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Mini-review

Curcumin for chemoprevention of colon cancer

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Abstract

The most practical approach to reduce the morbidity and mortality of cancer is to delay the process of carcinogenesis through the use of chemopreventive agents. This necessitates that safer compounds, especially those derived from natural sources must be critically examined for chemoprevention. A spice common to India and the surrounding regions, is turmeric, derived from the rhizome of *Curcuma longa*. Pre-clinical studies in a variety of cancer cell lines including breast, cervical, colon, gastric, hepatic, leukemia, oral epithelial, ovarian, pancreatic, and prostate have consistently shown that curcumin possesses anti-cancer activity *in vitro* and in pre-clinical animal models. The robust activity of curcumin in colorectal cancer has led to five phase I clinical trials being completed showing the safety and tolerability of curcumin in colorectal cancer patients. To date clinical trials have not identified a maximum tolerated dose of curcumin in humans with clinical trials using doses up to 8000 mg per day. The success of these trials has led to the development of phase II trials that are currently enrolling patients. Overwhelming *in vitro* evidence and completed clinical trials suggests that curcumin may prove to be useful for the chemoprevention of colon cancer in humans. This review will focus on describing the pre-clinical and clinical evidence of curcumin as a chemopreventive compound in colorectal cancer.
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Keywords: Curcumin; Turmeric; Colon; Cancer; Chemoprevention; COX-2

Abbreviations: 5-FU, 5-fluorouracil; ATF-2, activating transcription factor 2; AP-1, activator protein-1; AIF, apoptosis inducing factor; AHR, aryl hydrocarbon receptor; Arnt, aryl hydrocarbon receptor nuclear translocator; AUC, area under the curve; JNK, c-jun N-terminal kinase; CYP1, cytochrome P450-1 family; EGFR, epidermal growth factor; FAP, familial adenomatous polposis; GADD153, growth arrest and DNA damage; HNPCC, hereditary nonpolyposis colorectal cancer; IκB, IkappaB; IL-1, interleukin-1; LPS, lipopolysaccharide; MTHFR, methylenetetrahydrolfolate reductase; MAPK, mitogen activated kinase; NAT1 and NAT2, *N*-acetyltransfereases; NSAIDs, non-steroidal anti-inflammatory drugs; NF-κB, nuclear factor-kappa B; PPAR-γ, peroxisome proliferator activator receptor-gamma; PKC, protein kinase C; Smac, second mitochondria derived activator of caspase; SCC, squamous cell carcinoma; SULT1A1 and SULT1A3, sulfotransferase; TNF-α, tumor necrosis factor-alpha; UGTs, UDP-glucuronosyltrasferases.

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1. Cancer chemoprevention

Cancer is a multi-step process typically occurring over an extended period beginning with initiation followed by promotion and progression. The goal of cancer chemoprevention is to slow, block, or reverse the process of carcinogenesis through the use of natural or synthetic compounds. For a variety of reasons naturally occurring dietary substances over synthetic agents are preferred by patients to prevent cancer. This approach has largely focused on targeting deregulated intracellular pathways that have been implicated in abnormal cellular function. As a result there has been an increasing interest in dietary compounds that have an innate ability to modify these pathways thereby delaying process of carcinogenesis [1]. Pre-clinical studies of curcumin have shown the ability to inhibit carcinogenesis in cell lines that include breast, cervical, colon, gastric, hepatic, leukemia, oral epithelial, ovarian, pancreatic, and prostate cancer [2]. Epidemiological research has suggested the possible role of curcumin to prevent or delay the diagnosis of colorectal cancer as evidenced by ethnic groups that consume curcumin. The purpose of this review will describe the pharmacological activity of curcumin in colon cancer models (Fig. 1) and detail published clinical trials of curcumin for it use in colon cancer.

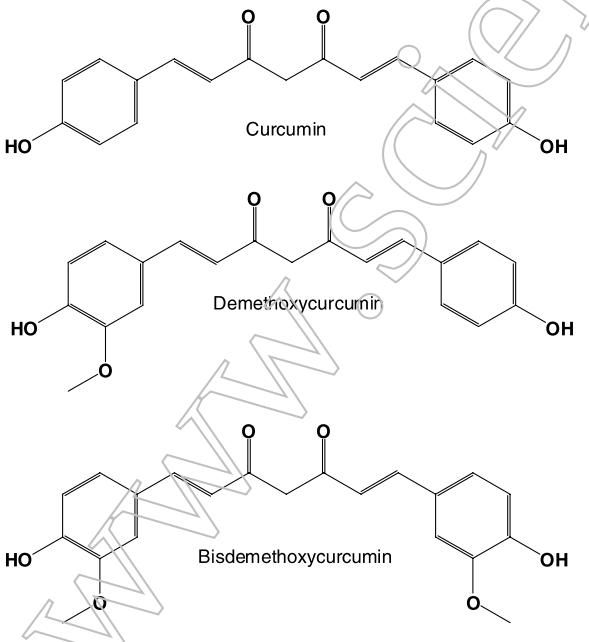

Fig. 1. Fractions of turmeric known as curcuminoids (curcumin, demethoxycurcumin and bisdemethoxycurcumin).

