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Review

Curcumin: From ancient medicine to current clinical trials

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Abstract. Curcumin is the active ingredient in the traditional herbal remedy and dietary spice turmeric (*Curcuma longa*). Curcumin has a surprisingly wide range of beneficial properties, including anti-inflammatory, antioxidant, chemopreventive and chemotherapeutic activity. The pleiotropic activities of curcumin derive from its complex chemistry as well as its ability to influence multiple signaling pathways, including survival pathways such as those regulated by NF-κB, Akt, and growth factors; cytoprotective pathways dependent on Nrf2; and metastatic and angiogenic pathways. Curcumin is a free radical scavenger and hydrogen donor, and exhibits both pro- and antioxidant activity. It also binds metals, particularly iron and copper, and can function as an iron chelator. Curcumin is remarkably non-toxic and exhibits limited bioavailability. Curcumin exhibits great promise as a therapeutic agent, and is currently in human clinical trials for a variety of conditions, including multiple myeloma, pancreatic cancer, myelodysplastic syndromes, colon cancer, psoriasis and Alzheimer's disease.

Keywords. Curcumin, inflammation, antioxidant, angiogenesis, anti-tumor, anticancer.

History and traditional uses of curcumin

The polyphenol curcumin is the active ingredient in the herbal remedy and dietary spice turmeric (*Curcuma longa* Linn). This vibrant yellow spice, derived from the rhizome of the plant (Fig. 1) [1], has a long history of use in traditional medicines of China and India [2]. The rhizome of turmeric has been crushed into a powder and used in Asian cookery, medicine, cosmetics, and fabric dying for more than 2000 years [2]. Early European explorers to the Asian continent introduced this important spice to the Western world in the 14th century [3].

Use of curcumin as a folk remedy continues today. As part of the ancient Indian medical system, Ayurveda, a poultice of turmeric paste is used to treat common eye infections, and to dress wounds, treat bites, burns, acne and various skin diseases [4]. The American pharmaceutical company Johnson & Johnson even makes turmeric Band-Aids™ for the Indian market [5]. In Northern India, women are given a tonic of fresh turmeric paste with powder of dried ginger roots and honey in a glass of hot milk to drink twice daily after childbirth. A poultice of turmeric is also applied to the perineum to aid in the healing of any lacerations in the birth canal [6]. Powdered turmeric is taken with boiled milk to cure cough and related respiratory ailments [4], and roasted turmeric is an ingredient used as an antidysenteric for children [4]. This ancient remedy is

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also used to treat dental diseases, digestive disorders such as dyspepsia and acidity, indigestion, flatulence, ulcers, as well to alleviate the hallucinatory effects of *hashish* and other psychotropic drugs [7]. In food and manufacturing, curcumin is currently used in perfumes and as a natural yellow coloring agent, as well as an approved food additive to flavor various types of curries and mustards [7, 8].

Recent emphasis on the use of natural and complementary medicines in Western medicine has drawn the attention of the scientific community to this ancient remedy. Research has revealed that curcumin has a surprisingly wide range of beneficial properties, including anti-inflammatory, antioxidant, chemopreventive and chemotherapeutic activity. These activities have been demonstrated both in cultured cells and in animal models, and have paved the way for ongoing human clinical trials. Studies documenting the activities of curcumin, its mechanisms of action, and its chemical and clinical features are summarized in this review. Given the explosive growth of interest in curcumin and the extensive literature that has developed on this topic, reports cited in this review should be considered as illustrative rather than comprehensive.

Figure 1. *Curcuma longa* (from Koehler's Medicinal-Plants).

Activities of curcumin

Anti-inflammatory and antioxidant activities of curcumin

Many of the activities associated with curcumin relate to its ability to suppress acute and chronic inflammation [8]. *In vitro* studies have shown that curcumin inhibits lipo-oxygenase and cyclo-oxygenase activities in phorbol 12-myristate 13-acetate (PMA)-induced inflammation of mouse fibroblast cells [9], xanthine oxygenase activities in NIH3T3 cells [10], nitric oxide production in RAW264.7 murine macrophages [11, 12], and reactive oxygen species (ROS) generation in activated rat peritoneal macrophages [13]. Curcumin also inhibits the production of pro-inflammatory monocyte/macrophage-derived cytokines [interleukin-8 (IL-8), monocyte inflammatory protein-1 (MIP-1), monocyte chemotactic protein-1 (MCP-1), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF- α)] in PMA- or LPS-stimulated peripheral blood monocytes and alveolar macrophages [14]. A recent study revealed that oxidative stimulation of G proteins in human brain membranes by metabolic prooxidants, homocysteine and hydrogen peroxide, can be significantly depressed by curcumin [15]. Curcumin was shown to inhibit lipid peroxidation in a rat liver microsome preparation [16] as well as in rat brain homogenates, where curcuminoids actually exhibited more potent antioxidant activity than alpha-tocopherol [17].

In vivo studies have also demonstrated an inhibitory effect of curcumin on inflammation. For example, curcumin inhibited inflammation induced by carrageenan [18, 19] and acute lung injury induced by cyclophosphamide [20]. In rats, curcumin had comparable activity to phenylbutazone, a commonly used anti-inflammatory agent [18]. Further, whereas phenylbutazone produced a significant leukopenia and lymphyocytopenia, curcumin did not [18]. Rats that were fed curcumin for 7 days prior to being treated with cyclophosphamide to induce lung injury, exhibited an increase in antioxidant defense mechanisms [20]. Topical application of curcumin markedly inhibited TPA- and arachidonic acid-induced epidermal inflammation (ear edema) in mice [21]. Thus, curcumin exhibits substantial antioxidant properties in a wide variety of experimental settings.

