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Colorectal Cancer: Chemopreventive Role of Curcumin and Resveratrol

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Abstract

Colorectal cancer (CRC) is a second leading cause of cancer deaths in the Western world. Currently there is no effective treatment except resection at a very early stage with or with-out chemotherapy. Of various epithelial cancers, CRC in particular has a potential for prevention, since most cancers follow the adenoma-carcinoma sequence, and the interval between detection of an adenoma and its progression to carcinoma is usually about a decade. However no effective chemopreventive agent except COX-2 inhibitors, limited in their scope due to cardiovascular side effects, have shown promise in reducing adenoma recurrence. To this end, natural agents that can target important carcinogenic pathways without demonstrating discernible adverse effects would serve as ideal chemoprevention agents. In this review, we discuss merits of two such naturally occurring dietary agents—curcumin and resveratrol—for chemoprevention of CRC.

BACKGROUND

Colorectal cancer (CRC) is the fourth most common form of cancer worldwide. In the United States, colon cancer ranks second among the cancer related deaths. It occurs with equal frequency in both men and women. The number of new cases of CRC has been rapidly increasing since 1975. It is estimated that nearly 150,000 new cases of CRC are diagnosed in the United States each year (1). The increased incidence of colon cancer in the Western world has partly been attributed to dietary factors such as a high-fat and low-fiber diet (2).

Most of CRCs are sporadic, whereas 10% have a clear genetic background. These include familial adenomatous polyposis (FAP), the Hamartomatous polyposis syndrome (e.g., Peutz–Jeughars, juvenile polyposis), hereditary nonpolyposis CRC (Lynch 1) and the cancer family syndrome (Lynch 2) (3). These conditions are associated with the high risk of developing CRC. Most CRCs are thought to develop through an orderly series of events known as adenoma carcinoma sequence. Here, normal colonic mucosa is transformed into

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adenoma, which then transforms into adenocarcinoma (4). In 1990, Fearon and Vogelstein (5) described the molecular basis of CRC as a multistep process that requires germ line and somatic mutations for malignant transformation. The APC gene is a negative regulator of β-catenin and is considered to be the "gatekeeper" in the adenoma to carcinoma sequence. Inactivation of APC gene results in increased accumulation of cytoplasmic levels, loss of membranous expression, and nuclear accumulation of β-catenin (6). Mutations in the APC gene occur early in the development of CRC as is seen in aberrant crypt foci (ACF), which are the earliest malignant lesions, considered to be precursors for adenoma and carcinoma of the colon. Mutations in p53 tumor suppressor gene are a relatively late event in colorectal tumorigenesis (7).

There are two distinct pathways in the development of CRC: 1) chromosomal instability, which is characterized by loss of heterozygosity (LOH), is responsible for 80–85% of sporadic colorectal adenomas and carcinomas; and 2) Microsatellite instability (MSI), which is responsible for 15–20% of sporadic CRCs (8). Mutations in DNA mismatch repair (MMR) genes including hMSH2, hMLH1, hPMS1, hPMS2, and hMSH6 that are required for correcting the nucleotide base mispairings that occur during the replication of the genome have been linked to MSI (9). Cells with MMR mutations accumulate abnormalities in short sequences of nucleotide bases that are repeated dozens to hundreds of times within the genome and are called microsatellites (10). Several oncogenes have also been implicated in sporadic CRCs. The most important one is K-RAS, which has been implicated in tumor invasion and metastasis (11). Point mutations in deleted in colon cancer have been implicated in CRC. The inhibitory influence of TGF-β on tumorigenesis is lost through mutations in SMAD-4 gene (12).

CHEMOPREVENTION

Chemoprevention is defined as the use of pharmacological or natural agents to prevent, stop, or reverse the development of cancers (13). The concept of chemoprevention has been key in the reduction of cancer-related morbidity and mortality. Many naturally occurring agents such as lycopene, soy isoflavones, pomegranate phenolics, selenium, curcumin, and resveratrol have been shown to possess chemopreventive potential (14). The properties of an effective therapeutic agent include one that has little or no toxicity to normal or healthy cells, availability in an oral form, and low cost (15). However, of many naturally occurring chemopreventive agents, only resveratrol and curcumin are reviewed in this article.

