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Natural products and colon cancer: current status and future prospects

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Abstract

Carcinogenesis is a multistage process consisting of initiation, promotion and progression phases. Thus, the multistage sequence of events has many phases for prevention and intervention. Chemoprevention, a novel approach for controlling cancer, involves the use of specific natural products or synthetic chemical agents to reverse, suppress or prevent premalignancy before the development of invasive cancer. Several natural products, such as, grains, nuts, cereals, spices, fruits, vegetables, beverages, medicinal plants and herbs and their various phytochemical constituents including, phenolics, flavonoids, carotenoids, alkaloids, nitrogen containing as well as organosulfur compounds confer protective effects against wide range of cancers including colon cancer. Since diet has an important role in the etiology of colon cancer, dietary chemoprevention received attention for colon cancer prevention. However, identification of an agent with chemopreventive potential requires *in vitro* studies, efficacy and toxicity studies in animal models before embarking on human clinical trials. A brief introduction about colon cancer and the role of some recent natural products in colon cancer chemoprevention with respect to multiple molecular mechanisms in various *in vitro, in vivo* and clinical studies are described in this review.

Keywords

Colon cancer; chemoprevention; natural products; *in vitro* studies; *in vivo* studies

Introduction

Carcinogenesis is a multistage process consisting of initiation, promotion and progression phases involving sequential generations of cells that exhibit continuous disturbance of cellular and molecular signal cascades [Vincent and Gatenby, 2008]. Thus, the multistage sequence of events has many phases for intervention to inhibit, reverse and/or delay each process of carcinogenesis before the development of invasive malignancy. Agents that can suppress these multiple pathways have great potential for chemoprevention [Krzystyniak, 2002]. An ideal chemopreventive agent should have (i) little or no toxicity, (ii) high efficacy in multiple sites, (iii) capability of oral consumption, (iv) known mechanisms of action, (v) low cost, and (vi) human acceptance. In recent years, natural products have received great attention for cancer prevention owing to their various health benefits, noticeable lack of toxicity and side effects, and the limitations of chemotherapeutic agents [Manson et al., 2005].

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Overall, natural products have been used worldwide as traditional medicines for thousands of years to treat various forms of diseases including cancer. Several studies have revealed that natural products exhibit an extensive spectrum of biological activities such as, stimulation of the immune system, antibacterial, antiviral, anti-hepatotoxic, anti-ulcer, anti-inflammatory, antioxidant, anti-mutagenic, and anti-cancer effects [Miyata, 2007; Espín et al., 2007]. A variety of grains, cereals, nuts, soy products, olives, beverages such as tea and coffee, and spices including turmeric, garlic, ginger, black pepper, cumin and caraway confer a protective effect against cancer [Lila, 2007; Williams and Hord, 2005]. Several studies have also documented the relationship between decreased cancer risk and high consumption of vegetables, including cabbage, cauliflower, broccoli, brussels sprout, tomatoes, and fruits such as, apples, grapes, and berries [Vainio and Weiderpass, 2006; Gordaliza, 2007]. In addition, a number of medicinal plants and herbs such as milk thistle have also been reported to reduce the risk of cancer in multiple sites [Park and Pezzuto, 2002; Kroll et al., 2007]. In particular, natural products consist of a wide variety of biologically active phytochemicals including phenolics, flavonoids, carotenoids, alkaloids and nitrogen containing as well as organosulfur compounds, which have been shown to suppress early and late stages of carcinogenesis [Nishino et al., 2007]. Several epidemiological studies have validated the inverse relation between the consumption of natural products and the risk of wide range of human cancers including colon cancer [Lila, 2007; Williams and Hord, 2005; Vainio and Weiderpass, 2006; Giovannucci, 2003; Satia-About a et al., 2004]. A brief introduction about colon cancer and the role of some recent natural products in colon cancer chemoprevention with respect to multiple molecular mechanisms in various *in vitro*, *in vivo* and clinical studies are described in following sub-sections.

Colon Cancer: Pathology, Risk Factors and Genetics

Colon cancer is defined as any malignant neoplasm arising from the inner lining of the colonic epithelium, and is the third most common cancer and the third leading cause of cancer related deaths for both men and women in United States [American Cancer Society, 2008]. Although the mortality rate has fallen dramatically over the last two decades, 108,070 new colon cancer cases and 49,960 deaths from colon cancer are estimated for 2008 [American Cancer Society, 2008]. The 5-year survival rate of colon cancer after diagnosis at an early and localized stage is 90 per cent; however, when distant metastasis has occurred, the 5-year survival rate drops to 10 per cent [American Cancer Society, 2008].

The occurrence of colon cancer is mainly associated with the incidence of aberrant crypt foci (ACF), an earliest neoplastic lesion, which are clusters of mucosal cells with an enlarged and thicker layer of epithelia than the surrounding normal crypts that progress in to polyps followed by adenomas and adenocarcinomas [Cappell, 2007]. These sequences of events are considered to be a consequence of the accumulation of multiple genetic alterations in colonic epithelium [Humphries and Wright, 2008]. Though all ACF do not progress in to colon cancer, several studies have reported that all colon cancer arises from ACF [Cappell, 2007].

