-bearing mice (CBRH7919-TK or CBRH7919-WT cells) with GCV and resveratrol at a ratio of 2:3 produced a marked reduction in tumor weight and size when compared to GCV or resveratrol alone [301].

Based on these findings, the authors conclude that when resveratrol is administered in low doses, it works synergistically with HSV-TK/GCV therapy to induce HCC cell killing, and the underlying mechanism mainly involves GJIC [301].

Qin Jiang et al. looked at the effects of paclitaxel in combination with resveratrol in order to minimize the dose and side effects of paclitaxel, while still maintaining the anti-tumor effect [302]. The researchers compared the anti-tumor effect of resveratrol and paclitaxel in HepG2 human liver cancer cells in vitro. They concluded that resveratrol could improve the anti-tumor effect of paclitaxel in HepG2 cells, and that resveratrol may be an effective paclitaxel sensitizing agent [302].

Feng Gao and colleagues discovered that the c-Met signaling pathway played an important role in the anti-cancer effect of resveratrol in HCC cells. Inhibiting the activation of HGF-c-Met signaling could be an approach for HCC prevention and treatment, according to their findings [303]. Resveratrol suppressed the HGF-c-Met signaling pathway, contributing to its anti-tumor effect in HCC cells. Resveratrol suppressed both anchorage-dependent and anchorage-independent HCC cell growth in a concentration-dependent manner. The activation of the HGF-induced c-Met signaling pathway was reduced by short-term resveratrol exposure, whereas long-term resveratrol treatment suppressed c-Met expression on the cell membrane. In addition, treatment with resveratrol suppressed HGF-induced cell invasion, while c-Met knockdown reduced HCC cell sensitivity to resveratrol treatment. Finally, the anticancer effect of resveratrol was confirmed in a xenograft tumor model, where resveratrol reduced tumor development in vivo. Their data suggested that c-Met could be a useful molecular target for HCC treatment [303].

The effects of resveratrol and IFN-α on the apoptosis, proliferation, and cell cycle of SMMC7721 cells were studied by Zhanchun Yang and colleagues. Their findings suggested that phytoestrogens affected the SIRT1/STAT1 pathway, which could lead to a new approach to reduce tumor resistance to IFN-α by targeting STAT1. They discovered that IFN-α inhibited SMMC7721 proliferation and induced apoptosis, which could be increased by resveratrol, and prevented by EX527 (a Sirt-1 inhibitor). Resveratrol was shown to be able to activate SIRT1 as well

Table 6
Effects of resveratrol in hepatocellular cancer.

Dose	Targets	Results	Model (in vitro/ *in vivo*/ human)	Cell line	Ref.
0–10 μg/mL	caspase-3,8,9, Bax, p53, p21, IκB-α, TIMP-1,2, Bcl-2, Bcl-xL, HIAP-1,2 cIAP-1, cIAP-2, NF-κB, COX-2,MMP-2,9, EGF, VEGF, Fit 1	Increased the anti-tumor effect of paclitaxel	*In vitro*	HepG2	[302]
30 mg/kg	HGF-c-Met	Inhibited tumor growth in vivo using a xenograft model	*In vitro,* in vivo	Hep3B, MHCC9L	[303]
0, 25, 50, 75, 100 μM	ADRB-2-HIF-1α axis	Inhibited proliferation under chronic stress	*In vitro*	HepG2	[306]
12.5, 25, 50, 100 μM	p53	Inhibited proliferation	*In vitro*	HepG2	[200]
20, 50, 80, 110, 140, 170, 200 μM	Bax, PARP, Bcl-2, caspase-3, caspase-7, SIRT1, PI3K, AKT, p-Fox O3a, PCNA, Ac-FoxO1, DLC1	Inhibited proliferation & migration	*In vitro*	HepG2, Bel-7402, SMMC7721	[307]
10, 20, 30 μM	STAT1, SIRT1	Increased the response of HCC to IFN-α treatment	*In vitro*	SMMC7721	[308]
0, 10, 20, 40, 60, 80, 100, 150, 200 μM	Beclin1, LC3 II/I, p62, p53, p-Akt	Inhibited proliferation & migration	*In vitro*	MHCC9H	[309]
12.5, 25, 50, 100, 200 μg/mL	ASCT2, cytochrome c, caspase-3, and caspase-9	Sensitized human hepatoma cells to cisplatin	*In vitro*	C3A, SMCC7721	[140]
80 μM	IL-6, CXCR4, Gli-1, MMP-9, uPA	Inhibited proliferation	*In vitro*	HepG2	[310]
100, 150 mg/kg	Cx26, Cx43	Enhanced intercellular gap junction communication	*In vitro,* in vivo	CBRH7919	[311]
50, 100 mg/kg	cyclin D1, Akt, and $p70^{S6K}$	Inhibited proliferation.	*In vitro,* in vivo	HBV X- Huh7	[312]
0.39, 0.78, 1.56, 3.13, 6.25, 12.5, 25 μg/mL	Caspase3, 7	Inhibited proliferation in a time & dose-dependent manner.	*In vitro*	HepG2	[313]
0, 5, 10, 25, 50, 100 μM	XBP1, CHOP, caspase-3, SCD1	Inhibited saturated FA content primarily by reducing triglyceride accumulation	*In vitro*	HepG2	[314]
10–160 μM	caspase-3, 8, 9, XIAP, survivin	Inhibited proliferation in a concentration & time-dependent manner.	*In vitro*	Hepa1–6	[315]
20, 40, 80 μM 10 mg/kg bw	HK2, lactate, caspase-3, 9, cleaved PARP, PKM2, Bax	Sensitized aerobic glycolytic cells to apoptosis	*In vitro,* in vivo	Bel-7402, HepG2, HCCLM3	[316]
0, 10, 20, 40 μM	VEGF	Inhibited proliferation, suppressed VEGF gene expression	*In vitro*	HepG2	[317]
20 mg/kg	PARP, caspase-3, p53, cytochrome-c, Bax, Bcl2	Activated apoptosis in male Wistar rats	*In vivo*	–	[318]
0, 25, 50, 75, 100, 200 μM	u-PA, JNK1/2, SP-1, PAI-1	Upregulated SP-1 pathway transcription factors	*In vitro*	Huh7	[319]
0, 10, 100, 200 μM	SIRT1, cyclin D1, VEGF, MMP-9,	Inhibited proliferation	*In vitro*	HepG2	[320]
10, 15 mg/kg	5-FU	Inhibited murine hepatoma 22 tumor growth	*In vivo*	Hepatoma 22	[321]
50, 75, 100, 125, 150, 175, 200, 225, 300 μM	cyclin D1, p38, Akt, Pak1, p-ERK1, p-ERK2, PCNA, GSK3β	Chemopreventive agent against liver cancer	*In vitro*	HepG2	[322]
10, 20, 40, 60 μg/mL	p21/WAF1, cyclin E, cyclin A, CDK 2, caspase 8, 9, Atg5, Atg7, Atg9, Atg12, Bcl-2, Bcl-xL	Chemopreventive agent against hepatitis C virus-induced hepatoma	*In vitro*	Huh-7	[323]
20, 40, 80 μM	caspase-3	Promoted apoptosis, inhibited proliferation	*In vitro*	Hepa 1–6	[324]
–	IL-8	Chemotherapeutic potential & immunomodulation activity	*In vitro,* in vivo	Bel-7402	[325]
–	MMP-9	Inhibited proliferation, down-regulated gene expression.	*In vitro*	SMMC-7721	[326]
10^{-12}, 10^{-11}, 10^{-10}, 10^{-9}, 10^{-8}, 10^{-6} M	ROS, eNOS, iNOS	Promoted apoptosis, inhibited proliferation, decreased ROS levels	*In vitro*	HepG2	[327]
200 mM	PTEN, Bcl-xl	Inhibited proliferation	*In vitro*	HepG2	[328]
2.5, 5, 10, 20, 40, 80, 160, 320 μM	–	Inhibited proliferation in a dose & time-dependent manner	*In vitro*	HepG2	[329]
5, 10, 20, 50, 100 μM	HDACs	Concentration-dependent anti-proliferation effect on all cell lines. Inhibited HDACs only in HepG2 cells	*In vitro*	HepG2, Hep3B, HuH7	[330]
0.2, 0.4, 2, 4, 6.25, 12.5, 25, 50, 100 μM	–	Slight increase in viability at all doses except 100 μM	*In vitro*	HepG2	[331]
5, 10, 20, 25, 50, 100, 200 μM	PARP-1, caspase-9, 3,Bax, Bcl-2, p53	Decreased viability	*In vitro*	HepG2	[332]
50, 100 and 300 mg/kg	nitric oxide synthase, 3-NT, Nrf2	Prevented diethylnitrosamine (DENA)-induced liver carcinogenesis in rats	*In vivo*		[333]
6.25, 12.5, 25, 50, 100 μM	MEK, phospho-CDK2, chk 2, CDK4, CDK6, Cyclin D1, D3, E, p21, caspase-7, PARP, Bax, Bim, Puma, phospho-ERK, -PDK-1, -Raf, Akt	Inhibited proliferation & DNA synthesis, induced apoptosis & cell cycle arrest	*In vitro*	HepG2	[334]
10, 50, 100 μM	MMP-9, NF-kappa B	Inhibited TNF-α-induced MMP-9 & invasion	*In vitro*	HepG2	[335]
50, 100, 300 mg/kg	Bax, Bcl-2	Induced apoptosis signaling	*In vivo*	Induced HCC	[336]
15 mg/kg	CAV1, caspase-3, ERK, p-p38	Induced HepG2 cell death in a concentration & time-dependent manner	*In vitro,* in vivo	HepG2	[337]
10, 50 ppm	Total chol, HDL, VLDL, LDL	Increased fecal excretion of neutral sterols & bile acids	*In vivo*	AH109A	[338]
			In vitro	SK-Hep-1	[339]

