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Prevention and Treatment of Colorectal Cancer by Natural Agents From Mother Nature

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Abstract

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the United States after cancers of the lung and the breast/prostate. While the incidence of CRC in the United States is among the highest in the world (approximately 52/100,000), its incidence in countries in India is among the lowest (approximately 7/100,000), suggesting that lifestyle factors may play a role in development of the disease. Whereas obesity, excessive alcohol consumption, a high-calorie diet, and a lack of physical activity promote this cancer, evidence indicates that foods containing folates, selenium, Vitamin D, dietary fiber, garlic, milk, calcium, spices, vegetables, and fruits are protective against CRC in humans. Numerous agents from “mother nature” (also called “nutraceuticals,”) that have potential to both prevent and treat CRC have been identified. The most significant discoveries relate to compounds such as cardamonin, celastrol, curcumin, deguelin, diosgenin, thymoquinone, tocotrienol, ursolic acid, and zerumbone. Unlike pharmaceutical drugs, these agents modulate multiple targets, including transcription factors, growth factors, tumor cell survival factors, inflammatory pathways, and invasion and angiogenesis linked closely to CRC. We describe the potential of these dietary agents to suppress the growth of human CRC cells in culture and to inhibit tumor growth in animal models. We also describe clinical trials in which these agents have been tested for efficacy in humans. Because of their safety and affordability, these nutraceuticals provide a novel opportunity for treatment of CRC, an “old age” disease with an “age old” solution.

Keywords

nutraceuticals; CRC; curcumin; gingerol; piperine

Introduction

Colorectal cancer (CRC), the third most commonly diagnosed cancer in the United States, develops through a multistep process in which normal mucosa first transitions to adenomatous polyps and then eventually to invasive carcinoma. CRC is a major cause of

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morbidity and mortality in the United States, with an estimated 143,460 new cases diagnosed and 51,690 deaths occurring in 2012[1]. It is estimated that 5-10% of all CRCs are due to inherited gene defects, but the great majority are sporadic and exhibit no heritable tendency. Life style has been shown to play a major role in the incidence of most cancers, especially CRC. Almost 70% incidence of CRC, has been linked to diet. Since certain type of diets accelerate CRC while others prevent CRC. We will focus in this review on the dietary agents that have been implicated in preventing this cancer.

Regardless of whether a cancer specifically results from a heritable mutation, extensive research within the last few years has indicated that most cancers are caused by dysregulation of as many as 500 gene products. These gene products include growth factors (e.g., EGF, VEGF, and IGF-1), growth factor receptors (e.g., EGF receptor), protein kinases (e.g., Src), inflammatory cytokines (e.g., TNF, IL-1, IL-6), inflammatory enzymes (e.g., COX-2, 5-LOX, PLA-2), proapoptotic proteins (e.g., TNF, Fas, TRAIL), antiapoptotic proteins (e.g., bcl-2, bcl-xL, cFLIP, IAP-1, IAP-2, survivin), tumor suppressors (e.g., p53, Rb), and transcription factors (e.g., NF-κB, AP-1, STAT3, HIF-1, PPARγ). Most of these gene products and the associated signaling pathways have been linked with CRCs. Perhaps one of the most important pathways in most CRCs is the pro-inflammatory pathway activated through the transcription factor NF-κB. This transcription factor has been shown to be activated by most risk factors linked to CRCs, including grilled meat, fried foods, saturated fatty acids, chemical and physical stress, and environmental pollutants [2]. Furthermore, constitutively active NF-κB has been encountered in most CRCs. Once activated, NF-κB regulates the expression of gene products that mediate survival (e.g., anti-apoptotic proteins bcl-2, bcl-xL, cFLIP, IAP-1, IAP-2, and survivin), proliferation (e.g., COX-2, c-myc, and cyclin D1), invasion (e.g., 5-LOX, MMP-9, ICAM-1, ELAM-1, and VCAM-1), and neo-angiogenesis (e.g., VEGF, IL-8, TNF, and IL-1) [3]. Most currently available agents that downregulate these pathways are highly specific for their targets (e.g., inhibitors of COX-2, VEGF, and EGFR). Such agents are unlikely to prevent diseases such as CRC which is caused by dysregulation of multiple gene products. Moreover, these agents are expensive and have numerous side effects [4-7]. A multi-targeted approach is therefore required for both treatment and prevention. It is worth noting that the same molecular targets are used for both prevention and treatment strategies [2, 8].

The incidence of CRC in the US (530 cases per million) is among the highest in the world. This contrasts with regions such as the Indian subcontinent (30 cases per million), in which CRC incidence is among the lowest in the world. Epidemiological and migration studies of Indians suggest that, to a large extent, these dramatic international differences in incidence rates can be explained by differences in environment, lifestyle, and diet. What is so unique about the Indian environment, lifestyle and/or diet that CRC risk in India is disproportionately lower than in the US? Given that food-derived compounds are constantly present in the intestine and may regulate the homeostasis of intestinal mucosa, one likely explanation is the nature of the Indian diet. Based on statistical and epidemiological data, Richard Doll and Richard Peto have postulated that 10–70% (average 35%) of human cancer mortality is attributable to diet [9]. Multiple lines of compelling evidence from epidemiological, clinical, and laboratory studies link cancer risk to nutritional factors. A feature of the Indian diet that distinguishes its from the Western diet is its higher proportion of dietary fiber, due largely to greater consumption of vegetarian food and lower intake of red meat than is the case with a typical Western diet. However, the preponderance of evidence suggests that, after accounting for other dietary risk factors, high dietary fiber intake is not associated with a reduced risk of CRC [10-12] and indeed, dietary fiber supplementation fails to reduce the risk of recurrence of colorectal adenomas in multiple randomized trials [13-16]. An alternative hypothesis is that distinctive spices routinely used in Indian cuisine confer protective effects against CRC. Evidence from multiple laboratories

indicates that spices prevent CRC development by modulating proinflammatory pathways closely linked with tumorigenesis.

