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REVIEW

Mechanisms of resveratrol in the prevention and treatment of gastrointestinal cancer

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Abstract

Gastrointestinal (GI) cancer is one of the leading causes of cancer-related deaths worldwide. According to the Global Cancer Statistics, colorectal cancer is the second leading cause of cancer-related mortality, closely followed by gastric cancer (GC). Environmental, dietary, and lifestyle factors including cigarette smoking, alcohol intake, and genetics are the most important risk factors for GI cancer. Furthermore, infections caused by *Helicobacter pylori* are a major cause of GC initiation. Despite improvements in conventional therapies, including surgery, chemotherapy, and radiotherapy, the length or quality of life of patients with advanced GI cancer is still poor because of delayed diagnosis, recurrence and side effect. Resveratrol (3, 4, 5-trihydroxy-trans-stilbene; Res), a natural polyphenolic compound, reportedly has various pharmacologic functions including anti-oxidant, anti-inflammatory, anti-cancer, and cardioprotective functions. Many studies have demonstrated that Res also exerts a chemopreventive effect on GI cancer. Research investigating the anti-cancer mechanism of Res for the prevention and treatment of GI cancer has implicated multiple pathways including oxidative stress, cell proliferation, and apoptosis. Therefore, this paper provides a review of the function and molecular mechanisms of Res in the prevention and treatment of GI cancer.

Key words: Gastrointestinal cancer; Resveratrol; Function; Molecular mechanisms; Prevention; Treatment

Core tip: Gastrointestinal (GI) cancer is a serious disease that affects people late in their lives and represents a global health burden. Despite improvements in conventional

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therapies, including surgery, chemotherapy, and radiotherapy, the length or quality of life of patients with advanced GI cancer is still poor. Many studies have demonstrated that resveratrol also exerts a chemopreventive effect on GI cancer. In this review, we describe the function and molecular mechanisms of resveratrol in the prevention and treatment of GI cancer.

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INTRODUCTION

Gastrointestinal (GI) cancer is one of the leading causes of cancer-related deaths worldwide and represents a global health burden. To date, most research attention has been directed towards the prevention of gastric cancer (GC) and colorectal cancer (CRC), the most common forms of GI cancer. According to Global Cancer Statistics[1], CRC is the second leading cause of cancer-related mortality, closely followed by GC. GC was responsible for more than one million new cancer cases in 2018 and an estimated 783000 deaths, which equates to 1 in every 12 deaths globally. More than 1.8 million new CRC cases and 881000 deaths were estimated to occur in 2018. Environmental, dietary, and lifestyle factors, as well as family history, are the most important risk factors for GI cancer. Despite improvements in current cancer therapies, including surgery, chemotherapy, and radiotherapy, the length or quality of life (QoL) of patients with advanced GI cancer is still poor because of delayed diagnosis, recurrence, and medication side effect[2-4]. Therefore, the identification of novel therapeutic strategies to enhance the therapeutic effect and survival rate of patients with GI cancer is urgently needed.

Recently, traditional medicines, which are derived from natural compounds, have been reported as promising therapeutic agents. In particular, flavonoids and polyphenols have been recognized as potential therapeutic agents for cancer. Resveratrol (3, 4, 5-trihydroxy-trans-stilbene; Res), a natural polyphenolic compound, is widely found in grapes, cranberries, peanuts, and red wine[5]. Previous reports have demonstrated that Res has various valuable pharmacological effects including anti-oxidant, anti-inflammatory, anti-carcinogenic, anti-bacterial, and cardiovascular protective effects[6-9]. The anti-tumor effect of Res was first reported in 1997[9]. Since then, many studies have indicated that Res exerts a wide range of preventive and therapeutic actions against various types of cancer including lung, colorectal, gastric, breast, and liver cancers. Moreover, many studies have demonstrated that Res might also exert chemopreventive effects when combined with other chemotherapeutic drugs. To date, the various anti-cancer molecular mechanisms of Res in the prevention and treatment of GI cancer have implicated multiple pathways in its effects including oxidative stress, cell proliferation, and apoptosis[10].

In this review, we summarize the principal findings supporting the anti-tumor properties of Res and describe its molecular mechanisms in GI cancer, either as a preventive or a therapeutic agent.