The occurrence of colon cancer is strongly related to age, with 90% of the cases arising in people who are 50 years or older; until age 50, both men and women have equal risk for colon cancer, but in later life males predominate with this malignancy [American Cancer Society, 2008]. Epidemiological studies have suggested that colon cancer is a manifestation of a number of inherited cancer predisposition syndromes, including familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, and personal or family history of colorectal cancer and/or polyps and inflammatory bowel disease [Rowley, 2005]. Furthermore, other factors such as obesity, lack of exercise, smoking, alcohol consumption, diet rich in high fat, red and processed meats and inadequate intake of dietary fiber, fruits and vegetables are also associated

with increased colon cancer risk [Cappell; 2007; Papapolychroniadis. 2004; Kim and Milner, 2007].

Vogelstein et al. [1988] first described the time dependent accumulation of genetic mutations and sequential phenotypic correlation in the colonic epithelium. Mutations due to loss of heterozygosity as well as chromosal instability in oncogenes such as *k-ras*, *c-erb2* or *c-myc*, or tumor suppressor genes such as *adenomatous polyposis coli* (APC), delete in colon cancer (DDC) or *p53* have been implicated in 80% of sporadic colon cancer [Mutch, 2007]. Microsatellite instability associated mutations in mismatch repair genes resulting in replication errors have also been suggested to play a key role in colon cancer development [Niv, 2007]. Gene abnormalities and aberrant expression of cell cycle regulators and cell-cell adhesion molecules are the other genetic events which have been involved in the pathogenesis of colon cancer [Mutch, 2007].

Colon Cancer Chemoprevention: Biological Endpoints and Associated Mechanisms

Several epidemiological studies have reported inverse correlation between a high intake of fruits, vegetables, and phytochemicals such as carotenoids and flavonoids and reduced risk of colon cancer [Lila, 2007; Williams and Hord, 2005; Vainio and Weiderpass, 2006; Giovannucci, 2003; Satia-About a et al., 2004; Nishino et al., 2007]. Plant-based chemopreventive agents and their constituent phytochemicals have been known to interfere with various molecular pathways involved in colon cancer initiation and progression [Gustin and Brenner, 2004]. Colon cancer development is associated with an excessive cell proliferation and a dysregulation of both cell cycle progression and apoptosis [Mutch, 2007]. Moreover, “neo angiogenesis” is an essential process in the development, growth and metastasis of colon tumor [Kumar, 2005]. Cyclooxygenase -2 (COX-2), an inducible prostaglandin G/H synthase, is know to play a major role in prostaglandin (PG) synthesis. Over expression of COX-2 and subsequent prostaglandin (PG) production from free arachidonic acid, have also been implicated in colon carcinogenesis [Spychalski et al., 2007]. In particular, COX-2-mediated increased PGE2 levels have been believed to enhance tumor promotion by promoting cell proliferation, angiogenesis and apoptotic evasion, stimulating tumor metastasis, and decreasing immune surveillance [Eisinger et al., 2007]. An abnormal activation of the Wnt/β-catenin pathway has also been implicated in the development of human colon cancer, and therefore is considered as a hallmark for this malignancy [Spychalski et al., 2007]. Over expression of Wnt ligand and/or mutations in the downstream molecules in the Wnt signaling cascade have been implicated in the activation of Wnt pathway [Luu et al., 2004]. Increased phosphorylation of extra cellular regulated kinases (ERK1/2) is required for PGE2 to stimulate cell proliferation of human colon cancer cells [Gustin and Brenner, 2004]. Deregulation of phosphatidylinositol 3 kinase (PI3K)/Akt signaling pathway and its downstream transcription factors are the other molecular events that have been implicated in cancer development [Bode and Dong, 2004]. A number of natural products and their active phytochemicals have been found to exert their chemopreventive effects by inducing cell cycle arrest and apoptosis, decreasing cell proliferation and angiogenesis, inhibiting tumor cell invasion and metastasis, and modulating various signal transduction as well as COX-2/PGE2 and Wnt/β-catenin pathways, involved in colon cancer development [Dragnev et al., 2007]. Herein, the potentials of several natural products targeting the above mentioned molecular pathways leading to colon cancer prevention and/or intervention are described. Figure 1 shows mechanisms of actions of various natural products and their constituent phytochemicals in colon cancer chemoprevention.