The Role of Nutraceuticals in Cancer Prevention

The use of plant-derived products (also called dietary botanicals) for the welfare of humankind is extends back as far as recorded history. The quest for plants, parts of plants, and components of parts of plants, that confer health benefits has perennially inspired human curiosity. At one time, the major source of medicine was the plants consumed by humans—prompting Hippocrates to preach almost 25 centuries ago, “let food be thy medicine and medicine be thy food.” This adage also calls to mind the common saying, “we are what we eat.” This philosophy is consistent with the position of both the National Cancer Institute and the American Cancer Society that eating more fruits and vegetables daily can reduce an individual’s risk of developing cancer. However, an accurate determination of the precise mechanisms by which the components of fruit and vegetables prevent cancer is needed before their inclusion in dietary supplements or evaluation in prospective clinical trials can be recommended. It is estimated that over 70% of cancers are preventable, with dietary agents making a 35% contribution. It remains unclear what specific dietary agents or nutraceuticals can prevent cancer. It is notable that more than half of all drugs approved by the Food and Drug Administration for cancer therapy within the last 4 decades have been either natural products, natural product derivatives, compounds based on natural products, or mimics of natural products [17]; indeed, cancer chemoprevention with botanicals is increasingly recognized as a promising research strategy [18]. In the current review, we show that that numerous nutraceuticals have potential as treatments for CRC (see table 1, 2 and 3). These include acetoxychavicol acetate, anacardic acid, berberine, betulinic acid, boswellic acid, butein, camptothecin, capsaicin, caffeic acid phenethyl ester, cardamonin, celastrol, chalcones, coronarin, curcumin, deguelin, diosgenin, elephantopin, emodine, embelin, escin, fisetin, flavopiridol, flavonoids, gambogic acid, garcinol, gossypol, gossypin, guggulsterone, indole-3-carbinol, morin, naphthoquinone, nimbolide, noscapine, oleandrin, piperine, piceatannol, pinitol, plumbagin, pomegranate, retnoids, honokiol, sanguinarine, sesamin, silymarin, simvastatin, terpenoid, thymoquinone, tocotrienol, triptolide, ursolic acid, withanolides, xanthohumol, and zerumbone. Various molecular targets modulated by these nutraceuticals are shown in Table 1. These targets include growth factors and their receptors, protein kinases, inflammatory biomarkers, and various transcription factors. Various biomarkers that are downregulated by nutraceuticals are shown in Figure 1. Those that are upregulated are shown in Figure 2. The use of these nutraceuticals for both prevention (Table 2) and treatment (Table 3) of CRC can be envisioned. The modulation of various biomarkers has been observed not only in colon cancer cells in culture but also in animal models of CRC (tables 2 and 3).

Role of nutraceuticals in CRC prevention

There are numerous reasons to conclude that most cancers, and CRCs in particular, are preventable. First, CRCs are more common in developed countries than in developing countries The causes of this disparity are not fully understood but numerous studies have indicated that lifestyle contributes as much as 95% to the incidence of all cancers. What is so unique about the Indian subcontinent lifestyle is uncertain. There is evidence to suggest that first, vegetarianism and certain spices unique to the diets of Indian people may contribute to a lower incidence of CRC. Second, grilled meat, fried foods, environmental pollutants, and certain viruses have been linked to colorectal tumorigenesis in rodent models. Third, dietary components derived from fruits and vegetables have been shown to suppress colorectal carcinogenesis in animals. Fourth, epidemiological studies and limited clinical trials in humans suggest that increased consumption of fruits and vegetables reduces the risk of

developing CRCs and improves clinical outcomes in those diagnosed with CRC. The foods and active agents from Indian spices that have been linked with prevention of CRCs include curcumin from *Curcuma longa*; piperine from *Piper nigrum*; [6]-gingerol from *Zingiber officinale*; resveratrol from grapes, peanuts, and berries; catechins from tea; genistein from soybeans; caffeic acid from mustard seeds and olive oil; quercetin from onions; ellagic acid from pomegranate; diallyl disulfide from garlic; sulforaphane from broccoli; lycopene from tomatoes; and indole-3-carbinol from cruciferous vegetables. Extensive studies have provided "proof of concept" that these agents have potent anticancer and chemopreventive effects against CRC and that they mediate their effects by targeting multiple molecular targets. Only a select few agents that have been examined extensively are described below.

Curcumin

The active principle of *Curcuma longa*, curcumin, is perhaps the dietary agent about which most is known with respect to gastrointestinal cancers. This agent gives curry powder (turmeric) its yellow color; its active ingredient has been identified as diferuloylmethane. Curcumin has been shown to protect animals from a wide variety of carcinogens that cause gastrointestinal cancers. The protective effects of curcumin have also been reported in patients with Crohn's disease, ulcerative colitis, familial adenomatous polyposis (FAP), and tropical pancreatitis. For instance, in one clinical trial of five FAP patients, polyps decreased by approximately 60% in number and 50% in polyp size between baseline and after treatment with curcumin [177]. A similar study involving 77 patients treated with celecoxib showed reductions of only 28 and 30% in polyp number and burden, respectively [178].

Curcumin's mechanism of action has been studied extensively [179]. Our group showed that curcumin downregulated the activation of NF-κB [180], thus leading to the downregulation of the expression of anti-apoptotic, cell-proliferative, invasive, and angiogenic gene products [181]. In addition to downregulating NF-κB activation, curcumin can suppress activation of STAT3 [182], HIF-1 [183], and PPAR-[184]. Curcumin also downregulates the activity and expression of both cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) [185] as well as the expression of TNF, IL-1, and IL-6. It additionally inhibits both the anti-apoptotic activating transcription factor [186] and EGF receptor signaling [187]. In spite of interfering with all of these targets, curcumin has been found to be relatively safe pharmacologically at very high doses [188]. Moreover, no dose-limiting toxicity has been established in previously published clinical trials.

