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TOPIC HIGHLIGHT

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Molecular mechanisms of chemopreventive phytochemicals against gastroenterological cancer development

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Abstract

Cancer is one of the leading causes of death worldwide. Commonly used cancer treatments, including chemotherapy and radiation therapy, often have side effects and a complete cure is sometimes impossible. Therefore, prevention, suppression, and/or delaying the onset of the disease are important. The onset of gastroenterological cancers is closely associated with an individual's lifestyle. Thus, changing lifestyle, specifically the consumption of fruits and vegetables, can help to protect against the development of gastroenterological cancers. In particular, naturally occurring bioactive compounds, including curcumin, resveratrol, isothiocyanates, (-)-epigallocatechin gallate and sulforaphane, are regarded as promising chemopreventive agents. Hence, regular consumption of these natural bioactive compounds found in foods can contribute to prevention, suppression, and/or delay of gastroenterological cancer development. In this review, we will summarize natural phytochemicals possessing potential antioxidant and/or anti-inflammatory and anti-carcinogenic activities, which are exerted by regulating or targeting specific molecules against gastroenterological cancers, including esophageal, gastric and colon cancers.

Key words: Curcumin; Resveratrol; (-)-Epigallocatechin gallate; Isothiocyanates; Sulforaphane; Gastroenterological cancers; Molecular target

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INTRODUCTION

Cancer is a leading cause of death worldwide. Surgery, chemotherapy and radiation therapy are commonly used cancer treatments. However, these can cause a number of side effects, and complete cure is often infeasible for most patients suffering from specific cancers. Epidemiological studies have suggested that regular consumption of vegetables, fruits, red wine and tea is associated with lower incidences of many chronic diseases, including cancers[1-4]. A recent review reported that natural bioactive compounds found in various foods can activate or deactivate molecular signaling cascades by targeting small molecules in cancer cells[5]. A number of natural phytochemicals, including isoflavones, gingerol, (-)-epi-

gallocatechin gallate (EGCG), quercetin, resveratrol, and curcumin have been identified to be chemopreventive and their significant health benefits are an active field of research[5]. In particular, gastroenterological cancers are closely associated with lower consumption of fruits or vegetables. Therefore, in this review, we will summarize the natural phytochemicals possessing potential antioxidant and/or anti-inflammatory and anti-carcinogenic activities, which act by regulating or targeting specific molecules against gastroenterological cancers, including esophageal, gastric and colon.

PHYTOCHEMICALS IN ESOPHAGEAL CANCER

Esophageal cancer is the eighth most common cancer and is the sixth most common cause of cancer-related deaths[6]. Due to the lack of symptoms, individuals are rarely aware of their condition until the metastatic stages of the disease[7]. Despite developments in current cancer treatments, including chemotherapy, radiation therapy, and surgery (esophagogastric resection), patients with esophageal adenocarcinoma are not often cured of the disease[8]. Statistical analysis for the past 5 years shows that Americans and Europeans with esophageal cancer have relatively low survival rates, 10%-15% and 10% respectively[9]. Moreover, this suggests that the esophageal tumors are resistant to regular therapies and, thus, alternative strategies for the treatment and/or prevention of esophageal cancer are required.

Major risk factors for esophageal cancer are chewing and smoking tobacco, drinking alcoholic beverages[10], low consumption of fruits and vegetables[1] and consumption of salt-cured, salt-pickled, and moldy foods[11]. Therefore, quitting cigarette smoking, reducing alcohol consumption, increasing fruit and vegetable consumption, and avoiding foods containing nitrosamines and nitrosamine precursors are critical for the prevention of this disease. In addition to such lifestyle changes, identifying foods or food constituents that can help to prevent, suppress, and/or delay the onset of esophageal cancer is essential[12,13]. Recent attention has focused on the beneficial actions of natural phytochemicals, such as isothiocyanates, curcumin, and resveratrol, against esophageal cancer (Table 1). Although the underlying molecular mechanisms have not been fully understood, such natural chemicals are known to protect against disease progression by targeting specific proteins.