GC

Res as a preventive agent against Helicobacter pylori

Helicobacter pylori (H. pylori) infection in the stomach induces a mucosal inflammatory response, oxidative stress, and changes to cell proliferation, which lead to GC[11-13]. Almost 90% of new cases of noncardia GC are attributed to this bacterium[14-16]. There are several mechanisms thought to be involved in the association between *H. pylori* and GC[17-20]. First, *H. pylori* can induce inflammatory mediators such as interleukin-8 (IL-8), IL-6, and tumor necrosis factor-α (TNF-α)[16]. Among these mediators, IL-8 plays a crucial role in the host inflammatory response to *H. pylori*[21-24]. The upregulation of IL-8 in *H. pylori* infection may lead to the generation of free radicals, and the release of proteolytic enzymes from activated neutrophils ultimately affects

mucosal integrity[25]. Second, *H. pylori* can induce oxidative stress and generate reactive oxygen species (ROS) in gastric epithelial cells, which can lead to altered epithelial proliferation and oxidative DNA damage[26]. When cells were pretreated with Res, both IL-8 secretion and *H. pylori*-stimulated ROS generation were suppressed[27]. Third, the gastric mucosal inflammation and damage caused by *H. pylori* infection are mediated by the overproduction of nitric oxide (NO), which is generated by inducible NO synthase (iNOS). Constant overproduction of NO may lead to DNA and tissue damage, ultimately increasing the risk of developing cancer[28]. Activation of the nuclear factor kappa B (NF-κB) signal transduction pathway is also an important event linked to tumorigenesis[29]. Res exerts significant effects against *H. pylori*-induced oxidative stress and inflammation by suppressing the expression levels of IL-8 and iNOS, blocking the activation of NF-κB, and activating the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 pathway[30].

Res in the inhibition of cancer cell proliferation

Cell proliferation plays an important role in the development of cancer. Cells acquire an increasing number of defects in key genes that enable persistent cell growth when the cells start to divide. Thus, compounds with anti-proliferative activities may be cancer chemopreventive[31]. Evidence suggests that Res can inhibit the proliferation of several transformed cells in culture[32-34]. Protein kinase C (PKC), which is associated with tumor suppression and cell proliferation[35,36], and mitogen-activated protein kinases (extracellular signal-regulated kinase 1 [ERK1] and ERK2), are regulated by growth factors controlling the proliferation of normal cells. Res inhibits the growth of gastric adenocarcinoma cells through a PKC-mediated mechanism[34] and the MEK1/2-ERK1/2-c-Jun signaling pathway[37]. Res also induces cell cycle arrest through regulation of the phosphatase and tensin homolog/phosphatidylinositol 3-kinase/Akt (PTEN/PI3K/Akt) signaling pathway and the Wnt/β-catenin signal pathway[38]. Res lowers the expression of related proteins in signaling pathways such as cyclin D1 (an important protein related to the G0/G1 cell cycle)[38,39]. Additionally, Res exerts its anti-proliferative action by interfering with the action of endogenously produced reactive oxygen. Res effectively inhibits hydrogen peroxide-stimulated proliferation and superoxide generation[25].

Inhibition of cancer cell invasion and metastasis

Cancer cell invasion and metastasis are interconnected processes that involve cell proliferation, cell migration, cell adhesion, and proteolytic degeneration of tissue barriers[40]. GC exhibits high motility due to its strong invasion and metastasis ability. The hedgehog (Hh) signaling pathway plays an important role in vertebrate development, the homeostatic process, and tumorigenesis. Res suppresses invasion and metastasis *via* inhibition of the Hh signaling pathway and epithelial-mesenchymal transition (EMT), which is also associated with cancer metastasis and invasion. Res was found to produce decreased expression of GLI family zinc finger 1, a key component of the Hh signaling pathway, as well as decreased expression of Snail and N-cadherin and increased expression of E-cadherin, which are key components of the EMT[41]. In addition, Res can inhibit metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) expression[42].