2. Introduction to colon cancer

Colon cancer is the third leading cause of cancer death in the United States [3]. The incidence of colon cancer worldwide can vary up to 20-fold with the highest prevalence in areas such as North America, Europe, Australia, and New Zealand. The lowest incidence is seen in India and lesser developed areas such as South America and Africa. Epidemiological studies suggest that economic development and dietary habits are implicated in colon cancer incidence. Several areas of nutrition that have been suggested to increase colon cancer risk are low fiber intake, high fat diet, and low calcium/micronutrient intake.

Within these populations a clear genetic susceptibility is seen within certain families [4]. Three genetic patterns have been categorized into the following groups: sporadic, inherited (~10%), and familial (~25%). The two most common forms of inherited colon cancer are the result of germline mutations which include: familial adenomatous polposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC). Genetic studies have focused on polymorphisms in *N*-acetyltransfereases (NAT1 and NAT2), cytochrome P450, and methylenetetrahydrolfolate reductase (MTHFR) enzymes due to their possible role in colon cancer [5,6].

Curative therapy for localized disease and palliative treatment for metastatic cancer are the primary treatment goals [7]. Complete surgical resection of the diseased tissue is the primary objective when treatment intent is curative. Further therapy may include adjunctive chemotherapy and/or radiotherapy depending on the extent of disease. In metastatic colon cancer the primary option is systemic chemotherapy and may include radiotherapy for palliative treatment. Surgery is rarely considered an option in metastatic colorectal cancer due to the inherent difficulty of removing metastatic lesions. Should chemotherapy be an option this is typically done with combination regimens such as FOLFIRI or FOLFOX. The FOLFIRI regimen contains the following agents: folinic acid, 5-fluorouracil, and irinotecan. FOLFOX is another option containing folinic acid, 5-fluorouracil, and oxaliplatin. In 2004, the FDA approved the use of Avastin® (bevacizumab), the recombinant, humanized monoclonal antibody in fluorouracil based regimens for the treatment of colorectal cancer. The addition of this biologic therapy targets metastasis through the inhibition of vascular endothelial growth factor (VEGF).

Overexpression of cyclooxygenase-2 (COX-2) expression is seen in up to 90% of sporadic colon carcinomas and 40% of colon adenomas. As a result of COX-2 overexpression compounds that target this deregulated pathway have been studied for chemoprevention in colon cancer. NSAIDs, and specific COX-2 inhibitors are the most studied agents clinically for the chemoprevention of colon cancer. Celebrex® (celexcoxib) has been FDA approved as a chemopreventive agent for colon cancer in patients displaying an FAP genotype. Post-market analysis has shown that chronic administration of these agents has been linked to an increase in the risk of acute myocardial infarction. Subsequently, this has led to the removal valdecoxib and rofecoxib from the market with continuing questions about the safety of specific COX-2 inhibitors as a whole [8].

3. Curcumin

A spice common to India and the surrounding regions, is turmeric, being derived from the rhizome of *Curcuma longa*. Fractions of turmeric known as curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin) are considered the active compounds and possess a yellowish orange color. Curcumin is the primary curcuminoid being studied in a host of areas including antioxidant potential, Alzheimer's disease, inflammation, chemoprevention, and chemotherapy. Pre-clinical studies in a variety of cancer cell lines have consistently shown that curcumin possesses anti-cancer activity *in vitro* [2]. In addition, *in vitro* studies using colon, gastric, hepatic, leukemia, ovarian, pancreatic, and prostate cancer cell lines have been performed showing that curcumin displays a potentiating effect with traditional pharmaceuticals such as 5-fluoruouracil (5-FU), all-trans retinoic acid, cisplatin, celecoxib, and doxorubicin [9–16]. The antioxidant potential of curcumin is well established with the ability to sequester the mutagenic/carcinogenic reactive oxygen species (e.g. superoxide anions, hydroxyl radicals, peroxides, and nitrite radicals) [17]. In addition to its antioxidant activity, curcumin has many pharmacological targets in different cancers where it has been shown to be effective. As a result, there is extensive interest in the clinical development of this compound as a cancer chemopreventive and/or chemotherapeutic agent as evidenced by the development of phase I clinical trials and current enrollment in phase II clinical trials.