Isothiocyanates

Isothiocyanates are naturally occurring phytochemicals in cruciferous vegetables, including Chinese watercress, cabbage, Brussels sprouts, turnips and cauliflower[14]. In the gastrointestinal tract, isothiocyanates are released from their precursor *via* hydrolysis catalyzed by myrosinase. Of its metabolites, phenethyl isothiocyanate (PEITC) has been reported to be rapidly absorbed and distributed in mice following oral administration[15]. Studies have demonstrated that PEITC (> 1.0 μmol/g diet) protects against esophageal cancer by inhibiting tumor incidence and multiplicity in rats treated with N-nitrosobenzylmethylanime (NMBA), the most potent inducer of esophageal tumors and is commonly used to study the pathogenesis of esophageal cancer[16].

Several studies of the molecular mechanism whereby PEITC inhibits NMBA-induced esophageal tumorigenesis have revealed that PEITC suppresses the activity of cytochrome P450 enzymes in rats with NMBA-induced esophageal cancer[11,17,18], and also inhibits DNA methylation by inhibiting the formation of the pro-mutagenic adduct O^6-methylguanine in rat esophageal DNA[16]. Significant correlations between DNA adduct formation and tumor multiplicity have been observed in rat lungs as well as esophagi[18], indicating that DNA adduct formation probably contributes to tumor incidence and multiplicity. Collectively, PEITC is likely to have anti-carcinogenic activity *via* regulation of P450 enzyme activity and inhibition of DNA damage, contributing to the prevention of esophageal cancer. However, no direct target has been identified. Hence, future investigation is needed to elucidate the molecular target(s) of isothiocyanates or their metabolites in the prevention and/or treatment of esophageal cancer.

EGCG

Polyphenols are major components of tea. One-third of the dry weight of green or black tea is composed of polyphenols, which have powerful antioxidant and anti-inflammatory potential[19]. Wang *et al*[20] reported that both decaffeinated green and black tea consumption reduced esophageal tumorigenesis and molecular events in rats treated with N-nitrosomethylbenzylamine, which is probably due to the suppression of tumor incidence and multiplicity[21]. EGCG is the most abundant and active constituent among tea polyphenols. In general, the anti-carcinogenic activities of EGCG are mediated *via* multiple mechanisms, including the inhibition of mitogen activation protein kinases (MAPK), activator protein-1 and cell transformation[22-24], inhibition of epidermal growth factor receptor (EGFR) phosphorylation[25], induction of cell cycle arrest (G0/G1)[26,27] and apoptosis[28], and inhibition of DNA methyltransferase (DNMT) activity[29].

EGCG also regulates multiple targets and mechanisms in protecting against esophageal cancer. EGCG (40 μmol/L) inhibits phosphorylation of ERK1/2, c-Jun, and cyclooxygenase-2 (COX-2), which are increased in the human esophageal cancer cell lines SKGT-4 and TE-8 as well as in esophageal tissue specimens obtained from patients[30]. *In vivo* analysis using nude mouse xenograft models also confirmed that lower tumor formation and growth are associated with the decreased expression levels of phosphorylated extracellular-signal-regulated kinase (ERK) and COX-2 induced by EGCG treatment(50 μg/kg per day)[30]. Together these suggest that EGCG may protect against esophageal cancer by reducing pro-inflammatory mediators, including ERK, c-Jun

Table 1 Chemopreventive phytochemicals and their actions and targets/mechanisms during the development of esophageal cancer, gastric cancer and colon cancer