Colon Cancer Chemoprevention: Effects on Molecular Events Associated with Proliferation and Apoptosis

Studies have shown the antiproliferative as well as apoptosis inducing ability of natural products in colon cancer chemoprevention. For example, blackberry, black raspberry, blueberry, cranberry, red raspberry, and strawberry extracts have been shown to inhibit the growth and stimulate apoptosis in HT-29 and HCT-116 cells [Seeram et al., 2006]. In particular, black raspberry and strawberry extracts exhibit significant pro-apoptotic effects in HT-29 cells [Seeram et al., 2006]. Procyanidine enriched fraction of apple is shown to inhibit cell growth through G2/M phase arrest and induction of apoptosis as evidenced by caspase 3 activation [Gossé et al., 2005]. Previously, we have shown that grape seed extract treatment inhibits HT-29 and LoVo cell growth by inducing G1 phase cell cycle arrest and caspase 3-dependent apoptotic cell death, which was associated with an increase in Cip1/p21 protein expression and a decrease in G1 phase-associated cyclins and cyclin-dependent kinases [Kaur et al., 2006]. Resveratrol (3,4',5 tri-hydroxystilbene), a naturally occurring polyphenolic compound highly enriched in grapes and red wine, has been shown to induce apoptosis in HT-29 cells [Park et al., 2007]. Resveratrol has also been shown to down-regulate telomerase activity in HT-29 and WiDr human colon cancer cell lines together with inhibition of cell proliferation [Fuggetta et al., 2006]. Engelbrecht et al. [2007] have reported that grape seed proanthocyanidin extract inhibits cell viability and induces apoptosis by suppressing PI3-K pathway in CaCo2 cells.

Silibinin, an active constituent of milk thistle, has been reported to inhibit proliferation and induce cell-cycle arrest of human colon cancer cells, Fet, Geo, and HCT116 [Hogan et al., 2007]. Silibinin upregulates the expression of cyclin-dependent kinase inhibitors and induces cell cycle arrest and apoptosis in human colon carcinoma HT-29 cells [Agarwal et al., 2003]. Also in HT-29 cells, beta-escin, a principle component of horse chestnut, treatment induces growth arrest at the G1-S phase together with an induction of Cip1/p21 and an associated reduction in the phosphorylation of retinoblastoma protein [Patlolla et al., 2006]. Wheat bran and its phytosterols fraction, phytosterol ferulates and 5-alk(en)yl-resorcinols exhibit significant inhibitory effect on the growth of HCT-116 human colon cancer cells [Sang et al., 2006]. Wheat bran and its phytic acid administration have also been shown to significantly induce apoptosis and differentiation in azoxymethane (AOM) – induced colonic preneoplastic lesions [Jenab and Thompson, 2000].

Tian and Song [2006] have documented that inositol hexaphosphate (IP6, also known as phytic acid) has potent inhibitory effect on proliferation of HT-29 cells by modulating proliferating cell nuclear antigen (PCNA) and Cip1/p21 expression. Treatment with chokeberry juice inhibits CaCo2 cell proliferation by promoting G2/M cell cycle arrest [Bermúdez-Soto et al., 2007]. Hong et al. [2007] have reported that Chinese red yeast rice, a food herb, inhibits cell growth and induces apoptosis in HCT-116 cells.

Diallyl sulfide (DAS), an organosulfur component of garlic has been reported to induce cell cycle arrest at G2/M phase as well as apoptosis in Colo 320 DM colon cancer cells by increasing caspase 3 expression and decreasing ERK-2 activity [Sriram et al., 2008]. Treatment of HT-29 and CaCo2 cells with diallyl disulfide (DADS), a garlic constituent, results in the inhibition of histonedeacetylase activity and histone hyperacetylation together with an increase in Cip1/p21 expression [Druesne et al., 2004]. Thiacremonone, another sulfur compound isolated from garlic, is found to induce apoptotic cell death in colon cancer SW620 and HCT-116 cells by suppressing NF-kappaB (NF-κB)-mediated anti-apoptotic genes, Bcl-2, cIAP1/2, and XIAP and inducing Bax, cleaved caspase 3 and cleaved PARP [Ban et al., 2007].

Curcumin, the yellow pigment in turmeric, also induces apoptosis in human colon cancer colo205 cells through the production of reactive oxygen species, Ca^{2+} and the activation of

caspase 3; it also enhanced the expression of bax, cytochrome C, p53 and Cip1/p21 but inhibited the expression of Bcl-2 [Su et al., 2006]. Studies have shown the anti-proliferative and apoptosis inducing effects of curcuminoids, a mixture of demethoxycurcumin and bisdemethoxycurcumin, against primary colon cancer cells isolated from Taiwanese patients [Hsu et al., 2007]. Recently, Watson et al. [2008] have reported a p21-independent inhibition of cell proliferation and induction of apoptosis by curcumin in both $p21^{(+/+)}$ and $p21^{(-/-)}$ HCT-116 cells. β-Ionone, a precursor for carotenoids present in many fruits and vegetables, also induces cytotoxicity, G1 phase cell cycle arrest and apoptosis in HCT-116 cells [Janakiram et al., 2008]. Together, the above summarized studies clearly and convincingly show that there are a vast range of phytochemicals from different sources, which exert potent cell growth inhibitory, cell cycle arrest inducing and apoptosis causing effects is a wide panel of human colon cancer cell lines with varying degree of genetic alterations/defects by targeting various molecular pathways.