4. Induction of apoptosis and cell cycle arrest by curcumin

The pro-apoptotic effect of curcumin is well established in a variety of cancer cell lines [2]. Recently, there has been evidence suggesting that c-jun N-terminal kinase (JNK) and p38 mitogen activated kinase (MAPK) as well as inhibition of constitutive nuclear factor-kappa B (NF-κB) transcriptional activity play a role in apoptosis [18]. HCT-116 colonocytes were exposed to curcumin at concentrations of 10 μM causing DNA damage in the form of single-strand breaks [19]. The novel finding in this study was that curcumin caused increased expression of growth arrest and DNA damage gene (GADD153) that has been implicated in apoptosis possibly through the modulation of protein kinase C (PKC) [20–22]. Sustained activation of JNK by curcumin at concentrations of 35 μM led to apoptosis of HCT116 cells accompanied by p38 activation and NF-κB inhibition [23]. Recently, it has been demonstrated that curcumin (100 μM) in HCT 116 cells leads to an increase in ceramide generation appearing to peak at the induction of apoptosis (50 μM) [24]. These findings suggest that curcumin can induce apoptosis by the production of reactive oxygen species and downstream activation of JNK and to a lesser extent by ceramide generation through the *de novo* pathway.

Curcumin was shown to activate caspases 9, 3, and 8 in the colon cancer cell lines SW480 and SW620 [25]. In the presence of heat shock proteins a reduction in the activation of both caspases 9 and 3, but not 8 in SW480 or SW620 cells was noted. Curcumin mediated the release of cytochrome *c*, the partial blocking of apoptosis inducing factor (AIF), and second mitochondria derived activator of caspase (Smac) was not blocked by heat shock proteins. Lovo cells and HCT-116 cells treated with curcumin were largely accumulated in G2/M phase which prevented cells from entering the next cell cycle [26–28].

5. Modulation of cell signalling by curcumin

5.1. Aryl hydrocarbon receptor (AHR) and detoxification enzymes

Under normal conditions AHR is localized in the cytoplasm and is typically complexed to hsp90, XAP2, and p23 [29]. Ligand binding of environmental toxins such as dioxin to AHR induces a

conformational change exposing a nuclear localization element. Translocation of AHR to the nucleus will lead to the dimerization of AHR to aryl hydrocarbon receptor nuclear translocator (Arnt) forming a functional transcriptional factor to the cytochrome P450-1 family (CYP1) of hemoproteins. CYP1 is involved in the metabolism of many drugs in addition to the bioactivation of pro-carcinogens to form mutagens. Treatment of oral squamous cell carcinoma (SCC) cells with 5 μM curcumin led to the nuclear localization of AHR, dimerization of AHR to Arnt and subsequent upregulation of CYP1A1 [30]. Interestingly, the inhibition of benzo(*a*)pyrene 7,8-dihydrodiol bioactivation to its carcinogenic counterpart benzo(*a*)pyrene 7,8-dihydrodiol 9,10-epoxide was noted when SCC cells and intact mucosa were treated with 5 μM curcumin. One possible explanation is that curcumin may act as a competitive substrate to environmental toxins in the CYP1 family. A competitive substrate mechanism suggests the role of curcumin as a chemopreventive against in individuals who have been exposed to pro-carcinogens.

Detoxification of dietary substrates, potential carcinogens, and endogenous substrates is carried out by the detoxifying enzymes UDP-glucuronosyltrasferases (UGTs). These enzymes are localized in the liver, bladder, and gastrointestinal tract [31]. The conjugation of glucuronide to curcumin by UGT facilitates elimination. In this study using colon cell lines LS180 and HT29 treated with 50 μM curcumin the down regulation of capsaicin glucouronidation by 50–90% in 15 minutes was observed with recovery after 24 h [32]. When 100 μM curcumin was used to treat the cell lines there was a more sustained inhibition with incomplete recovery after 24 h. Inhibition of UGT is not believed to be by direct targeting but rather a downstream effect of protein kinase C inhibition leading to the inhibition of UGT phosphorylation [33]. The clinical implications of this mechanism have not been studied, however, it is not unreasonable to suggest that a decreased clearance of UGT substrates such as irinotecan may be observed resulting in an increase in efficacy and/or toxicity.

5.2. Inhibition of serine/threonine kinases – protein kinase C (PKC) and c-jun N-terminal kinase (JNK)

Serine–threonine kinases have an important role in the regulation of signaling cascades that control cell proliferation and death and therefore represent targets for cancer therapy.

Upon activation, PKC is translocated to the plasma membrane by RACK proteins (membrane-bound receptor for activated protein kinase C proteins) [34]. Examples of PKC substrates include Ikappa B (IκB), MAPKs, and vitamin D_3 receptor. Substrates of PKC regulate these downstream targets through phosphorylation of tyrosine residues. PKC has different susceptible regions responding to antioxidant (i.e. cancer-preventive) and pro-oxidant (tumor promoter) compounds [35]. The action of curcumin to inhibit oncogenesis has been observed at the vicinial thiols on the catalytic domain leading to the inactivation of PKC. The downstream effects of this can be seen in NFκB, activator protein-1 (AP-1), epidermal growth factor (EGFR), and UGT1A1 (Fig. 1). Small molecule inhibitors of PKC such as calphostin C have been evaluated in the past for their potentiating effects of other chemotherapeutics suggesting that curcumin may possess the same potential [36].