Chemopreventive, chemotherapeutic, and chemosensitizing activity of curcumin

Curcumin inhibits cancer development and progression, targeting multiple steps in the pathway to malignancy (Fig. 2). Curcumin has activity as both a blocking agent, inhibiting the initiation step of cancer by preventing carcinogen activation, and as a sup-

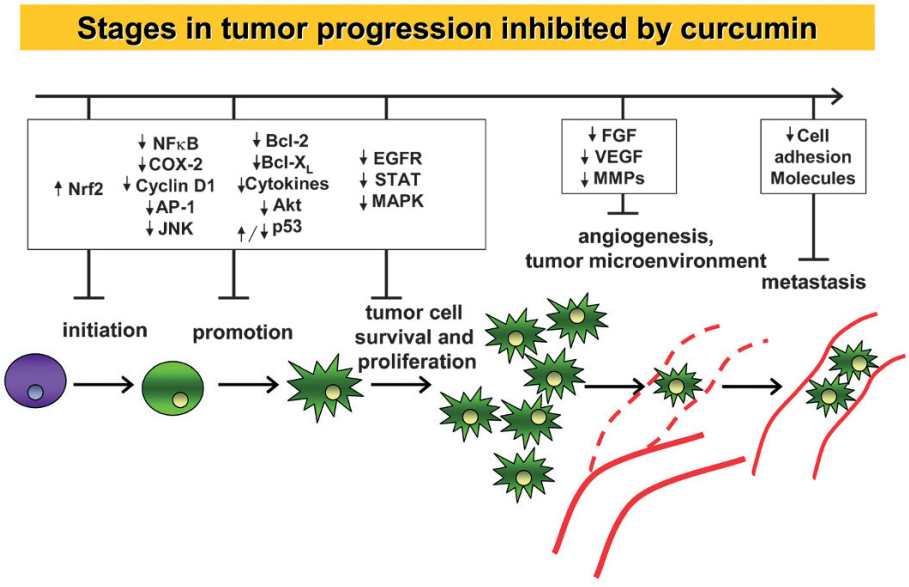

Figure 2. Stages in tumor progression inhibited by curcumin.

pressing agent, inhibiting malignant cell proliferation during promotion and progression of carcinogenesis [22]. Several animal studies have shown that curcumin has a dose-dependent chemopreventive effect in colon, duodenal, stomach, esophageal and oral carcinogenesis [23]. Curcumin reduces tumors induced by benz(a)pyrene and 7,12 dimethyl benz(a)anthracene [24–26], tumor promotion induced by phorbol esters on mouse skin [27], carcinogen-induced tumorigenesis in the forestomach, and *N*-ethyl-*N*'-nitro-*N*-nitrosoguanidine-induced duodenal tumors [28]. Curcumin not only reduced the number of tumors per mouse and the percentage of mice with tumors, but also reduced tumor size in forestomach and intestine [28]. Further studies demonstrated that curcumin inhibits cancer development in rat stomach initiated by *N*-methyl-*N*'-nitro-*N*-nitrosoguanisine (MNNG) [29] and reduces the incidence and/or multiplicity of esophageal tumors and preneoplastic lesions in rats with *N*-nitrosomethylbenzylamine-induced esophageal carcinogenesis [30]. Dietary curcumin significantly suppressed azoxymethane-induced colonic preneoplastic lesions and colon tumor incidence and tumor multiplicity [31]. Additionally, a marked preventive effect of curcumin on diethylstilbestrol (DES)-dependent promotion in radiation-initiated mammary tumorigenesis in rats was demonstrated [32, 33]. Curcumin was an effective cytotoxic agent against the mouse bladder tumor line MBT-2 and the UMUC human bladder tumor cell line, and effectively inhibited implantation and growth of bladder tumor cells in C3H mice [34].

In addition to its preventive activity against chemically induced tumors, orally administered curcumin has potent preventive activity during tumor promotion in radiation-initiated mammary tumorigenesis [32, 33]. In two separate studies, female Wistar-MS rats received whole body irradiation at day 20 of pregnancy. The animals were implanted with a DES (diethylstilbestrol) sustained release pellet at 1 month after weaning, a mammary tumor promoter regimen. In the first study, the experimental group was fed a diet containing 1 % curcumin immediately after termination of nursing for 12 months [32]. Rats fed curcumin were shown to have significantly decreased incidence of total mammary tumors over a 1-year period (28 %) compared to control (84.6 %) ($p<0.0001$), and the number of mammary tumors/tumor-bearing rat in the curcumin-fed group was half of that in the rats fed the control diet. Overall, the administration of curcumin together with DES implantation in the irradiated rats significantly decreased the cumulative incidence curve ($p<0.0001$) of mammary tumors for the 1-year period, compared with the control group [32]. In the second study by the same investigators, Wistar-MS rats were only fed the curcumin diet between day 11 of pregnancy and parturition (day 23 of pregnancy) [33]. Again, the number of mammary tumors significantly decreased ($p<0.0001$) from 70.3 % in the control group to 18.5 % in the curcumin-fed group. Both studies showed that the appearance of the first palpable tumors was delayed ~2.5 months in the curcumin-fed group [32, 33]. Compared to rats fed the control diet, body weight was significantly decreased in the rats fed the curcumin diet, in spite of similar intake of diet throughout the experiment [32, 33]. While not a toxic action of curcumin, the reduction in body weight is likely due a decreased concentration of serum triglycerides [32]. Curcumin was not shown to have adverse effects on fetuses or

dams, and the results suggest the possibility of clinical application of curcumin in radiation therapy to prevent mammary tumors.