(*continued on next page*)

Table 6 (*continued*)

Dose	Targets	Results	Model (in vitro/ *in vivo*/ human)	Cell line	Ref.
50, 100, 150, 200, 225, 250 μM	Ras-related protein Rab 37, annexin A8, thymidine kinase, maspin	Caused cytotoxicity, inhibited expression of antioxidant proteins			
0–200 μmol/l	phospho-AMPK, surviving	Induced apoptosis.	*In vitro*	HepG2	[340]
50 mg/kg bw	MLCK	Decreased MLCK expression, promoted apoptosis, inhibited liver carcinogenesis in a DENA-induced HCC rat model	*In vivo*	HCC	[341]
5, 10, 15 mg/kg	cyclin B1, D1, p34cdc2	Anti-tumor activity	*In vivo*	H22	[342]
500, 1000, 1500 mg/kg	IgG, PFC	Inhibited proliferation	*In vitro* in vivo	H22	[343]
10, 30 μM	UGT1A1, UGT2B7 and ST1E1	Increased mRNA expression levels of three metabolic enzymes	*In vitro*	HepG2	[344]
0–350 μM	caspases 2, 3, 7, 8, 10	Activated anticancer pathways	*In vitro*	H4IIE	[345]
1, 3, 10, 30, 50, 100, 150, 200 μM	–	Inhibited proliferation at μM range in a concentration and time-dependent manner	*In vitro*	HepG2, Fao	[346]
0–100 μM	HGF	Reversed the increase in peroxide levels & expression of HGF in ROS-stimulated tumor cells.	*In vitro,* in vivo	AH109A	[347]
1, 5, 10, 20 μg/mL	p53, p21, Bax	Induced cell cycle arrest at G1 phase, increased expression of p21 & Bax in p53 + Hep G2 cells	*In vitro*	Hep G2,Hep 3B	[348]
2.5, 5, 25 μM	HGF	Decreased growth factor expression, induced invasion	*In vitro*	HepG2	[349]
0, 1, 10, 50, 100 μM	PS	Decreased PS expression in an ER independent manner,	*In vitro*	HepG2	[350]
50, 100 or 300 mg/kg	IL-1, IL-6, and TNF-α	Normalized DENA-induced alterations, reduced expression of IL-1, IL-6, TNF-α	*In vivo*	hepatocarcinogenesis	[351]
1, 5, 10 μM	PON-1, AhR	Increased gene expression in primary human hepatocytes & hepatoma cell line	*In vitro*	HuH7	[352]
0–200 μM 1, 5, 10, 100 mg/100 g bw	–	Inhibited invasion, ROS potentiated invasion	*In vitro, ex vivo*	AH109A	[353]
1.25, 2.50, 5.0, 10.0, 20.0 μg/mL	–	Inhibited proliferation, induced apoptosis	*In vitro*	H22	[354]
0.01–500 μM	mTOR, S6K1 and eIF4E-BP1, eIF4F, eIF2α	Inhibited global protein synthesis.	*In vitro*	H4-II-E	[355]
50, 100, 300 mg/kg	HSP70, COX-2, NF-κB p65, IκBα	Suppressed DENA-induced increased expression of hepatic HSP70 & COX-2.	*In vivo*	–	[356]
0–20 μM	CYP1A1, AHR	Inhibited CYP1A1 expression	*In vitro*	HepG2	[357]
5, 10, 25, 50, 100 μM	HO-1, PON-1, Nrf2	Induced antioxidant enzymes heme oxygenase-1 & paraoxonase-1 in cultured hepatocytes.	*In vitro*	HUH7	[358]
1 mg/kg bw	–	Induced apoptosis, reduced cell number.	*In vitro, In vivo*	AH-130	[359]
0, 50, 100, 150, 200 μM	ZEB2	Decreased viability, promoted cell cycle arrest & apoptosis	*In vitro*	SNU398	[360]
100 mg/kg	Lactate dehydrogenase, sirtuin 1, catalase	Normalized the levels of urea, lipid peroxidation, lactate, lactate dehydrogenase, downregulated the increased expression of sirtuin 1	*In vivo*	–	[361]
100 mg/kg	Catalase, glutathione peroxidase, NF-κB, SIRT1, LPO	Restored the levels of catalase & glutathione peroxidase in alcohol-aflatoxin B1-induced HCC	*In vivo*	–	[362]

as phosphorylated STAT1. Inhibition of STAT1 reduced the combined anticancer effects of IFN-α and resveratrol, reduced apoptosis, and boosted the survival of SMMC7721 cells. On the other hand, overexpression of STAT1 increased the anticancer effect of the resveratrol and IFN-α combination. Their findings suggested that resveratrol could be a potential approach to improve HCC response to IFN-α therapy via the SIRT/STAT1 pathway [304].

Seungmo Park et al. evaluated the anti-tumor effect of resveratrol against HBV-induced HCC using Huh7-HBx human hepatoma cells overexpressing the HBV X-protein. They also assessed how resveratrol affected survivin expression, STAT3 downstream mediators, and cyclin D1 in BALB/c nude mice implanted with Huh7-HBx cells [305]. Resveratrol reduced cell viability according to the MTT assay. Resveratrol caused G1 cell cycle arrest without any effect on the sub-G1 cell population, according to flow cytometrty. As a result, they looked into how resveratrol affected cyclin D1 regulation, which is crucial during the G1/S cell cycle transition. The cyclin D1 signaling pathway, as well as the ERK, p90RSK, Akt, and p70S6K signaling pathways, were all suppressed by resveratrol, but not the ERK signaling pathway. In a xenograft mouse model, an intraperitoneal infusion of resveratrol decreased tumor volume. Downregulation of survivin was observed, although cyclin D1 expression was unaltered. The findings suggested that resveratrol administration may help the management of HBV-induced HCC by regulating survivin levels [305].

Effects of resveratrol in hepatocellular cancer is summarized in Table 6.