	Natural phytochemical	Chemopreventive action	Targets/mechanisms	Ref.
Esophageal cancer	Isothiocyanate	Inhibition of DNA damage	Inhibition of DNA methylation	[17]
		Inhibition of tumorigenesis	Inhibition of cytochrome P450 enzymes activity	[11,18]
	EGCG	Anti-inflammation	Inhibition of phosphorylated ERK1/2, c-Jun and COX-2 expressions	[30]
			Decreased COX-2 expression and PGE_2 production	[32]
		Growth inhibition	Inhibition of EGFR phosphorylation	[31]
		Induction of cell cycle arrest	Inhibition of cyclin D1	[32]
		DNA damage	Inhibition of DNA methyltransferase activity	[29]
	Curcumin	Antioxidant	Induction of SOD-1	[46]
		Anti-inflammation	Inhibition of COX-2	[46]
			Inhibition of NF-κB activity	[50-52]
			Inhibition of IL-8 mRNA expression	[52]
		Apoptosis and cell cycle arrest	Inhibition of Notch signaling	[57]
Gastric cancer	Curcumin	Chemoresistance	Downregulation of NF-κB	[61]
			Induction of apoptotic genes *Bcl-2* and *Bcl-xL*	[61]
		Suppression of cell proliferation and invasion	Downregulation of EGFR-PAK1	[62]
			Reduction of cyclin D1 expression	[62]
	Resveratrol	Inhibition of cell cycle progression	Inhibition of PKC	[72,73]
			MEK1/2-ERK1/2-c-Jun	[74]
		Induction of apoptosis	Reduction in Bcl-2, enhancing *Bax* gene	[76,77]
	Sulforaphane	Protection against oxidative stress	Stimulation of Nrf2	[78-80]
			Enhancement of GST and glutathione levels	[78,81]
		Anti-bacterial activity	Decrease in gastric bacterial colonization	[82]
			Reduction in the expression of TNF-α and IL-1β	[82]
Colon cancer	Curcumin	Growth inhibition	EGFR/IGFR	[102]
			ERK/Egr-1/EGFR	[87,96]
		Suppression of tumorigenesis	AMPK-COX-2	[101]
			Wnt/β-catenin	[102,106]
	Resveratrol	Anti-proliferation Apoptosis	IGF-1, p53	[108]
			PPP-FAK signaling	[109]
		Apoptosis growth inhibition	AMPK	[110]

ERK: Extracellular-signal-regulated kinase; COX-2: Cyclooxygenase-2; PGE_2: Prostaglandin E2; EGFR: Epidermal growth factor receptor; EGCG: Epigallocatechin gallate; SOD: Superoxide dismutase; NF-κB: Nuclear factor κB; IL-8: Interleukin-8; PKC: Protein kinase C; MEK: Mitogen-activated protein kinase; Bcl-2: B-cell lymphoma 2; GST: Glutathione S-transferase; TNF: Tumor necrosis factor; IGFR: Insulin-like growth factor receptor; PPP: Pentose phosphate pathway; FAK: Focal adhesion kinase; AMPK: Adenosine monophosphate-activated potein kinase.

and COX-2 in *in vitro* carcinogenesis and *in vivo* tumorigenesis models, and cancer patients.

EGCG inhibits phosphorylation of EGFR and HER-2/neu in KYSE 150 esophageal squamous cell carcinoma, leading to the inhibition of growth factor receptor and, thus, exerting anti-carcinogenic activity[31]. Another study demonstrated that EGCG (4 mg/kg *i.p.*) attenuates cyclin D1 and *COX-2* gene expression, thereby reducing the production of prostaglandin E2 (PGE_2) in rats treated with NMBA[32]. This suggests that cyclin D1 and COX-2 may act as partial targets of EGCG. EGCG-mediated decrease in PGE_2 production following NMBA treatment was further supported by another study using F344 rats[33]. Lastly, EGCG also inhibits DNA methylation, thereby suppressing the onset of esophageal cancer. Indeed, hypermethylation of DNA is associated with critical events during cancer progression, such as cell cycle regulation, DNA repair, and apoptosis[34-36]. In particular, methylation of CpG by DNMT is known to cause chromosome condensation and transcription repression[37,38]. The importance of DNA demethylation has been emphasized in strategies to develop cancer therapies and was further supported by studies using DNMT inhibitors. Treatment with DNMT inhibitors leads to the inhibition of cancer cell growth, induction of cancer cell apoptosis, and attenuation of tumor volume in mice[39-42]. In fact, Fang *et al*[29] demonstrated that EGCG acts as a potent DNA methylation inhibitor by suppressing DNMT activity, leading to the demethylation of CpG and reactivation of methylation-silenced genes in the human esophageal cancer cell line KYSE 510.

Curcumin

Curcumin is a yellow pigment derived from turmeric, the powdered rhizome of Curcuma longa Linn. Accumulating evidence suggests numerous health benefits of curcumin, including antioxidant, anti-inflammatory, and anti-carcinogenic properties[43,44], which are probably mediated by regulation of multiple intracellular targets[5]. Multiple molecular targets have been identified using various cancer cell lines and xenograft animal models of esophageal cancer.