Colon Cancer Chemoprevention: Effects on Molecular Events Associated with Angiogenesis

Numerous natural products with “angiopreventive” effects have been considered as chemopreventive agents [Dragnev et al., 2007]. Under serum starved condition in HT-29 cells, epigallocatechin gallate (EGCG) treatment is shown to inhibit the increase in the expression of vascular endothelial growth factor (VEGF), which is a potent angiogenic factor [Jung et al., 2001]. Lu et al. [2006] have reported that down-regulation of VEGF expression is one of the key mechanisms of chemoprevention by black raspberries. Liposomal curcumin preparation exhibits anti-angiogenic effects in Colo205 and LoVo xeografts by decreasing VEGF, CD31, and interleukin-8 [Li et al., 2007]. Treatment with ethanolic extract of Ka-mi-kae-kyuk-tang a formula of ten Chinese oriental herbs has been shown to inhibit the invasiveness of the mouse colon 26-L5 cancer cells *in vitro* [Lee et al., 2006]. Aged garlic extract has been reported to inhibit invasive activities of SW480 and SW620 cells [Matsuura et al., 2006].

Recently, it has been reported that, soybean saponin significantly inhibits the invasion of HT-29 cells through a Matrigel-coated membrane [Kang et al., 2008]. In addition, two weeks pretreatment with dietary soybean saponin decreased the incidence of CT-26 colon metastatic tumor colonization in lungs of mice which receive tail vein injection of CT-26 cells [Kang et al., 2008]. Recent studies in our laboratory clearly showed that silibinin decreases hypoxia inducible facter-1 alpha and VEGF expression thereby exerting its angiopreventive effects in HT-29 xenografts [Singh et al., 2008]. Curcumin has been found to inhibit cell migration of human colon cancer colo205 cells by decreasing matrix metalloproteinase (MMP)-2 expression [Su et al., 2006]. Together, these reports suggest that various phytochemicals, which exert anti-proliferative and pro-apoptotic effects in colon cancer cells, are also effective as anti-angiogenic agents. This is an important observation because angiogenesis is the most important event for cancer growth including colon cancer beyond a restricted size in to a full-blown malignancy [Jain, 2002].

Colon Cancer Chemoprevention: Effects on Cyclooxygenase Pathway

Plant based chemopreventive agents and their active constituents are reported to interfere with COX-2 activity and PGE2 synthesis. Hong et al. [2004] have documented the modulation of arachidonic acid metabolism by curcumin and its related beta-diketone derivatives, tetrahydrocurcumin and dibenzoylmethane, in HT-29 cells. EGCG showed dose-dependent inhibition of PGE2 synthesis and down-regulation of genes involved in inflammatory pathways in tumor necrosis factor (TNF)-alpha-stimulated HT-29 and T84 cells [Porath et al., 2005]. Moreover, EGCG treatment significantly decreased PGE2 synthesis and cellular levels of both COX-2 protein and mRNA as well as transcriptional activation of COX-2 by inhibiting

epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases (RTKs) in HT-29 cells [Shimizu et al., 2005a]. EGCG has also been shown to modulate AMP-activated protein kinase followed by the reduction in COX-2 expression and PGE2 secretion in HT-29 colon cancer cells [Hwang et al., 2007].

Thiacremonone, a garlic sulfur compound, has been reported to suppress inflammatory genes such as inducible nitric oxide synthase (iNOS) and COX-2 in SW620 and HCT-116 cells [Ban et al., 2007]. More recently, Zykova et al. [2008] have demonstrated that resveratrol and its analogues, 3,3',4',5',5-pentahydroxy-trans-stilbene inhibit COX-2 mediated PGE2 production in HT-29 cells. Dietary administration of Perilla oil significantly decreased AOM-induced ACF formation and PGE2 levels in colonic mucosa indicating its protective effect in the early stage of colon carcinogenesis [Onogi et al., 1996]. Modulatory effects of green tea on arachidonic acid metabolism during AOM-induced colon carcinogenesis have been documented [Ju et al., 2003]. Sengupta et al. [2005] have reported that dietary cardamom inhibits the formation of AOM-induced colonic aberrant crypt foci and reduces COX-2 and iNOS expression in mice model. Soybean saponin has been found to inhibit both protein and mRNA levels of COX-2 and PGE2 secretion via NF-κB dependent pathway [Kang et al., 2008].

Treatment with tricin, a rice bran flavone reduces PGE2 production in both HCEC and HCA-7 cells. Moreover, Dietary supplementation of 0.2% tricin reduced number of intestinal adenomas by 33% by decreasing PGE2 production [Cai et al., 2005]. Interestingly, wheat bran fractions are also reported to decrease iNOS and COX-2 expression during experimental colon carcinogenesis [Reddy et al., 2000]. Anthocyanin-rich extracts of bilberry and grape are also shown to down-regulate COX-2 mRNA expression in AOM-treated rat colon [Lala et al., 2006].