3.7. Resveratrol and biliary tract cancer

Resveratrol strongly decreased the acetylation of FOXO1 (Forkhead Box O1) and the interaction between Ac-FOXO1 and Atg7, preventing autophagy in human cholangiocarcinoma QBC939 cells and triggering apoptosis and decreasing viability. In vitro findings show that treatment of these cells with resveratrol suppressed autophagy progression and enhanced the oxidative stress and mitochondrial dysfunction (MtD). Likewise, pharmacological suppression of autophagy worsens resveratrol-induced oxidative stress, MtD, and apoptosis whereas rapamycin promotion autophagy and mitigates these effects. As a result, one of the mechanisms by which resveratrol triggers apoptosis in QBC939 cells is oxidative stress and MtD caused by autophagy suppression [363].

Suyanee et al. showed that resveratrol could suppress the ability of IL-6 to stimulate growth and migration in CCA cells and immortalized cholangiocytes. Resveratrol stimulated autophagy and increased the expression of E-cadherin over N-cadherin in migrating cells. They showed that resveratrol had anticancer effects through affecting pro-tumorigenic metabolic and cytokine-mediated cross-talk between CAFs

Table 7
Effects of resveratrol in biliary tract cancer.

Dose	Targets	Results	Model (in vitro/ *in vivo*/ human)	Cell line	Ref.
–	bcl-2, c-myc, p53	Suppressed proliferation, induced apoptosis	*In vitro*	GBC	[368]
20 μM	FOXO1, Atg7, LC3, p62	Decreased viability, promoted apoptosis.	*In vitro*	QBC939	[369]
20 mg/kg	Cyp1b1	Decreased gene expression in cells & tumors.	*In vitro,* in vivo	Mz-ChA-1	[370]
0, 8, 16, 32, 64 μM	LDH, ALP, TG	Inhibited proliferation in both cell lines, produced 40 times more ALP and LDH activity in culture medium	*In vitro*	SK-ChA-1	[367]
32, 64 μM	TG2	In both cell cultures inhibited proliferation by 24–76 %.	*In vitro*	SK-ChA-1, MZChA1	[365]
50, 100 μM	IL-6, N-cad, E-cad	Abolished the secretion of pro-migratory factors, inhibited autophagy.	*In vitro*	CCA KKU-213, KKU-100	[364]

and cancer cells. They also revealed that conditioned media from cholangiocarcinoma-derived CAFs contained IL-6, which increased CCA cell migration. Surprisingly, resveratrol could prevent CAFs from secreting IL-6, essentially removing the pro-migration effect of their conditioned medium. The latter effect was linked to the induction of autophagy in CCA cells. They discovered that while IL-6 did promote the cell migration of invasive CCA cells, resveratrol strongly inhibited migration in both immortalized cholangiocytes and CCA cells. IL-6-mediated CCA cell motility was greatly enhanced by CAF-conditioned medium, while CAF-conditioned medium pre-treated with resveratrol fully prevented cancer cell motility and reversed the N-cadherin to E-cadherin switch in migrating cells. This was the first evidence that CAF secreted products could affect autophagy and CCA cell behavior, and that a nutraceutical such as resveratrol could reverse cancer cell malignancy by affecting CAF metabolism and secretion [364].

Leda Roncoroni et al. investigated whether inhibition of transglutaminase 2 (TG2) could abolish the cytotoxic effect of resveratrol on cholangiocarcinoma and gallbladder cancer cell lines [365]. The addition of resveratrol to both cell lines resulted in a considerable decrease in proliferation, ranging from 24 % to 76 %. The TG2 inhibitors successfully lowered TG2 activity while leaving the protein quantity unchanged. After TG2 suppression, the proliferation that had been inhibited by resveratrol was restored to normal. Furthermore, morphologic study indicated that RES had a cytotoxic effect and that this effect was reduced when TG2 was inhibited. The researchers discovered a relationship between the cytotoxic effects of resveratrol and TG2 enzyme activity in cholangiocarcinoma and gallbladder cancer cell lines [365].

Gabriel and colleagues found that the addition of low doses of resveratrol to cholangiocarcinoma cells was associated with minor toxicity, and increased sensitivity to several chemotherapeutic drugs that are currently used in clinical settings. They also demonstrated that this sensitivity was linked to a reduction in expression of Cyp1b1, and knockdown of Cyp1b1 in these cells was also associated with increased sensitivity to chemotherapeutic drugs [366]. They looked at how resveratrol affected cholangiocarcinoma cell chemosensitivity and found a relationship between Cyp1b1 expression and chemosensitivity. Resveratrol was administered to cholangiocarcinoma cell lines before they were given mitomycin, gemcitabine, or 5-fluorouracil (5-FU). In vitro, resveratrol co-treatment with each chemotherapeutic drug reduced proliferation and enhanced apoptosis more compared to each chemotherapeutic drug alone. They found that treatment with 5-FU plus resveratrol produced a more pronounced reduction in tumor volume and higher TUNEL staining in vivo compared to treatment with 5-FU alone. Moreover, in Mz-ChA-1 cells and cholangiocarcinoma tumors, resveratrol reduced Cyp1b1 expression. In vitro investigation using stable-transfected cells with Cyp1b1 expression knocked down (Mz-Cyp1b1) showed that Mz-Cyp1b1 cells had higher sensitivity to chemotherapeutic drugs compared to mock-transfected cells, and Mz-Cyp1b1-induced tumors were more sensitive to 5-FU treatment in vivo than mock-transfected tumors. They suggested that resveratrol administration could be an adjuvant treatment for improving chemosensitivity in patients suffering from cholangiocarcinoma [366].

Leda Roncoroni et al. investigated the effects of resveratrol on a human cholangiocarcinoma cell line (SK-ChA-1) in two and three-dimensional cultures [367]. Resveratrol inhibited cell growth in both types of cell culture, and led to 40 times higher ALP and LDH activity in the culture medium. Transglutaminase (TG) activity was increased in cell lysates, and cell cycle arrest was produced in the G(1)/S phase. Their findings suggested that resveratrol could be used as a chemotherapeutic/chemopreventive agent for cholangiocarcinoma [367].

Table 7 summarizes the effects of resveratrol in biliary tract cancer.

4. Resveratrol and gastrointestinal cancer clinical trials

The Clinicaltrials.gov showed more than 150 ongoing human clinical trials of resveratrol, 14 of which were associated with resveratrol against cancer. Numerous trials were performed to evaluate the safety, pharmacokinetics, and bioavailability of resveratrol, and the only limited recorded trials focused on evaluating the efficacy of resveratrol in some cancers. Although the majority of the studies were focused on colorectal cancer, it also covered cancers such as breast cancer, multiple myeloma, follicular lymphoma, liver cancer, and neuroendocrine tumors. *In vitro* studies indicated that resveratrol suppresses growth and triggers apoptosis in human colon cells, and murine models of colorectal cancer revealed that resveratrol decreased colorectal carcinogenesis and inflammation [371].

Nguyen et al. conducted the first phase I clinical trial on resveratrol treatment in colon cancer patients [372]. They compared the use of low-dose plant-based resveratrol (20 or 80 mg/day; $n = 2$ and 1, respectively) with freeze-dried grape power resveratrol (80 or 120 g/day; $n = 3$ and 2, respectively) in patients with colorectal cancer ($n = 8$) who had normal and cancerous intestinal mucosal samples biopsied at the time of diagnosis and two weeks after daily oral supplementation. The Wnt signaling pathway, which is known to be implicated in colon cancer formation, was assessed in normal and malignant mucosa before and after resveratrol or grape powder administration. The authors noted that after administration of resveratrol and grape powder, the inhibition in expression of Wnt, myc, and cyclin D1 genes were notable in cases of normal colon mucosa, while no changes were observed in cancer cells [372]. The low-dose grape powder had the most significant results. As a result, the authors concluded that resveratrol, in combination with other compounds found in grapes, could potentially be utilized to lower the risk of colon cancer formation by reducing Wnt signaling pathway, although it might not be as effective against established colon cancer [372].

Since, despite all colorectal cancer research done with resveratrol, the optimal dose has not yet been discovered, one phase I clinical trial (NCT00433576) lunched to investigate the side effects and determine the optimal dose of resveratrol that will result in bioactive levels in patients with colorectal cancer [373].