Curcumin is a well-known antioxidant[43]. Excess amounts of reactive oxygen species (ROS) lead to the initiation, progression, and promotion of various cancers[45]. Therefore, the role of antioxidants is critical dur-

ing the development of cancers. In fact, treatment with curcumin (10-100 μmol/L) reversed suppression of the powerful antioxidant superoxide dismutase (SOD)-1 and induction of *COX-2* gene expression following treatment with bile acid in an esophageal epithelial cell line (HET-1A)[46]. This suggests that the antioxidant capacity of curcumin contributes to the prevention of esophageal cancer by increasing the activity and/or expression levels of antioxidant enzymes, including SOD, and reducing pro-oxidant enzymes, such as COX-2.

In addition to its antioxidant capacity, curcumin exerts its anti-cancer activities *via* its anti-inflammatory activity. Nuclear factor κB (NF-κB) is a well-known pro-inflammatory transcription factor involved in the initiation, promotion and progression of cancers[47]. It is also known that increased NF-κB activity is associated with greater cell proliferation, invasion, angiogenesis, metastasis, suppression of apoptosis, and chemoresistance in various types of cancer[48,49]. Several studies have demonstrated that curcumin inhibits NF-κB activity in esophageal adenocarcinoma[50,51]. Rawat *et al*[52] reported that curcumin (50 μmol/L) protects against bile acid-induced enhanced NF-κB activity in an esophageal cell line (OE33), which in turn reduces the expression levels of NF-κB target genes, including interleukin (IL)-8. In addition, patients with Barrett's esophagus supplemented with curcumin (a 500 mg curcumin tablet daily for 7 d) showed decreased IL-8 mRNA expression, suggesting that curcumin can act as a potential chemopreventive agent against esophageal cancer[52].

Recently, it was demonstrated that curcumin induces cell death (apoptosis) and cell cycle arrest by blocking Notch signaling pathways. Notch signaling was recently found to be upregulated in esophageal cancer and is as a therapeutic target for esophageal cancer due to its critical roles in tumor cell proliferation, apoptosis and stem cell maintenance and renewal[53-56]. Inhibition of Notch signaling in oral squamous carcinoma cells by curcumin also contributes to downregulation of NF-κB, which in turn reduces the expression of target genes of NF-κB, including Bcl-2, cyclin D1, vascular endothelial growth factor, and matrix metalloproteinase-9[57].

PHYTOCHEMICALS IN GASTRIC CANCER

Gastric cancer is the seventh most common cause of cancer-related mortality in the world. Exposure to chemical carcinogens or *Helicobacter pylori* (*H. pylori*) infection causes several events which may lead to the development of gastric cancer[58]. In particular, *H. pylori* infection results in infiltration of neutrophils and macrophages into the gastric mucosa. Infiltration of neutrophils and macrophages leads to the production of free radicals, including superoxide and nitric oxide. ROS-mediated stress responses result in gastric mucosal injury, ulcers, and ultimately gastric cancer[59]. Therefore, agents that have powerful antioxidant potential *via* scavenging ROS or enhancing antioxidant capacity may help to protect against gastric cancer development (Table 1).

Curcumin

It has been suggested that curcumin inhibits *H. pylori* infection in mice by reducing its growth[60]. The mechanisms of cellular growth and potential therapeutic capacity of curcumin have been further investigated by *in vitro* studies using multiple gastric cancer cell lines. Curcumin protects against chemoresistance in human gastric cancer cells by downregulating NF-κB and subsequent NF-κB-mediated anti-apoptotic genes, such as Bcl-2 and Bcl-xL in the human gastric cancer SGC 7901 cell line[61].

In addition, curcumin reduces EGFR expression and the activity of p21-activated kinase (PAK)1, a downstream regulator of EGFR. Curcumin also reduces NF-κB activity, regulated by PAK1, leading to decreases in cell proliferation by reducing the mRNA and protein expression of cyclin D1 and suppresses cell cycle progression from the G1 to S phases. Therefore, curcumin inhibits the proliferation and invasion of various gastric cancer cells[62].

Resveratrol

Resveratrol is a highly abundant polyphenol found in red grapes and red wine. Epidemiological studies have revealed an inverse relationship between red wine consumption and the incidence of cardiovascular disease[63,64]. The cardioprotective effect of red wine was attributed to resveratrol[65]. During the last two decades, extensive research has focused on the antioxidant, anti-inflammatory and anti-carcinogenic health benefits of resveratrol[66]. Specifically, resveratrol was found to have antibacterial effects[67] by inhibiting the growth of multiple *H. pylori* strains[68-70]. Increased expression of IL-8 and increased production of ROS were detected in the gastric mucosa following exposure to *H. pylori*. Furthermore, *H. pylori*-mediated infection increases motility and leads to morphological changes in co-cultured cells, known as the hummingbird phenomenon. Treatment with resveratrol (1-100 μmol/L) significantly attenuated IL-8 secretion, ROS formation, and markedly inhibited morphological changes in cells infected with *H. pylori*[71]. Hence, resveratrol is a candidate therapeutic agent against gastric cancer.