Increased activity in the c-jun N-terminal kinase (JNK) pathway, which is a member of the mitogen activated protein kinases (MAPKs) leads to the synthesis of inflammatory mediators which is known to be a factor in cancer [37]. Transient activation of the JNK pathway by inflammatory cytokines leads to an anti-apoptotic effect. Interestingly, apoptosis can be observed when the JNK pathway is activated by NF-κB inhibition [38,39]. To contrast, sustained inhibition of the JNK pathway has been found to be pro-apoptotic. The role of activated JNK is to phosphorylate and activate c-jun and other transcription factors such as activating transcription factor 2 (ATF-2) and Elk-1, however, its role in apoptosis remains controversial. In human colon cancer cells (HCT116) treated with 35 μM curcumin a sustained activation of JNK dependent apoptosis was observed [18]. The ability of curcumin to modulate JNK dependent apoptosis was confirmed using the JNK signaling inhibitor SP600125 resulting in an attenuation of curcumin induced apoptosis.

5.3. Activator protein-1 (AP-1)

Transcriptional and post-translational regulation of AP-1 is controlled through the MAPKs (ERK 1/2, SAPK/JNK, and p38). The modulation of the

JNK pathway with curcumin is well established and subsequently leads to the inhibition of AP-1 [18]. In HT-29 cells treated with 35 μM curcumin using a luciferase reporter assay a dramatic reduction of luciferase activity was seen even in the presence of a known stimulator of AP-1 [40].

5.4. Nuclear factor-kappa B (NF-κB)

NF-κB is a transcription factor derived from the family of Rel proteins that has been implicated in the proliferation of cancer [2,41]. Generally speaking, the activation of NF-κB protects cells from apoptotic stimuli possibly through the regulation of survival genes. NF-κB is stimulated by tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), T and B cell mitogens, bacterial lipopolysaccharide (LPS), viruses, UV light, gamma rays, and oxidative stress. Curcumin was shown to inhibit NF- κB and COX-2 expression in oral cancer cells exposed to smokeless tobacco extract [42]. Jeong et al., assessed the trend of NF-κB modulation by curcumin in HT-29 colon cancer cells after stimulation by LPS [43]. A reduction of NF-κB was seen at 10 μM curcumin as evidenced through the use of a luciferase reporter assay. The down stream effects of this have been shown to modulate multiple genes including the down regulation of COX-2 [44]. A more recent study has been able to elucidate the subtype of NF-κB that is inhibited by curcumin as NF-κB/p65 in a time-dependent manner but not NF-κB/p50 [45]. Aggarwal and colleagues have shown that curcumin has the ability to inhibit paclitaxel-induced nuclear factor-kappaB pathway in addition to inhibiting lung metastasis of breast cancer and may in the future prove useful in cancers displaying resistance to chemotherapy [46].

5.5. Early growth response gene product

Early growth response (Egr-1) gene products modulate the activity of many genes including EGFR. Interruption of the ERK signalling pathway by curcumin (15 μM) led to a reduction in transactivation of Egr-1 as evidenced in Caco-2 and HT-29 cells [47]. Promoter deletion assays and site-directed mutagenesis identified a binding site for the transcription factor early growth response-1 (Egr-1) in EGFR promoter as a putative curcumin response element in regulating the promoter activity of the gene in Moser cells.

5.6. Cycloxygenase-2 (COX-2)

Epidemiological studies have shown a correlation between patients taking NSAIDs such as aspirin and a reduction in the incidence of colorectal cancer. This finding led to an interest in using curcumin which displays COX-2 inhibition for the chemoprevention of colon cancer [48,49]. In four colon cancer cell lines (HT-29, IEC-18-k-ras, Caco-2, SW-480) the use of curcumin (10–15 μM) and celecoxib (5 μM) inhibited the proliferation and induced apoptosis through the COX-2 and non-COX-2 pathways [50]. A potentiating effect of COX-2 inhibition of curcumin when used in combination with celecoxib was noted in cancer cells. The authors concluded that this may be due to activity in the COX-2 pathway and possibly through unknown mechanisms in non-COX-2 pathways. The mechanism of the COX-2 inhibitor class (valdexocib, celecoxib, and rofecoxib) is through the direct binding and subsequent antagonism of COX-2 [51]. The mechanism of curcumin to inhibit COX-2 activity is through the regulation of transcription factors and is fundamentally different than the mechanism of the COX-2 inhibitor class whose mechanism is through competitive inhibition of the COX enzyme [52].