Colon Cancer Chemoprevention: Effects on Wnt/β-catenin Pathway

The Wnt/β-catenin pathway has been considered as an attractive target for colon cancer chemoprevention. In HT-29 cells, treatment with EGCG increases protein levels of E-cadherin by 27% to 58%, induces the translocation of β-catenin from nucleus to cytoplasm and plasma membrane, and decreases c-Myc and cyclin D1 [Ju et al., 2005]. EGCG has also been shown to effectively inhibit intestinal tumorigenesis in Apc min mice, possibly through the attenuation of the carcinogenic events, which include aberrant nuclear β-catenin and activated Akt and ERK signaling [Ju et al., 2005]. Rajakangas et al. [2008] have reported that dietary administration of white currant, a family of berries suppresses intestinal tumors in min mice by decreasing nuclear β-catenin and NF-κB proteins. In SW480 cells, methanolic extract of *Polysiphonia japonica* attenuates Wnt/β-catenin signaling without altering the levels of β-catenin protein, and reduces the expression of cyclin D1 [Gwak et al., 2006].

Thearubigins, the most abundant polymeric black tea polyphenols, inhibit dimethylhydrazine (DMH)-induced cell proliferation by suppressing Wnt/β-catenin pathway. Treatments with polymeric black tea polyphenols (PBP) extract showed decreased levels of COX-2, c-MYC and cyclin D1 proteins which aid cell proliferation probably by regulating β-catenin and thereby maintaining expression of APC and decreasing inactivation of GSK3β [Patel et al., 2008]. In APC min mice, treatments with Polyphenon E and EGCG are shown to significantly reduce the number of polyps by decreasing β-catenin nuclear expression [Hao et al., 2007]. Mahmoud et al. [2000] have shown that both curcumin and caffeic acid phenethyl ester (CAPE) significantly decrease tumor formation and decrease β-catenin expression in APC Min mice.

Colon Cancer Chemoprevention: Effects on Signal Transduction Pathways

Natural products and their active phytochemicals have also been known to modulate mitogen activated protein kinases (MAPKs) and PI3K/Akt pathways. DMH-induced activation of

MAPKs such as ERK and c-Jun N-terminal kinase (JNK) was found to be inhibited by treatments with thearubigins extract [Patel et al., 2008]. Sulforaphane (SFN), an isothiocyanate which is present abundantly in broccoli and cauliflower, has been shown to reduce small intestinal polyps and proliferative index and induce apoptosis, together with a down-regulation in the phosphorylation of JNK, ERK and Akt, which were found to be highly expressed in the adenomas of Apc Min mice [Hu et al., 2006]. Other studies have shown that EGCG and Polyphenon E decrease the phosphorylated forms of EGFR, HER2, ERK and Akt proteins thereby inhibiting the growth of CaCo2, HCT-116, HT-29, SW480, and SW837 colon cancer cells [Shimizu et al., 2005b]. Furthermore, polyphenon E and EGCG reduced phospho-Akt levels thereby decreasing cell proliferation and inducing apoptosis in APC min mice [Hao et al., 2007].

Collett and Campbell [2004] have reported that curcumin treatment induces JNK-dependent apoptosis by enhancing sustained phosphorylation of c-jun and stimulation of activator protein-1 transcriptional activity. It has been known that curcumin inhibits CaCo-2 and HT-29 human colon cancer cells growth by suppressing gene expression of EGFR through reducing the trans-activation activity of Egr-1 [Chen et al., 2006]. DAS decreases ERK activity thereby suppressing the growth of Colo 320 DM colon cancer cells *in vitro* [Sriram et al., 2008]. Grape seed proanthocyanidin extract is shown to attenuate PI3-kinase (p110 and p85 subunits) and decrease Akt phosphorylation at Ser473 thereby inducing apoptosis in CaCo2 cells [Engelbrecht et al., 2007]. More recently we have shown that silibinin treatment inhibits both ERK1/2 and Akt signaling in HT-29 xenograft [Sigh et al., 2008]