Although curcumin does exhibit activity against CRC in various preclinical models, it has several limitations. First and foremost, its bioavailability and tissue distribution are very poor [189], although piperine, a component of *Piper nigrum* that is often consumed with turmeric, has been shown to enhance the bioavailability of curcumin [190]. Second, it is not curcumin but turmeric that is consumed routinely by people in the Indian subcontinent where the incidence of CRC is relatively low. Third, people consuming turmeric do not consume turmeric alone but rather in combination with other spices such as *Piper nigrum* (black pepper) and *Zingiber officinale* (ginger). Fourth, turmeric exhibits activities that are different from those of curcumin [191, 192]. Fifth, the activity of curcumin is potentiated by turmerones and other minor components of turmeric [193]. For all of these reasons, further in-depth exploration of turmeric is warranted.

[6]-Gingerol

Ginger, the rhizome of *Zingiber officinale*, is as reputed for its medicinal properties as is turmeric. Ginger has traditionally been used in different parts of the world for various human ailments and in particular to aid digestion and treat nausea and vomiting in pregnancy [194]. Some pungent constituents present in ginger and other zingiberaceous

plants have potent antioxidant, anti-inflammatory, antiemetic, antiulcer, cardiotonic, antihypertensive, hypoglycemic, antihyperlipidemic, and immuno-stimulant properties. Additionally, some of these constituents exhibit cancer-preventive activity in experimental studies and clinical trials [195, 196]. These properties of ginger are attributed to the presence of certain pungent vallinoids, specifically [6]-gingerol and [6]-paradol, as well as other constituents such as shogaols and zingerone. Experimental studies have also revealed that ginger and its most active constituent, [6]-gingerol, regulate the molecules in cellular signal transduction pathways, including NF-κB, AP-1, growth factors, chemokines, MAPK, p53, cyclin D1, VEGF, COX-2 and iNOS pathways [197-203]. By modulating multiple cell signaling pathways, these components inhibit cancer development and/or progression. Both [6]-gingerol and [6]-paradol have been found to induce cancer cell apoptosis [204]. [6]-gingerol has also been shown to inhibit phorbol ester-induced inflammation, epidermal ornithine decarboxylase activity, and skin tumor promotion in mice [205]. Specifically in CRC, [6]-gingerol has been shown to reduce the incidence of CRCs in a rat azoxymethane (AOM) model [206], and to inhibit CRC cell proliferation, and endothelial cell tube formation [207], and G1 cell cycle arrest. [6]-gingerol inhibits these processes through downregulation of cyclin D1 via inhibition of -catenin translocation [201]. [6]-shogaol has been shown to induce apoptosis via reactive oxygen species (ROS) production, caspase activation, and GADD153 expression [208]. The chemopreventive properties of both ginger and turmeric have been linked in part to the upregulation of MAP kinase phosphatase-5 [209]. Ginger thus appears to contain a variety of constituents that may ultimately be of use in cancer prevention and treatment.

Piperine

Black pepper (*Piper nigrum*), a native Indian botanical, has been used in Indian cooking for centuries. It is valued for its distinctive sharp, stinging quality, which has been attributed to its active ingredient, the alkaloid piperine. Since the discovery of *Piper nigrum*'s active piperine, the use of black pepper has captivated the interest of modern medical researchers. Many physiological effects of *Piper nigrum*, its extracts, or its bioactive compound piperine, have been reported in recent decades. By stimulating the digestive enzymes of the pancreas, piperine enhances digestive capacity and significantly reduces gastrointestinal transit time for food [210]. Piperine has been shown to enhance the bioavailability of a number of therapeutic drugs as well as phytochemicals through its inhibitory influence on enzymatic drug biotransforming reactions in the liver and intestine [211]. Piperine strongly inhibits the activity of hepatic and intestinal aryl hydrocarbon hydroxylase and uridine dinucleotide phosphate-glucuronyl transferase [211]. Most clinical studies on piperine have focused on its effect on drug metabolism as a means of improving the bioavailability of other botanicals [189, 212, 213]. Piperine's bioavailability-enhancing property is also partly attributed to increased absorption caused by its effect on the ultrastructure of the intestinal brush border [214, 215]. Piperine has been demonstrated, in *in vitro* studies, to protect against oxidative damage by inhibiting or quenching ROS. *Piper nigrum* or piperine treatment has also been found to lower lipid peroxidation *in vivo* and beneficially influence antioxidant status in several experiments involving oxidative stress [215, 216].

1′-Acetoxychavicol Acetate

1′-Acetoxychavicol acetate (ACA), which is obtained from the rhizomes of *Alpinia galanga*, is a component of traditional Asian condiments. It has both chemopreventive and chemotherapeutic potential in animals as well as *in vitro* models of CRC. ACA has been shown to induce apoptosis in CRC cell lines. It has also been reported that ACA inhibits DNA synthesis, thereby inhibiting cell proliferation [217]. In rat intestine epithelial cells (IEC6), ACA induced glutathione S-transferase (GST) and NAD(P)H: quinone

oxidoreductase 1 (NQO1) activities, increased intracellular glutathione levels, and upregulated intranuclear Nrf2 and cytosolic p21 [19]. It also has the ability to inhibit azoxymethane (AOM)-induced colon tumorigenesis in rats [151]. Feeding these rats with ACA significantly reduced the incidence of colon carcinoma by suppressing proliferation biomarkers such as ornithine decarboxylase activity and colonic mucosal polyamine contents. Such inhibition was also associated with elevated levels of activity of phase II enzymes, including GST and QR, in the rat colon [151].

Berberine

Berberine is an isoquinoline natural alkaloid found in the roots, rhizomes, stem, and bark of a wide variety of traditional herbs, including goldenseal, barberry and Oregon grape. Numerous studies have shown that it can prevent and treat CRC. In *in vitro* assay, berberine inhibited proliferation and induced apoptosis of various CRC cells. It induced cell cycle arrest at the G2/M phase and caused apoptosis as evidenced by the loss of mitochondrial membrane potential, release of cytochrome c, suppression of c-IAP1, Bcl-2, Bcl-xL, induction of p21 expression, activation of caspases, and cleavage of PARP [22, 20]. In addition, berberine-induced apoptosis was accompanied by phosphorylation of JNK and p38 MAPK, increases in FasL and t-BID levels, and ROS generation [22]. Berberine's anti-proliferative and apoptotic activity was found to be associated with the inhibition of NF-κB and Wnt/β-catenin signaling pathways [152, 20]. Moreover, berberine modulated pgp-170 expression in cancer cells, which was associated with changes in drug resistance [25] and inhibited arylamine N-acetyltransferase (NAT) activity in a human colon tumor cell line [218]. In an AOM-induced colon carcinogenesis rat model, berberine significantly inhibited the increases in lipid peroxidation, protein bound carbohydrates, and enhanced antioxidative status [153]. Oral administration of berberine was also found to inhibit COX-2 activities without inhibiting COX-1 activity in AOM-induced rat colon [154]. Thus, berberine inhibits neoplastic transformation in rat colon.