5.7. Nitric oxide synthase

Nitric oxide is involved in the expression of COX-2 subsequently leading to the activiation of proinflammatory prostaglandins which have been linked to cancer. Male F344 rats were chemically induced by AZO to form pre-cancerous lesions, aberrant crypto foci [53]. *S,S′*-1,4-Phenylene-bis-(1,2-ethanediyl)bis-isothiourea (PBIT), a selective iNOS inhibitor was compared to curcumin for chemopreventive properties. PBIT suppressed the formation of aberrant cryptic foci formation by 58% ($P < 0.001$) while the curcumin group had a 45% formation ($P < 0.001$).

5.8. Epidermal growth factor receptor (EGFR)

EGFR is known to be highly expressed in colorectal cancer as well as other solid tumors. FDA approval of cetuximab (Erbitux®), a chimeric monoclonal antibody binding EGFR for EGFR positive colon cancer patients is evidence of the interest of EGFR as a therapeutic target for cancer [54]. Through the inhibition of the Egr-1 by curcu-

min (15 μM), a known transcription factor, a reduction was seen in EGFR expression in Caco-2 and HT-29 cells [55]. A second pathway has been reported to suppress the expression of EGFR. Moser cells treated with curcumin in a dose dependent manner, saw an increase in peroxisome proliferator activator receptor-gamma (PPAR-γ) [56]. Stimulation of PPAR-γ led to a reduction in cyclin D1 which is known to play a role in cell cycle progression and proliferation.

6. Inhibition of cell signaling associated with angiogenesis, metastasis, and migration by curcumin

6.1. Matrix metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) are members of the zinc-dependent endopeptidases which have been implicated in the degradation of extracellular matrix [57]. MMP-2 and MMP-9 are often over expressed in various cancers and studied as therapeutic targets. This process is considered to be a pivotal role in metastasis and was aggressively studied by pharmaceutical companies in the 1990s. Broad spectrum MMP inhibitors based on hydroxamic acid were developed with limited success in Phase III trials due to adverse effects [58]. The ability of curcumin to inhibit MMP-9 is well established in other areas such as prostate and breast cancer [59,60]. The colo 205 cell line when treated with curcumin was noted to decrease levels of MMP-2, promote MMP-9 activity, and had no effect on MMP-7 as determined by western blot assays and mRNA levels [45].

7. Pharmacokinetics of curcumin

The low bioavailability of oral curcumin is well established. Typically, quantifiable serum levels are not achieved until doses of up to 3600 mg are used. The alkaloid piperine from the *Piper* species is a known inhibitor of glucouronidation (i.e. UGT1A1) in the liver and small intestine and has been studied to assess the modulation of curcumin bioavailability [61,62]. Ten healthy volunteers received 2000 mg of curcumin with and without 20 mg of piperine in a randomized controlled fashion [62]. An increase in bioavailability of 2000% was seen with a curcumin and piperine combination compared to curcumin alone ($P < 0.001$). Employing liposome drug delivery technology has also successfully been performed *in vitro* and *in vivo* studies to enhance bioavailability (i.e. murine model) [63]. Another drug delivery system successfully used curcumin encased in natural biodegradable polymers (bovine serum albumin and chitosan) in Wistar rats [64]. Also, a group has formulated a β-cyclodextrin formulation of curcumin to enhance bioavailability [65].

Curcumin is a large lipophilic molecule that undergoes extensive gastrointestinal and hepatic metabolism after oral dosing. Phase I metabolism is through a reduction reaction forming tetrahydrocurcumin, hexahydrocurcumin, and hexahydrocurcuminol. Phase II metabolism consists of glucouronidation and sulfation by O-conjugation to form curcumin glucuronide and curcumin sulfate and rapidly excreted. One *in vitro* study of curcumin was found to inhibit UGT1A1 between 80% and 98% [66]. With concomitant administration of mycophenolic acid, a known substrate for UGT1A1, no cellular toxicity in LS180 cells was observed by MTT assay, however, *in vivo* studies are lacking. Curcumin has also been shown to be a substrate and inhibitor for the sulfotransferase enzymes (SULT1A1 and SULT1A3) [67,68]. The majority of curcumin elimination is via alcohol dehydrogenase to form hexahydrocurcumin in fecal matter [2].

Interestingly, there is evidence that curcumin metabolites display a similar potency to curcumin, however, further pharmacologic studies of these metabolites are needed [69].