IL-6 is a multifunctional cytokine that plays a vital role in host defense mechanisms and the growth of various cancer cells[43]. Yang found that Res inhibited IL-6-induced cell invasion and matrix metalloproteinase activation by blocking Raf/mitogen-activated protein kinase signaling activation[44].

Induction of cancer cell apoptosis and senescence

Apoptosis induced by Res appears to be one of the inhibitory mechanisms involved in GC treatment. Res is a slow inducer of apoptosis; prolonged treatment with high concentrations of Res may result in apoptotic cell death and loss of cells[25,34]. The apoptosis may be attributed to the accumulation of peroxynitrite arising from the production of significant levels of NO[25]. Additionally, Res induces cell apoptosis *via* downregulating the expression of the apoptosis-inhibiting protein survivin[45], increasing generation of ROS[46], and downregulating senescence pathways such as cyclin D1, cyclin-dependent kinase 6 (CDK 6), CDK4, p16, and p21[47].

Apoptosis is usually mediated through two major pathways: The intrinsic pathway, induced by destabilization of mitochondria; and the extrinsic pathway, activated when extracellular ligands interact with receptors of the TNF family (TNF, FAS, and TRAIL). With mitochondria as the central gateway controllers and the B-cell lymphoma 2 (Bcl-2) family of proteins as executioners, the mitochondrial pathway is complex[48,49]. The Bcl-2 family plays an important role in the control of apoptosis, including anti-apoptotic proteins such as Bcl-2 and B-cell lymphoma-extra large (Bcl-xl), as well as pro-apoptotic proteins such as Bcl-2-associated X (Bax) and Bcl-2-

associated agonist of cell death (Bad)[50,51]. Res was found to induce apoptosis by downregulating the anti-apoptotic gene *Bcl-2* and upregulating the pro-apoptotic gene *Bax*[52,53]. It is also clear that activation of caspases is a hallmark of apoptosis promotion in response to death-inducing signals originating from mitochondria[53-55]. After treatment with Res, expression of the proapoptotic proteins cleaved caspase3 and cleaved caspase-8 are upregulated. Res also induces apoptosis by suppressing NF-κB activation[55]. Additionally, Res produces time- and concentration-dependent increases in the mitotic inhibitor p21$^{(cip1/WAF-1)}$ and the tumor suppressor p53[56]. The specific cell death signals engaged by Res appear to be cell type-dependent, particularly with respect to the p53 status of the cell[35,57]. Upregulation of both Fas and Fas-L proteins has been observed after Res treatment of p53-expressing SNU-1 cells, whereas in p53-deficient KATO-III cells, only Fas-L is increased[57]. Res and the sphingosine kinase inhibitor dimethylsphingosine (DMS) may be part of a common apoptotic signaling pathway. Res increases the cytotoxicity and p53 expression when combined with DMS[58].

Res reverses the multidrug resistance of cancer cells

Chemotherapy is considered to be the most effective treatment for patients with inoperable cancer; it provides palliative treatment of symptoms and improves patient QoL and survival[59]. However, conventional chemotherapeutic drugs such as doxorubicin (DOX) and platinum have been criticized due to their negative effects, including the development of drug resistance and the occurrence of tumors[60,61]. Xu *et al*[62] found that Res could reverse DOX resistance by reversing the EMT process *via* modulation of the PTEN/Akt signaling pathway.

Res may reduce the drug resistance of cancer cells by affecting the expression of several genes and proteins associated with multidrug resistance (MDR), including *ATP binding cassette subfamily B member 1*, *annexin A1*, and *thioredoxin* genes, as well as the proteins encoded by these genes[63]. Res can also reduce the expression levels of the aforementioned genes in the human GC cell line EPG85-257RDB and human GC cell line EPG85-257RNOV, which are resistant to daunorubicin and mitoxantrone, respectively[63].

CRC

Res as an anti-inflammatory agent in CRC

Many studies have demonstrated that Res has promising preventive and therapeutic effects on CRC *in vitro* and *in vivo*. Cyclooxygenase-2 (COX-2) enzyme expression is usually upregulated during inflammation in most human adenocarcinomas and colonic tumors[64-66]. Res decreases COX-2 protein expression in CRC cells[67]. Chronic colitis is associated with CRC risk, and Res mixed with food ameliorates a dextran sulfate sodium mouse model of colitis[68]. Sirtuin 1 (SIRT-1) may induce inflammatory cytokines through the activation of NF-κB. Hofseth *et al*[69] found that Res can also reverse the downregulation of SIRT-1 during colitis.