Resveratrol inhibits cell cycle progression of nitrosamine-stimulated KATO-Ⅲ and RF-1 cells by inducing cell cycle arrest in the G0/G1 phase through inhibiting kinase C-mediated mechanisms and induces apoptotic cell death in various gastric adenocarcinoma cell lines[72,73]. Another mechanism by which resveratrol regulates cell proliferation is associated with the MEK1/2-ERK1/2-c-Jun signaling cascade, a critical signaling pathway in the proliferation and growth of human adenocarcinoma gastric cells. Resveratrol was found to suppress the phosphorylation of MEK1/2-ERK1/2, which subsequently inhibits translocation of c-Jun into the nuclear compartment, leading to inhibition of cell proliferation[74].

In addition to the inhibition of cell proliferation, resveratrol (50-200 μmol/L) induces apoptosis in human gastric cancer SGC7901 cells by producing ROS, which can be reversed by treatment of cells with SOD or catalase, leading to the attenuation of resveratrol-mediated

cellular apoptosis[75]. Resveratrol induces apoptosis in esophageal carcinoma (EC-9706) cells, mediated by reducing the expression of Bcl-2 and enhancing that of the pro-apoptotic gene Bax[76]. Resveratrol can induce apoptosis of transplanted tumor cells, probably mediated by downregulation of the anti-apoptotic gene bcl-2 and upregulation of the apoptotic gene Bax by resveratrol in implanted primary human gastric cancer cells in nude mice[77].

Sulforaphane

The natural chemical compound sulforaphane is an isothiocyanate and is abundant in cruciferous vegetables, especially broccoli[59]. Sulforaphane is present as sulforaphane glucosinolates (SGS), which is biologically inactive. SGS is hydrolyzed by the action of myrosinase in the oral cavity and small intestine to produce sulforaphane. Biologically active sulforaphane is ultimately absorbed into the systemic circulation, where it exerts various activities[59]. Although sulforaphane is not itself an antioxidant, it exerts antioxidant activity by stimulating Nrf2-depedent antioxidant enzymes, such as glutathione S-transferase (GST), thereby protecting cells against oxidative stress[78-80]. Compared to other strong antioxidants, such as vitamin C or polyphenols, sulforaphane maintains the activities of antioxidant enzymes, including NAD(P)H: quinone oxidoreductase (NQO1) and GST in the gastric mucosa of Nrf2-/- mice infected with *H. pylori* and fed a high salt diet[59]. This renders sulforaphane a more potent antioxidant substance and mediates its protection of the gastric mucosa against oxidative stress.

Sulforaphane increases detoxification as well as antioxidant enzymes in a Nrf2-dependent manner. Fahey *et al*[78] demonstrated that sulforaphane suppresses benzo-[a]pyrene-evoked forestomach tumors in ICR mice. This is probably mediated by inducing phase 2 detoxification enzymes, including NQO1 and GST, and upregulating antioxidant enzymes, which are abrogated in mice without the *Nrf2* gene[78]. In patients with *H. pylori*-associated gastritis, *H. pylori* eradication increased or restored the activity of GST and glutathione levels in the antral mucosa[81]. This further emphasizes the importance of antioxidants during the development of gastric cancers associated with *H. pylori* infection.