CURCUMIN

Introduction

Curcumin is an active ingredient of turmeric, a well known Indian spice that is derived from the dried roots of the plant *Curcuma longa*. In many Southeast Asian countries it has been consumed in the diet on a daily basis for centuries. This daily consumption not only speaks for its safety but has been said to be responsible for the low incidence of CRC in these countries. Ancient Chinese and Indian Ayurvedic medicine literatures have described the usefulness of turmeric in the treatment of a variety of ailments such as joint pain, wound dressing, hepatic and biliary disorders, anorexia, and sore throat (16). In studies performed over the past several decades, curcumin has been shown to be nontoxic for use in a variety of disorders such as Alzheimer's disease, diabetes mellitus, pancreatitis, cystic fibrosis, inflammatory bowel disease, arthritis, multiple sclerosis, drug and alcohol induced liver injury, drug induced nephrotoxicity, drug induced myocardial injury, hyperlipidemia, and in ischemic heart disease and atherosclerosis, to name a few (17-22). From the point of view of cancer, it has been shown that curcumin inhibits carcinogenesis. This effect is mediated in part by inhibition of angiogenesis, downregulation of several transcription factors, and

suppression of proliferation and induction of apoptosis in a variety of cancer cells including colorectal cells (23).

However, as we discuss later, owing to low oral bioavailability and minimal distribution in tissues other than the gastrointestinal (GI) mucosa, the usefulness of curcumin in diseases other than those involving the GI mucosa remains an active subject of investigation (24). At the same time, it is potentially the ideal agent for prevention and treatment of diseases of the GI tract (25).

Chemical Composition

Curcumin is a yellow crystalline molecule with a molecular weight of 368.37. It was first isolated in its crystalline form in 1860, and its diferuloylmethane structure was identified in 1910. As shown in Fig. 1, the chemical formula of curcumin is 1,6-heptadiene-3,5-dione-1,7-bis(4-hydroxy-3-methoxyphenyl)-(1E,6E) (26). In alkaline conditions, it exists in a stable enol form and appears reddish in color; whereas in neutral or acidic conditions, it assumes an insoluble keto form. Curcumin is insoluble in water but soluble in organic solvents such as dimethylsulfoxide and alcohol (27).

The yellow color of turmeric is attributed to 4 curcuminoid photochemicals, namely, curcumin (curcumin 1), demethoxycurcumin (curcumin 2), bisdemethoxycurcumin, and cyclocurcumin, the last yet to be identified. These curcuminoids are also the active ingredients of turmeric (28). Naturally occurring turmeric has only 2% to 5% of curcumin, whereas commercially available curcumin has 77% curcumin-1 and the rest is curcumin-2 and curcumin-3 (28).

Absorption and Metabolism

Most preclinical and clinical studies have demonstrated a poor oral bioavailability of curcumin. Orally administered curcumin undergoes extensive first pass metabolism in the liver by conjugation to glucuronide and sulphate. With intravenous/intraperitoneal (ip) administration, curcumin is metabolized into dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol (29).

In mice, with oral administration of 1 g/kg, the peak plasma concentration reached was found to be much lower than that noted following ip administration of 0.1 g/kg. However, curcumin was detectable for up to 6 h after oral administration; whereas after ip administration, it was detectable for only an hour (30).

In a clinical study, 12 patients scheduled for hepatic surgery for liver metastasis from colon cancer were given curcumin in doses between 0.45 and 3.6 g/day for 7 days prior to surgery. On Day 7, 6 to 7 h after the dose, trace levels of curcumin and its metabolites were found in peripheral blood and portal blood, but none were detected in the resected hepatic tissue (31). In another study by the same group, oral curcumin (3,600 mg/day) was administered to patients about to undergo surgery for colon cancer. The concentration of curcumin in the resected normal tissue was 12.7 ± 5.7 nmol/g, and in malignant tissue, it was 7.7 ± 1.8 nmol/g. However, at both these levels, curcumin was pharmacologically active as evidenced by the reduction in COX-2 expression and M(1)G adduct formation (32).

In a preclinical study, the aim of which was to determine whether products of curcumin biotransformation have biological activity similar to curcumin, 4 curcumin metabolites—tetrahydrocurcumin, hexahydrocurcumin, curcumin sulphate, and hexahydrocurcuminol—were compared with curcumin in their ability to inhibit phorbol ester induced prostaglandin E2 (PGE2) production in human epithelial cells (33). It was observed that although the first 3 metabolites moderately inhibited inducible PGE2 production, hexahydrocurcuminol had

no significant effect on inducible PGE2 production (33). These studies have suggested that after first pass metabolism, curcumin's biological activity is significantly reduced; hence there is a need to search for analogues of curcumin with better oral absorption and lower first pass metabolism. The problem of poor bioavailability and tissue distribution can be circumvented by use of phospholipid and micelles as well as liposomes and nanoparticles, all of which help to improve the distribution of hydrophobic drugs, or by combining curcumin with other pharmacological agents that may alter its metabolism (34,35). One such agent is piperin, which inhibits intestinal and hepatic glucuronidation. In a Phase 1 clinical trial, it was observed that the oral bioavailability of curcumin increases by 2,000% 1 h after administering 2 g of curcumin in combination with 20 mg/kg of piperin. On the other hand, curcumin alone was undetectable or minimally detectable in serum (36).

