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TOPIC HIGHLIGHT

2015 Advances in Colorectal Cancer

Role of phytochemicals in colorectal cancer prevention

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Abstract

Although the incidence of colorectal cancer (CRC) has been declining in recent decades, it remains a major public health issue as a leading cause of cancer mortality and morbidity worldwide. Prevention is one milestone for this disease. Extensive study has demonstrated that a diet containing fruits, vegetables, and spices has the potential to prevent CRC. The specific constituents in the dietary foods which are responsible for preventing CRC and the possible mechanisms have also been investigated extensively. Various phytochemicals have been identified in fruits, vegetables, and spices which exhibit chemopreventive potential. In this review article, chemopreventive effects of phytochemicals including curcumin, polysaccharides (apple polysaccharides and mushroom glucans), saponins (Paris saponins, ginsenosides and soy saponins), resveratrol, and quercetin on CRC and the mechanisms are discussed. This review proposes the need for more clinical evidence for the effects of phytochemicals against CRC in large trials. The conclusion of the review is that these phytochemicals might be therapeutic candidates in the campaign against CRC.

Key words: Phytochemicals; Fruits; Vegetables; Spices; Colorectal cancer; Cancer prevention

Core tip: Colorectal cancer (CRC) remains a major public health issue as a leading cause of cancer mortality and morbidity worldwide. Chemoprevention is one milestone for this disease. A diet consisting of fruits, vegetables, and spices has the potential to prevent CRC. This manuscript reviews the phytochemicals in these dietary foods that are responsible for preventing CRC and the possible mechanisms. Various phytochemicals have been identified in fruits, vegetables, and spices which exhibit chemopreventive potential. This work will further promote the importance of phytochemicals in CRC prevention.

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INTRODUCTION

Colorectal cancer (CRC) continues to be a worldwide killer, despite that the past decade has witnessed enormous amount of research and rapid development. According to recent statistics, CRC is the fourth most common malignant tumor worldwide, with an annual incidence of 1.2 million new cases and over 600000 deaths[1]. CRC mortality has been increasing in many Western countries[2]. In 2014, there were an estimated 136830 new cases of CRC and 50310 patients died from CRC in the United States[1]. In several areas at low risk historically, including Spain, and some countries in Eastern Europe and Eastern Asia, the incidence of CRC is rapidly increasing[2,3]. The number of CRC cases and the mortality are increasing in China as well, where more than 170000 new cases of CRC are diagnosed each year[4].

Considerable advances in neoadjuvant chemotherapy and surgical techniques have been achieved in the past decades. *e.g.*, the median survival period of CRC patients of stage Ⅳ was prolonged to 17.9 mo by adding bevacizumab to the program of 5-fluorouracil/calcium folinate[5]. However, the 5-year survival rate of colon cancer of stage Ⅳ was only 8.1% after treatments[6].

Anand *et al*[7] pointed out that only 5%-10% of all cancer cases are caused by genetic defects and the remaining 90%-95% are caused by environment and lifestyle, providing great opportunities for cancer prevention. Therefore, chemoprevention, which is defined as the intake of foreign agents in order to restrain induction, prevent or slow the progression of cancer, or reverse carcinogenesis at a premalignant stage has drawn more and more attention from both the scientific community and the general public[8]. Among cancers, CRC is a good candidate for chemoprevention owing to the long precancerous stage that provides individuals with an opportunity to interfere before adenomas develop into cancer. Various pharmacologic or dietary agents have been evaluated for their chemopreventive effects against cancer[9,10]. Unlike other cancer cells, CRC cells are exposed directly to the agents. Then, there is a growing interest to investigate how these agents are associated with CRC. Celecoxib, a cyclooxgenase-2 (COX-2) inhibitor, is approved for preventing familial adenomatous polyposis (FAP). However, the chemopreventive benefit of celecoxib is at the expense of its serious cardiovascular adverse effect[11]. The serious side effects of the FDA approved chemopreventive drugs are usually paid particular attention when taking into account long-term use of a drug in healthy people who may or may not develop cancer. This clearly indicates the need for agents, which are effective as well as safe in preventing CRC. Diet derived phytochemicals will be potential candidates for this purpose. It is widely believed that a diet high in fruits, vegetables, spices, and grains possesses beneficial effects on the intestine, particularly the colon. The substances in these dietary foods that are responsible for preventing CRC and the mechanisms by which they achieve this have been extensively studied. A large number of studies have shown that a proper diet can help protect against CRC. Many phytochemicals have been isolated and identified in fruits, vegetables, spices, and grains that show chemopreventive potential[12-15]. Below is a description of selected phytochemicals which have been studied extensively to determine their role in CRC prevention.