Colon Cancer Chemoprevention: *In Vitro* Studies

Natural products and their active constituents have been reported to exert their chemopreventive effects in a wide range of colon cancer cell lines, namely HT-29, LoVo, CaCo2, SW480 and 620, HCT-116 [Table 1]. Various *in vitro* studies showed that, extracts from various fruits including black raspberry, strawberry, apple, grape seeds induce apoptosis in HT-29 cells [Seeram et al., 2006;Gossé et al., 2005;Kaur et al, 2006]. Aged garlic extract as well as number of organo sulfur compounds from garlic, DAS, DADS and thiacremonone have been documented to exert anti-cancer effects by modulating various carcinogenic mechanisms in Colo 320 DM, HT-29, CaCo-2, SW620 and HCT-116 cell lines [Sriram et al., 2008;Druesne et al., 2004;Ban et al., 2007;Matsuura et al., 2006]. Curcumin has been shown to inhibit colon cancer cells growth by arresting them at various phases of cell cycle and inducing apoptosis [Su et al., 2008; Hsu et al., 2007;Watson et al., 2008]. Treatment with EGCG has been found to modulate VEGF expression, PGE2/COX-2 as well as beta-catenin pathways in colon cancer cells under *in vitro* conditions [Jung et al., 2001; Shimizu et al., 2005; Ju et al., 2005]. In particular, EGCG treatment decreased phospho EGFR, HER2, ERK and Akt levels in various colon cancer CaCo2, HCT-116, HT-29, SW480, and SW837 cells [Shimizu et al., 2005]. *In vitro* chemopreventive potential of various natural products has also been summarized above in previous sections.

Colon Cancer Chemoprevention: *In Vivo* Studies

Experimental carcinogenesis models are useful to understand multistage nature of carcinogenesis and different ways to interfere with the process under *in vivo* conditions [Reddy, 1998]. In this regard DMH- or AOM- induced experimental colon carcinogenesis models in rodents are ideal experimental models for colon cancer and have been extensively used for colon cancer chemoprevention research. Besides these models, genetic models of intestinal carcinogenesis (APC min) as well as xenograft models have also been widely used to test the chemopreventive efficacy of natural products.

Sengupta et al. [2008] have reported synergistic chemoprotective effects of garlic and tomato on AOM-induced colon carcinogenesis in Sprague-Dawley rats. Similarly, a 5% dried onion dietary feeding is shown to significantly reduce AOM-induced ACF formation [Taché et al., 2007]. Protective effects of wheat bran have been documented against AOM-induced experimental carcinogenesis [Reddy et al., 2000]. Soy protein consumption has been demonstrated to reduce the risk of developing colon tumors in animal models [Hakkak et al., 2001]. Chemoprotective effects of cooked navy beans have been reported during AOM-induced colon carcinogenesis in obese ob/ob mice [Bobe et al., 2008]. Dietary administration of 0.025% or 0.05% β-escin has shown dose dependent inhibition of AOM-induced ACF formation in F344 rats [Patlolla et al., 2006]. Raju et al., [2005] have shown that low doses of β-carotene and lutein inhibit AOM-induced ACF formation whereas high doses enhance ACF incidence. Three weeks treatment with phenethyl isothiocyanate (PEITC), a constituent of cruciferous vegetables significantly reduced the number of polys in APC min mice by modulating cyclins D1, A and E as well as P21 expression [Khor et al., 2008]. Chemopreventive effects of SFN as well as PEITC have been documented against AOM-induced ACF formation in Fischer rats [Chung et al., 2000].

Several other studies have revealed chemopreventive effects of various spices including cumin, caraway, black pepper, fenugreek seeds, ginger on DMH-induced colon carcinogenesis [Nalini et al., 2006; Kamaleeswari et al., 2006; Manju and Nalini, 2005; Devasena et al., 2007]. Cloudy apple juice has been demonstrated to reduce DMH-induced colonic crypt proliferation, ACF formation and DNA damage in rats [Barth et al., 2005]. Resveratrol has been shown to decrease AOM-induced ACF formation by increasing bax and Cip1/p21 expression [Tessitore et al., 2000]. Recently, white currant, a family of berries was found to reduce intestinal tumors in min mice [Rajakangas et al., 2008]. Dietary feeding of anthocyanin-rich tart cherry extract in combination with suboptimal levels of the nonsteroidal anti-inflammatory drug sulindac to APC Min mice for 19 weeks is shown to inhibit intestinal tumorigenesis in APC(Min) mice [Bobe etal., 2006].

Beneficial effects of green tea on ACF formation in AOM-induced colon carcinogenesis have also been documented [Ju et al., 2003]. Treatment with green tea selectively decreases initial stages of intestinal carcinogenesis in the AOM-APC Min mouse model [Issa et al., 2007]. Similarly, EGCG administration is shown to effectively reduce the number of small intestinal tumors, increased E-cadherin expression and to decrease nuclear β-catenin, c-Myc, phospho Akt and phospho-ERK1/2 expression in APC min mice [Ju et al., 2005]. Dietary supplementation of green tea extract has also been demonstrated to inhibit HCT-116 cancer cells growth in athymic male nude mice. Inhibition by green tea is evidenced by the inhibition of mitotic index, MMP-9 and VEGF secretion [Roomi et al., 2005].

Our xenograft studies showed that eight weeks of grape seed extract treatment significantly decreases HT-29 tumor xenograft volume by 44% by decreasing cell proliferation and inducing apoptosis as evidenced by decreased PCNA expression, increased Cip1/p21 protein levels as well as TUNEL positive cells and poly(ADP-ribose) polymerase cleavage [Kaur et al., 2006]. Recent studies from our laboratory have also demonstrated *in vivo* anticancer efficacy of silibinin on HT-29 human colon cancer xenograft growth in nude mice. These findings suggested that antiproliferative, proapoptotic, and antiangiogenic activities of silibinin may be responsible for its *in vivo* antitumor efficacy [Singh et al., 2008]. Chemopreventive effects of various natural products and their active constituents in various *in vivo* models are summarized in Table 2.