In a pharmacokinetic study (NCT00920803) by Howells et al., they

Table 8
Novel formulations of resveratrol for gastrointestinal cancer.

Type of cancer	Formulation	Dose	Targets	Results	Model (in vitro/ *in vivo*/ human)	Cell line	Ref.
Breast, pancreatic, prostate	Resveratrol-conjugated gold nanoparticles	6.3 – 200 μg/mL	–	Gum Arabic increased the corona of resveratrol on the surface of AuNPs	*In vitro*	PANC-1	[380]
Pancreatic cancer	Resveratrol-loaded albumin nanoparticles		HAS, RGD	Highest inhibitory activity among tested drugs, good biocompatibility, no recurrence, no significant toxicity	*In vivo*		[381]
Hepatic carcinoma	Resveratrol loaded chitosan nanoparticles	0.25 mg/kg	–	Improved anticancer activity, superior cytotoxicity than B-CS	*In vitro,* in vivo	HepG2	[382]
Hepatic carcinoma	Pterostilbene	12.5, 25, 50, 100 μM	P53, SOD2	Increased ROS production, activated mitochondrial apoptosis pathway	*In vitro,* in vivo	HepG2	[383]
Liver cancer	Resveratrol nanoparticles	6 mg/kg	FA-HSA-RESNPs	Demonstrated folate-receptor targeting	*In vitro,* in vivo	HepG2	[376]
Hepatocellular carcinoma	Resveratrol-loaded CS-TPP, R-CS-1, R-CS-5	5, 10, 20, 30, 40 μg/mL	–	Showed stability to long-term storage & UV light	*In vitro*	SMMC 7721	[384]
Liver cancer	GL-HSA-RES-NPs	5 mg/kg	–	Displayed efficient targeting to liver tumors, sustained-release property	*In vitro,* in vivo	HepG2	[385]
Liver cancer	Res-GNPs	1, 4, 8, 12 μg/mL	pro-caspase-9, − 3, PI3K, Akt, caspase-8, Bax, VEGF	Stimulated apoptosis, inhibited proliferation	*In vitro,* in vivo	HepG2	[377]
Colon cancer	RES loaded colloidal (MCM-48-RES)	48, 100, 200, 400 μM	PARP, cIAP1, NF-κB	Enhanced solubility by ~95 %, increased in vitro release kinetics, demonstrated anti-inflammatory activity	*In vitro*	HT-29, LS147T	[386]
Colorectal cancer	Resveratrol-loaded calcium-pectinate beads	1:1, 2:1, 3:1, 4:1 μg/mL	–	Optimized Ca-pectinate beads	*In vitro*	–	[387]
Colorectal cancer	Resveratrol-loaded Zn-pectinate beads	1.1, 2.1, 3.1, 4.1 μg/mL	–	Displayed improved delayed drug release pattern compared to Ca-pectinate beads.	*In vitro*	–	[388]
Colon cancer	Resveratrol-LNC	–	–	Gradual increase in target to non-target uptake with time	*In vitro*	HT29	[389]
Colon cancer	Technetium-99 m labeled resveratrol loaded AuNPs ($^{99\ m}$Tc-Res-AuNP)	5, 6.5, 10, 12.5, 22.5, 40, 50, 80, 100,160 μg/mL	–	Induced cancer cell uptake	*In vitro,* in vivo	HT29	[378]
Colorectal cancer	RCRL	50, 100, 200 μM	–	Enhanced cytotoxicity profile of liposomes	*In vitro*	HT-29	[390]
Colorectal cancer	RV-SLN, LNA-RV-SLN, DHA-RV-SLN	5, 10, 50 μM	caspase-3	Enhanced PUFA incorporation into cells, inhibited proliferation	*In vitro*	HT-29, HCT116	[391]
Colorectal cancer	Resveratrol loaded INU-F68-SA nanomicelles (RSNM)	3.75, 7.5, 15, 30, 60, 90 μg/mL	–	Increased cytotoxicity to CRC cells, stimulated apoptosis, altered mitochondrial membrane potential	*In vitro,* in vivo	HCT 116	[392]
Colon cancer	3,5,4′-trimethoxy-trans-stilbene loaded PEG-PE micelles	0.25, 2.25, 4.97, 11.05 μM	caspase-3	Suppressed tumor growth, increased survival with very low damage to normal tissue	*In vitro,* in vivo	CT26	[393]
Hepatic cancer	NP-0S, NP-50S, NP-100S	0.025, 0.25, 0.05, 0.125 mg/mL	–	Improved cell uptake, reduced CCl4-induced hepatotoxicity by decreasing oxidative stress	*In vitro,* in vivo	Caco-2, CCl-13	[394]
Colon cancer	As_2O_3 combined with resveratrol	1, 3, 5, 25, 50 μM	hERG, Bcl-2, Bax	Inhibited proliferation, promoted apoptosis	*In vitro,* in vivo	HCT116	[395]
Colon cancer	Resveratrol-ferulic acid (FER), resveratrol -FER-FA-SLNs	0.25, 0.5, 1.0, 5, 10, 15, 20, 25, 30 μg/mL	cyclin D1, E, CDK4, CDK2, CDK-6, Bcl-2, p53, Bax, cytochrome C, caspase 3, 9	Increased cytotoxicity, Induced apoptosis	*In vitro*	HT-29	[396]
Colon cancer	Albumin loaded$^{99\ m}$Tc-resveratrol, AuNP loaded$^{99\ m}$Tc-resveratrol	–	–	Single-photon emission computed tomography (SPECT).	*In vivo*	colon cancer	[397]
Colorectal cancer	NLCs, CSNLCs	2.5, 5, 7, 10, 12 μg/mL	caspase-3, death receptor (DR-4)	Inhibited proliferation, both NLC and CSNLC induced apoptosis in hepatocytes	*In vitro,* in vivo	Hep-G2, HCT-116	[398]
Colorectal cancer	RBT/Res, Ru-CeO_2-RBT/Res, Ru-CeO_2-RBT/Res-DPEG	20 μg/mL, 5 mg/kg	HIF-1α	Good tumor penetration depth, antitumor effects, alleviated tumor hypoxia, inhibited metastasis	*In vitro,* in vivo	Caco-2, SW480, HCT116, CT26	[399]
Colorectal cancer	Curcumin plus resveratrol	0, 5, 10, 20, 25, 30 μM	–	Improved bioavailability, anticancer activity	*In vitro*	HCT-116	[400]

observed the impacts of resveratrol or SRT501 therapy in colorectal cancer patients with hepatic metastasis scheduled to undergo hepatectomy (n = 9) [374]. Following daily administration of 5 g of micro-ionized resveratrol SRT501 for 10–21 days (n = 6), a significant increase in the expression of cleaved caspase-3 in tumor tissue compared with equivalent tissue from subjects on placebo-treated (n = 3) indicates increased apoptosis of cancerous cells. In this study, researchers reported higher levels of resveratrol in plasma (1942 ± 1422 ng/mL) and hepatic tissues (1098 ± 1393 ng/g) after SRT501 administration in the patients. No significant change was observed in the other biomarkers tested, including AKT1, survivin, GSK-3, and PARP. It seems that micronized resveratrol was better tolerated by patients, with all adverse events evaluated as mild when compared to nonmicronized resveratrol. The researchers hypothesized that the doses would need to be slightly greater in order to induce meaningful apoptosis [374].

The other colon cancer trial (NCT00578396) was using seedless red grapes to identify the highest dietary doses of resveratrol that may be obtained. This is very relevant for colon cancer prevention since new dietary advice for the human population might be quickly provided/created.

These trials should provide some relevant information for future extensive human investigations targeted at introducing resveratrol to clinics for disease management. Furthermore, resveratrol-rich diets may be promoted for improved health and disease prevention. It is important to note that small sample sizes and potentially confounding effects of drugs limit conclusions, and that there is still insufficient human data on the effectiveness of resveratrol in the treatment of cancer.