NATURAL COMPOUNDS WITH CHEMOPREVENTIVE POTENTIAL

CURCUMIN

Curcumin is a hydrophobic polyphenol derived from turmeric, the rhizome of the herb Curcuma longa, and has a potential in suppressing inflammation and inhibiting the growth of neoplastic cells[16]. Many *in vitro* studies have proven that curcumin could be used as a therapeutic agent for CRC through affecting numerous target molecules.

Both survivin and insulin like growth factor-1 (IGF-1) could lead to inhibition of apoptosis and prolonged survival of colon cancer cells by suppressing the mitochondria-mediated pathway. Curcumin down-regulates the expression of survivin and IGF-1 by activating the expression of p53 and reducing tumor necrosis factor-α (TNF-α) levels, leading to activation of apoptotic signal[17]. Guo *et al*[18] assessed the effects of curcumin and investigated its mechanism in LoVo cells. Cells incubated with 2.5-30 μg/mL of curcumin for 24, 48 or 72 h had a significantly decreased growth rate. Curcumin treatment not only induced cell cycle arrest of LoVo cells at S phase and apoptosis

accompanied by ultra-structural changes and release of lactate dehydrogenase in a dose-dependent manner, but also decreased the mitochondrial membrane potential and activated caspase-3 and caspase-9 in a dose- and time-dependent manner. Furthermore, curcumin increased Bax and p53 and reduced Bcl-2 and survivin expression, and triggered the release of cytochrome c in LoVo cells. The results indicate that curcumin suppressed the growth of LoVo cells, at least in part, by inducing apoptosis through a mitochondria-mediated pathway. Nuclear factor-kappa B (NF-κB) is one of the most important molecules involved in innate immunity and inflammation and has emerged as an important endogenous tumor promoter[19]. NF-κB plays an important role of supervision in controlling the transformation of inflammation in the context of inflammatory cells and cancer. Under resting condition, the NF-κB dimmers reside in the cytoplasm. Upon activation, it translocates to the nucleus, where it triggers the expression of more than 200 genes that exhibit the ability of suppressing apoptosis and inducing proliferation, cellular transformation, invasion, metastasis, inflammation, radio-resistance, and chemo-resistance. NF-κB activation in cancer cells would lead to inflammation-induced tumor growth, and inhibition of NF-κB activation could prevent tumor growth[20]. Various studies have demonstrated the pivotal role of NF-κB in tumor initiation and progression in CRC[21]. Curcumin could mediate its therapeutic effects partly through regulating the transcription factor NF-κB and NF-κB-regulated gene products including cyclin D1, TNF-α, Bcl-2, Bcl-XL, inducible nitric oxide synthase and matrix metallo-preteinases (MMPs)[22]. Curcumin inhibited the TNF-induced activation of inhibitor of nuclear factor kappa-B kinase (IKK), bringing about the suppression of TNF-dependent phosphorylation, degradation of IκBα and translocation of the p65 subunit. Curcumin also blocked hydrogen peroxide- and phorbol ester-induced activation of NF-κB[23].