Biological Actions In Vitro

Inhibition of cell proliferation—Curcumin has been shown to inhibit the proliferation of numerous cancer cell lines by causing arrest in G1/M phase (37). By suppressing ornithine decarboxylase (ODC) activity, curcumin has been shown to inhibit proliferation of breast cancer cells and also induce their arrest in the G1/S phase (38). Cyclin D1 is necessary for cells to progress through the G1 phase of the cell cycle. Cyclin D1 gene expression is downregulated by curcumin via decreased activation of nuclear factor-κB (NF-κB) (39,40). Studies have also demonstrated that the effects of curcumin on colon cancer cells are dose dependent (41,42).

Additionally, from the point of view of cancer angiogenesis, it is important to note that curcumin arrests the proliferation of human vascular endothelial cells (HUVEC) cells by accumulating them in the S phase (43). It is important to note that as curcumin causes cell cycle arrest in the G2/M phase, it raises the possibility whether curcumin could render the cells sensitive to radiation and thus could be a potential radiosensitizer (37, 44).

Proapoptotic property—Curcumin induces apoptosis in various transformed cells in vitro including immortalized NIH 3T3 fibroblasts and colon cancer cells (41,45). Moreover, it has been shown to induce apoptosis of cancer cells without any significant cytotoxic effects on healthy cells (46). Some of the proapoptotic mechanisms include generation of reactive oxygen species, induction of p53 and proapoptotic proteins such as BAX while downregulating antiapoptotic genes Bcl-2 and BclXL (47,48). Curcumin stimulates the release of cytochrome c from mitochondria leading to caspase 3 activation, which results in cleavage of polyadenosine ribose polymerase (PARP) and inhibitor of caspase activated deoxyribonuclease (ICAD) (48). Loss of growth promoting signals via inhibition of transcription factors NF-κB, activating protein-1 (AP-1), and c-JUN and downregulation of proto-oncogenes Erg1 and c-MYC play a significant role in curcumin induced apoptosis (48). Thus, curcumin induced apoptosis can be mediated by both mitochondria dependent and independent mechanisms. In hepatocyte stellate cells (HSC) and colon cancer Moser cells, curcumin induced apoptosis and antiproliferative action via an increase in peroxisome proliferator activated protein-γ (PPAR-γ), resulting in suppression of cyclin D1 and EGFR (49,50).

Inhibition of angiogenesis—Curcumin inhibits proliferation of HUVEC and HVSMC cells at micromolar concentrations, resulting in inhibition of vascular tubule formation (43). This is mediated in part by downregulation of proangiogenic factors such as VEGF and angiopoetin 1 and 2 (51). It has also been shown to inhibit platelet derived growth factor (PDGF) induced proliferation of vascular smooth muscle cells (VSMC) in vitro (52).

Inhibition of carcinogenesis—Carcinogens are hydrocarbon compounds that are activated by cytochrome p-450 (CYP450) enzymes upon entering the body. Curcumin inhibits the activity of CYP450 as demonstrated by a decrease in the alkylation of ethoxyresorufin in rat liver and decrease in aflatoxin induced DNA adduct formation, processes that require the CYP450 system (53). DMBA, like other hydrocarbon carcinogens, binds to the Aryl Hydrocarbon receptor (AhR); and this dimer binds to the response element (RE) on the promoter region of the CYP gene, thus increasing its transcription (54). Curcumin binds to AhR, thus preventing it from binding to the RE of the CYP gene (54).

The effect of curcumin on Phase 2 reactions is concentration dependent, activating glutathione transferase (GST) at low doses and inhibiting at high doses (55). Curcumin's effect on GST also depends on the presence of carcinogens. It has been shown to inhibit GST in cells treated with carcinogens and activates it in normal cells (55). Overall, the data support inhibition of carcinogenesis by curcumin at initiation phase by inhibiting activation of carcinogens through CYP450 enzymes and increasing clearance by making them water soluble.