8. Clinical trials

Sharma and colleagues assessed the pharmacodynamic and pharmacokinetic properties of curcumin in 15 Caucasian patients with a history of colorectal cancer in a phase I clinical trial [70]. All subjects had received a 5-FU based therapy in addition to undergoing surgery with measurable disease beyond the colon. Only 1 of the 15 patients had measurable disease in the colon with the other patients having complete surgical resection of cancerous lesions. Patients were stratified to receive 440, 880, 1320, 1760, or 2200 mg of *Curcuma* extract once daily by mouth as a capsule (P54FP, Phytopharm). Lymphocytic glutathione-*s*-transferase (GST) activity and M_1G levels was assessed as a biomarker to curcumin activity. Three patients who received the lowest dose saw a decrease from 64 ± 19 nmol/min/mg protein to 26 ± 13 nmol/min/mg protein. Interestingly, the other 12 patients receiving higher doses

did not observe any change in GST activity. It is unknown if there is a correlation between GST activity in lymphocytes versus GST activity in the colon epithelium. Correlation was not observed with levels of M_1G based on a variety of different stratifications. Levels of curcumin and its metabolites were not observed in plasma, urine, or blood cells. This finding is not surprising as it is well established that curcumin undergoes rapid glucouronidation in the small intestine explaining the unobservable levels [62,67]. Adverse events were minimal with 1 patient taking 1320 mg/day experiencing nausea (NCI grade I) during the first month of treatment with spontaneous clearing even with continuation of *Curcuma* extract. Two patients experienced diarrhea with 1 patient taking 880 mg/day (NCI Grade II) and a second subject taking 2200 mg/day (NCI grade I) developed after four months and one month into treatment, respectively. The cause of the diarrhea was not determined before both patients withdrew from the study. The one patient who had local colon disease saw a decline in cancer biomarker carcinoembryonic antigen (CEA) of 310 ± 15 to 175 ± 9 after two months of receiving curcumin capsules (i.e. 440 mg/day). A computed tomography (CT) scan revealed that disease of the colon was stabilized, however, metastasis was observed in the liver. A partial explanation may be explained by the low bioavailability observed with curcumin. This study showed the safety and tolerability of doses up to 2.2 g for four months of *Curcuma* extract in patients with colorectal cancer.

A phase I clinical trial assessed the tolerability of curcumin in 25 subjects from Taiwan with high risk or pre-malignant lesions [71]. Curcumin was provided as a 500 mg tablet for three months with 24/25 subjects completing the three month treatment regimen. A trend was seen with an increase in the area under the curve (AUC, nMole h/ml), maximum concentration (C_{max}, μM), and T_{max} (time at maximum concentration, h) as dose increased. Five subjects receiving 4000 mg of curcumin had an AUC of 2.55 ± 1.76, C_{max} of 0.51 ± 0.11, and a T_{max} of 1.67 ± 0.58. Two subjects received 8000 mg of curcumin had an AUC of 13.74 ± 5.63, C_{max} of 1.77 ± 1.87, and a T_{max} of 1.75 ± 0.35. Subjects who consumed 2000 mg or less had curcumin levels barely detectable in serum with no detectable levels in urine. Histological improvements independent of dose were observed in precancerous lesions in 7 of the 25 subjects. Frank malignancies were observed in 2 of the 25 subjects during the three month treatment regimen. This study showed the possible activity of chemoprevention, safety and tolerability in doses up to 8000 mg per day warranting further studies.

A second phase I clinical trial by Sharma and colleagues assessed curcumin biomarkers for systemic activity [72]. Fifteen patients were enrolled in the study who displayed histologically proven adenocarcinomas of the colon or rectum. Two of the patients had measurable disease in the colon while all others displayed measurable disease beyond the colon. Patients were assigned to receive 450, 900, 1800, or 3600 mg of curcumin daily and directed to consume the capsules after a two hour fast in the morning with a glass of water. The test compound was well tolerated with minor gastrointestinal events (i.e. diarrhea and nausea). One subject consuming 450 mg per day had NCI grade 1 diarrhea while another subject (3600 mg per day) experienced NCI grade 2 diarrhea. A third patient (900 mg) experienced NCI grade 1 nausea which resolved spontaneously. A rise in serum alkaline phosphatase in 4 patients was observed with 2 patients at NCI grade 1 and the other 2 patients at NCI grade 2. A 150% rise in serum lactate dehydrogenase compared to pre-treatment values was seen in 3 patients. Patients consuming 3.6 g of curcumin saw a 46% decrease in PGE2 levels ($P = 0.028$). Mean plasma levels of 11.1 ± 0.6 nmol/L at the one hour time point were seen in 3 patients consuming 3.6 g of curcumin. Curiously, curcumin levels were ~1/40th of those observed in a previous study [71]. A possible explanation presented by the authors was that Cheng et al., used a synthetic version while Sharma et al., used a natural curcumin with other curcuminoids present. Another possibility that was not considered is that pharmacogenomic studies have shown that different single nucleotide polymorphisms are present in different ethnic groups (i.e. Taiwan versus European) in the UGT1A1 gene which is known to metabolize curcumin [73]. Serum markers GST activity and M1G levels were assessed and determined to be unsatisfactory as biomarkers in the future. No partial responses were seen and no reductions in tumor markers were observed. Safety and tolerability was observed in this study with doses of curcumin up to 8000 mg per day.