In addition to its antioxidant capacity, sulforaphane exerts chemoprotective effects which are attributed to its *in vitro* anti-bacterial activity[59]. In a clinical study of *H. pylori*-infected patients (n = 48), the group that consumed broccoli (70 g/d; containing 420 μmol/L sulforaphane precursor) for 8 wk showed decreased levels of markers of *H. pylori* colonization (*i.e.*, urease level and *H. pylori* stool antigen) and markers of gastric inflammation (*i.e.*, serum pepsinogens Ⅰ and Ⅱ) compared to the placebo group[82]. An *in vivo* study using C57BL/6 female mice infected with *H. pylori* Sydney strain 1 and maintained on a high-salt (7.5% NaCl) diet confirmed the anti-bacterial activity of sulforaphane. Mice treated with broccoli rich in sulforaphane showed decreased gastric bacterial colonization as well as reduced expression of tumor necrosis factor (TNF)-α and IL-1β in the gastric mucosa, contributing to amelioration of inflammation and, thus, prevention of high salt-induced gastric corpus atrophy[82]. Interestingly, the anti-bacterial and anti-inflammatory activities of sulforaphane were not observed in mice with *Nrf2* gene depletion, suggesting that sulforaphane exerts its effect *via* Nrf2[82].

PHYTOCHEMICALS IN COLORECTAL CANCER

Colorectal cancer is one of the most commonly diagnosed cancers in both males and females[83]. The mortality rate of males with colon and rectal cancer was the third highest for cancers in the United States between 1930 and 2007[84]. Consumption of a high-calorie diet that is high in fat leads to obesity. Many studies have investigated the contribution of obesity to colorectal diseases[85-88]. The colon is one of the first organs to encounter various factors in foods and, thus, the effects of natural bioactive compounds in the diet on colorectal tissue are the subject of extensive investigation.

The Wnt signaling pathway is a primary factor in colorectal cancer. Among several Wnt signaling proteins, β-catenin is a key regulator, which turns on and off cell proliferation proteins. In the normal state, the "destruction" complex comprising axin, APC, and glycogen synthase kinase-3β, phosphorylates β-catenin, which subsequently becomes degraded[89]. However, after activation of the Wnt signaling pathway, the "destruction" complex is suppressed and β-catenin is not degraded by ubiquitination. Accumulated β-catenin then translocates into the nucleus and binds directly to the T-cell factor (TCF)/lymphoid enhancer factor (LEF) family molecules. These interactions stimulate TCF/LEF target genes involved in cellular proliferation, such as c-myc and cyclin D1[90,91].

More importantly, the Wnt signaling pathway is stimulated by obesity[92] and is a secondary factor in the development of colon cancers[93,94]. Obesity is associated with chronic inflammation[85]. In obesity-related cancers, phosphoinositide-3-kinase (PI3K)/Akt, MAPK, and their downstream signaling proteins, including mammalian target of rapamycin (mTOR), are activated as the severity of obesity increases[95]. Overall, it is commonly accepted that suppression of the inflammatory signaling pathway may represent an important strategy for inhibition of both Wnt- and obesity-related colon cancers. Several lines of evidence have reported the anti-colon carcinogenic effects of natural compounds, which act as small molecule inhibitors of the inflammatory signaling pathway. Among them, curcumin and resveratrol are the most significant anti-carcinogenic compounds (Table 1).

Curcumin

Curcumin is the yellow pigment of turmeric and numerous studies using various carcinogenesis models have

shown its chemopreventive effects. One clinical study reported that curcumin has anti-colon carcinogenic effects. Indeed, oral intake of curcumin (4 g for 30 d) decreased the number of aberrant crypto foci in the colon in this Phase Ⅱ a clinical trial of curcumin for the prevention of colorectal neoplasia.

A number of studies have investigated the mechanisms underlying the inhibition of colon cancer development by curcumin. The major targets of the signaling pathways regulated by curcumin are EGFR[96,97], AMPK-COX-2[98], MAPK[99] and Wnt/β-catenin[100]. EGFR is one of four family erbB receptors and is involved in many malignancies, including colorectal cancer[97], by modulating multiple signaling pathways. Specifically, ligand-activated EGFRs are autophosphorylated and activate Ras and other signaling pathways, which in turn increase the expression of EGFR target genes. Indeed, increased levels and function of EGFR are closely associated with the metastatic potential of human colon carcinoma cells. Chen *et al*[96] reported that curcumin inhibits colon cancer cell growth by reducing the ERK/Egr-1/EGFR signaling pathway and decreasing the expression of EGFR. Curcumin was also demonstrated to prevent the emergence of chemoresistant colon cancer cells *via* inhibition of EGFR and insulin-like growth factor (IGF)-1R.