Whole botanical is better than a single active principle

Whether genistein, lycopenes, statins, catechins, or resveratrol; evidence indicates that the original sources of these nutraceuticals (soy, tomato, red yeast rice, green tea, and red grapes, respectively) may exhibit activity *in vivo* superior to that of their isolated active components. Indeed, numerous lines of evidence suggest that the whole botanical may be better than its active principle. For instance, *Curcuma longa* contains curcumin, demethoxy curcumin (DMC), bisdemethoxy curcumin (BDMC), turmeric oil (also known as turmerones), cyclocurcumin, and other constituents. Although curcumin is a major constituent (2-6%) of *Curcuma longa*, other components exist in minor but significant amounts. *Curcuma longa* oil consists of aromatic turmerone (ar-turmerone), -turmerone, and -turmerone. *Curcuma longa* oil has been linked with antifungal [219, 220], antibacterial [221], insecticidal [222], mosquitocidal [223], antioxidant [224], antimutagenic [224], and anticancer [225] activities. This oil has also been found to inhibit oral submucous fibrosis, a precancerous condition for oral cancer in healthy volunteers [225]. Additionally, turmeric oil has been shown to enhance the bioavailability of curcumin in human volunteers [193, 226].

A synergy has been observed between curcumin, DMC, and BDMC. Specifically, it has been shown that the ability of curcumin to inhibit peroxidation of linoleic acid by 15-lipoxygenase is synergistically enhanced by DMC and BDMC. Furthermore, we showed that the anti-inflammatory activity of curcumin is enhanced when curcumin is combined with DMC and BDMC [227]. Similarly, nematocidal activity levels have been reported to be higher in turmeric than in curcumin alone [228]. Curcumin-free aqueous turmeric extracts have been shown to suppress 7,12-dimethylbenz[α]anthracene (DMBA)-induced rat

mammary tumor formation [192] and to inhibit benzo(a)pyrene-induced forestomach papillomas in mice [191]. Consistent with evidence that a whole botanical may potentially be more effective than its active principle, there is also an evolving body of evidence to suggest that whole botanicals exhibits potent antitumor activity at clinically meaningful doses. Various reports indicate that turmeric alone blocks glucuronidation and sulfation in Caco-2 cells *in vitro* [229], inhibits early activation of the Epstein-Barr-virus antigen [230], inhibits benzo(a)pyrene-derived DNA adduct formation [231], and suppresses the growth of *Helicobacter pylori* [232]. In rodents, 1% dietary turmeric was found to inhibit DMBA-induced carcinogenesis [233], abrogate croton oil-induced skin tumor formation [234], and suppress nitrosodiethylamine-induced hepatocarcinogenesis [235]. In addition, turmeric was found to prevent benzo[a]pyrene-induced forestomach tumors in Swiss mice and methyl-(acetoxymethyl)-nitrosamine-induced oral mucosal tumors in Syrian golden hamsters [236]. In a study of DMBA-induced mammary tumorigenesis in C3H (Jax) mice and Wistar rats, dietary turmeric suppressed mammary tumor virus-related reverse transcriptase activity, abrogated preneoplastic changes in the mammary glands, and decreased tumor incidence and tumor burden [237].

Combination of botanicals is expected to be superior to a single botanical alone

There is considerable interest in evaluating the likelihood that a combination of key botanicals might exhibit synergistic protective activity against CRC. A wide variety of botanicals and their phenolic compounds and flavonoids possesses potent antioxidant, antimutagenic, and anticarcinogenic activities. Multiple studies have suggested that a combination of botanicals and/or their active principles might be more efficacious than any one botanical alone. Piperine has been shown to enhance the bioavailability of curcumin in rodents and humans in part through the inhibition of glucuronidation [190]. We have also confirmed that piperine enhances the bioavailability of curcumin in human subjects [189]. In one study testing this combination, oral curcumin with piperine reversed lipid peroxidation in patients with tropical pancreatitis [212]. In another study, the combination of piperine plus curcumin significantly enhanced anti-immobility, neurotransmitter-enhancing (serotonin and dopamine), and monoamine oxidase inhibitory effects compared with curcumin alone [213]. When 5-lipoxygenase, the key enzyme involved in biosynthesis of leukotrienes, was evaluated in human polymorphonuclear leucocytes, the order of inhibitory activity was noted to be quercetin > eugenol > curcumin > cinnamaldehyde > piperine > capsaicin > allyl sulfide [238]. Furthermore, the inhibitory potency of aqueous extracts of these botanicals correlated with the active principles of their respective botanicals, with the combination of active principles or extracts synergistically inhibiting 5-LOX activity [238].

Human Studies

Clinical trials of nutraceuticals for CRC prevention and treatment in humans have established a larger body of knowledge about curcumin than about all other nutraceuticals. This agent has been examined in patients with ulcerative colitis (UC) and Crohn's disease (CD) [239]. In an open-label study, curcumin was administered to five patients with ulcerative proctitis and five with CD. All proctitis patients improved, with reductions in concomitant medications in four, and four of five CD patients had lowered Crohn's Disease Activity Index scores and sedimentation rates. Curcumin was also examined in a randomized, multicenter, double-blind, placebo-controlled trial of a maintenance therapy for UC [240]. Eighty-nine patients with quiescent UC were recruited. Forty-five patients received curcumin (1g after breakfast and 1g after the evening meal) plus sulfasalazine or mesalamine for 6 months, and 44 patients received placebo plus sulfasalazine or mesalamine for 6 months. Clinical activity index and endoscopic index were determined at entry, then

every 2 months, at the conclusion of the 6-month trial, and at the end of 6-month follow-up. Of 43 patients who received curcumin, two relapsed during 6 months of therapy, whereas eight of 39 patients in the placebo group relapsed. These results indicate a significant difference between curcumin and placebo. Furthermore, curcumin improved both the clinical activity index and endoscopic index levels in patients, thus suppressing the morbidity associated with UC. A 6-month follow-up was conducted during which patients in both groups were on sulfasalazine or mesalamine. Eight additional patients in the curcumin group and six patients in the placebo group relapsed.