COX-2 is one of the most important molecules involved in inflammation and cancer. Elevated expression of COX-2 has been detected in the majority of colorectal carcinomas[24-28], and in a subset of adenomas. Inhibition of COX-2 activity, either by genetic disruption or pharmacological methods, leads to reduced size and number of adenomas in murine models of intestinal tumorigenesis[29,30]. Curcumin markedly inhibited the mRNA and protein expression of COX-2, but not COX-1. Lev-Ari *et al*[31] conducted a study to investigate whether curcumin enhances the anti-growth effects of celecoxib, a specific COX-2 inhibitor, in human colon cancer cell line HT-29. This study revealed that in the presence of 10-15 μmol/L of curcumin, a physiologic dose of celecoxib at 5 μmol/L was sufficient to restrain cell growth by suppressing proliferation and promoting apoptosis through the COX-2-dependent and -independent pathways. This effect was similar to what can be achieved by using a 10-fold higher concentration of celecoxib (50 μmol/L) when administrated alone. Curcumin potentiated the growth inhibitory effect of celecoxib by shifting the dose-response curve to the left. The clinical importance of this effect lies in the fact that it can be achieved in the serum of patients treated with standard anti-inflammatory (200-400 mg) or antineoplastic (400-800 mg) doses of celecoxib[31]. The phosphorylated form of cortactin (cortical actin binding protein) or CTTN, a monomeric protein located in the cytoplasm of cells (pTyr^{421}) plays a crucial role in cancer cell migration and invasion. Upregulated pTyr^{421}-cortactin has been detected in colon cancer. Curcumin significantly downregulated pTyr^{421}-CTTN in HCT116 cells and SW480 cells, but had no effect in HT-29 cells. Curcumin physically interacted with PTPN1 tyrosine phosphatases to increase its activity, which resulted in dephosphorylation of pTyr^{421}-CTTN. PTPN1 inhibition could abolish the effects of curcumin on pTyr^{421}-CTTN. Curcumin decreased migration of HCT116 and SW480 cells which highly express PTPN1, but not of HT-29 cells with significantly reduced endogenous PTPN1 level. Adenovirally encoded CTTN increased migration of all three cell lines. Further study showed that curcumin significantly reduced the physical interaction of CTTN and pTyr^{421}-CTTN with p120 catenin (CTNND1). In summary, curcumin mediates the activity of PTPN1 phosphatase to reduce cortactin phosphorylation and interaction with CTNND1, and finally to reduce cell motility in colon cancer[32].

Curcumin, therefore, is a promising chemopreventive natural agent with multiple targets and no reported adverse or toxic events.

The pharmacodynamic and pharmacokinetic effects of oral curcuma extract in patients with CRC have been investigated. In one study, curcumin was administered to 126 patients with CRC before undergoing surgery. Patients either received 360 mg of curcumin or placebo three times daily. Results demonstrated that curcumin treatment was accompanied by increased body weight, decreased serum TNF-α level, modulated tumor cell apoptosis and enhanced p53 expression[17]. A dose-escalation pilot study of Curcuma extract at doses of 0.45-3.6 g in 15 patients with advanced CRC for a period of 4 mo showed a dose dependent inhibition of COX-2 activity, measured as basal and lipopolysaccharide (LPS)-mediated prostaglandin E_2 (PGE_2) production in blood, demonstrating the efficacy of curcumin in CRC. A daily dose of 3.6 g of curcumin was related to a 62% and 57% decrease of inducible PGE_2 on days 1 and 29, respectively ($P < 0.05$)[33]. In one pharmacodynamic and pharmacokinetic study of oral Curcuma extract, 15 patients with advanced CRC refractory to standard chemotherapies were given Curcuma extract at doses ranging from 440 to 2200 mg/d. Curcuma extract including 36-180 mg of curcumin was given for 4 mo. The doses were well tolerated with no obvious toxicity observed.

Table 1 Current clinical trials of curcumin and resveratrol

ClinicalTrials.gov Identifier	Title	Design/phase	Intervention	Primary purpose
NCT01294072	Study investigating the ability of plant exosomes to deliver curcumin to normal and colon cancer tissue	Phase Ⅰ	Dietary supplement: curcumin Dietary supplement: curcumin conjugated with plant exosomes Other: no intervention	Treatment
NCT00295035	Phase Ⅲ trial of gemcitabine, curcumin and celebrex in patients with metastatic colon cancer	Phase Ⅲ	Drug: celecoxib Drug: curcumin	Treatment
NCT00027495	Curcumin for the prevention of colon cancer	Phase Ⅰ	Dietary supplement: curcumin	Prevention
NCT00973869	Curcumin in preventing colorectal cancer in patients undergoing colorectal endoscopy or colorectal surgery	Phase Ⅰ	Dietary supplement: curcumin Other: high performance liquid chromatography Other: laboratory biomarker analysis Other: pharmacological study Procedure: diagnostic endoscopic procedure Procedure: therapeutic conventional surgery	Prevention
NCT00365209	Phase ⅡA trial of curcumin among patients with prevalent subclinical neoplastic lesions (aberrant crypt foci)	Phase Ⅱ	Other: laboratory biomarker analysis Other: pharmacological study Drug: curcumin	Prevention
NCT01490996	Combining curcumin with FOLFOX chemotherapy in patients with inoperable colorectal cancer	Phase Ⅰ Phase Ⅱ	Drug: oral complex C3 curcumin+ chemotherapy Drug: chemotherapy only	Treatment
NCT01859858	A prospective evaluation of the effect of curcumin on dose limiting toxicity and pharmacokinetics of irinotecan in patients with solid tumors	Phase Ⅰ	Dietary supplement: curcumin Drug: Irinotecan	Basic science
NCT00118989	Curcumin for the chemoprevention of colorectal cancer	Phase Ⅱ	4 g curcumin daily for 4 mo or placebo	Prevention
NCT00256334	Resveratrol for patients with colon cancer	Phase Ⅰ	Drug: resveratrol	Treatment
NCT00578396	Phase I biomarker study of dietary grape-derived low dose resveratrol for colon cancer prevention	Phase Ⅰ	Dietary supplement: grapes	Prevention Phase Ⅰ
NCT00433576	Resveratrol in treating patients with colorectal cancer that can be removed by surgery	Phase Ⅰ	Patients with colorectal adenocarcinomas received resveratrol for days 1 to 8 and on day 9 underwent colorectomy Tumor biopsy will be retrieved	