Colon Cancer Chemoprevention: Clinical Trials

Insulin-like growth factor-I (IGF-1) has been considered as a risk factor for various types of cancer including colon cancer. The plasma concentration of IGF-1 decreased significantly by 25% after tomato lycopene extracts [Walfisch et al., 2007]. Results from a preliminary double-blind, randomized clinical trial showed that 12 months treatment with aged garlic extract significantly reduced size and number of colonic adenomas in patients with colorectal adenomas [Tanaka et al., 2006]. Phase I clinical trial has been completed to determine the curcumin dose that can be tolerated to help in preventing colon cancer in healthy men and women [Cheng et al., 2001]. Grubben et al. [2000] have reported in their randomized trial in healthy volunteers that unfiltered coffee intake increase the detoxification capacity and anti-mutagenic properties in the colorectal mucosa through an increase in glutathione concentration but does not influence proliferation in colonic epithelium.

Conclusion and Future Prospective

This review summarized chemopreventive efficacy of natural products and their constituent phytochemicals in various *in vitro* and *in vivo* colon cancer models. All these results strengthen the fact that natural products can modulate various molecular pathways involved in cancer initiation and progression. Studies described here and elsewhere clearly highlight the use of natural products as novel chemopreventive agents for colon cancer intervention. It is expected that future studies with natural products will define various molecular mechanisms and targets for tumor growth inhibition, apoptosis, and especially angioprevention. To date, chemoprevention clinical trials with natural products conducted in colon cancer are very limited. Extensive clinical research is warranted to evaluate further safety and chemopreventive efficacy of natural products either alone or in combination with chemotherapeutic agents against colon cancer.

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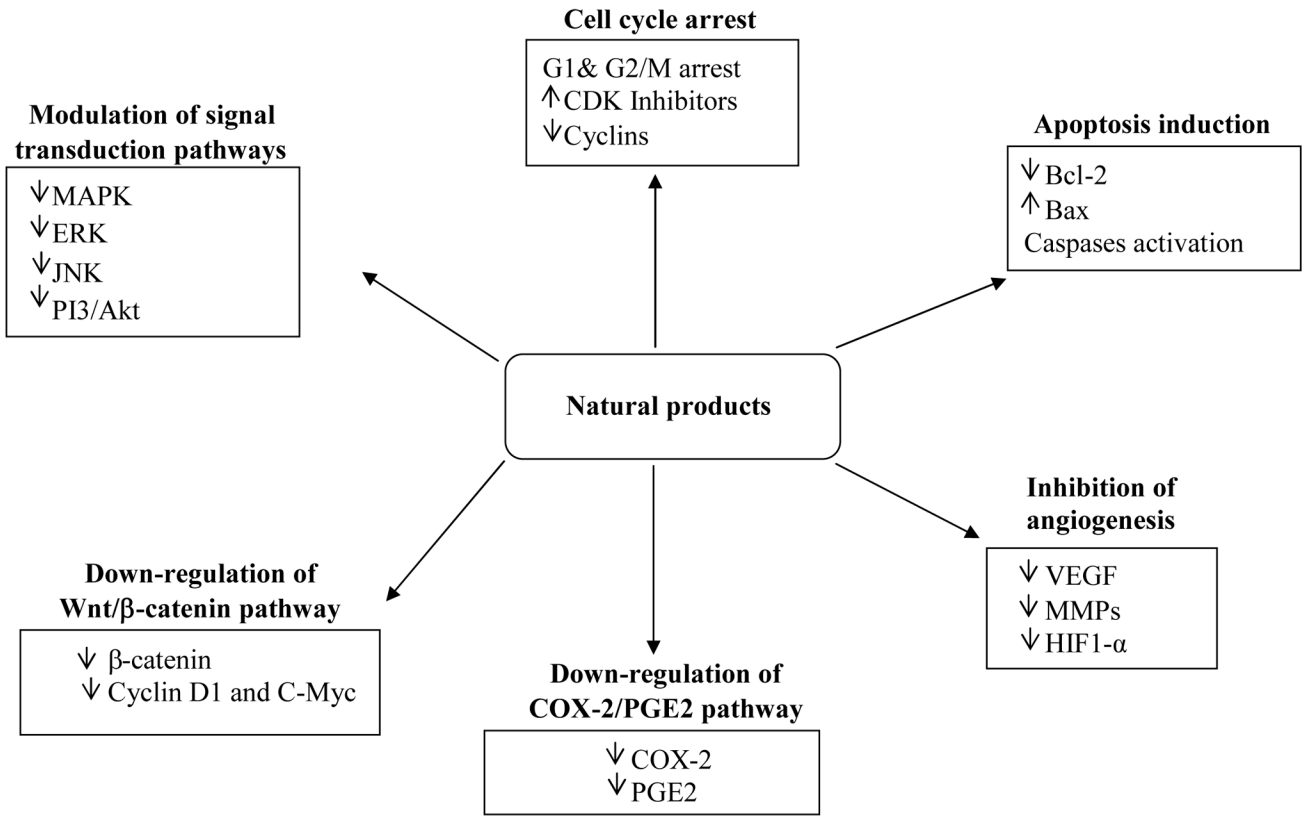

Figure 1.
Mechanisms of action of natural products and their constituent phytochemicals in colon cancer chemoprevention.