Familial adenomatous polyposis is an autosomal-dominant disorder characterized by the development of hundreds of colorectal adenomas and eventual colorectal cancer. Regression of adenomas in this syndrome occurs with the administration of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors, both of which can have considerable side effects. Curcumin was examined in combination with quercetin in FAP patients [177]. Five FAP patients with prior colectomy received curcumin 480 mg and quercetin 20 mg orally 3 times a day. All 5 patients' polyps had decreased in number and size from baseline after a mean of 6 months of treatment with curcumin and quercetin. The mean percentage decreases in the number and size of polyps from baseline were 60.4% and 50.9%, respectively.

Recently, Carroll and colleagues trialed the use of curcumin for the prevention of colorectal neoplasia [241]. The group examined the effects of oral curcumin (2g or 4g per day for 30 days on prostaglandin E2 (PGE_2) within aberrant crypt foci (ACF; primary endpoint), 5-HETE, ACF number, and proliferation in a non-randomized, open-label clinical trial of 44 eligible smokers with eight or more ACF on screening colonoscopy. Forty-one subjects completed the study. A significant reduction (40%) in patients' ACF numbers occurred in the 4g dose group, whereas ACF numbers were not reduced in the 2g dose group. Interestingly, neither dose of curcumin reduced PGE_2 or 5-HETE within ACF or normal mucosa or reduced Ki-67 in normal mucosa.

Numerous studies have also considered the use of curcumin for the treatment of CRC. A dose escalation study conducted in healthy volunteers showed insignificant serum levels of curcumin even when as much as 12,000 mg of curcumin was consumed daily [188]. Sharma and colleagues have examined both pharmacodynamic and pharmacokinetic properties with oral curcumin in patients with CRC [242]. Interestingly, Sharma and colleagues showed that daily ingestion of 440mg of curcumin for 29 days (with 15 patients) was accompanied by a 59% decrease in lymphocytic glutathione S-transferase activity, but this was not the case at a higher dose (2200mg). Another study [243] showed that a daily dose of 3.6g curcumin on days 1 and 29 caused 62% and 57% decreases, respectively, in inducible PGE_2 production in blood samples taken 1 hour after dose administration compared with levels observed immediately before predose. Garcea and colleagues [244] found that administration of curcumin (3,600mg) decreased DNA adduct 3-(2-deoxy-beta-di-erythro-pentafuranosyl)-pyr[1,2-alpha]-purin-10(3H)one M(1)G levels in malignant colorectal tissue from 4.8 +/- 2.9 adducts per 107 nucleotides to 2.0 +/- 1.8 adducts per 107 nucleotides. COX-2 protein levels in malignant colorectal tissue were not affected by curcumin. In another study, 106 colorectal cancer patients were given 360mg of curcumin orally 3 times/day and then monitored for cancer-induced weight loss, serum TNF levels, tumor cell apoptosis, and other biomarkers on days 10, 20, and 30 after treatment [245]. The authors showed that curcumin administration increased body weight, decreased serum TNF-levels, increased numbers of apoptotic tumor cells, enhanced the expression of p53 molecules in tumor tissue, and modulated tumor cell apoptotic pathways, as indicated by upregulation of bax and downregulation of bcl-2. They concluded that curcumin treatment improves the general health of patients. All these studies therefore indicate that curcumin is quite safe when

consumed in large quantities. Paradoxically, however, its effect in patients is unrelated to serum levels. Lower doses also appear to be more effective than higher doses in modulating biomarkers in human subjects.

Conclusion

Thus, this review clearly demonstrates that various nutraceuticals provided by the Mother Nature have a huge potential for both prevention and treatment of CRC. However, more clinical trials are required to prove neutraceuticals' potential against this highly lethal disease. Since these agents can be administered chronically without any concern for safety and are highly affordable, their use has been the wave of the past and is likely to continue as the wave of the future.

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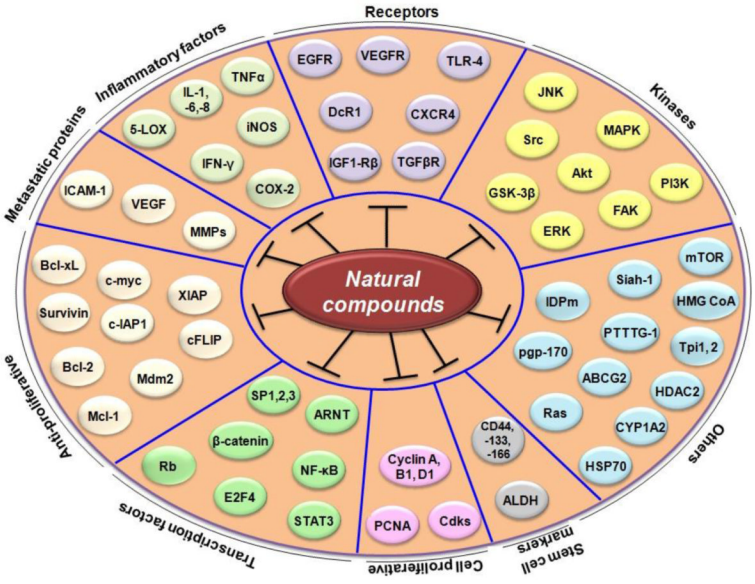

Fig. 1.
Molecular targets in colorectal cancer that are downregulated by natural compounds.