Inhibition of COX-2—Curcumin is a potent inhibitor of COX-2. This action on COX-2 is most likely mediated by NF-κB downregulation, which is one of the major inducers of COX-2 promoter activation (56). Celecoxib and curcumin, when administered together, synergistically inhibit human colon cancer cells (57). Four different cell lines of human colon cancer, namely, HT29, IEC-18-Kras, Caco-2, and SW-480, were treated with celecoxib, curcumin, or both. It was demonstrated that the combination of celecoxib and curcumin synergistically inhibited proliferation and induced apoptosis by downregulating COX-2 expression (57).

Downregulation of EGFR and human epidermal growth factor receptor 2 (HER2)/neu mediated signal transduction—EGFR family of proto-oncogenes encodes tyrosine kinases, which are downregulated by curcumin to inhibit growth in neoplastic cells. Curcumin has been shown to downregulate both intrinsic tyrosine kinase activity of EGFR as well as EGF-mediated phosphorylation of the receptor (58,59). HER2/neu tyrosine kinase activity is also decreased upon treatment with curcumin (60). Moreover, curcumin induces intracellular degradation of HER2/neu like geldanamycin (61). Curcumin also leads to the decreased levels of total EGFR and HER2 through inhibition of promoter transcriptional activity and by dissociating its binding to the chaperone molecule (GRP94), respectively (62,63).

Curcumin increases the gene expression of and activates the nuclear hormone receptor PPAR-γ in hepatic stellate cells. PPAR-γ antagonists reduce the ability of curcumin to inhibit cell proliferation (49). In Moser cells, the activation of PPARγ by curcumin leads to downregulation of cyclin D1 and EGFR gene expression (50).

Downregulation transcription factor NF-κB—NF-κB is a nuclear transcription factor for genes encoding inflammatory cytokines, major histocompatibility complex (MHC) genes, adhesion molecules, cyclooxygenease-2 (COX2), and genes responsible for resistance to chemotherapy. Curcumin inhibits both constitutive and H_2O_2, tumor necrosis factor (TNF) and phorbol acetate induce NF-κB activation (63). Curcumin inhibits NF-κB activity via blocking NF-κB from binding to DNA and IKK complex activation, which blocks Iκ-$\beta\alpha$ phosphorylation (64,65). This leads to downregulation of NF-κB mediated gene expression of adhesion molecules intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (ELAM-1), thus suppressing tumor metastasis (66).

In addition, matrix metalloprotein-9 (MMP-9) is downregulated by curcumin again via downregulation of NF-κB (67,68). Matrix metalloproteinase are proteases that contribute to metastasis, and thus MMP-9 downregulation contributes to curcumin mediated inhibition of metastasis.

Telomerase is an enzyme that splits the telomeres located at chromosomal terminals at the end of each cell division, thus restricting the total number of cell divisions that the cell can undergo. Telomerase activity is decreased in many cancers. Curcumin treated breast cancer cells showed a marked inhibition of telomerase activity (69). This inhibition was due to a decrease in hTERT expression, probably mediated by NF-κB inhibition. Inhibition of telomerase by curcumin has been demonstrated in other cancer cell lines as well (70,71). Thus, attenuation of NF-κB activity is considered central to many of curcumin's anticancer properties.

AP-1 inhibition—AP-1 is a transcription factor that regulates genes involved in carcinogenesis, cell proliferation, and progression of benign tumors to malignancy and in metastasis. It is formed by dimerization of activated c-Jun, and c-FOS (72). Curcumin inhibits c-Jun N terminal kinase activation by carcinogens, thus inhibiting c-Jun phosphorylation and consequently AP-1 activation (73,74). Curcumin has also been shown to downregulate tumor promoting agent (TPA) induced activation of both c-Jun and c-FOS (75). Further, by directly interacting with the DNA binding motif of AP-1, curcumin prevents its actions on gene expression (76).

Curcumin in combination with other chemotherapeutic drugs—The combination of curcumin and various other chemotherapeutic drugs has been studied. As we have discussed, curcumin possesses the ability to inhibit cell proliferation and stimulate apoptosis. This, along with the fact that curcumin sensitizes cancers to chemotherapy and that it is nontoxic, makes it an ideal agent to combine with standard chemotherapeutic drugs, most of which are highly toxic. Curcumin has been shown to sensitize prostate cancer cells to chemotherapy and radiotherapy (77). It sensitizes multidrug resistant (MDR) HEK 293 cells to etoposide and colon cancer in nude mice to oxaliplatin (78,79). The combination of curcumin and cisplatin is synergistic in inhibiting hepatic cancer HA22T/VG cells (80). By downregulating doxorubicin induced NFκB activation, curcumin augments the cytotoxic potential of doxorubicin (81).