Lipopolysaccharide (LPS), a principal component of the outer membrane of Gram-negative bacteria, plays a critical role in triggering an early inflammatory response. Res reduces the LPS-induced inflammatory response by interfering with LPS-induced NF-κB activation[70]. Nrf2 is recognized as a drug target for the prevention of CRC[71]. Res supplementation suppresses tumorigenesis in colitis-associated tumorigenesis mice. Downregulation of Nrf2 and its target genes have been observed in adenomas from adjacent normal tissue[72].

Res inhibits oxidative stress in CRC

CRC is a pathological consequence of persistent oxidative stress, resulting in mutations and DNA damage in cancer-associated genes in which the cellular overproduction of ROS is implicated[73,74]. Sengottuvelan *et al*[74] demonstrated that 1,2-dimethylhydrazine (DMH)-induced DNA damage and oxidative stress were effectively suppressed by chronic Res supplementation. Particularly, entire-period Res supplementation increases enzymatic (glutathione reductase, superoxide dismutase, glutathione peroxidase, catalase and glutathione S-transferase) and non-enzymatic (reduced glutathione, vitamin C, vitamin E and β-carotene) anti-oxidant status with a corresponding decrease in the extent of lipid peroxidation markers such as thiobarbituric acid reactive substances, diene conjugates, and lipid hydroperoxides.

Res inhibits cell proliferation in CRC

Res also exerts anti-proliferative activity in CRC similar to GC. There are several mechanisms involved in the anti-proliferative effects of Res. First, Res may inhibit the expression of ornithine decarboxylase, a key enzyme of polyamine biosynthesis that is

enhanced in cancer growth[75]. Second, Res inhibits cell proliferation through modulating cyclin and CDK activities such as telomerase activity[76,77]. Relatively high concentrations (higher than 2.5 μg/mL) of Res have been found to downregulate telomerase activity[78]. Third, obesity is associated with elevated insulin-like growth factor-1 (IGF-1), which is related to various types of cancer including CRC[79]. Res inhibits IGF-1R protein levels, and the downstream Akt/Wnt signaling pathway, which plays a critical role in cell proliferation, is attenuated[80]. Finally, Liu *et al*[81] found that the anti-proliferative effects of Res may be mediated by regulation of the PTEN/PI3K/Akt and Wnt/β-catenin signaling separately. The exogenous expression of PTEN suppresses PI3K/Akt signaling and promotes the anti-proliferative effects of Res. The protein and mRNA expression of β-catenin is also decreased in a concentration-dependent manner[81].

Res induces cell apoptosis in CRC

Similar to GC, Res induces cell apoptosis in CRC through both intrinsic and extrinsic pathways[82]. In the intrinsic or mitochondrial pathway, Res can induce Bax-mediated and Bax-independent mitochondrial apoptosis. Res induces the co-localization of cellular Bax protein with mitochondria, collapse of the mitochondrial membrane potential, activation of caspases 3 and 9, and finally, apoptosis[83]. Res can also induce an early increase in mitochondrial ROS production upstream of caspase activation[84].

In the extrinsic pathway, Res induces redistribution of the Fas receptor in membrane rafts to trigger apoptosis[85]. Res also induces clustering and redistribution of Fas, which is associated with formation of a death-inducing signaling complex in cholesterol and sphingolipid-rich fractions of SW480 cells, together with Fas-associating protein with death domain and procaspase-8[85]. Apoptosis can also be initiated by lysosomes and the endoplasmic reticulum[86].

In addition, the mechanism by which Res induces apoptosis involves ROS-triggered autophagy. Inhibition of Res-induced autophagy causes significant attenuation in apoptosis accompanied by the decreased cleavage of casapse-8 and caspase-3[87]. Res-induced apoptosis can be partially mediated through the PKC-ERK1/2 signaling pathway[88-90]. Res significantly upregulates phosphorylation of PKCα and ERK1/2. Pre-treatment with PKCα and ERK1/2 inhibitors (Gő6976 and PD98059, respectively) promotes apoptosis[90].