Ingestion of 440 mg for 29 d was correlated with a 59% decrease in lymphocytic glutathione S-transferase activity. This effect was not seen at higher doses. Neither curcumin nor its metabolites were detected in blood or urine. Despite the results, it is difficult to figure out whether curcumin at this dose is an effective chemopreventive agent in CRC because of the small number of subjects[34].

In another study, curcumin capsules (450, 1800, and 3600 mg) were given to patients with CRC daily for 7 d. Trace levels of curcumin were found outside the circulation. Level of M1G, a marker of DNA adduct formation, was significantly reduced by curcumin at a dose of 3600 mg. The study showed that curcumin at a dose of 3.6 g for daily use is pharmacologically efficacious[35]. In a phase IIa clinical trial, curcumin at doses of 2 g or 4 g was administered to 44 eligible smokers with 8 or more aberrant crypt foci (ACF) over a 30-d period. Results demonstrated that at a dose of 4 g, curcumin was able to reduce the ACF number by 40% ($P < 0.005$), whereas at a dose of 2 g, curcumin did not show the effect[36]. Other clinical trials of curcumin are listed in Table 1.

POLYSACCHARIDES

Polysaccharides are a structurally diverse class of biological macromolecules, which are composed of monosaccharide polymers linked through glycosidic bonds. They range in structure from linear to highly branched form, and are used extensively as foods and pharmaceuticals. Furthermore, the enormous variety of polysaccharides has resulted in a constantly evolving group of potential bioactive compounds.

Apple polysaccharides

Apples are a kind of healthy food, and the consumption of which may decrease the risk of CRC[37]. It has been found that cloudy apple juice could decrease ACF development, hyperproliferation, and DNA damage in the distal colon of dimethylhydrazine (DMH)-initiated rats[38]. One component that makes the apple juice cloudy is saccharide. We thus extracted polysaccharides from apple and evaluated their effects on CRC. A microarray was used to investigate the effects of apple polysaccharides (AP) on human colon carcinoma cells (HT-29). Treatment of HT-29 cells with AP caused

the expression of 333 genes over the cutoff value (⩾ 2-fold). Cell cycle pathways were mainly influenced. At concentrations from 0.001 to 0.1 mg/mL, AP induced a G_0/G_1 phase arrest in HT-29 cells dose-dependently. Administration of AP could protect ICR mice against CRC effectively. The results of Western blot suggested that AP induced cell-cycle block in a p53 independent manner[39]. Galectin-3, a member of the family of β-galactoside-binding lectins, is involved in different stages of inflammation, generally viewed as a promoter of inflammatory response[40-42], as well as the processes of tumorigenesis and metastasis[43-45]. Galectin-3 is a prognostic marker, and its alteration is correlated with tumor pathogenesis, progression and/or metastasis in various kinds of cancers including CRC[46,47]. In our previous study, we have found that AP moderately triggered apoptosis of colonic epithelial cells, indicating that the anti-CRC potency of AP was probably due to its apoptosis inducing ability. Western blot analysis revealed that galectin-3 changed in both the nucleus and the cytoplasm during the process from colitis to colon cancer in the model. Furthermore, AP could suppress the binding of galectin-3 to its ligands, which is partly the possible mechanism for AP to enhance apoptosis and prevent tumorigenesis[48].