Earlier studies from this laboratory have demonstrated that curcumin in combination with EGFR-related protein (ERRP), a pan-ERB inhibitor, causes a greater inhibition of growth of colon cancer cells than either agent alone. This was associated with a concomitant inhibition of NF-κB (82). For colon cancer, 5-FU or a combination of 5-FU and oxaliplatin (FOL-FOX) are the standard forms of chemotherapy. Recent in vitro studies from this laboratory have demonstrated that curcumin in combination with FOLFOX results in significantly greater apoptosis and growth inhibition than either curcumin, 5-FU, FOLFOX, or curcumin with 5-FU. The combination also produced a fivefold increase in IGF-binding protein-3 (IGFBP-3) which sequesters IGF-1, thus making it unavailable for binding to activating IGF-1R (83). In addition, the expression and phosphorylation of IGF-1R, EGFR, HER2, and HER3, as well as their downstream effectors COX-2 and Akt, were significantly decreased by the combination of curcumin and FOLFOX (83). The results suggest that curcumin synergizes with colon cancer chemotherapeutics.

Clinical Studies With Curcumin

Safety—As mentioned earlier, curcumin has been consumed on a daily basis in numerous south Asian countries for centuries, which points toward the safety of this compound. In

over a dozen clinical studies, which have included both Phase 1 and Phase 2 clinical trials, curcumin has been found to be safe and well tolerated. In 3 clinical trials, curcumin doses of up to 12 g/day have been shown to be without much adverse effects (84,85,36).

In one of these studies, 25 patients with premalignant and malignant but early invasive lesions were given between 500 and 12,000 mg/day for 3 mo, starting at 500 mg/day and increasing up to 12,000 mg/day; no significant toxicity was observed (84). It was observed that curcumin at 8,000 mg/day had minimal toxicities. Also, histological improvement in lesions was seen in 7 patients, whereas 2 patients developed frank malignancy despite treatment (84). In another dose escalation trial in which 24 healthy volunteers were given 500 to 12,000 mg/day of curcumin, only nontreatment related toxicity was seen in 7 volunteers (85).

Clinical trials of curcumin in cancer—There have been numerous Phase 1 and 2 clinical trials with curcumin. However, a complete description of each of them is beyond the scope of this review; instead, we review those that deal with anticancer actions of curcumin, especially in CRC.

In a study of 15 patients with advanced CRC refractory to standard chemotherapy, curcumin was administered in doses ranging from 0.45 to 3.6 g/day for 4 mo. No systemic biological activity was observed at doses between 0.45 and 1.8 g/day. However, in 6 patients receiving a dose of 3.6 g/day, lipopolysaccharide induced PGE2 levels in blood were decreased 1 h postdose of curcumin (86). In another study involving 15 patients with CRC, curcumin was given in doses ranging from 36 to 180 mg/day for 4 mo (87). Of the 15 patients, 5 had radiologically stable disease for 3 mo or longer. At 36 mg of curcumin/day, the levels of leukocyte GST declined; but no such decline was observed at higher doses. In one patient, a significant decrease in the level of carcinoembryonic antigen (CEA) was noted (87). In yet another trial, 12 patients with CRC undergoing surgery were given 0.45, 1.8, or 3.6 g/day of curcumin for 7 days prior to surgery (88). The concentration of curcumin and its metabolites was determined in serum and resected colon, for both normal and malignant tissues. In patients taking 3.6 g/day, significant levels were reached in both normal and malignant tissues, with higher levels seen in normal tissues. At this dose, curcumin was also detectable in blood. In the same study, it was noted that MiG adduct levels were 2.5 times higher in malignant tissue vs. normal colorectal tissue. On Day 7, it was noted that curcumin decreased MiG adducts in malignant tissue but had no effect on normal tissue (88).

Curcumin has been shown to be effective in FAP. Fifteen FAP patients who had previously undergone colectomy were administered with a combination of 480 mg of curcumin and 20 mg of ovrectin 3 times/day for an average of 6 mo. A mean decrease of 60.4% was noted in the number of polyps and a mean decrease of 50.9% was noted in the polyp size. Besides the aforementioned trials, a number of other trials are currently under way to further explore both the chemopreventive and/or therapeutic role of curcumin in various cancers, especially CRC.