A phase 1 trial assessed the presence of curcumin and metabolites in hepatic tissue and portal blood. Twelve patients received 450, 1800 or 3600 mg of curcumin capsules for seven days prior to surgery.

Only 3 of the 12 subjects receiving 3600 mg per day of curcumin had levels at the threshold of detection (~3 nm). Curcumin, curcumin sulfate, and curcumin glucuronide were not present in bile or liver tissue in any patient. Two reductive forms of curcumin (hexhydrocurcumin and hexahydrocurcuminol) were seen in one patient. A significant increase ($P < 0.05$) was seen in M1G levels in normal and malignant tissues. M1G levels in normal tissue rose from 4.3 ± 0.4 (pre-treatment) to 6.3 ± 3.8 (post-treatment) while malignant tissue saw an increase from 2.5 (pre-treatment) $\pm$ 1.5–6.3 $\pm$ 5.2 (post-treatment). Speculation by the authors was that this increase may have been a response to the surgical procedure. The authors concluded that curcumin in its present form has a low oral bioavailability and the potential feasibility as an oral agent to treat distant metastasis of the gastrointestinal tract.

Garcea et al., studied curcumin levels in the colorectum and the pharmacodynamics in 12 patients with confirmed colorectal cancer [74]. The staging of patients was as follows: 2 patients were Dukes