In addition to a role as a chemopreventive and chemotherapeutic agent, curcumin may also function as a chemosensitizer, enhancing the activity of other anti-neoplastic agents, in part by inhibiting pathways that lead to treatment resistance [35]. *In vitro*, curcumin inhibited the Fanconi anemia (FA)/BRCA pathway, a DNA-damage response pathway required for repair of cisplatin cross-links, in ovarian tumor lines and MCF7 breast tumor cell lines. This sensitized these cell lines to cisplatin through apoptotic cell death [36]. Moreover, curcumin had no effect on the dose-dependent paclitaxel cytotoxicity profile of these cells, indicating that curcumin seems to specifically sensitize cells to cisplatin-mediated DNA damage rather than microtubular damage [36]. Additionally, curcumin sensitized LNCaP, DU145 and PC3 tumor cell lines to the death ligand TRAIL (TNF-related apoptosis inducing ligand) [37]. Cells treated with low concentrations of curcumin (10–30 μM) or low concentration of TRAIL (20 ng/ml) did not induce appreciable cell death; however, combined treatment with subtoxic concentration of each agent (10–40 μM curcumin and 20 ng/ml TRAIL) for 48 h reduced viability of each cell line [37]. Additionally, subtoxic concentrations of curcumin sensitize human renal cancer cells to TRAIL-mediated apoptosis [38]. Results from this study demonstrated a critical role of curcumin-induced ROS in mediating the up-regulation of death receptor 5 (DR5) to render cells more sensitive to the cytotoxic activities of TRAIL [38]. An earlier study showed that curcumin potentiated the cytotoxic effects of several common chemotherapeutic agents in prostate cancer cells, PC3 and DU145, by inducing $p21^{WAF1/CIP1}$ and CCAAT enhancer binding protein beta (C/EBP_{β}) expressions and suppressing NF-κB activation [39]. Pretreatment with curcumin (10 μM) caused a time-dependent inhibition of doxorubicin-induced NF-κB activity in the hepatocellular carcinoma (HCC) cell line Hep-3B [40]. In other *in vitro* studies, the presence of curcumin enhanced the cytotoxic effects of chemotherapeutic drugs, including doxorubicin [41], tamoxifen [42], cisplatin and camptothecin, daunorubicin, vincristine (VCR) and melphalan [43]. The human multiple myeloma (MM) cell line, U266, was least sensitive to VCR, but the presence of curcumin enhanced cytotoxicity from below 10% to greater than 70% [43]. Pretreatment with 5 μM curcumin dramatically lowered the concentration of paclitaxel required to induce a cytotoxic response in the human cervical cancer cell line HeLa [44]. The authors of this study further demonstrated that curcumin pretreatment augments membrane flip-flop, caspase activation, PARP cleavage, and cytochrome *c* release by paclitaxel [44]. Furthermore, when pretreated with 20 μM curcumin, the HCC cell line, HA22T/VGH, which constitutively expresses activated NF-κB, was sensitized to the antitumor and apoptotic effects of cisplatin through changes in the levels of NF-κB as well as decreased expression of 'inhibitory of apoptosis' proteins (IAPs) [45]. Additionally, curcumin treatment of dexamethasone-resistant MM.1R cells enhanced the cytotoxic effects of both chemotherapeutic agents on these chemoresistant cells [43]. A multidrug-resistant (MDR) cervical carcinoma cell line (KB-V1) and a drug-sensitive cervical carcinoma cell line (KB-3–1), which overexpress the drug export protein Pgp (p-glycoprotein), showed enhanced sensitivity to vinblastine-induced cytotoxicity because curcumin inhibited Pgp efflux activity [46] and MDR-1 gene expression [47]. Curcumin, at concentrations of 5.0 μmol/l, 10.0 μmol/l and 20.0 μmol/l, was able to decrease the IC_{50} of VCR in VCR-resistant gastric cancer SGC7901/VCR cells in a dose-dependent manner, suggesting that curcumin is able to reverse MDR in these cells [48]. Similarly, curcumin (50 μM) induced cell death in MDR CEM(P-gp4) and LoVo(P-gp4) cells in the absence of caspase-3 activation [49]. Recently, chemosensitization by curcumin has also been further demonstrated *in vivo*. Curcumin dissolved in cottonseed oil given by gavage at doses of 5 mg/day, 5 days per week for 4 weeks inhibited the growth of PC3 xenografts in nude mice by 50% compared to controls; moreover, curcumin enhanced the antitumor effects of gemcitabine and radiation [50]. Analysis of the tumors revealed reduced expression of murine double minute 2 (MDM2), a major ubiquitin E3 ligase of p53, in xenografts treated with curcumin alone [50]. Thus, curcumin may provide an effective therapy for treating many chemoresistant and MDR cancers.

Radiosensitization and radioprotection

An interesting aspect of curcumin's activity is the ability to exert both radioprotective effects in normal cells and radiosensitizing effects in cancer cells (see [51] for recent review). Although the mechanism(s) enabling curcumin to exerts these opposing effects are not entirely understood, it has been suggested that curcumin's ability to reduce oxidative stress and inhibit transcription of genes related to oxidative stress and inflammatory responses may afford protection against the harmful effects of radiation, whereas the radiosensitizing activity might be due the up-regulation of genes responsible for cell death [51]. Curcumin at 2 and 4 μM concentrations in combination with radiation showed significant enhancement to radiation-induced clonogenic inhibition and apoptosis

in the prostate cancer cell line PC3 [52]. Radiation induces pro-survival factors such as increased NF-κB activity and up-regulation of Bcl-2 in PC3 cells; however, curcumin treatment in combination with radiation showed inhibition of TNF-α-mediated NF-κB activity, resulting in down-regulation of Bcl-2 [52]. Additionally, results from this same study showed significant activation of cytochrome *c* and concurrent increase in caspase-9, which confirmed the involvement of the mitochondrial pathway of apoptosis following curcumin treatment to enhance the radiation-induced sensitivity in PC3 cells [52]. In another study, PC3 cells were exposed to 0 or 15 μmol/l curcumin for 24 h followed by exposure to 10 Gy γ-irradiation [50]. Radiation-induced increase of MDM2 was blocked by curcumin; furthermore, when control PC3 cells and PC3 cells with MDM2 knockdown or overexpression were exposed to curcumin (5 μmol/l) for 24 h then irradiated with varying doses of radiation (0, 5, or 10 Gy) decreased viability was seen compared to radiation alone [50].