RESVERATROL

Background

Phytoalexins are toxic compounds that are synthesized by plants in response to stress and invasion of other pathogens. Resveratrol (trans 3,5,4 trihydroxystilbene) is a phytoalexin found in at least 75 plant species that belong to the Cassia Quinquangulata family (89). Chemical structure of resveratrol is shown in Fig. 2. Resveratrol is formed by a condensation reaction between 3 molecules of malonyl coA and a molecule of 4-coumaroyl coacatalyzed by resveratrol synthase (90).

Both the cis and trans forms coexist; however, trans is the biologically active form. It is classified as a polyphenol compound with more than one phenol group. Polyphenols are antioxidants, which by reacting with free radicals makes them less toxic and suppresses tumor development through the removal of reactive oxidant species. The dietary sources are red wine (up to 13.4 mg/l); peanuts, around 1.79 micrograms/g); grapes; mulberries; and cranberries.

Absorption and Metabolism

Resveratrol is readily and rapidly absorbed along the length of the GI tract, which has been demonstrated in the isolated rat small intestine perfusion model and human intestinal epithelial cell line (Caco2) (91). Bulk (>96%) of absorbed resveratrol on the serosal side is in the conjugated form, most of which is conjugated by the addition of glucuronide; and this is catalyzed by UDP glucuronyl transferase, forming 3-O and 4′-O glucuronides. A small fraction of absorbed resveratrol is conjugated by the addition of sulfate and is catalyzed by sulfonyl transferase (92). These findings were further supported by studies that have used microsomes prepared form the different parts of GIT and human intestinal cell lines Caco-2 and PD-7 (93). Transcellular absorption of resveratrol increased with the concentration. However, the linearity was found to be limited, suggesting extensive metabolism of resveratrol (94). Studies performed by using human liver and duodenum models indicated that resveratrol is glucuronidated as well as sulfated in these tissues; and flavonoids, possibly by competing for the same xenobiotic enzyme system, inhibit the process of conjugation and might be useful in increasing the bioavailability of free resveratrol (95). Finally, studies that have been conducted using human hepatoblastoma cell line (Hep G2) and normal human hepatocytes showed that hepatic uptake of resveratrol probably takes place by passive as well as a carrier-mediated process (96). Also, resveratrol was found to be trapped by the plasma protein, albumin, which might be involved in delivering it to the hepatocytes in the carrier-mediated pathway; and the association of resveratrol with albumin is enhanced in the presence of fatty acids (96). Later studies that have been performed by orally administering ^{14}C labeled –trans resveratrol in rats, have confirmed the aforementioned metabolic fates of resveratrol and accumulation of resveratrol mainly in the liver and then in the kidney, which is the organ responsible of resveratrol excretion (97,98).

Biological Actions In Vitro

Even though the exact mechanism responsible for the chemopreventive property of resveratrol is not clear, various studies have implicated its involvement in modulating a variety of pathways or processes leading to tumor development, resulting in inhibition of cellular events associated with all 3 stages of cancer development, namely, initiation, promotion, and progression (13). The number of studies toward understanding the role of resveratrol in preventing or reversing colon cancer progression has been growing. A significant number of these studies have shown that induction of apoptotic cell death and inhibition of cell cycle progression are the two major pathways responsible for the chemopreventive role of resveratrol in colon cancer. Resveratrol induces apoptosis by clustering FAS and forming a death inducing signaling complex in SW480 human colon cancer cell line (99). Resveratrol induced dose dependent apoptotic cell death in a colon cancer cell line (HT 27), and this is caused by induction of endoplasmic reticulum stress response as indicated by the induction of ER stress markers such as eIF-2 (eukaryotic initiation factor 2a) (100). Vaticanol C, tetramer of resveratrol, markedly suppresses cell growth and induces apoptosis as indicated by nuclear condensation and fragmentation causing DNA ladder formation in colon cancer SW480, DLD-1, and COLO201 cells (101). Release of cytochrome c and activation of caspase-9 in this study indicated that the apoptosis is caused by loss of mitochondrial membrane potential. Studies using the human colonic adenocarcinoma cell line Caco-2 and the colon carcinoma cell line HCT-116

showed that the chemopreventive effects on colonic cancer cells is by inhibition of cell cycle as indicated by decreased levels of cyclin D1 and cdk4 and by induction of apoptosis as indicated by increased caspase activity (102). Subsequently, another study used a resveratrol analog, piceatanol, and found similar results (103). A study using multiple colon cancer cell lines showed that resveratrol has direct dose dependant antiproliferative activity (104). The study also indicated that telomerase activity is downregulated. Telomerase is a eukaryotic ribonucleoprotein (RNP) complex that helps to stabilize telomere length in human stem cells, reproductive cells, and cancer cells by adding TTAGGG repeats onto the telomeres using its intrinsic RNA as a template for reverse transcription. Also, resveratrol significantly inhibited the growth (70%; dose: 25 micromoles) and decreased ODC activity, which is a key enzyme in polyamine synthesis and is implicated as a risk factor in CRC (105).