LPS, a glycolipid from the outer membrane of Gram-negative bacteria, activates toll-like receptor 4 (TLR4) to stimulate intracellular signaling cascades including NF-κB pathways and mitogen activated protein kinases (MAPKs), and results in a substantial increase in the production of chemokines, cytokines, and the synthesis of a wide group of lipid inflammatory mediators[49,50]. By observing the effect of AP on LPS-activated HT-29 and SW-620 CRC cells and an azoxymethane/dextran sodium sulfate (AOM/DSS) induced mouse model, we found that AP reduced AOM/DSS caused toxicities, prevented carcinogenesis, and downregulated the expression of TLR4, MD2, myeloid differentiation protein88 (MyD88), TRIF-related adapter molecule (TRAM) interferon-β, interleukin-6, and TNF-α. The protective effects of AP may be associated with the suppression of TLR4/MD2-mediated signaling, including MyD88 and TRIF, as well as the inhibition of NF-κB-mediated inflammatory signaling pathways.

The data above may provide another molecular basis for understanding how apple acts to prevent CRC and suggest that AP has the potential in treating colitis and preventing carcinogenesis[51].

Mushroom glucans

Medicinal mushrooms have been traditionally used as a healthy food or supplement for the prevention and treatment of several health statuses or diseases, *e.g.*, cancer, atherosclerosis, hypertension, and diabetes. Polysaccharides extracted from many edible mushrooms show promising effects in preventing and treating CRC. It has been found the expression of the proliferating-associated marker proliferating cell nuclear antigen (PCNA) in colorectal adenocarcinomas of mice was significantly reduced by oral administration of *P. pulmonarius* glucans. This indicates that *P. pulmonarius* glucans inhibited colorectal carcinogenesis by suppressing the abnormal proliferative activity of preneoplastic and neoplastic cells[52]. Xie *et al*[53] reported that *Ganoderma lucidum* glucan extract inhibited proliferation of CRC SW480 cells. A soluble α-glucan from *P. ostreatus* got by Lavi *et al*[54] suppressed colon cancer cell proliferation *via* direct interaction of the glucan with the colon cancer cells and their apoptosis induction.

Induction of cell apoptosis has been a target mechanism for cancer treatments[55]. Certain mushroom polysaccharides have proapoptotic functions in many tumor cell lines *in vitro*. Hu *et al*[56] showed that the mushroom *Inonotus obliquus* induced apoptosis with differing sensitivity in human colon cancer DLD-1 cells. Lavi *et al*[52] observed that feeding mice with *P. pulmonarius* glucans increased the expression of active-caspase-3 and Bax. And these effects were found in *P. pulmonarius* glucans treated colon carcinoma cell lines (HCT-116 and HT29) as well. In the *P. pulmonarius* glucans treated colon carcinoma cell lines, there was an increase in the level of cytosolic cytochrome c and a decrease of the anti-apoptotic protein Bcl-2.

SAPONINS

Saponins, a major family of secondary metabolites containing a sugar moiety glycosidically linked to a hydrophobic aglycone (sapogenin), are a class of bioactive compounds naturally present in particular abundance in various plant species[57,58], including ginseng or red ginseng (Panax, Araliaceae) in a form called ginsenosides. This class of chemical compounds are found in different parts of the plant: stems, roots, bulbs, leaves, blossom and fruit[59]. Saponins of several plants are known to induce apoptosis in some cancer cells[60].

Paris saponins

We investigated the growth inhibitory effect of *Trillium tschonoskii* steroidal saponins (TTS), which were extracted from *Trillium tschonoskii* Maxim, in a mouse model of colitis-associated CRC and HT-29 cells. Forty male ICR mice were administered with 1, 2-dimethyl-hydrazine (DMH) and dextran sodium sulfate (DSS). Ten mice were given no further treatment, and the rest were administered with different doses of TTS (5, 10, and 20 mg/kg) orally, every three days from the 9th week to the 20th week. TTS effectively protected ICR mice from DMH/DSS-caused tumorigenesis. The incidence of tumor development was 90% (9/10) in the mice treated with DMH/DSS, but that was reduced to 50% (5/10), 40% (4/10), and 20% (2/10), respectively, in the mice treated with 5%,

10%, and 20% of TTS. Results of Ki-67 staining, TUNEL assay and caspase-3 activity assay revealed that TTS moderately decreased abnormal proliferation and increased apoptosis of colonic epithelial cells. TTS inhibited the growth and triggered the apoptosis of HT-29 cells, partly through suppressing MAPKs and triggering mitochondrial-mediated apoptotic pathway. Further, we isolated a monomer, namely, Paris saponin VII (PSVII), from TTS and evaluated its effect on human CRC cell lines HT-29 and SW-620. The results showed that PSVII inhibited growth of these cells effectively. It could not only induce cell cycle arrest in G_1 phase, but also trigger apoptosis in a caspase-3-dependent manner. One possible mechanism may be through inhibition of Ras activity by PSVII. We further proved that PSVII effectively prevented colitis associated-colorectal carcinogenesis in an ICR mouse model, and significantly reduced xenograft tumor size in a murine CRC model. These preclinical studies suggest that PSVII has potentials in the treatment of CRC[61].