Effect of curcumin on the tumor microenvironment: Inhibition of angiogenesis and metastasis

Angiogenesis, a fundamental process by which new blood vessels are formed from existing vessels, is essential in reproduction, development, and wound repair [53]. Tumor growth and metastasis are dependent upon the formation of new blood vessels to sustain growth and to allow tumor cells to enter the circulation and metastasize to distant sites [53]. Curcumin has been shown to interfere with many of the processes involved in angiogenesis [54]. Early studies demonstrated that curcumin inhibits fibroblast growth factor (FGF)-induced neovascularization [54–56]. The angiogenic ligands vascular endothelial growth factor (VEGF) and angiopoietin 1 and 2, which act in a coordinated fashion in angiogenesis, were inhibited by curcumin in Ehrlich ascites tumor (EAT) cells, and VEGF and angiopoietin 1 gene expression were inhibited in NIH3T3 cells [56]. Moreover, the same study showed that curcumin had an inhibitory effect (*in vitro*) on the angiogenic receptor kinase-insert domain receptor (KDR) on human umbilical vein endothelial cells (HUVECs) [56]. Additional effects of curcumin on angiogenesis and metastasis may be mediated by its ability to regulate cell adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (ELAM-1), cell surface proteins involved in tumor metastasis [57]. Thus, curcumin completely blocked the adhesion of monocytes to endothelial cells as well as the cell surface expression of ICAM-1, VCAM-1, and ELAM-1 [58].

Curcumin inhibits proteinases involved in extracellular matrix (ECM) remodeling [57]. The urokinase plasminogen activator system (uPA) affects the migration of endothelial cells through the regulation of several angiogenic factors, such as basic FGF, transforming growth factor (TGF), TNF, hepatocyte growth factor (HGF), and VEGF [57]. Curcumin inhibited TGF-β-mediated induction of uPA in transformed keratinocytes, resulting in a reduction in cell migration and invasiveness [59]. Curcumin also modulates matrix metalloproteinases (MMPs), which regulate endothelial cell attachment and migration [60]. In addition, curcumin was shown to inhibit cellular migration and invasion of the highly invasive SK-Hep-1 cell line of human HCC, and this effect was associated with curcumin's inhibitory action on MMP-9 secretion [61]. *In vivo*, curcumin inhibits metastases of B16F-10 melanoma cells in mice [62]; this inhibition may be due to the inhibition of metalloproteinases [63].

Curcumin as a signaling molecule

The pleiotropic activities of curcumin are likely linked to its ability to influence multiple signaling pathways (Fig. 2) as well as to its complex chemical properties (discussed in the following section). Among signaling pathways affected by curcumin are key survival pathways regulated by NF-κB and Akt, as well as cytoprotective pathways dependent on Nrf2.

Inhibition of NF-κB by curcumin

Curcumin modulates numerous targets including the transcription factor NF-κB and NF-κB-regulated gene products such as cyclo-oxygenase-2 (COX-2), cyclin D1, adhesion molecules, MMPs, inducible nitric oxide synthase, Bcl-2, Bcl-X_L and TNF [8]. NF-κB plays a critical role in signal transduction pathways involved in chronic and acute inflammatory diseases and various cancers [64–67]. The NF-κB proteins reside in the cytoplasm in an inactive state, but they are translocated to the nucleus upon activation, which requires activation of various kinases and the phosphorylation and degradation of IκB, the NF-κB cytoplasmic inhibitor [68]. Curcumin was shown to inhibit TNF-dependent NF-κB activation in human myeloid ML-1a cells [69], as well as activation induced by various other agents including phorbol ester and hydrogen peroxide. The effect of curcumin was not due to any chemical modification of NF-κB proteins. As all three inducers of NF-κB used in this study are known to produce reactive oxygen intermediates (ROI), curcumin may exert its effect by quenching of ROI [69]. Curcumin was further shown to abolish

the phosphorylation and degradation of IκB induced by TNF, indicating that the step in the signal transduction pathway of NF-κB activation inhibited by this agent coincides with or precedes the phosphorylation step of NF-κB [69]. Another study concluded that the inhibitory effect of curcumin is through the IκB/NF-κB system in intestinal epithelial cells of rat and human origin, including IEC-6, HT-29, and Caco-2 [68].

Curcumin was shown to have an anti-metastatic role through the inhibition of NF-κB in the highly invasive and metastatic breast cancer cell line MDA-MB-231 [70]. At a concentration of 25 μM, curcumin treatment reduced the viability and induced apoptosis in MDA-MB-231 cells *via* disruption of the NF-κB activation pathway as a consequence of diminished IκB and p65 phosphorylation [70]. Similar observations were reported for U937 (human myeloid leukemia) and A293 (human embryonic kidney) cells treated with curcumin [71]. The inhibition by curcumin of the transcription factors NF-κB and activator protein-1 (AP-1) resulted in concomitant reduction in MMP expression [70]. Since enhanced production of MMPs is associated with aggressive tumor growth, a higher metastatic potential, and poor clinical outcome of malignant tumors [72–75], NF-κB inhibition is likely to contribute to the chemopreventive and chemotherapeutic activity of curcumin.