Res inhibits cell invasion and metastasis in CRC

Similar to GC, Res leads to the downregulation of MALAT1, consequently the invasion and metastasis of CRC can be inhibited. MALAT1 is also correlated with the Wnt/β-catenin signaling pathway, which regulates tumor cell invasion and metastasis[91]. Treatment with Res can also decrease the nuclear localization of β-catenin, resulting in attenuation of Wnt/β-catenin signaling. Morin *et al*[92] and Jeong *et al*[93] reported that transcription factor 4 (TCF4) is a molecular target of Res in the prevention of CRC. Res treatment downregulated the expression of TCF4 through ERK- and p38-dependent pathways[93]. In addition, decreased expression of tristetraprolin (TTP) is observed in patients with CRC[94]. Res suppresses the proliferation and invasion/metastasis by activating TTP[94]. It can reverse the proliferation and invasion induced by TNF-β, which is linked to suppression of the TNF-β-stimulated NF-κB signaling pathway[95-99]. In addition, Res suppresses TNF-β-promoted NF-κB-mediated gene biomarkers associated with proliferation, apoptosis, and invasion[95], induces morphological changes associated with the expression of EMT parameters (elevated vimentin and slug, reduced E-cadherin), and increases migration/invasion[100].

Vascular endothelial growth factor (VEGF) is an important angiogenic factor secreted by tumor cells, which stimulates tumor neo-angiogenesis and vascular permeability[101]. Res may decrease the level of VEGF in many cancer cells such as human leukemia (U937) cells, ovarian carcinoma cells, and breast cancer cells (MDAMB-231)[102-104]. Fouad *et al*[105] reported that Res can inhibit angiogenesis. VEGF protein secretion was significantly reduced in both Caco2 and HCT116 cells.

Res reverses MDR in CRC

MDR is a common phenomenon in the clinic that requires immediate resolution. Several findings have indicated that Res chemosensitizes the anti-tumor effects of fluorouracil (5-FU) by inhibiting the EMT phenotype *via* the upregulation of intercellular junctions and downregulation of the NF-κB pathway[99]. Genotoxicity and apoptosis are increased when 5-FU-resistant cells are treated with Res and 1,3-Bis (2-chloroethyl)-1-nitrosourea[106]. In addition, this combined treatment decreases the levels of DNA polymerase beta, flap endonuclease 1, and DNA damage-binding protein 2, which are overexpressed in 5-FU-resistant cell lines[106]. Res also synergizes the invasion inhibitory effects of 5-FU. Res significantly attenuates drug resistance *via*

suppression of EMT factors (decreased vimentin and slug, increased E-cadherin), diminished NF-κB activation and its translocation to the nucleus, and abolished NF-κB-regulated gene end products (matrix metalloproteinase 9, caspase-3)[107]. Further, Res can chemosensitize TNF-β-induced increased capacity for survival and invasion of HCT116R cells in response to 5-FU[108].

Moreover, Res can downregulate the expression of MDR1 to ameliorate cisplatin resistance[106,109]. Wang *et al*[110] also found that Res inhibits MDR1 expression in oxaliplatin (L-OHP)-resistant CRC cells HCT116 cells through inhibition of the NF-κB signaling pathway and activation of cAMP-response element binding protein in an 5' AMP-activated protein kinase-dependent manner. Table 1 summarizes the effect and targets/mechanisms of Res in GC and CRC.

FUTURE OUTLOOK

Despite all of the documented potential anti-cancer effects of Res in cell culture models and animal models, we cannot assume that the potential properties of Res can be translated to humans because of the low bioavailability of Res. Due to the rapid metabolism and glucuronidation and sulfation in the intestine and liver, the bioavailability of Res in humans is considerably less than 1%[111,112] despite high absorption of almost 70%[113,114]. The poor bioavailability of Res is an important problem in terms of extrapolating its potential clinical application. Several methods have been developed to improve its bioavailability, such as utilizing it in combination with an additional phytochemical curcumin or using nanotechnological formulations[115,116].