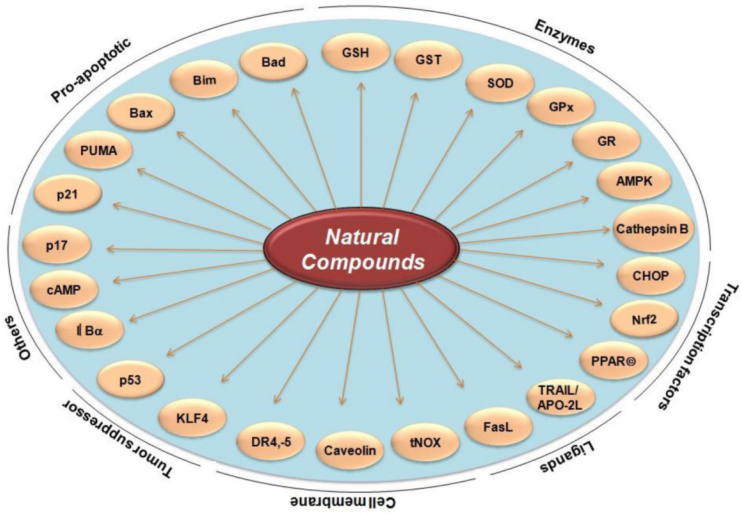

Fig. 2.
Molecular targets in colorectal cancer that are upregulated by natural compounds

Table 1

Molecular target of natural compound in in vitro models of colorectal cancer

Cell lines/animals	Targets	References
Acetoxychavicol acetate		
IEC6	GST, NAD(P)H, NQO1, GSH, Nrf2, p21	[19]
Berberine		
SW480	NF-κB, COX-2, VEGF, p21, Bcl-2, survivin	[20]
HT-29	Survivin	[21]
SW620	BID, c-IAP1, Bcl-2, Bcl-xL, JNK, p38 MAPK, FasL	[22]
Colon 26	IL-6	[23]
HCT116	Cyclin B1, cdc2 kinase	[24]
COLO 205,CT26	pgp-170	[25]
DLD-1	COX-2	[26]
Betulinic Acid		
Colo-205	Glyco-genes	[27]
RKO, SW480	Sp-1,-2,-3, survivin, VEGF, EGFR, cyclin D1, PTTG-1, NF-κB	[28]
SW948, HCT116	Topoisomerase I and IIα	[29]
PTC	CYP1A2	[30]
SNU-C5	Bcl-2, Bad	[31]
SW480	Caveolin-1 KLF4, PPARγ	[32]
HT29	Bcl-2, cyclin D1, Bax	[33]
Colo-205	p17	[27]
AKBA		
HT29	Akt	[34]
HCT116	Cyclin D1, cyclin E, CDK 2, CDK4, Rb, p21	[35]
Butein		
CLL.220.1	GSH	[36]
COLO 320HSR, CLL.220.1	GST	[37]
Capsaiscin		
HCT116	tNOX	[38]
Colo 205	Bcl-2, Bax	[39]
HCT116	p53, Mdm2, DR4, Fas (CD95), Bax, Bcl-2	[40]
HT29	AMPK, ACC	[41, 42]
HT29	PPARγ	[42]
CAPE		
HCT116, SW480	β-Catenin, cyclin D1, c-myc	[43]
CT26	MMP-2, -9, VEGF	[44]
Cardamonin		

Cell lines/animals	Targets	References
HCT116	DR-4, -5, DcR1, CHOP	[45]
CDDO		
SW480	PPARγ	[46]
Colon fibroblasts	IFN-γ, IL-1, TNFα, iNOS, COX-2	[47]
Celastrol		
HCT116	CXCR4	[48]
SW620	TRAIL/APO-2L	[49]
Deguelin		
COLO205, HCT116	IL-8, IκBα, NF-κB, cFLIP, Bcl-2, Bcl-xL	[50]
Diosgenin		
HT29	p38 MAPK, DR5, COX-2	[51]
HT29, HCT116	COX-2, 5-LOX	[52]
HCT116	HMG-CoA reductase, p21 ras, β-catenin	[53]
HT29	Bcl-2	[54]
HCT15	Bcl-2, Bax	[55]
Emodin		
LS1034	Bcl-2, Bax	[56]
WiDr	MMP-2, -9, RhoB, NF-κB, VEGF	[57]
DLD-1	PRL-3, ezrin	[58]
DLD-1, HT2	SOD, GST, tGPx, LDH	[59]
HCT116	VEGFR-1, -2	[60]
Escin		
HT29	p21 (WAF1/CIP1)	[61]
Fisetin		
HCT116	p53	[62]
HCT116	Bcl-xL, Bcl-2, Bak, Bim, FasL, DR5, TRAIL, p53	[63]
HT29	COX2, EGFR, PGE2, β-catenin, NF-κB, Wnt, cyclin D1, MMP-7	[64]
HT29	CDK-2, -4, CDC25C, cyclin E, cyclin D1, p21 (CIP1/WAF1)	[65]
Flavopiridol		
HCT116	p53, Rad51, Cdk9	[66]
HCT116	Cdc2, survivin	[67]
HCT116	p21	[68]
HCT116	p21, XIAP	[69]
HCT116	Rb	[70]
T84	cAMP	[71]
Garcinol		
HCT116	DR4, DR5, survivin, Bcl-2, XIAP, cFLIP, Bid, Bax	[72]
HT29, HCT116	ERK1/2, survivin	[73]