Downstream of NF-κB: Inhibition of COX-2

COX-2, the inducible form of COX, predominates at inflammatory sites [76], and several lines of evidence indicate a critical role of COX-2 in tumor promotion [77–79]. For decades, it has been known that curcumin can inhibit COX activity in rat peritoneal and human platelets [80]. Furthermore, the addition of curcumin to homogenates of mouse epidermis inhibited the metabolism of arachidonic acid to 5-hydroxyeicosatetraenoic acid (5-HETE), of arachidonic acid to 8-HETE, and of arachidonic acid to prostaglandin (PG) E2, PGF2 alpha, and PGD2 [21]. COX-2 is selectively overexpressed in colon carcinogenesis [81]; moreover, pharmacological inhibition of COX-2 has been shown to protect against development of colonic tumors in mice [82, 83]. Treatment with curcumin suppressed chenodeoxycholate (CD)- or phorbol ester (PMA)-mediated induction of COX-2 protein and synthesis of PGE2 in several gastrointestinal cell lines [84]. In human colon epithelial cells, curcumin was shown to inhibit COX-2 induction by the colon tumor promoters TNF or fecapentaene-12 through the inhibition of NF-κB [85]. While nonsteroidal anti-inflammatory agents (NSAIDs) directly inhibit COX-2 activity [86], chronic administration causes serious side effects [87]. Therefore, given its long history of consumption without adverse health effects, curcumin could be an important alternative for chemoprevention of colon cancer [85].

Downstream of NF-κB: Inhibition of cyclin D1

Cyclins are the major control switches of the cell cycle, and cyclin D1, a component subunit of cyclin-dependent kinase CDK4/6, is a critical target of proliferative signals in G1 phase of the cell cycle [88]. Cyclin D1 is a proto-oncogene that is overexpressed as a result of gene amplification or translocation in many cancers [89]. Curcumin is a potent inhibitor of cyclin D1 expression through both transcriptional and post-transcriptional mechanisms [43, 89]. Curcumin targets cyclin D1 through multiple pathways, including NF-κB. Expression of cyclin D1 was down-regulated due to the suppression of NF-κB activity by curcumin, resulting in the decreased formation of the cyclin D1/Cdk4 holoenzyme complex and the subsequent suppression of proliferation and induction of apoptosis in human MM [43]. Additionally, curcumin was found to induce G0/G1 and/or G2/M phase cell cycle arrest in HUVECs along with up-regulation of CDK inhibitors (CDKIs) and slight down-regulation of cyclin B1 and cdc2 [90]. Proliferation of prostate and breast cancer cells in culture was blocked by curcumin and correlated with the down-regulated expression of cyclin D1 protein [89]. The suppression of cyclin D1 by curcumin led to inhibition of CDK4-mediated phosphorylation of retinoblastoma protein and blocked cell cycle progression from G1 to S phase [89]. Using rat hepatic stellate cells (HSCs), which are used to model chronic liver disease, the cyclin D1 gene was significantly down-regulated by curcumin treatment through the activation of peroxisome proliferator-activated receptor γ (PPARγ), which in turn inhibited HSCs proliferation [91].

Downstream of NF-κB: Suppression of Bcl-2 and Bcl-X_L

Bcl-2 and Bcl-X_L are anti-apoptotic proteins that are regulated by NF-κB [92], and suppression of these proteins is linked to apoptosis. Curcumin induces apoptosis in various cancer cell lines including acute myeloblastic leukemia (HL-60), chronic myelogenic leukemia (K-562), breast adenocarcinoma (MCF-7), cervical epithelial carcinoma [93] and (PC3) prostate cancer [94]. Curcumin induces apoptosis *via* mitochondrial pathway involving caspase-8, BID cleavage, cytochrome *c* release, and caspase-3 activation [95]. Curcumin induced apoptosis in human MM cells [43] and human mantle cell lymphoma (MCL), an aggressive B cell non-Hodgkin's lymphoma by suppressing the constitutive expression of Bcl-2 and Bcl-X_L [96].

Downstream of NF-κB: Inhibition of cytokines

Blockade of NF-κB may contribute to curcumin-dependent inhibition of cytokines and their downstream actions. Cytokines inhibited by curcumin include IL-1, -2, -6, -8, and -12 [97–100], TNF [97, 99–101], and interferon-γ (IFN-γ) [100].

Inhibition of Akt by curcumin

In addition to inhibiting NF-κB, curcumin also inhibits the pro-survival kinase Akt. Akt is a protein kinase that promotes cell survival by inhibiting apoptosis, in part through phosphorylation of Bad [102]. Akt is activated by phosphorylation [103, 104]. In human renal carcinoma cells (Caki), curcumin-induced apoptosis was associated with inhibition of Akt activity [105]. The expression and phosphorylation of Akt in Caki cells were significantly decreased in response to curcumin (75 μM) [105]. Treatment with an antioxidant, *N*-acetyl-cysteine (NAC), inhibited curcumin-induced apoptosis and prevented the release of cytochrome *c* from the mitochondria, suggesting a role for ROS in this process [105].