Ginsenosides

Ginseng, a plant of the Araliaceae family named scientifically Panax ginseng[62], has a great reputation in the treatment of cancer. Growing evidence has shown that ginseng, especially the ingredients of which, namely, ginsenosides, possesses beneficial effects in the treatment and prevention of CRC[63-65]. Studies on ginsenosides especially Rh2 and Rg3 demonstrated that they are most effective anti-cancer compounds identified in ginseng[66-68].

Treatment of HCT116 and SW480 cells with ginsenoside Rh2 activated the p53 pathway, upregulated the level of the pro-apoptotic regulator Bax, and downregulated the level of anti-apoptotic protein Bcl-2. The anti-cancer effect of Rh2 could be enhanced by antioxidants[69]. Ginsenoside Rg3 is a single compound isolated from American ginseng (Panax quinquefolius L., Araliaceae) and Asian ginseng (Panax ginseng C. A. Meyer). Rg3 inhibited cell proliferation and viability of cancer cells *in vitro*. Allelic deletion of the oncogenic β-catenin in HCT116 cells made the cells more sensitive to Rg3-induced growth inhibition. He *et al*[70] also demonstrated that Rg3 effectively inhibited the growth of HCT116 xenograft tumors . Histologic examination revealed that Rg3 inhibited cancer cell proliferation, decreased PCNA expression and diminished nuclear staining intensity of β-catenin. The possible mechanisms could be partly attributed to Rg3 blocking nuclear translocation of the β-catenin protein and hence inhibiting β-catenin/Tcf transcriptional activity. Yuan *et al*[71] found that Rg3 induced apoptosis of HT-29 cells indicated by DNA fragmentation and cleavage of poly(ADP-ribose) polymerase (PARP). Rg3 downregulated the expression of anti-apoptotic protein Bcl-2, upregulated the expression of pro-apoptotic proteins p53 and Bax, and induced the release of mitochondrial cytochrome c, PARP, caspase-9 and caspase-3. However, suppression of AMPK with its inhibitor compound C or small interfering RNA for AMPK (siAMPK) completely abolished Rg3-induced apoptosis. In addition, STO-609 (CaMKKβ inhibitor) attenuated Rg3-induced AMPK activation and apoptosis. These results suggest that Rg3-induced apoptosis in HT-29 cells is mediated *via* the AMPK signaling pathway.

Rh2 and Rg3 exhibited anti-proliferative and anti-angiogenesis effects *in vivo* and *in vitro* through inhibition of the NF-κB pathway, suppression of cell proliferation and induction of apoptosis. This beneficial effect of ginsenosides might be due to cell cycle arrest in cancer. It seems that the G_1 phase and G_1/S checkpoint were blocked by different mechanisms of ginsenosides[72,73], which involved upregulation of p53 and p21 and downregulation of cyclin and CDK including CDK2, cyclin E and cyclin D1 in G_1 phase and G_1/S checkpoint[73].

Soy saponins

Frequent consumption of soy and soy-based products is related with reduced cancer incidence particularly for colon cancer. Kim *et al*[74] examined the effect of crude soy saponins extract on PMA (phorbol 12-myristate 13-acetate)-induced inflammatory responses. They found that crude saponin extract suppressed cell growth in a dose- and time-dependent manner. In addition, crude soy saponins extract suppressed the degradation of IKKBα in PMA-stimulated cells, while COX-2 and PKC expression was significantly downregulated.

Tsai *et al*[75] treated WiDr human colon cancer cells, the same cell line as HT-29 with 150, 300, 600 or 1200 ppm of soy saponin. They found that soy saponin decreased the number of viable cells in a dose-dependent manner and suppressed PMA-induced PKC activity. Cells treated with saponins developed cytoplasmic vesicles with the cell membrane being rougher and more irregular in a dose-dependent manner, and eventually disassembled. At 600 and 1200 ppm, the activity of AP was increased ($P < 0.05$). These findings provide another molecular basis for understanding how soy acts to prevent inflammation and cancer.