5. Novel formulations of resveratrol for gastrointestinal cancer

Velaphi C Thipe et al. investigated whether gold nanoparticles (AuNPs) could be used to adsorb resveratrol onto their surface to form a phytochemical corona [375]. Their overall goal was to create a synergistic anti-cancer nanosystem combining the intrinsic pro-apoptotic qualities of AuNPs with resveratrol in a new class of green nanotechnology-based phytochemical-embedded AuNPs for oncology applications. Gum arabic (GA) was used to improve the overall stability and provided a protein matrix support for greater trans-resveratrol loading onto the surface of the AuNPs. For the preparation of Res-AuNPs, resveratrol was used to convert Au3 + to Au0 at room temperature, and GA was employed to further encapsulate the nanoparticulate surface, enhancing the overall stability. They reported a 3-fold increase in the resveratrol corona on the Res-conjugated AuNPs, which resulted in enhanced anti-cancer activity. Dark-field microscopy (CytoViva) images showed that the Res-AuNPs achieved optimum cellular uptake during a 24-hour incubation period. They carried out the synthesis and thorough characterization, and measured the in vitro stability of Res-AuNPs in various biological conditions. They proposed their use as anti-tumor drugs for prostate (PC-3), breast (MDAMB-231), and pancreatic (PANC-1) cancer cells [375].

Bolin Lian et al. [376] used folic acid (FA)-conjugated HSA to encapsulate RES, and produce RES-loaded NPs (FA-HSA-RESNPs), as a tailored drug delivery system for treating HCC (Fig. 1). A noninvasive live animal imaging system was used to evaluate the activity of the FA-HSA-RESNPs against tumors in vivo. They investigated factors such as, HSA concentration, aqueous-to-organic phase volume ratio, and the speed, time, pressure, and frequency of the high-pressure fluid nano-homogeneous emulsification process to optimize particle size and drug loading efficiency. An in vitro drug-release study showed that the NPs could reliably and slowly release resveratrol [376].

Duoduo Zhang et al. hypothesized that AuNPs loaded with resveratrol (RES-AuNPs) would have a greater anti-cancer effect than RES alone. To test this hypothesis, a series of experimental studies were conducted [377]. The RES-GNPs were characterized using UV-Prove, zetasizer, and transmission electron microscopy. The RES-GNPs had a better anticancer effect than free RES both in vitro and in vivo, which they proposed could be because the AuNPs carried more resveratrol into the cells and localized it in the mitochondria. They proposed this system could be useful in the treatment of liver cancer in the clinic [377].

Rozy Kamal et al. sought to overcome the low bioavailability and retention of resveratrol in biological systems, due to its limited aqueous solubility, poor absorption, and rapid metabolism. They hypothesized that adsorption of resveratrol onto AuNPs, which are biocompatible water-soluble carriers, could improve its solubility in biological fluids as well as provide chemical and biological protection against degradation in vivo [378]. Technetium-99 m labeled resveratrol-loaded AuNPs (RES-AuNP) were synthesized, characterized, and evaluated for their cancer targeting ability in HT29 colon cancer cells and in a rat xenograft cancer model. The results were compared to 99mTc-AuNP and 99mTc-RES results. Internalization by cancer cells was substantially higher with 99mTc-RES-AuNP than with 99mTc-AuNP or 99mTc-RES. Furthermore, after i.v. injection of 99mTc-RES-AuNPs to colon tumor-bearing rats, a gradual increase in target to nontarget uptake ratio was seen, indicating that 99mTc-RES-AuNP showed better in vivo targeting of colon adenocarcinoma than 99mTc-RES [378].

Simona Serini et al. speculated that the encapsulation of omega-3 PUFA (polyunsaturated fatty acids) in solid lipid nanoparticles (SLN) composed of stearic acid (C18H36O2) esterified with resveratrol (RV-SLN), could increase their delivery to CRC cells, and could protect omega-3 PUFA against degradation and oxidation, thus increasing the anti-cancer effects. They evaluated the physicochemical properties and antioxidant activity of the newly developed RV-SLN. Furthermore, they investigated whether encapsulating the PUFAs, linoleic acid or docosahexaenoic acid in RV-SLN could alter the uptake of these omega-3 PUFAs in human HT-29 CRC cells, and thereby increase their anti-cancer effects [379].

Below we have summarized Novel formulations of resveratrol for gastrointestinal cancer in Table 8.

6. Analogues of resveratrol for gastrointestinal cancer treatment

DMU-281 (4'-hydroxy-3,4,5-trimethoxystilbene, a metabolite of resveratrol) was found to have very little anti-proliferative activity in liver and breast cancer cell lines. However, Magorzata Józkowiak et al. found that this metabolite had high cytotoxicity in LOVO and DLD-1 colon cancer cells. They also elucidated the mechanism of DMU-281 anticancer activity in both cell lines [401]. They demonstrated that DMU-281 triggered cell cycle arrest at G2/M phase and stimulated apoptosis, which was shown by activation of caspases-3, 7, and 8. Furthermore, they found that DMU-281 could alter the expression pattern of proteins and genes involved in both intrinsic and extrinsic apoptosis pathways. Therefore, DMU-281 might be useful for colon cancer treatment by inducing apoptosis [401].

Hsu YH et al. investigated whether pterostilbene (PTE) could increase the sensitivity of pancreatic ductal carcinoma (PDAC) cells to gemcitabine (GEM) [402]. They found that PTE could play an important role in the modulation of the MDR1 efflux pump for PDAC treatment. Their findings showed that PTE stimulated apoptosis, autophagic cell death, and cell cycle arrest at S-phase, and inhibited the expression of MDR1 via down-regulating RAGE/PI3K/Akt signaling in wild type MIA PaCa-2 and GEM-resistant MIA PaCa-2 cells. It is known that RAGE (receptor for advanced glycation end products) is involved in the GEM resistance process, and transfection of small interfering RNA against RAGE increased GEM sensitivity. Their findings showed that PTE increased chemosensitivity in PDAC cells via inhibiting proliferation and the expression of MDR1, which was modulated by the RAGE/PI3K/Akt axis [402].

Yu CL et al. investigated whether PTE caused autophagic cell death in HCC cells via ER stress signaling pathways [403]. They found that PTE inhibited HCC cell growth by triggering autophagy and ER stress, but did not induce apoptosis. Further efforts revealed that salubrinal (an inhibitor of eIF2α dephosphorylation) in combination with PTE could

Table 9
Analogues of resveratrol for GI cancer treatment.