Effects of curcumin on tumor suppressor p53

The tumor suppressor and transcription factor, p53, is a critical regulator in many cellular processes including cell signal transduction, cellular response to DNA-damage, genomic stability, cell cycle control, and apoptosis [106]. p53, which mediates apoptosis under many stress conditions, and its downstream targets, p21waf1/cip1 and growth arrest and DNA damage-inducible gene 45, are overexpressed during curcumin-induced apoptosis in a human basal cell carcinoma [107]; and p53 and c-myc were up-regulated in a human hepatoblastoma cell line after curcumin treatment [108]. In human breast cancer cells, curcumin induced apoptosis through p53-dependent Bax induction [109, 110]. Curcumin was found to up-regulate cyclin-dependent kinase inhibitors (CDKIs), p21WAF1/CIP1, p27KIP1, and p53 in immortalized HUVECs (ECV304) [90]. In other studies, however, p53 was decreased, with a concomitant increase of the heat-shock protein 70, HSP70, after curcumin treatment in colorectal carcinoma cells [111, 112]. Curcumin caused the growth arrest and apoptosis of BKS-2 immature B cell lymphoma by down-regulation of growth and survival promoting genes (*egr*-1, c-*myc,* Bcl-X_L, and NF-κB) as well as p53 [113]. Curcumin caused cell death in a p53-independent manner in eight melanoma cell lines, four with wild-type and four with mutant p53 [114]. Therefore, the role of p53 tumor suppressor in curcumin-induced apoptosis appears to be tissue specific [114].

Induction of phase II enzymes by curcumin

In addition to inhibiting NF-κB, Akt, and other pathways important to tumor cell survival, curcumin also exerts a cytoprotective effect on non-cancer cells through the transcriptional induction of phase II enzymes. This latter effect may be critical to its chemopreventive activity. Phase II enzymes protect cells from stress by detoxifying carcinogens or reducing oxidant stress [115]. Curcumin has been shown to elevate activities of phase II enzymes such as glutathione transferases [116], NAD(P)H:quinone reductase (QR) [117], and heme oxygenase [118, 119], while inhibiting procarcinogen activating phase I enzymes, such as cytochrome P4501A1 [120]. Curcumin has been further been shown to increase levels of glutathione (GSH), an important antioxidant [121]. Low-dose exposure of curcumin led to an adaptive response, with both an immediate increase in GSH, and the ability to rapidly generate more glutathione [121]. Effects of curcumin were attributable to its ability to induce mRNA of the GSH biosynthetic genes *Gclc* and *Gclm* [121]. The effects of curcumin on phase II enzymes are due, at least in part, to its ability to alter the pool of transcription factors that bind to the electrophilic response element, (EpRE), a *cis*-acting element that mediates the transcription of cytoprotective phase II genes in response to chemopreventive agents [121, 122]. Prominent among these transcription factors regulated by curcumin is Nrf2 (NF-E2-related factor-2) [118].

Modulation of growth factors and their signaling pathways by curcumin

Curcumin is a potent inhibitor of ligand-induced activation of epidermal growth factor receptor (EGFR) [123], suggesting the potential to block the cascade of intracellular signals associated with mitogenesis and cell proliferation [123]. Curcumin exerts its effect by inhibiting the tyrosine phosphorylation of EGFR, which occurs extensively in established cancers [124]. The *erbB2*/*neu* gene-encoded $p185^{neu}$ tyrosine kinase is a potent oncoprotein that is overexpressed in about 30% of breast cancers and is associated with poor prognosis [125]. Using the human breast cancer cell line AU-565, it was observed that curcumin inhibits $p185^{neu}$ tyrosine kinase activity *in vitro* and depletes mature $p185^{neu}$ *in vivo*, which resulted in suppression of cell growth [125]. Additional growth factor pathways modulated by curcumin include TGF-β1, platelet-derived growth factor (PDGF) [126], FGFs [55], hypoxia-inducible factor (HIF)-1α [127], insulin-like growth factor (IGF) [128], and colony-stimulating factors (CSFs) [129].

Inhibition of STAT3 activation by curcumin

Signal-transducer-and-activator-of-transcription-3 (STAT3) is a member of a family of transcription factors that play major roles in cytokine signaling [130, 131]. Constitutive activation of STAT3 has been reported in many cancers, including breast cancer, prostate cancer, head and neck squamous cell carcinoma, MM, pancreatic cancer, and others [132, 133]. The role of STAT3 in tumorigenesis is mediated through effects on various anti-apoptotic genes, such as Bcl-X_L [134]. STAT3 has also been shown to induce VEGF, thereby promoting angiogenesis [135]. Due to the critical role of STAT3 in tumorigenesis, inhibitors of STAT3 have potential in both prevention and treatment of cancer [132]. Curcumin, along with several other plant polyphenols, has been shown to suppress STAT3 activation [136, 137]. Curcumin proved to be a potent inhibitor of STAT3 phosphorylation resulting in suppressed proliferation of MM cells [43]. Moreover, in comparison to AG490, probably the best-known inhibitor of STAT3 phosphorylation, a longer exposure (12 h *versus* 30 min) and higher dose (100 μM *versus* 10 μM) of AG490 was needed to suppress STAT3 phosphorylation [43]. Since constitutively active STAT3 can contribute to oncogenesis by protecting cancer cells from apoptosis, curcumin's suppression of STAT3 activation could facilitate apoptosis [43].

Effect of curcumin on mitogen-activated protein kinases

The mitogen-activated protein kinase (MAPK) signaling pathway, which uses mitogen-activated, extracellular regulated kinase (ERK)-activating kinase (MEK) and ERK isoforms, c-Jun N-terminal kinases/stress-activated protein kinases (JNKs/SAPKs), and p38 kinases, is a major pathway used in growth factor signaling to trigger proliferation and cell differentiation [138]. The SAPKs and p38 are activated most vigorously by the inflammatory cytokines, TNF-α, and IL-1α, and by a diverse array of cellular stresses, such as heat shock, UV, and ionizing radiation [139]. Using a murine model of colitis, Salh *et al.* [140] reported that a diet consisting of 0.25% curcumin was able to attenuate inflammatory activity in this experimental model of inflammatory bowel disease (IBD) through a reduction in the activity of p38 MAPK. In *in vitro* assays using human Jurkat T (leukemia) cells, MCF-7 (breast cancer) cells and human embryonic kidney 293 cells, curcumin effectively inhibited JNK activation [141]. Therefore, through inhibition of the JNK signaling module, curcumin can effectively block both AP-1 [142] and NF-κB [142, 143] signaling pathways.