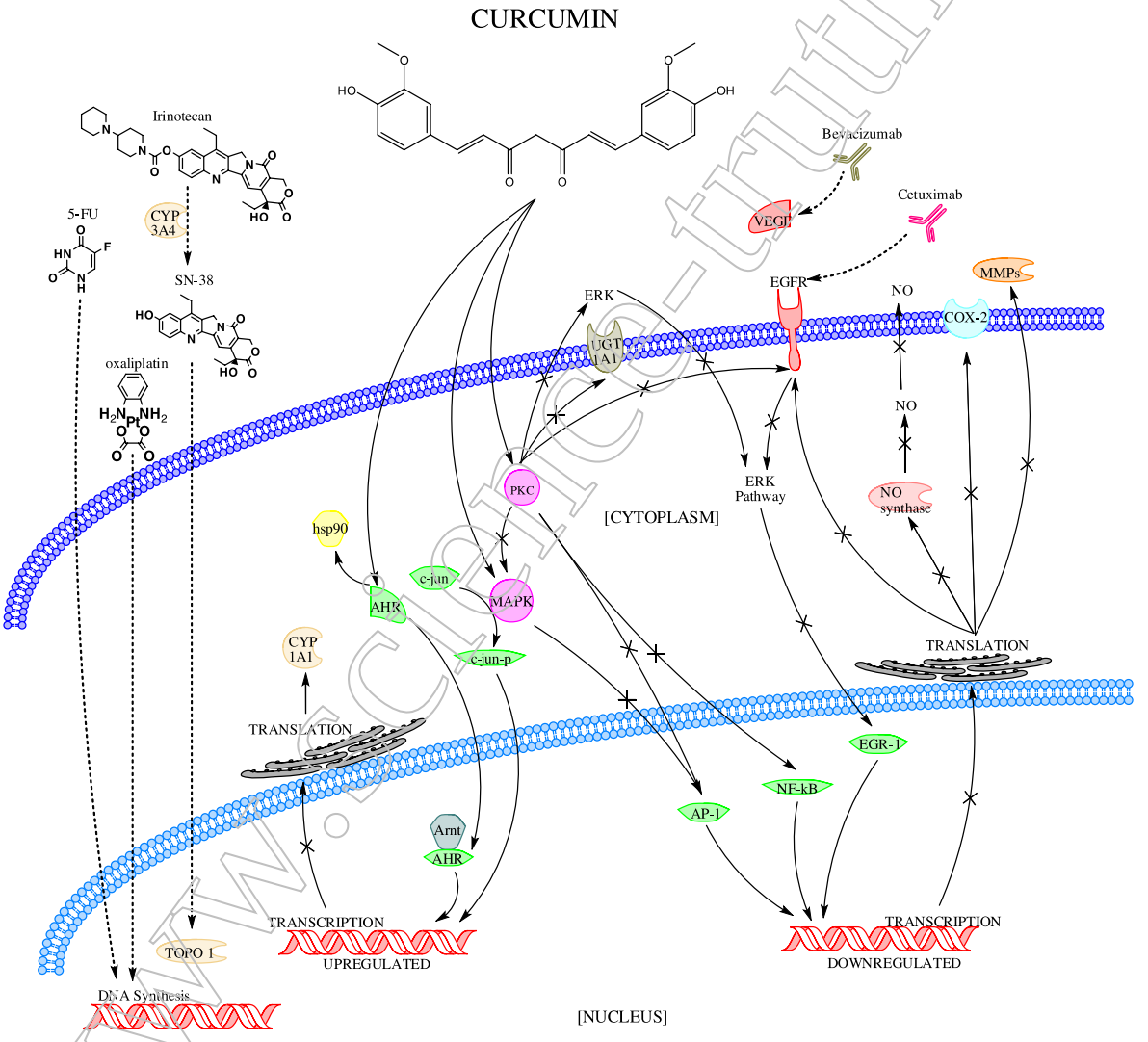

Fig. 2. Curcumin mechanism of action in colon cancer. Direct activity of curcumin occurs at AHR, MAPK, and PKC. Ligand binding of environmental toxins such as dioxin to AHR induces a conformational change exposing a nuclear localization element. Translocation of AHR to the nucleus will lead to the dimerization of AHR to aryl hydrocarbon receptor nuclear translocator (Arnt) forming a functional transcriptional factor to the cytochrome P450-1 family (CYP1) of hemoproteins. The down stream effects of MAPK include the downregulation of phosphorylation of c-JUN and inhibition of AP-1 to act as a transcription factor. The down stream effects of PKC include the inhibition of the ERK pathway, UGT, and EGFR.

A, 3 patients were Dukes B, and 7 patients were Dukes C. Patients were assigned to 450, 1800 or 3600 mg of curcumin per day for seven days prior to surgery. Detectable curcumin levels were seen in the serum of only 1 patient (3600 mg). Every patient had detectable curcumin levels in normal and malignant colorectal tissue ranging from 7 to 20 nmol/gram tissue. Curcumin levels were the highest in normal tissue of the caecum and ascending colon as opposed to the transverse, splenic flexure, and descending colon suggesting a local effect. COX-2 levels were undetectable in normal tissue while detectable in malignant colorectal tissue. Curcumin was not found to modulate the expression of COX-2 in malignant tissue. At baseline, M1G levels were found to be 2.5× higher in malignant tissue (4.8 ± 4.9 per 10^7 nucleotides) compared to normal tissue (2.3 ± 1.1 per 10^7 nucleotides, $P < 0.05$). Curcumin had no effect on the levels of M_1G in normal colorectal mucosa however colorectal M_1G levels in malignant tissue was significant ($P < 0.05$) in patients who had received the highest dose. Doses of 3600 mg of curcumin are safe and sufficient to see pharmacodynamic changes in the gastrointestinal tract.

9. Conclusions and future prospects

Currently, there is a need for compounds that target multiple molecular and cellular pathways in cancer. Curcumin is a compound that displays those traits in cell models as well as animal models and appears to be an attractive compound for chemoprevention/chemotherapy (see Fig. 2) [2]. As a result five human clinical trials have been conducted in colon cancer patients and are attempting to answer basic questions like safety, tolerability, pharmacokinetic, and pharmacodynamic issues. Every clinical trial has concluded that curcumin is safe and poses minimal adverse effects. Doses up to 8000 mg per day of curcumin were well tolerated and in some cases evidence would suggest that some patients displayed a pathological change.

An area of concern for some may be the inhibition of COX-2 by curcumin leading one to ponder the safety of this compound for chronic use and will require further study. The mechanism of curcumin to inhibit COX-2 is fundamentally different than the COX-2 inhibitors class (celecoxib, valdecoxib, and rofecoxib) suggesting that curcumin will not be a risk factor for cardiovascular events. Further studies are also needed to assess the potential for drug interactions of curcumin with known substrates of UGT enzymes along with the role of single nucleotide polymorphisms in this enzyme. Specifically, the chemotherapeutic irinotecan used in colon cancer poses as a theoretical risk since this compound is metabolized by the UGT enzyme system. One could argue that curcumin displays poor bioavailability resulting in a minimal inhibition of UGT enzymes in organs beyond the gastrointestinal tract such as the liver, however, if compounds that enhance bioavailability such as piperine are used systemic effects of UGT inhibition may be seen. Further evaluations in this area may resolve some of the confusion that has been seen in pharmacokinetic studies. Another area of interest is the use of curcumin as a lead compound for medicinal chemists [75–77]. However, an advantage of curcumin over its synthetic counterparts is that curcumin has an established record of safety with an understanding of its mechanism of action.

With questions revolving around the chronic use of COX-2 inhibitors the need for new chemopreventive agents for colorectal cancer is necessary. Curcumin is a compound that has been shown to target multiple pathways *in vitro* and has been shown to be safe in oncology patients. The use of curcumin in oncology patients to assess its efficacy is an exciting and emerging area and warrants further studies in colon cancer as well as other cancers.

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