Type of cancer	Resveratrol compound	Dose	Targets	Results	Model (in vitro / *in vivo* /human)	Cell line	Ref.
Pancreatic	Triacetylresveratrol	0, 5, 50, 100, 150, 200 μM	STAT3, NFκB, Mcl-1, Bim, Puma, PARP, caspase-3	Reduced viability, stimulated apoptosis	*In vitro*	PANC-1 BxPC-3	[92]
Pancreatic, breast cancer	Cis-3,4',5-trimethoxy-3'-hydroxystilbene	5, 10, 25, 50 μM	Aurora B, Cyclin B, BubR1, phosphorylated histone H3 (p-HH3)	Increased expression of mitotic checkpoint proteins; Cyclin B, Aurora B, BubR1, phosphorylated histone H3.	*In vitro*	PANC-1, AsPC-1, Colo-357	[107]
Melanoma, pancreatic	Resveratrol 4'-acetate & 4'-palmitoate esters	50 μM	–	Selective cytotoxicity to cancer cells compared to normal cells	*In vitro*	DM443, DM738, normal NHDF	[122]
Gastrointestinal, colorectal, pancreatic	3,3',4,4',5,5'-Hexahydroxy-trans-stilbene	0, 0.1, 0.5, 1, 10, 50, 100 μM	Cyclin D, E	Inhibited proliferation, accelerated senescence	*In vitro*	PSN-1, SW480	[406]
Leukemia, pancreatic	Digalloylresveratrol, arabinofuranosylcytosine	4, 5 μM	–	Inhibited proliferation, additive effects in combination	*In vitro*	BxPC-3, PANC-1	[407]
Pancreatic, ovarian, colorectal	DHS (trans-4,4'-dihydroxystilbene)	0.137 – 100 μM 0, 1, 5, 10, 20, 50 μM	RRM2 (ribonucleotide reductase regulatory subunit M2) of Ribonucleotide reductase (RNR)	Suppressed DNA replication & tumor growth, inhibited DNA replication, induced apoptosis, cell cycle arrest at S-phase, and DNA damage	*In vitro,* in vivo	PK9, RPK-9, HCT116, KB-Gem, KB-Hu	[408]
Hepatocellular	RES-ASA hybrid (RAH)	0, 20, 40 60 μM	Cyclin D1, Cyclin E, caspase-3, Bim, Bax, Bad, Bak, Bcl2, BclXL and cytochrome *c*	Enhanced anticancer activity	*In vitro,* in vivo	HCT-116, HT29	[409]
Colon	Piceatannol (3, 3', 4, 5'-trans-tetrahydroxystilbene)	100, 200 μM	ODC, c-Myc, SAMDC, SSAT, c-Fos	Inhibited polyamine synthesis, caused growth arrest	*In vitro*	Caco-2	[254]
Colon	Melinjo seed extract (resveratrol & gnetin c)	50, 100 mg/kg/d	caspase 3/7	Inhibited proliferation, induced early & late apoptisis	*In vivo*	CT26	[410]
Pancreatic, melanoma	Pterostilbene	30 mg/kg	ACTH	Downregulated antioxidants by a glucocorticoid & Nrf2 dependent mechanism	*In vitro, In vivo*	ASPC-1, BxPC-3	[411]
Pancreatic	Pterostilbene	10,20,30, 40,50, 75 100 μM	Caspase-3/7	Inhibited proliferation, cell cycle arrest, mitochondrial membrane depolarization	*In vitro*	MIAPaCa, PANC-1	[412]
Pancreatic	N-hydroxy-N′-3,4,5-trimethoxy-benzamidine (resveratrol analog)	5, 7.5, 10, 20, 40, 80 160 μM	Ribonucleotide reductase	Inhibited proliferation, stimulated concentration-dependent apoptosis in both cell lines.	*In vitro*	AsPC-1, BxPC-3	[413]
Pancreatic	Digalloylresveratrol (DIG)	1–100 μM	Ribonucleotide reductase, Erk1/2, p38, ATM, Chk2, Cdc25A	Decreased number of cells in S phase	*In vitro*	AsPC-1, BxPC-3	[414]
Glioma, breast, pancreatic	(E)− 4-(3,5-dimethoxystyryl)phenyl acetate	0, 5, 15, 20 μM	Bcl-xL, cyclin D1, B1, survivin	Reduced colony formation, induced cell cycle arrest	*In vitro*	PANC-1	[415]
Pancreatic	Triacetyl resveratrol	0, 1, 5, 10, 20 μM	miRNA200, E-cadherin, N-cadherin, Snail, Slug, Zeb1, cyclin D1, Bcl2, Gli1	Inhibited colony formation & EMT, Induced apoptosis	*In vitro*	AsPC1, PANC1	[404]
Oral	Pinostilbene hydrate	0, 20, 40, 80 μM	MMP-2, ERK1/2, p38	Suppressed MMP-2 by inhibiting p38/ERK1/2 signaling pathway	*In vitro*	SCC-9 SASHSC3	[416]
Oral	Polydatin (resveratrol 3-β-mono-D-glucoside)	0 – 150 μM	AHR, CYP1A1, HSP-90	Decreased protein expression.	*In vitro*	CAL-25	[417]
Oral	Pterostilbene	25, 50, 75, 100 μM	–	Reduced tumor volume by 22 % compared to control group	*In vitro,* in vivo	CAL27	[418]
Oral	Pterostilbene	0, 5, 10, 25, 50, 75, 100 μM	Atg5, Atg7, Atg12, LC3-II,Beclin-1, caspase 3, 7, 9, MDR1, AKT, Bax, cytochrome c, Bcl-2	Cell membrane rupture, autophagic vacuole formation, reduced viability, increased autophagy & apoptosis	*In vitro*	CAL27	[419]
Gastric	Caragaphenol A (resveratrol trimer)	0, 1, 2.5, 3, 5, 10 μM	Cdk2, Cdk4, Cdk6, p27, CyclinB1, Cdk1, PARP, XIAP and Bcl-2	Promoted apoptosis & cell cycle arrest	*In vitro*	AGS-5FU	[420]
Esophageal	Pterostilbene	5, 10, 15, 50, 100, 150 μM	Caspase 3, 9, 12, GRP78, p-PERK, ATF6, CHOP, p-eIF2α, PUMA, Bcl-2, cytochrome c, Sp-1	Reduced viability, adhesion & migration, increased apoptotic index	*In vitro,* in vivo	EC109, TE1	[421]
		20, 50 mg/kg			*In vivo*	–	[422]

(*continued on next page*)

Table 9 (*continued*)