Curcumin chemistry

As discussed above, curcumin is a demonstrated antitumor agent, chemopreventive [144] and antioxidant [145]. To better understand and improve these properties, considerable effort has been expended on studies of curcumin's chemistry. These include studies of its physical properties, studies to improve the bioavailability of curcumin or to prepare more effective derivatives of curcumin, and studies on the relationship between curcumin's redox and metal-binding properties and biological effects. To date, however, direct chemical connections between curcumin structure and mode of action remain incompletely understood.

Structure and pharmacology

Curcumin was first isolated by Vogel in 1842 and structurally characterized by Lampe and Milobedeska in 1910 [146]. It was synthesized and confirmed in 1913 [147]. Typical extracts of *Curcuma longa* L. contain the structures I–III, of which I is the most common [148] (Fig. 3). Reports conflict as to whether I or III is the most potent as an antioxidant and anti-tumor agent [145, 148]. Curcumin exists in its enol-tautomer form [149] (Fig. 3), and it exhibits limited solubility in water, slight solubility in MeOH, and good solubility in DMSO and chloroform [149], a property that may be responsible for its low bioavailability as described later in the clinical trials section. Curcumin possesses three protons that are ionizable in water: the enolic proton with a pKa of approximately 8.5 and two phenolic protons withe pKa of 10–10.5 (in mixed alcoholic/water solvent). Due to the low aqueous solubility of curcumin, some workers dissolve it in base for study; however, this approach does not address the alkaline decomposition of curcumin as described below.

The stability of curcumin toward chemical degradation by alkali has been investigated by several laboratories with varying results, possibly due to differences in the media used [150–153]. Tonnesen *et al.* [151] identified degradation products including ferulic acid and feruloylmethane, and studied kinetics of degradation in a MeOH/aqueous buffer medium (1:9), with phosphate buffer (pH 6–9) or carbonate buffer (pH 9–10). The rate behavior was complex showing several peaks and valleys in the 7–10 pH regime, and was second order in curcumin. Wang *et al.* [152] found that curcumin decomposed 90% within 30 min in 0.1 M phosphate buffer at pH 7.2 at 37°C, and tentatively identified the decomposition product trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal, from which they identified vanillin as a final product along with ferulic acid and feruloylmethane.

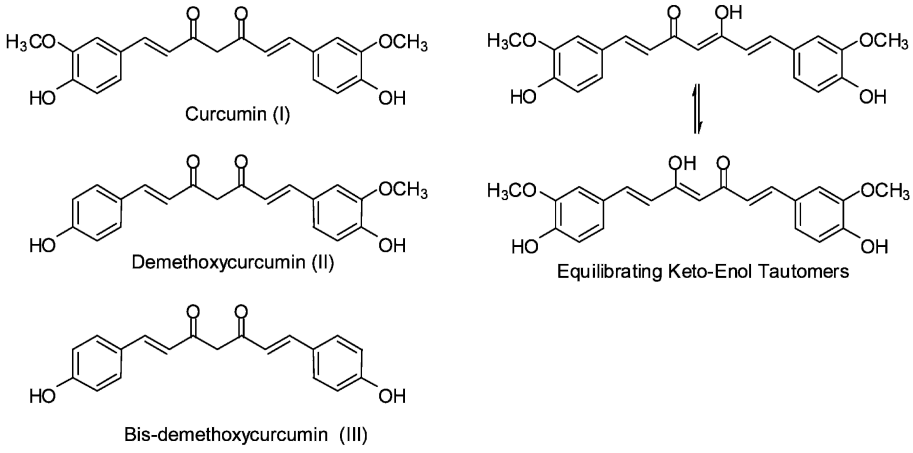

Figure 3. Curcumin I, II, III (curcumin, demethoxycurcumin, bis-demethyoxy curcumin), and keto-enol tautomers of curcumin.

Stability in cell culture medium containing 10 % fetal calf serum or in human blood was greater, but 50 % of curcumin had still decomposed after 8 h [152]. Another study found pseudo-zero-order kinetics of curcumin decomposition when working in unbuffered aqueous medium of pH 10–13.5, with a rate constant of 1.39×10^{-9} M/min [150]. A recent study showed first-order kinetics of degradation for curcumins I, II and III, where phosphate, borate, Tris and carbonate buffers were employed [153]. Curcumin III (bisdemethoxycurcumin) was the most stable, with a rate order of I > II > III. Curcumin is also photodegradable, as studied in isopropanol solution [154].

A number of studies of pharmacology and metabolites of curcumin exist [80, 155, 156]. The intestinal metabolites in human and rats have been identified as curcumin glucuronide, curcumin sulfate, tetrahydrocurcumin and hexahydrocurcumin [156]. Thus, both metabolic conjugation and reduction are observed. Traces of the aforementioned decomposition products of dihydroferulic acid and ferulic acid were found as biliary metabolites of oral curcumin administration in rats [157], which indicates that the chemical decomposition products of curcumin are present *in vivo*, and may be relevant to biological activity.

Curcumin is a lipophilic molecule and rapidly permeates cell membranes [158]. Curcumin was found to affect the structure and function of cellular membranes and mimic typical events occurring during apoptosis; however, the cellular response to curcumin contrasted with typical apoptotic cell death because loss of membrane integrity was immediate, partly reversible, and cells could recover in a relatively short time [158]. The authors suggested that membranous changes evoked by curcumin might underlie some of its effects [158, 159]. For example, by changing access to phosphatidylserine, curcumin might modulate the activity of enzymes such as protein kinase C.