Cell lines/animals	Targets	References
HT29	FAK, Src, MAPK, ERK, PI3K, Akt, Bcl-2, Bax, MMP-7	[74]
Gossypol		
HCT116	DR5, Bcl-xL, Bcl-2, survivin, XIAP, cFLIP, CHOP, ERK1/2	[75]
CT26	Bcl-2, Bcl-xL	[76]
HT29	p21, cyclin D1, Bcl-2, Bcl-xL, Bag-1, Mcl-1, Bak	[77]
HT29, LoVo	p53, Bcl-2, Bax	[78]
Guggulsterone		
HT29	p21, IGF1-Rβ	[79]
HT29	CBR3	[80]
HT29	cIAP-1, cIAP-2, Bcl-2, Bid, Fas, p-JNK, c-Jun	[81]
HT29	VEGF, ARNT, STAT3, MMP-2, -9	[82]
Nimbolide		
WiDr	NF-κB, ERK1/2, p38, JNK1/2, MMP-2, -9	[83]
HCT116	DR4, DR5, ERK, p38 MAPK, I-FLICE, cIAP-1, cIAP-2, Bcl-2, Bcl-xL, survivin, XIAP, p53, Bax	[84]
HT29	p21, cyclin D2, Chk2, cyclin A, cyclin E, Cdk2, Rad17	[85]
Noscapine		
LoVo	Survivin, Bcl-2, Bax	[86]
HCT116	p53, p21, Bcl-2, Bax	[87]
Piperine		
Caco-2	P-glycoprotein, CYP3A4	[88]
Gambogic acid		
LOVO	PI3K, Akt, Bad	[89]
Curcumin		
HuTu 80, Caco-2	GST, UGT	[90]
HCT116	p53, p21	[91]
Caco2	P-gp	[92]
HT29, HCT116	CD133, CD44, CD166, ALDH	[93]
HCT116	STAT3	[94]
HCT116	ERK1/2, p38 MAPK, JNK	[95]
HCT116	ABCG2, EGFR, IGF-1R, NF-κB, β-catenin, COX-2, c-myc, Bcl-xL, Bax	[96]
HCT116	IDPm	[97]
HCT116	E2F4, cyclin A, p21, p27	[98]
HCT116, HT29	p53, p21, PUMA	[99]
HCT116	EGFR, HER-2, IGF-1R,	[100]
Caco2	AKT, COX-2, cyclin D1 VDRE, GR, CYP3A4, CYP24, p21, TRPV6	[101]

Cell lines/animals	Targets	References
HT29, HCT116	CD44, CD166, EGFR	[102]
HCT116	NF-κB, EGFR, IGF-1R	[103]
HCT116	NF-κB, Akt, Bcl-2, Bcl-xL, IAP-2, COX-2, cyclin D1	[104]
HT29	Akt, COX-2, AMPK	[105]
HCT116	p53, p21 (CIP1/WAF1)	[106]
HCT116	PCNA, CDK2, CDK4, cyclin B, p21, p27, p53, NF-B, Akt	[107]
HCT116, SW480	20S & 26S proteasome	[108]
Plumbagin		
HT29, HCT116	EGFR, Akt, GSK-3β, PCNA, cyclin D1, COX-2	[109]
Reserpine		
HCT116	β-catenin, cyclin D1, c-myc, Siah-1	[110]
LS180	CYP3A5	[111]
Resveratrol		
Caco-2, SW480	iNOS, IκB, TLR-4	[112]
HCT116	JNK, p38	[113]
HT29, SW480	AKT, STAT3	[114]
HCT116	p53, Bax, Bcl-2	[115]
SW480, HT29	ERK, JNK, Akt, FAK, Fyn, Grb2, Ras, SOS	[116]
Caco-2	CYP1A1	[117]
SW480	PDCD4, PTEN, TGFβR, SMADs	[118]
HT29	p27, cyclin D1, p53, IGF-1R, Akt, Wnt	[119]
HT29	CHOP, GRP-78, XBP1	[120]
HCT116	DR4, Fas (CD95), p53, Bax, Mdm2	[40]
HCT116	NF-κB, EGFR, IGF-1R	[103]
Caco-2	Bak, FADD	[121]
Lovo	VEGF, MMP-9, HIF-1	[122]
RKO	β-catenin	[123]
HT29	COX-2, PGE2	[124]
Sanguinarine		
HT29	Bax, Bcl-2	[125]
Silibinin		
SW480	DR4, DR5, Mcl-1, XIAP	[126]
CSLC	AKT, mTOR, PP2Ac β-catenin, IGF-1Rβ, ILGBP-1, GSK-3β, PKB/Akt	[127]
SW480	β-catenin, GSK3, cyclin D1, VEGF, iNOS, c-myc, survivin	[128]
HCT116	Cyclin B1, -D1, CDK2, p21, p27, COX-2	[129]
LoVo	Flt-1	[130]

Cell lines/animals	Targets	References
Tocotrienol		
SW620	β-catenin, Wnt-1, cyclin D1, c-jun, MMP-7	[131]
HCT116	DR-4, DR5, ERK1, Bax, c-IAP2, Bcl-xL	[132]
HT29, HCT116	HMG-CoA reductase, RhoA	[133]
HT29	NF-κB, Bcl-2, Bax	[134]
RKO	p53, WAF1/p21, Bcl-2	[135]
Theaflavin		
Caco-2	COX-2, TNFα, ICAM-1, NF-κB	[136]
Thymoquinone		
HT29	HDAC2	[137]
HCT116	p53, CHEK1	[138]
HCT116	p53, p21WAF1, Bcl-2	[139]
Ursolic acid		
HCT116	Bcl-xL, Bcl-2, cFLIP, survivin, cyclin D1, MMP-9, VEGF, ICAM-1	[140]
HCT116	Sphingomyelinase	[141]
SW480	Bcl-2, Bcl-xL, survivin	[142]
HT29	EGFR, ERK1/2, p38 MAPK, JNK, Bcl-2, Bcl-xL	[143]
HCT116	DR4, DR5, DcR2, JNK	[144]
Withanolide		
HCT116	NF-κB, COX-2	[145]
Xanthohumol		
HCT116	CXCR4	[146]
HCT15	DNA topoisomerase I, MDR1	[147]
HCT116	Bcl-2	[148]
Zerumbone		
HCT116	DR4, DR5, cFLIP, ERK1/2, p38 MAPK, p53, Bax, p21	[149]
Caco-2, Colo320	IL-1, IL-1, IL-6, TNFα	[150]