Hepatic carcinogenesis	trans-3,4,5,4'-tetramethoxystilbene (DMU-212)		NF-κB (p65, p50), IκB, IKK, iNOS, STAT3, c-Fos	Suppressed NF-κB activation, reduced iNOS protein level		
Liver	Res-005 (3,5-dimethoxy-3′,4′-dihydroxy-trans-stilbene) Res-006 (3,5-diethoxy-3′,4′-dihydroxy-trans-stilbene)	0, 25, 50, 60, 65, 70, 75, 80, 90, 100, 150, 200, 250 μM	Caspase-3, PARP, IRE1α, JNK, *Xbp1, Erdj4,* PERK, eIF2α, *Chop,* ATF6α and *Grp78*	Altered mitochondrial dynamics, increased level of mitochondrial ROS, caused mitochondrial membrane potential collapse, triggered cell death & ER stress	*In vitro*	Huh-7, HepG2 [423]
Normal liver	Pterostilbene, piceatannol	25 mg/kg	Peroxisome proliferator-activated receptor α-isoform (PPARα)	Lowered lipid & glucose levels	*In vitro,* in vivo	H4IIEC3 [424]
Hepatocellular carcinoma	Pterostilbene	50, 250 mg/kg	VEGF, EGF, MMP-9	Increased enzyme activity, protein & mRNA levels, inhibited VEGF expression	*In vitro,* in vivo	$HepG_2$ [425]
Hepatoma	Piceatannol	5, 10 mg/kg	–	Promoted apoptosis & cell cycle arrest	*In vitro,* in vivo	AH109A [426]
Liver	Phoyunbene B (trans-3,4'-dihydroxy-2',3',5-trimethoxystilbene)	30, 50, 100 μM	Cyclin B1, Bcl-2, Bax	Inhibited proliferation, promoted apoptosis & cell cycle arrest	*In vitro*	HepG2, FHCC-98 [427]
Hepatocellular carcinoma	RESG (resveratrol-4-O-d-(2'-galloyl)-glucopyranoside	0, 2.5, 5, 10, 20, 40 μM	caspase 3, 9, p-JNK, p-ERK	Inhibited viability, induced apoptosis	*In vitro,* in vivo	HepG2, SMMC–7721, BEL-7402 [428]
Hepatic carcinogenesis	3,4,4',5-tetramethoxystilbene	20, 50 mg/kg	Caspase 4, 8, 9, 12	Increased mRNA of genes driving mitochondrial apoptosis, reduced mRNA of anti-apoptotic genes	*In vivo*	– [429]
Hepatocellular carcinoma	Pterostilbene	0, 10, 25, 50, 100, 250 μM	–	Marked increase in early apoptosis	*In vitro*	HepG2 [430]
Hepatocellular carcinoma	MR-3 (2,4',5',-trimethoxy-trans-stilbene) MR-5 (3,5,3',4',5'-pentamethoxystilbene)	1, 5, 10, 25, 50, 75, 100 μM	TIMP-1, TIMP-2, MMP-2, MMP-9,	Reduced MMP-9 & MMP-2 activity, increased TIMP-2 protein in a concentration-dependent manner	*In vitro*	HepG2, Hep3B [431]
Hepatocellular carcinoma	Oxyresveratrol	20, 25, 40, 50, 80, 100, 120, 160 μM	CD31, VEGFR3, VEGF-C	Inhibited proliferation & migration, inhibited tumor growth	*In vitro,* in vivo	QGY-7701, SMMC-7721 [432]
Colon, liver	(Z)− 3,5,4′-trimethoxystilbene (E)− 3,5,4′-trimethoxystilbene	0.1, 0.5, 1, 5, 10, 50, 100, 200, 500 μM	For E-isomer: cAMP, AMPK, SHP & SIRT1	Inhibited proliferation, caused S phase cell cycle arrest	*In vitro*	CaCo-2, HepG2, HT-29 [433]
Colon	DMU-212	0 – 20 μM	Bak1, Bik, Bok, Noxa, Bax, Bad, Apaf1, p53, Bcl-xL, Bcl-2, Bag1	Up-regulated pro-apoptotic mRNAs	*In vitro*	DLD-1, LOVO [434]
Colorectal	3,4,4′trimethoxystilbene 3,5,4′trimethoxystilbene	0, 10, 20, 40, 80 μM	γ-tubulin	Inhibited proliferation, induced apoptosis	*In vitro*	HCT116, SW620 [435]
Colorectal	Piceatannol	0.5, 1, 1.5, 2, 2.5, 3 μM	miRNA-129, Bcl-2	Inhibited proliferation, induced apoptosis	*In vitro*	HCT116, HT29 [436]
Colon	R3A (3,5,4'-triacetylresveratrol)	10, 30, 50 μM	cyclin A, CDK2, H1 histone	Increased cells in early S phase, inhibited proliferation	*In vitro*	SW480, SW620, HCT116 [437]
Intestinal epithelial cancer	trans-resveratrol, cis-resveratrol, transtrimethoxy-resveratrol	0.25, 0.5, 0.1, 1, 10, 25, 50, 100, 200 μM	–	Showed antioxidant activity, inhibited eicosanoid synthesis & proliferation	*In vitro*	Caco-2 [438]
Colon	trans 3,4,5,4′-tetramethoxystilbene (DMU-212)	0.1, 1, 5, 10, 20, 25, 30, 40, 50 100 μM	PGE-2 COX-2 (only for resveratrol)	Decreased number of adenomas, decreased PGE-2 production	*In vitro,* in vivo	HCA-7 [439]
Colon	Polydatin (3,4′,5-trihydroxystilbene-3-β-D-glucoside)	0 – 500 μM	Hsp27, p21, ALP, PARP, Erk-1, Erk-2, Akt	Modulated oxidative stress, cell cycle, differentiation, induced apoptosis	*In vitro*	Caco-2 [440]
Colorectal	(*E*)-N-(2-(4-methoxystyryl) phenyl) furan-2-carboxamide (CS)	3, 6, 12 μM	Fas, FADD, caspase 8, 3, PARP, p53, p21	Caused cytotoxicity	*In vitro*	HT-29, HCT116 [441]
Colon	Bakuchiol (4-[(1E,3 S)− 3-ethenyl-3,7-dimethylocta-1,6-dien-1-yl]phenol)	0, 1,5, 10 μg/mL	DR4, DR5, cFLIP, survivin, XIAP, Bcl2, caspase-3, 8, 9, PARP, JNK	Increased expression of cell death receptor, Inhibited proliferation	*In vitro*	HCT116, HT-29 [442]
Ovarian, colorectal, breast, cervical	3,3′,4,4′,5,5′-trans-hexahydroxystilbene (M12)	1.5 – 100 μM	mitochondrial superoxide dismutase (MnSOD)	IC50 values for M12 correlated with MnSOD expression	*In vitro*	DLD-1, LOVO [443]
Colon	Pterostilbene (PTE) Pinostilbene (PIN)	0 – 100 μM	p53, cleaved PARP, Bax, cleaved caspase-3, $p21^{Cip1/Waf1}$, cyclin E and p-Rb	Inhibited proliferation, caused S phase cell cycle arrest, induced apoptosis	*In vitro,* in vivo	HCT116, HT29 [444]
Colon	R3S (resveratrol-3-sulfate) R3G (resveratrol-3-glucuronide)	10, 20, 30 μM	cyclin E, cyclin B, cyclin A, Cdk1, Cdk 2, H2AX, p53, p21, PARP, caspase-3	Inhibited proliferation, caused S phase, cell cycle arrest	*In vitro*	SW480, SW620 [445]

(*continued on next page*)

Table 9 (*continued*)

	R4G (resveratrol-4-glucuronide)						
Colon	resveratrol 3-O-D-sulfate, resveratrol 3-O-D-glucuronide, resveratrol 4'O-D-glucuronide	1–500 μM	cyclin D1, A3 adenosine receptors, AMPK	Inhibited proliferation (IC50 9.8–31 μM) caused S phase cell cycle arrest, reversed by inhibitor of AMP-activated protein kinase	*In vitro*	Caco-2, HCT-116, SW480	[446]
Colorectal	caffeic acid-conjugated resveratrol (UHA6052)	0, 2.5, 5, 10, 20, 40, 80 μM	KRAS	Inhibited proliferation, no effect on HKe3 cell spheroids	*In vitro*	HCT116. HKe3	[447]
Colorectal	Ferulic acid-resveratrol adducts UHA023 UHA024 UHA025	0.625, 1.25, 2.5, 5, 10, 20 μM	p15, KRAS	Inhibited proliferation & CDK activity, inhibited oncogenic KRAS-signaling pathway	*In vitro*	HCT116, HKe3	[448]
Colon	(*Z*)− 3,5,4'-trimethoxystilbene	0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 1, 2.5, 10, 20, 30 μM	ornithine decarboxylase, S-adenosyl methionine decarboxylase	Decreased activity of ornithine decarboxylase & S-adenosyl methionine decarboxylase	*In vitro*	Caco-2, SW-480, SW-620	[449]
Colon	3,5-O-Digalloylresveratrol (DIG)	1, 2, 4, 5, 8, 10, 20, 40, 80, 160 μM	Ribonucleotide reductase (RR)	Inhibited RR, decreased incorporation of ^{14}C-labeled cytidine into DNA, inhibited progression from S to G2/M phase	*In vitro*	HT-29	[450]
Colon	3,5,4'-trimethoxystilbene (MR-3)	0, 5, 10, 25, 50, 100 μM	cytochrome-c, caspase 3, 9, p21, PCNA, p53, Bax, Bcl-2, Fas	Induced apoptosis, decreased proliferating cell nuclear antigen (PCNA)	*In vitro,* in vivo	HT-29, COLO 205	[451]
Colon	R3A (resveratrol triacetate) ε-viniferin (resveratrol dimer) ε-viniferin penta-acetate	3, 30, 60, 100 μM 5, 10, 20, 50 μM	–	Induced cell cycle arrest, inhibited proliferation	*In vitro*	SW480	[452]
Colorectal	3,4,5,4′-tetramethoxy-trans-stilbene, 3,4,5,4′- tetramethoxy-cis-stilbene	0.5, 1, 2.5, 5, 50, 100, 500, 1000 μM	cytochrome c	Stimulated mitochondrial membrane permeability transition, rapid perinuclear mitochondrial clustering, cytochrome c release, inhibited apoptosis	*In vitro*	HCT116, Caco-2	[453]
Colon	Vaticanol C (resveratrol tetramer)	1.56, 5, 12.5, 25, 50, 100 μg/mL	–	Inhibited proliferation, promoted apoptosis	*In vitro*	SW480, DLD-1, COLO201	[454]
Colon	(Z)− 3,5,4′-trimethoxystilbene (R3) [*cis & trans*]	0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 1, 2.5, 5, 10, 20, 30 μM	ornithine decarboxylase, s-adenosylmethionine decarboxylase	Inhibited proliferation, caused cell cycle arrest	*In vitro*	CaCo-2, SW480, SW620	[455]
Colorectal	Piceatannol	12.5, 25, 50, 100, 200 μM	cyclin D1, B1, cdk4, $p27^{Kip1}$, cyclin E, cyclin A	Reduced proliferation, caused cell cycle arrest	*In vitro*	Caco-2, HCT-116	[456]
Colon	4-(6-hydroxy-2-naphthyl)−1,3-benzenediol (HS-1793)	12.5, 25, 50, 100 μM	AKT, pro-caspase-8, pro-caspase-3, PARP, Bcl-2, Bax, cytochrome c, cyclin B1, Cdc2, Cdc25C, CDK2, CDK4, CDK6, ERK1/2	Inhibited proliferation, promoted apoptosis	*In vitro*	HCT116	[457]
Colorectal	Resveratrol, nano-diamino-tetrac	1, 10 μM	RRM2, ERK1/2, COX-2 (protein & mRNA), tp53, p53 (serine 15), CDKN1A (p21)	Inhibited proliferation.	*In vitro,* in vivo	HCT 116, HT-29	[458]
Colorectal	Trans-scirpusin A (resveratrol oligomer)	12.5, 25, 50, 100 μM	TNF-α mRNA, CD25, FoxP3, MDSCs, LC3, p-AMPK (T172), mTORC1, p-p70S6K	Inhibited proliferation, increased autophagy proteins, stimulated apoptosis	*In vitro,* in vivo	CT26	[459]
Hepatocellular carcinoma	Pterostilbene	0, 25, 50, 75, 100 μM	p-eIF2α, Beclin-1, p62, LC3-II, Bip, PERK, ATF4, CHOP and Ki-67	Inhibited proliferation without apoptosis, caused ER stress & autophagy	*In vitro,* in vivo	Huh-7, SK-Hep1, HA22T VGH, HepG2	[403]
Pancreatic	Pterostilbene	0, 5, 10, 25, 50, 75 μM	RAGE, PI3K, Akt, MDR, Bcl-xL, Bax, Atg, Beclin-1, LC3-II	Stimulated apoptosis, S-phase cell cycle arrest, autophagic cell death, inhibited proliferation	*In vitro*	MIA PaCa-2	[460]
Colon	DMU-281 (3,4,5,4′-tetramethoxystilbene) DMU-214 (3′-hydroxy-3,4,5,4′-tetramethoxystilbene) DMU-291 (4-hydroxy-3,5,4'-trimethoxystilbene) DMU-807 (3-hydroxy-4,5,4′-trimethoxystilbene)	10, 20 μM	caspase-9, 8, 3/7, procaspase-3, Bik, Tnf, Hmgb1, Birc2, Stat5b, Tnfsrf10c, Traf-1, Tnfsrf1b, Traf-3,Traf-5, Bad, Bak1, Fas, Tnfsrf10b,11b, Tnfsf8, Bcl-2, Bcl-2L1, Stat5a, Smac/Diablo, Bcl-xL, Hsp60, Fadd, Hsp27	Induced cell cycle arrest & apoptosis, decreased anti-apoptotic proteins	*In vitro*	DLD-1, LOVO, CaCo-2	[461]