In Vivo Studies With Resveratrol

Several in vivo studies have been conducted. Oral administration of resveratrol on tumorigenesis in Min mice (which are genetically predisposed to develop intestinal tumors as a result of mutation of APC gene) starting from 5 wk of age prevented the development of colon cancer and reduced the formation of intestinal tumors by 70% in comparison with the control group (105). A comparison of the gene expression profile showed that resveratrol downregulated the genes directly involved in cell cycle progression and proliferation (e.g., Cyclin D1 and D2) and upregulated the genes involved in recruitment and activation of immune response (105). Studies on the effects of resveratrol on azoxymethane-induced (AOM) carcinogenesis revealed a significant reduction in the number and multiplicity of ACF in the colorectal mucosa (106). Also, resveratrol was found to differentially regulate the expression of BAX and p21 in mucosa with ACF and non-ACF peripheral mucosa (106). In the xenograft gastric tumor model, 6 injections of high doses of resveratrol at an interval of 2 days near the tumor site inhibited tumor progression (107). Studies performed on in Wistar rats found a significant reduction in tumor incidence and the occurrence of histological lesions following administration of resveratrol (8 mg/kg body weight for 30 wk) (108).

COMBINATION OF CURCUMIN AND RESVERATROL FOR PREVENTION OF COLORECTAL CANCERS

As discussed earlier, both curcumin and resveratrol target certain common pathway of colon carcinogenesis such as NF-κB and growth factor receptors that play a critical role in development and progression of colon cancer. Hence, we hypothesized that combination of curcumin and resveratrol would be an effective preventive and/or therapeutic strategy for colon cancer. Indeed, the combination of curcumin and resveratrol was found to be more effective in inhibiting growth of p53-positive (wt) and p53-negative colon cancer HCT-116 cells in vitro and in vivo in SCID xenografts of colon cancer HCT-116 (wt) cells than either agent alone. Moreover, the combination was found to be synergistic in inhibiting the growth of colon cancer cells as calculated using calcusyn software (109). The inhibition of tumors in response to curcumin and/or resveratrol was associated with the reduction in proliferation and stimulation of apoptosis. Moreover, in vitro studies have further demonstrated that the combinatorial treatment caused a greater inhibition of constitutive activation of EGFR and its family members as well as IGF-1R and attenuation of NF-κB activity (109). Taken together, the combination of curcumin and resveratrol could be an effective chemoprevention strategy for CRC without the risk of prohibitive side effects.

CONCLUSION

Numerous studies, both preclinical and clinical, have well established the anticancer potential of curcumin and resveratrol. In both of these naturally occurring compounds, newer analogues and/or drug delivery systems need to be explored. Also, the optimal dose and half-life of both of these agents in human beings have yet to be determined. The obvious advantage of naturally occurring agents compared to standard chemotherapy is absence of side effects. Most importantly, they need of a chemopreventive agent for CRC in the Western world is pressing. The experience with curcumin in the Indian subcontinent over hundreds of years and the low incidence of colorectal cancer in this region, along with the vast scientific evidence accumulated over the past few decades, warrant a large scale clinical trial of curcumin as well as resveratrol in the treatment of CRC, either as single agents or in combination with conventional chemotherapy.

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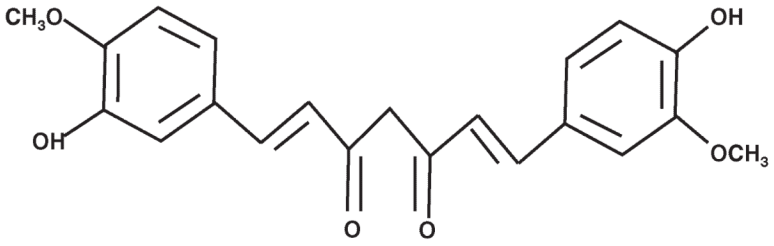

FIG. 1.