Xu *et al*[117] reported that combined treatment with curcumin and Res in DMH-treated GC rats led to regulation of both p53 phosphorylation and acetylation, which activated stable tumor suppressor p53 against GC. Gavrilas *et al*[118] also investigated cell proliferation inhibitory effect of the combined treatment of curcumin and Res, and found synergistic effects in both DLD-1 and Caco-2 cells. The expression of several apoptosis regulatory genes including PMAIP1, BID, ZMAT3, and FAS was significantly increased, representing novel targets of combined treatment with curcumin and Res[117,118].

Lipid-core nanocapsules (LNCs) also reportedly stabilize the incorporated drugs, control their release pattern, and increase the activity of the drugs in the body[119]. Feng *et al*[120] prepared Res-loaded LNCs (RSV-LNCs) and found that they exerted a remarkable reduction in cell apoptosis of approximately 36%. This suggests that RSV-LNCs have superior anti-cancer effects and promising potential to increase the therapeutic efficacy of Res[120].

CONCLUSION

GI cancer, particularly CG and CRC, is a highly prevalent cancer and one of the leading causes of cancer-related deaths worldwide. Multiple molecular mechanisms, including inflammation, oxidative stress, cell proliferation, and apoptosis, are associated with its incidence and progression[121,122]. Res is a polyphenol compound with a variety of properties including anti-inflammatory, cell proliferation inhibition, and apoptosis properties[123,124]. Multiple studies have demonstrated the potential effects of Res for the treatment of GC and CRC. This phytochemical has multiple advantages, is comparatively safe, and is able to target multiple cell signaling pathways. However, the bioavailability of Res is very low in humans and a high dose may not reach a sufficient concentration of treatment due to the metabolic characteristics[125]. Res may be of benefit for digestive tract cancer treatment as it is efficiently absorbed in the GI tract and exerts local effects before its metabolization[126,127]. Although various methods have been developed to improve the bioavailability of Res, more studies are needed to verify the efficacy of Res in GI cancer.

Table 1 Effect and targets/mechanisms of resveratrol in gastric cancer and colorectal cancer

	Effect	Cell or animal model	Proposed targets/mechanisms	Ref.
Gastric cancer	Anti-*H. pylori*	MKN-45 cells	Inhibition of IL-8 secretion, inhibition of ROS generation	[27]
		Mice	Downregulation of IL-8 and iNOS, inhibition of NF-κB activity, activation of the Nrf2/HO-1 pathway	[30]
	Anti-proliferation	KATO-III cells	Inhibition of PKC activity	[34]
		ACS cells	The MEK1/2-ERK1/2- c-Jun signaling pathway	[37]
		SNU-1 cells	The PTEN/ PI3K/Akt signaling pathway	[25]
		MGC803 cells	The PI3K/Akt signaling pathway	[38]
		MGC-803 cells	Downregulation of β-catenin, c-myc, and cyclin D1, inhibition of the Wnt/β-catenin pathway	[39]
	Inhibition of invasion and metastasis	SGC7901 cells	Inhibition of the Hh signaling pathway and EMT	[41]
		SGC7901 cells	Inhibition of the Raf/MAPK signaling pathway	[44]
		BGC823 cells	Inhibition of MALAT1	[42]
	Induction of apoptosis and senescence	SGC7901 cells	Downregulation of survivin	[45]
		SGC-7901 cells	Increase of ROS	[46]
		AGS, BGC-823 and SGC-7901 cells	Downregulation of the senescence pathways such as cyclin D1, CDK 6 and CDK4, p16 and p21	[47]
		Nude mice	Downregulation of anti-apoptotic gene *bcl*-2, up-regulation of the pro-apoptotic gene *bax*	[52]
		SGC 7901 cells	Upregulation of *bax*, cleaved caspase 3 and cleaved caspase 8, downregulation of *bcl*-2, inhibition of NF-κB activity	[53]
		SGC-7901 cells	Activation of caspase-3 and pro-caspase 9 was downregulated, the expression ratio of *bax/bcl-2* was increased	[54]
		SNU-1 cells and KATO-III cells	Upregulation of both Fas and Fas-Lin SNU-1 cells, upregulation of Fas-L in KATO-III cells	[56]
		SNU-1, KATO- and RF-1 cells	SNU-1 cells: Upregulation of p53, downregulation of surviving; AGS cells: Upregulation of p53, stimulation of caspase 3 and cytochrome C oxidase activities; KATO-III cells (not expressing p53): Stimulation of caspase 3 and cytochrome C oxidase activities	[57]
		SNU-1 cells	Upregulation of p53 expression	[58]
	MDR	SGC7901/DOX	PTEN/Akt signaling pathway	[62]