RESVERATROL

Resveratrol (*trans*-3,5,40-trihydroxystilbene) is a phytoalexin found in plants including berries, grapes, and peanuts. Numerous *in vitro* studies have shown that resveratrol has anti-CRC effects by inhibiting both tumor initiation and progression. For example, resveratrol could suppress inflammatory responses through decreasing nitric oxide levels and inhibiting the phosphorylation of the IκB complex, thus suppressing the activation of NF-κB dependent mechanisms[76].

Serra *et al*[77] conducted a study by pretreating HT-29 colon epithelial cells with 25 mM of resveratrol and/or 500 mM of 5-aminosalicylic acid, and then exposing the cells to a combination of cytokines (IL-1α, TNF-α, IFN-c) for a certain period of time. The data demonstrated that resveratrol, at a concentration 20 times lower than 5-aminosalicylic acid, could significantly decrease PGE_2 and NO production, iNOS and COX-2 expression and reactive oxidant species formation induced by the cytokine challenge. And resveratrol downregulated JAK-STAT pathway by decreasing the levels of activated STAT1 in the nucleus. Liu *et al*[78] suggested that resveratrol exhibited growth inhibitory effects in human colon cancer cells by regulating separately the PTEN/PI3K/Akt and Wnt/β-catenin signaling. They found that resveratrol inhibited the proliferation and promoted apoptosis of HCT116 cells, and suppressed the xenograft tumor growth of colon cancer as well. Resveratrol upregulated the expression of phosphatase and tensin homolog (PTEN) and decreased the phosphorylation of Akt1/2. The exogenous expression of PTEN inhibited the PI3K/Akt signal and promoted the growth inhibitory effects of resveratrol in HCT116 cells. Knockdown of PTEN increased PI3K/Akt signal but reduced the growth inhibitory function of resveratrol. The mRNA and protein expression of β-catenin was both reduced by resveratrol in a concentration dependent way. Resveratrol could activate caspases-3 and -8 and increase the Bax/Bcl-2 ratio[79]. The process through which resveratrol promoted the cleavage of caspases-3 and -8 was by reactive oxygen species triggered autophagy[80]. Several *in vivo* studies have demonstrated that resveratrol possesses beneficial effects in preventing and treating colon tumor formation as well. Azoxymethane was used to induce colon tumorigenesis in 344 male Fisher rats, and then, resveratrol (daily intake calculated to be 200 mg/kg BW) was added into their drinking water for 100 d[81]. Tessitore *et al*[81] found that compared with control water treatment, resveratrol treatment reduced the appearance of ACF precursors for colon cancer. Resveratrol also decreased the appearance of large-sized ACF and increased the expression of Bax. In another study, adult male Wistar rats were given 1,2-dimethylhydrazine (DMH) once weekly for the first 15 wk. The DMH-treated rats were divided into three groups and then administrated daily with resveratrol (8 mg/kg BW; intragastric administration). The rats of group 1 were supplemented with resveratrol every day starting 2 wk before carcinogen treatment for the first 15 wk; the rats of group 2 were supplemented with resveratrol 2 d after the last injection of the carcinogen and continued to the end of the experiment; and the rats of group 3 were supplemented with resveratrol from the day of carcinogen treatment and continued to the end of the entire experimental period of 30 wk. All the rats were sacrificed 30 wk after the initial exposed DMH injection. In comparison to vehicle-treated DMH rats, resveratrol treatment decreased tumor incidence and the number of ACF[82]. Resveratrol could also reduce COX-2 activity and expression, decrease ornithine decarboxylase that is highly expressed in cells during cell proliferation and tumor promotion, and increase the level of cleaved caspase-3[83]. A genetically engineered mouse model for sporadic CRC, in which the APC locus was knocked out and KRAS was activated specifically in the distal colon, was used to investigate the effects of resveratrol in preventing and treating CRC. Feeding the mice with a diet containing 150 or 300 ppm resveratrol (105 and 210 mg daily human equivalent dose, respectively) before tumors were visible by colonoscopy, resulted in a 60% inhibition of tumor production. In the 40% of mice that developed tumors, KRAS expression was lost in the tumors. In a therapeutic assay where tumors were allowed to develop prior to treatment, feeding tumor bearing mice with resveratrol led to a complete remission in 33% of the mice and a 97% decrease in tumor size in the remaining mice. It was shown by the analysis of miRNA expression that resveratrol treatment caused increased expression of miR-96, a miRNA previously shown to regulate KRAS translation in non-tumoral and tumoral colonic tissues. These results indicate that resveratrol is able to inhibit the formation and growth of colorectal tumors by downregulating KRAS expression[84].