Bis-Keto form of Curcumin (neutral and acidic conditions) Chemical Formula: C21H20O6 Molecular Weight: 368.38 g/molFIG.

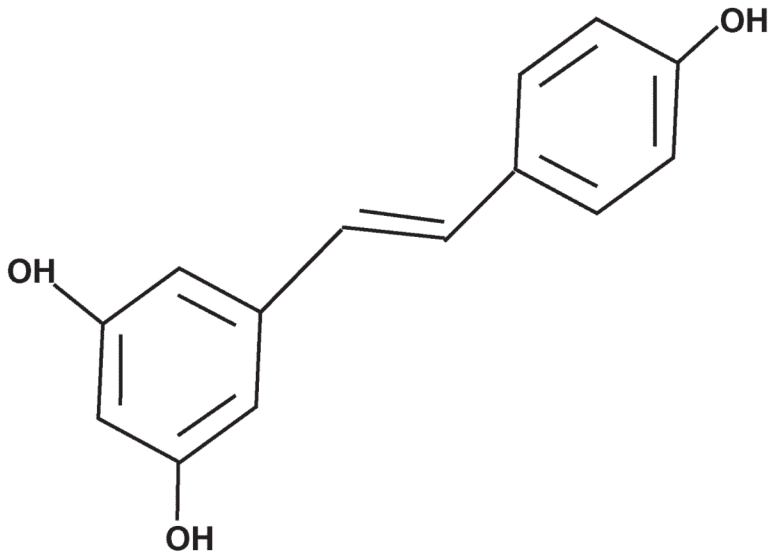

FIG. 2.
Trans-Resveratrol (biologically active form) Chemical Formula: C14H120O3 Molecular Weight: 228.25 g/mol

TABLE 1

Currently ongoing clinical trials of curcumin in colorectal neoplasia[a]

Trial No.	Phase	Target Population	Primary Objective
NCT00365209	II	Smokers with ACF	Mean percentage change in PGE2 within ACF from baseline to 30 days after treatment with curcumin
NCT00973869	I	Patients undergoing colorectal endoscopy or surgery	Determine curcumin concentration in the colonic mucosa
NCT00745134	II	Patients with locally advanced rectal cancer	Pathologic complete response rate following neoadjuvant radiation, capecitabine, and curcumin
NCT00295035	III	Patients with locally advanced or metastatic colorectal cancer	Improvement in progression free survival with addition of curcumin to gemcitiabine with or without celecoxib
NCT00927485	II	Familial adeomatous polyposis	Number and size of small and large intestinal polyps
NCT00118989	II	Patient with resected adenomatous polyps	Cellular proliferation and apoptosis in colonic mucosa in patient with resected polyps
NCT00248053	II	Familial adeomatous polyposis	Number and size of small and large intestinal polyps
NCT00176618	II	Subjects with ACF	To evaluate the effects of curcumin or the NSAID sulindac on the number of ACF in the left colon and rectum of normal volunteers

[a]Abbreviations are as follows: ACF, aberrant crypt foci; PGE2, prostaglandin E2; NSAID, nonsteroidal anti-inflammatory drug.

TABLE 2

Reported clinical trials of curcumin in colorectal neoplasia[a]

Reference	Phase	Target Population	Major Findings
Cruz-correa M et al. (110)	Pilot	FAP patients	Reduction in number (60.4%) and size (50.9%) of polyps with curcumin (1,440 mg/day) and quercetin (60 mg/day) compared to baseline
Sharma et al. (87)	I	Metastatic colon cancer, refractory to standard therapies	33% of the patients had radiologically stable disease
Sharma et al. (86)	I	Colorectal cancer refractory to standard chemotherapy	6/15 patients had decreased PGE2 levels in peripheral blood lymphocytes
Garcea et al. (88)	I	Colorectal cancer undergoing surgery	Significant level of curcumin detected in both malignant and normal colonic tissue; decreased MiG adducts in malignant tissue but had no effect on normal tissue

[a]Abbreviations are as follows: FAP, familial adenomatous polyposis; PGE2, prostaglandin E2.

TABLE 3

Currently ongoing clinical trials of resveratrol in colorectal neoplasia

Trial Number	Phase	Target Population	Primary Objective
NCT00256334	II	Colorectal cancer patients undergoing surgery	Modulation of Wnt signaling in malignant and normal colonic mucosa
NCT00433576	I	Patients undergoing colorectal cancer surgery	Determine resveratrol concentration in the colonic mucosa