ABCCG2, ATP-binding cassette sub-family G member 2; ACC, acetyl-CoA carboxylase; AKBA, acetyl-keto-beta-boswellic acid; AMPK, AMP-activated protein kinase; AR, aldose reductase; ARNT, aryl hydrocarbon receptor nuclear translocator; Bag-1, Bcl-2-binding protein; CAPE, Caffeic acid phenethyl ester; CBR3, Carbonyl reductase 3; CDDO, 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid; CDK, cyclin dependent kinase; CHOP, CCAAT/enhancer-binding protein-homologous protein; COX-2, cyclooxygenase-2; CXCR4, Cysteine X Cysteine (CXC) chemokine receptor 4; DcR, decoy receptor; DR, death Receptor; EGFR, Epidermal growth factor receptor; ERK, extracelluar signal- regulated kinases; FAK, focal adhesion kinase; GPx, glutathione peroxidase; GR, glucocorticoid receptor; GRP, glucose-regulated protein; GSH, glutathione; GSK-3β, Glycogen synthase kinase-3β; GST, glutathione S-transferase; HO-1, hemoxygenase-1; ICAM, intracellular cell adhesion molecule; IDPm, NADP(+)-dependent isocitrate dehydrogenase; IFN, interferon; IGF, insulin-like growth factor; IL, interleukin; iNOS, inducible nitric oxide synthase; IκBα, inhibitor of kappaB alpha; KLF, Krüppel-like factor; KLF4, Krüppel-like factor 4; LC3, microtubule-associated protein 1 light chain 3; MAPK, Mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF-κB, nuclear factor-kappaB; NQO1, quinone oxidoreductase 1; Nrf2, NF-E2-related factor 2; PCNA, proliferating cell nuclear antigen; PGE2, prostaglandin2; Pgp, phosphoglycoprotein; PI3K, phosphatidylinositol-3-kinase; PP2Ac, protein phosphatase 2Ac subunit; PPARgamma, peroxisome proliferator- activated receptor gamma; PRL-3, phosphatase of regenerating liver-3; PTC, Primary tumor cells of colon adenocarcinoma; PTTG, pituitary tumor transforming gene; QR, quinone reductase; SOD, superoxide dismutase; STAT3, signal transducers and activators of transcription 3; TNF, Tumor necrotic factor; tNOX, tumor-associated NADH oxidase; TRAIL, TNF related apoptosis-inducing ligand; VDRE, vitamin D responsive element; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; XIAP, X-linked inhibitor of apoptosis.

Table 2

Prevention of colorectal cancer with natural compounds

Targets	References
Rat Model	
Acetoxychavicol acetate	
GST, QR	[151]
Berberine	
β-Catenin	[152]
SOD, catalase, GST, GPx	[153]
COX-2	[154]
Capsaiscin	
GST, QR	[155]
HMG CoA reductase	[156]
Morin	
HMG CoA reductase	[157]
SOD, catalase, GST, GPx, GR	[158]
Curcumin	
HSP70	[159]
Resveratrol	
SOD, catalase, GPx, GST	[160]
Silibinin	
Bcl-2, Bax, IL-1β, TNFα, MMP7	[161]
CytochromeP450, GST	[162]
Theaflavin	
COX-2, iNOS	[163]
Thymoquinone	
Catalase, GPx, SOD	[164]
Zerumbone	
COX-2, prostaglandins	[165]
Mouse Model	
Curcumin	
TNFα, IL-6, COX-2, AMPK, NF-κB	[166]
iNOS, COX-2, ERK1/2, Wnt-1, β-catenin	[167]
TNFα, IFNγ, COX-2, β-catenin, p53	[168]
Resveratrol	
NF-κB, PKC-2, iNOS, COX-2, AR, HO-1, Nrf2	[169]
NF-κB, STAT3, iNOS, ERK	[170]
Silibinin	
PCNA, cyclin D1, Cip1/p21, iNOS, COX-2, VEGF	[171]

Targets	References
Zerumbone	
NF-αB, HO-1	[40]
Diosgenin	
IL-1β, lipoprotein lipase, triglyceride, HO-1, SOD-3	[172]
Noscapine	
β-Catenin, cyclin D1, c-myc, p21	[173]

AMPK, AMP-activated protein kinase; AR, aldose reductase; COX-2, cyclooxygenase-2; GPx, glutathione peroxidase; GST, glutathione S-transferase; ERK, extracelluar signal-regulated kinases; HO-1, hemoxygenase-1; HMG-CoA reductase, 3-hydroxy-3-methyl-glutaryl-CoA reductase; HSP, heat shock proteins; NF-κB, nuclear factor-kappaB; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; MMP, matrix metalloproteinase; Nrf2, NF-E2-related factor 2; PCNA, proliferating cell nuclear antigen; QR, quinone reductase; SOD, superoxide dismutase; STAT3, signal transducers and activators of transcription 3; TNF, Tumor necrotic factor; VEGF, vascular endothelial growth factor

Table 3

Therapeutic approach to colorectal cancer using natural compounds

Agent	Cells	Target	Reference
Curcumin	SW480	NF-κB, c-myc, cyclin D1, Bcl-2, CD31	[174]
Deguelin	COLO 205	Ki-67, NF-κB, VEGF	[50]
Guggulsterone	HT-29	Bcl-2	[81]
Plumbagin	HCT116	von Willebrand Factor	[175]
Silibinin	SW480	β-Catenin, GSK3β, cyclin D1, c-myc, survivin, VEGF, iNOS	[128]
Thymoquinone	HCT116	Ki-67	[139]
Ursolic acid	HCT116	NF-κB, STAT3, β-catenin, EGFR, CD31, p53, p21, Ki-67, Bcl-xL, Bcl-2, cFLIP, survivin, cyclin D1, MMP-9, VEGF, ICAM1	[140]
Resveratrol	HT-29	p21, PCNA	[176]

COX-2, cyclooxygenase-2; EGFR, Epidermal growth factor receptor; ERK, extracelluar signal-regulated kinases; GSK-3β, Glycogen synthase kinase-3β; NF-κB, nuclear factor-kappaB; ICAM, intracellular cell adhesion molecule; iNOS, inducible nitric oxide synthase; MMP, matrix metalloproteinase; PCNA, proliferating cell nuclear antigen; VEGF, vascular endothelial growth factor