Many clinical pilot studies have shown that large doses of resveratrol are comparatively safe. Twenty CRC patients were given resveratrol at a dose of 0.5 g or 1.0 g orally for 8 d prior to surgery. The results showed that resveratrol was well tolerated. Resveratrol and its metabolites were detected in CRC resection tissue. Resveratrol (0.5 g or 1.0 g) decreased tumor cell proliferation by 5% (P = 0.005) and was enough to elicit anticarcinogenic effects in colon tumors[85]. In this study, serum resveratrol concentrations of 86 and 674 nmol/mL were observed at 0.5 and 1.0 g dose levels. Moreover, parent resveratrol accounted for a much larger proportion of resveratrol species in colorectal tissue than in plasma. These data support the notion that the colorectum is a suitable target for chemoprevention by resveratrol. Resveratrol at doses of 0.5 and 1.0 g has the capacity to induce pharmacological effects in the gastrointestinal tract[86]. Other clinical trials of resveratrol are listed in Table 1.

QUERCETIN

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is one of the major dietary flavonoid and polyphenol found in several fruits, vegetables and beverages such as tea and wine. It has been shown that quercetin plays a role in inhibiting tumorigenesis in colon cells through antioxidant, anti-inflammatory, antiproliferative, and pro-apoptotic mechanisms. Quercetin downregulated Bcl-2 through inhibition of NF-κB[86] and inhibited phosphorylation of EGFR, thus

suppressing downstream signaling in colon carcinoma cells[87]. Mutoh *et al*[88] used a reporter gene assay to investigate the inhibitory effect of 12 flavonoids on the transcriptional activity of *COX-2* gene in human colon cancer DLD-1 cells. They observed that quercetin was the most potent suppressor of COX-2 transcription with an IC_{50} value of 10.5 mmol/L. Dysregulation of Wnt/beta-catenin pathway plays a key role in colorectal carcinogenesis. Park *et al*[89] indicated that quercetin may reduce nuclear beta-catenin and Tcf-4 proteins to downregulate β-catenin/Tcf transcriptional activity in SW480 cells. They found that quercetin downregulated the transcriptional activity of β-catenin/Tcf both in SW480 and in HEK293 cells which were transiently transfected with constitutively active mutant β-catenin gene. Both the electrophoretic mobility shift assay and immunoprecipitation results showed that binding of the Tcf complexes to its specific DNA-binding sites was significantly suppressed by quercetin. Results of Western blot suggested the decreased binding induced by quercetin was caused by decreased levels of β-catenin and Tcf-4 products in the nucleus. In another study, Shan *et al*[90] found that quercetin reduced cell viability in a dose- and time-dependent manner in SW480 cells. The percentages of apoptotic cells and cells in G_2/M phase were increased obviously after treatment with quercetin. Treatment with quercetin at a concentration of 160 μmol/L reduced β-catenin/Tcf transcriptional activity by about 18-fold. Quercetin reduced cyclin D1 and survivin expression in a dose-dependent manner at both mRNA and protein levels. Activation of AMP-activated protein kinase (AMPK), a physiological cellular energy sensor, strongly inhibits cell proliferation in tumor cells. Kim *et al*[91] found that treatment of HT-29 cells with quercetin significantly decreased cell viability, induced cell cycle arrest in the G1 phase and increased the expression of apoptosis-related proteins, such as AMPK, p53, and p21. *In vivo* studies demonstrated that quercetin treatment for over 6 wk led to a significant reduction in tumor volume. The study suggested that quercetin may trigger apoptosis *via* AMPK activation and p53-dependent apoptotic cell death in HT-29 cells.

CONCLUSION

Regular consumption of fruits and vegetables might protect against cancer. The protective role of certain components (phytochemicals) in fruits and vegetables against cancers occurring in different anatomical sites is now well supported. The objectives of this review were to document the chemopreventive effects of several phytochemicals including curcumin, polysaccharides (AP, and mushroom glucans), saponins (Paris saponins, ginsenosides and soy saponins), resveratrol, and quercetin on CRC and the possible mechanisms. These phytochemicals have advantages because they are comparatively safe and usually target multiple cell signaling pathways. As research continues, interventions in CRC using various phytochemicals might eventually become a specific treatment of choice.

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