AMPK is a highly conserved kinase in eukaryotes. Although its main function is in maintenance of energy homeostasis, novel roles for AMPK were discovered recently. The AMPK-COX-2 cascade is an important pathway associated with cancer growth. Previous studies demonstrated that a signaling cascade involving AMPK, pAkt and COX-2 is a promising target as it is regulated by curcumin during cancer cell growth. Over 80% of colonic adenomas and carcinomas exhibit mutations in the *APC* gene and constitutive activation of Wnt signaling[101]. Thus, Wnt/β-catenin signaling has been targeted for the development of novel anti-colorectal cancer drugs. Curcumin also inhibits the Wnt/β-catenin signaling pathway[102]. Curcumin impairs Wnt signaling and cell-cell adhesion pathways, subsequently inducing G_2/M phase and apoptosis in colon cancer cells.

Resveratrol

Resveratrol is a naturally occurring phenolic phytochemical, which is present in red grapes. Resveratrol exerts its chemopreventive and chemotherapeutic effects by modulating multiple biological activities. Daily *p.o.* doses of 0.5 g or 10 g resveratrol for 8 d inhibited tumor cell proliferation by 5% with no resveratrol-related adverse effects in patients with resectable colorectal cancer (n = 90)[103]. Another clinical study demonstrated that ingestion of grape powder suppresses the expression of Wnt target genes, including cyclin D1 and axin Ⅱ, in normal colonic mucosa. This suggests that dietary supplementation with resveratrol-containing products is a potential colon cancer preventive strategy and that Wnt/β-catenin is a potential target for resveratrol in normal colonic mucosa[104]. The anti-colonic tumor effects of resveratrol have been investigated in various *in vivo* studies[105-107]. Resveratrol (300 ppm) supplementation reduced levels of markers of DSS-mediated colitis inflammation, such as iNOS, COX-2 and TNF-α, in mice[105]. Resveratrol also inhibited the 1,2-dimethylhydrazine-induced tumor burden per animal, per group and over the three regimens of colon carcinogenesis (initiation, post-initiation and entire period)[107].

Resveratrol suppresses IGF-1-induced human colon cancer cell proliferation by activating p53 signaling pathways. Because the IGF signaling pathway is closely related to obesity-mediated colorectal carcinogenesis[108], resveratrol may be useful for suppressing obesity-induced colorectal cancers. Additionally, resveratrol inhibits human colon cancer cell proliferation and promotes apoptosis by suppressing the pentose phosphate pathway and focal adhesion kinase, a critical protein for cell-extracellular matrix communication. This supports the anti-colon-carcinogenic effect of resveratrol in obese individuals[109].

Furthermore, resveratrol exerts synergistic anti-cancer effects on chemoresistant cancer cells by regulating the AMPK signaling pathway. The HT-29 cell line has been used to develop anti-cancer drugs intended to overcome chemoresistance[110]. Although 100 μmol/L etoposide, an anti-cancer agent, did not inhibit the proliferation of HT-29 cells, pretreatment with resveratrol (50-400 μmol/L) induced cytotoxicity under 100 μmol/L etoposide[110]. Additionally, the phosphorylation level of acetyl-CoA carboxylase (ACC), the downstream molecule of AMPK, was increased by co-treatment with resveratrol and etoposide and increased phospho-ACC and pAMPK inhibition of cell viability. Compound C, an AMPK inhibitor, reduced resveratrol/etoposide-induced cytotoxicity on HT-29 cells[110].

CONCLUSION

Gastroenterological cancers, including those of the esophagus, stomach and colon, are closely associated with lifestyle factors, especially diet. Patients suffering from gastroenterological cancers often cannot be completely cured with regular chemopreventive strategies and, thus, prevention, suppression, and/or delaying the onset of these cancers are critical. A number of natural phytochemicals, including curcumin, resveratrol, isothiocyanates, EGCG, and sulforaphane have been shown to have anti-carcinogenic, anti-inflammatory, and antioxidant activities by targeting small molecules or regulating signaling cascades, thereby protecting against the development of gastroenterological cancers. Although most phytochemicals act as small molecule inhibitors, they often have low bioavailability following oral administration. Indeed, the concentration of resveratrol is lower than its major metabolite resveratrol sulfate glucuronide after daily administration of 0.5 g resveratrol for 8 d to colorectal cancer patients[103]. The majority of the phytochemicals are readily converted to their metabolites in the gastrointestinal tract. These metabolites may have similar or better effects than their parent compounds and, thus, may also represent primary therapeutic agents.

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