Table 1

In vitro studies showing chemopreventive potential of natural products.

Reference	Natural product	Cells	Mechanisms of action
Seeram et al., 2006	Blackberry, black Raspberry, Blueberry, Cranberry, red Raspberry, and Strawberry	HT-29 and HCT-116	Growth inhibition Apoptosis induction
Kaur et al., 2006	Grape seed extract	HT-29 and LoVo	G1 phase cell cycle arrest ↑Caspase 3 dependent apoptotic cell death. ↓Decrease in G1 phase-associated cyclins and cyclin-dependent kinases
Park et al., 2007	Resveratrol	HT-29	Apoptosis induction
Engelbrecht et al., 2007		CaCo2	↓PI3-K pathway
Zykova et al., 2008		HT-29	↓Cox-2 & PGE2
Agarwal et al., 2003	Silibinin	HT-29	Cell cycle arrest; CDKIs and Apoptosis induction
Hogan et al., 2007	Silibinin	Fet, Geo, and HCT116	Cell cycle arrest
Sang et al., 2006	Wheat bran and its phytosterols	HCT-116	Growth inhibition ↓PCNA
Tian and Song 2006	IP6	HT-29	↑p21 expression
Su et al., 2006	Curcumin	Colo205	Activation of caspase 3 ↑Bax, cytochrome C, p53 and p21 ↓Bcl-2 and MMP-2
Sriram et al., 2008	DAS	Colo 320 DM	G2/M phase arrest, ↑Caspase 3 activation ↓ERK-2 activity, ↑p21 expression
Druesne et al., 2004	DADS	HT-29 and CaCo2	Apoptosis induction,↓Cox-2 and iNOS
Ban et al., 2007	Thiacremonone	SW620 and HCT-116	↓Invasion
Matsuura et al., 2006	Aged garlic extract	SW480 and SW620	
Jung et al., 2001	EGCG	HT-29	↓VEGF expression
Porath et al., 2005		HT-29 and T84	↓PGE2 synthesis
Shimizu et al., 2005a		HT-29	↓EGFR,↓COX-2
Shimizu et al., 2005b		CaCo2, HCT-116, HT-29, SW480, and SW837	↓p-HER2, -ERK and -Akt
Ju et al., 2005		HT-29	↓c-Myc and cyclin D1
Kang et al., 2008	Soybean saponin	HT-29	↓Invasion

Table 2

Chemopreventive effect of natural products and their active constituents against colorectal cancer in various *in vivo* models.

References	Natural product	Animal models
Sengupta et al.,2004	Garlic and tomato	AOM
Taché et al., 2007	Onion	AOM
Tessitore et al., 2000	Resveratrol	AOM
Reddy et al., 2000 and Jenab and Thompson, 2000	wheat bran	AOM
Hakkak et al., 2001	Soy protein	AOM
Bobe et al., 2008	Navy beans	AOM
Lala et al., 2006	Bilberry and grape	AOM
Barth et al., 2005	Cloudy apple juice	DMH
Nalini et al., 2006 and	Cumin, and black pepper	DMH
Kamaleeswari et al, 2006	Caraway	DMH
Manju and Nalini, 2005	Ginger	DMH
Sengottuvelan and Nalini,2006	Resveratrol	DMH
Devasena et al. 2003 and 2007	Fenugreek seeds	DMH
Perkins et al., 2002 and Mahmoud et al.,2000	Curcumin	APC min mice
Li et al., 2007	Curcumin	HT-29 and LoVo xenografts
Kaur et al., 2006	Grape seed extract	HT-29 xenograft
Singh et al., 2008	Silibinin	HT-29 xenograft
Bobe et al., 2006	Tart cherry extract	APC min mice
Rajakangas et al., 2008	White currant	Min mice
Issa et al., 2007	Green tea	AOM-APC min mice
Roomi et al., 2005	Green tea	HCT-116 xenograft
Ju et al., 2005	EGCG	APC min mice
Hao et al., 2007	EGCG and polyphenon B	APC min mice
Patel et al., 2008	Thearubigins	DMH
Chung et al., 2000	Sulforaphane and PEITC	AOM
Hu et al, 2006	Sulforaphane	APC min mice
Khor et al., 2008	PEITC	APC min mice