moderate ER stress-related autophagy via the phospho-eukaryotic initiation factor 2/activating transcription factor-4/LC3 pathway, resulting in additional inhibition of eIF2 dephosphorylation and higher cell death. They also found that PTE inhibited tumor growth in a SK-Hep-1 tumor xenograft mouse model. The findings provided novel evidence that PTE could play a role in autophagy and ER stress-mediated cell death in HCC cells [403].

Junsheng Fu et al. investigated the molecular mechanisms by which TCRV, a resveratrol derivative, inhibited EMT and proliferation in PC cells, while inducing apoptosis. According to their findings, TCRV inhibited the growth of PC cells and stimulated apoptosis. TCRV inhibited the EMT by increasing the expression of E-cadherin and decreasing EMT-associated transcription factors. TCRV inhibited PC cell growth by affecting the sonic hedgehog (Shh) signaling pathway without any effect on normal human pancreatic ductal epithelial cells (HNPNE), implying that TCRV may be useful for PC prevention and treatment [404].

Chen C-W et al. investigated the anti-cancer effect of DHS (trans-4,4'-dihydroxystilbene) on a panel of human cancer cell lines compared to resveratrol and other synthetic resveratrol analogs. They found that DHS inhibited a broad spectrum of cancer cells more strongly than the other agents. The authors discovered that DHS bound to RRM2 (ribonucleotide reductase regulatory subunit M2), and caused degradation of RRM2 in proteasomes mediated by cyclin F. RRM2 degradation decreased cellular RNR activity, which reduced dNTP production, caused DNA damage, inhibited DNA replication, triggered cycle cell arrest at S phase and apoptosis. The addition of DHS to cisplatin or gemcitabine, synergistically enhanced their cytotoxicity to cancer cells. DHS increased the killing of ovarian cancer cells resistant to cisplatin, as well as PC cells resistant to gemcitabine [405].

Analogues of resveratrol for gastrointestinal cancer treatment is summarized in Table 9.

7. Conclusions

Significant amounts of research have been conducted to investigate the promising health benefits of resveratrol in a wide range of diseases, with much emphasis placed on its applicability to the prevention and treatment of cancer. Herein, the role of resveratrol in gastrointestinal cancer suppression and its underlying mechanisms were discussed. Resveratrol appears to be a promising option for prevention and GI therapy. Ongoing research into exact mechanism and interaction of resveratrol with different molecular pathways may provide new avenues for GI therapy. Although the vast majority of experimental studies have produced evidence in favor of the biological benefits of resveratrol, several obstacles still hinder its translation into clinical practice. Resveratrol displays very low toxicity, and despite having numerous molecular targets, it mainly affects regulatory and protective pathways that are often deregulated in many cancers. This suggests that it has the potential to be used as an anticancer agent alone as well as in combination with other anticancer treatments. Preventing carcinogenesis entails reducing inflammation, oxidative stress, and cancer cell growth, as well as restoring tightly controlled cell-death systems. However, owing to the intricacy and large number of cellular processes involved in carcinogenesis, additional research is merited to identify the mechanisms behind the chemopreventive properties of resveratrol. Besides, when it comes to translating experimental studies into novel treatments, the limited bioavailability of resveratrol in humans has been a long-standing problem. Despite the fact that clinical trials have achieved some promising findings, there have been numerous inconsistent results, which could be due in part to the formulations and dosage protocols employed. Further studies need to be carried out on resveratrol delivery methods, mixtures with other substances, and how its metabolism could be modified. Furthermore, the interactions of resveratrol with other compounds, and the development of more easily absorbed analogs of the chemical, could enhance its bioavailability to become a viable agent for cancer management. In addition, a new formulation of resveratrol with nano-delivery devices should be developed and tested pharmacokinetically and pharmacodynamically in cancer patients.

Finally, while the mentioned studies demonstrate that resveratrol has some pharmacological effects, it is unknown whether this effect is large enough to make it a helpful agent for GI cancer treatment. This will need a step back and many more pilot trials by researchers, but it will almost certainly result in a much more fruitful outcome for transferring resveratrol from the bench to the bedside.

Credit Author Statement

Hamed Mirzaei involved in conception, design, and drafting of the manuscript. Amirhossein Loghman, Amir Hossein Sheida, Taranomsadat Taghavi, Seyed Saeed Tamehri Zadeh, Michael R Hamblin and Mina Homayounfal contributed in data collection and manuscript drafting. All authors approved the final version for submission. Mohammad Roshani[1], and Ameneh Jafari critically revised the manuscript. Mohammad Tobeiha, Parastoo EsnaAshari were added in the first version wrongly and they were contributed in another one. All authors approved the new authorship changes. New authors checked the whole of manuscript, tables, figures and responded to reviewers comment. All author approved these changes and signed author agreement form.

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