		RDB and RNOV	In RDB cells, Res reduced the expression level of all analyzed genes, so were results at the protein level obtained for P-gp and TXN. In turn, in the RNOV cell line, Res reduced TXN expression at mRNA and protein levels	[63]
Colorectal cancer	Anti-inflammatory	HCA-7 cancer cells	Downregulation of *COX*-2 III	[67]
		Dextran Sulfate Sodium (DSS) mouse model of colitis	Decrease of CD3+ T cells, downregulation of p53	[68]
		Caco-2 and SW480 cells	Inhibition of iNOS, decrease of NO production, inhibition of NF-κB activity	[70]
		Mice	Downregulation of Nrf2	[72]
	Inhibit oxidative stress	Wistar male rats	Increase of the enzymic and non-enzymic antioxidant status	[74]
	Anti-proliferation	CaCo-2 cells	Inhibition of ODC expression	[75]
		SW480 cells	Modulation of cyclin and CDK activities	[76]
		HT-29 and WiDr cells	Downregulation of telomerase activity	[78]
		HT-29 cells	Inhibition of IGF-1R and the downstream Akt/Wnt signaling pathway	[80]
		HCT116 cells	Downregulation the PTEN/PI3K/Akt and Wnt/β-catenin signaling	[81]
	Induce apoptosis	HCT116 cells	Induction of *bax*, activation of caspases 3 and 9	[83]
		HT-29 cells	Production of O_2^{-}•, increase of mitochondrial ROS production	[84]
		SW480 cells	Redistribution of Fas	[85]
		HT-29 cells	Lysosomal cathepsin D demonstrated upstream of cytosolic caspase activation	[86]
		HT-29 cells	ROS-triggered autophagy, decrease of cleavage of casapse-8 and caspase-3	[87]
		HT- 29 cells	The PKC- ERK1/2 signaling pathway	[90]
	Inhibit invasion and metastasis	LoVo and HCT116 cells	Downregulation of MALAT1, decrease of β-catenin attenuation of Wnt/β-catenin signaling	[91]
		HCT116 cells	ERK and p38-dependent pathways, downregulation of TCF4	[93]
		HCT116 and SNU81 colon cancer cells	Increase of TTP expression	[94]
		HCT116 cells	Suppression of NF-κB signaling pathway	[98]
		HCT116, RKO and SW480 cells	Decrease of TNF-β/TNF-βR-induced EMT, suppression of NF-βB and FAK	[99]
	Inhibition of angiogenesis	Caco2 cell and HCT116 cells	Reduction of VEGF level	[105]
	Reversion of MDR	5-FU-sensitive HCT-116 cells	Decrease of the levels of POL-β, POLH, FEN1and DDB2	[106]
		5-FU chemoresistance-derived clones HCT116R cells	Upregulation of intercellular junctions and downregulation of NF-κB pathway	[107]
		HCT116R cells	Suppression of tumor-promoting factors (NF-κB, MMP-9, CXCR4) activity and EMT factors	[108]

	CIS-resistant HCT 116 cells	Increase in the early apoptosis fraction and enhance the subsequent apoptotic effects of CIS [109]
	HCT116/LOHP	Downregulation of mRNA and P-gp/MDR1 and MDR1 promoter activity [110]

IL: Interleukin; ROS: Reactive oxygen species; NO: Nitric oxide; iNOS: Inducible nitric oxide synthase; Nrf2: Nuclear factor erythroid 2-related factor 2; EMT: Epithelial-mesenchymal transition; Hh: Hedgehog; MALAT1: Metastasis-associated lung adenocarcinoma transcript 1; CIS: Cisplatin; NO: Nitric oxide; MDR1: Multi-drug resistance protein 1.

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