Derivatization and structure-activity relationships

To overcome its limited water solubility, a number of new approaches have been explored to deliver curcumin effectively, such as liposome encapsulation [160, 161]. The group of Saladini *et al.* [162] have sought to improve solubility by modifying the structure by covalent linking of a sugar to curcumin and have studied its potential as an agent for treatment of iron-overload disease. Many investigators have considered curcumin a lead compound for the design of new chemotherapeutic agents for treatment of cancers including colon [163], prostate [164], and others [165–167]. Application of synthetic organic chemistry has yielded many derivatives of curcumin. One study of anti-angiogenic properties focused on curcumin mimics whereby the diketone group was replaced by an α, β-unsaturated ketone and the phenolic groups were unsymmetrically replaced by substituted phenyls and other aromatics [168]. Some compounds were identified as more active inhibitors of HUVEC growth and tube formation, but no relation to chemical structure was apparent.

A study of effects on phase II detoxification enzymes utilized both curcuminoids closely related to the parent plus a variety of mimics [169]. The investigators concluded that placement of a hydroxyl group at the *ortho* position of the phenolic groups and the maintenance of the diketone group in the molecule improved the potency of the molecules as phase II enzyme inducers.

Metal-binding chemistry

Among studies of metal ion complexation of curcumin, those with the cations $[VO]^{2+}$ [170, 171], Mn^{2+} [172, 173], $Fe^{2+/3+}$ [162, 167, 174, 175] and Cu^{2+} [176–179] have findings of particular biological interest. Unfortunately, the metal ion complexation reactions of curcumin and characterization of complexes is most often conducted in nonionizing solvents such as

alcohols. Studies of aqueous metal ion speciation with curcumin under controlled pH conditions are of greater relevance to the biological environment. Because the acetylacetonate ($acac^-$) ligand (region A of curcumin, Fig. 4) is known to bind all the above metal ions, and the acac complexes have some kinetic or thermodynamic stability in polar and/or protic media [180], it is reasonable to assume that the interactions of these ions with curcumin *in vivo* is biologically significant.

Iron is the metal ion whose aqueous speciation with curcumin has been studied most thoroughly [174, 175]. Surprisingly, although the speciation studies were conducted at pHs that ranged to well over 7, there was rarely mention of the decomposition of curcumin at pH >7, nor were the appropriate checks for its decomposition made. The principal conclusion of the iron speciation work is that species such as [Fe^{III} (H_2curcumin-)$(OH)_2$] are readily found at pH 7 [174, 175]. These have formation constants nearly as great as that of transferrin (log $K_f = 22.06$). This formation constant must be compared to the pKa of curcumin (here indicated as H_3curcumin), which is 8.54. The values for Fe(II) are ~12 orders of magnitude smaller than those of Fe(III). There is no doubt that curcumin is a strong chelator of iron under neutral to slightly acidic conditions, although less is known of its affinity to other biometals.

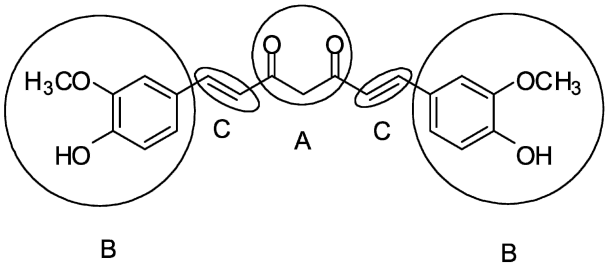

Figure 4. Nomenclature of regions of Curcumin l. (A) β-diketone or keto-enol (see Fig. 3); (B) phenolic; (C) alkene linker.

Redox chemistry

The most common chemical studies of curcumin, aside from the preparation of new derivatives, are those of its redox activity. The biological classification of curcumin as both pro- and antioxidant, depending on conditions, is well supported by studies showing it to be a free radical scavenger, a reducing agent and a DNA damage agent in the presence of Cu or Fe ions [176, 181–185]. The active site in curcumin and the mechanism underlying its antioxidant activity, however, are disputed. Most reports support a hydrogen atom transfer (HAT) mechanism and disagree on whether the hydrogen originates from the keto-enol group or the phenolic OH^- group [186–188]. In addition to this controversy, Litwinienko and Ingold [189, 190] have recently proposed that curcumin exhibits a single proton loss electron transfer (SPLET) mechanism of hydrogen donation in ionizing medium. The SPLET process involves deprotonation of the keto-enol group and electron transfer to form β-diketonyl radical, followed by proton donation from phenol. Finally, an electron migrates through the delocalized system to restore the keto-enol group and convert the phenolate to a phenoxyl radical. Thus, they assert that curcumin is a reducing agent *via* HAT in less-polar solvents, but that SPLET is the more biologically significant mode of curcumin action.

Although it is well established that curcumin is able to bind Fe, Mn and Cu as described above, there are relatively few studies of how such binding modulates the redox properties of curcumin. Studies involving the interaction of curcumin with Fe or Cu have indicated pro-oxidant effects, suggesting that the metal complexes are able to redox cycle, in analogy to the Fenton process [176, 183, 184]. Radical-scavenging effects are also noted for the Mn [172] and Cu [177] complexes of curcumin, either of hydroxyl radical or of superoxide.

Curcumin as an iron chelator *in vivo*

Consistent with its iron-binding chemistry, curcumin exhibits properties consistent with *in vivo* activity as an iron chelator [191]. Studies of the effects of curcumin on the induction of cytoprotective phase II enzymes in the mouse normal liver cell line BNL CL.2 revealed that curcumin induced ferritin L and ferritin H mRNA, as well as GSTα. Unexpectedly, however, although protein levels of GSTα rose in parallel to its mRNA, protein levels of ferritin H and L declined [191]. Ferritin is regulated by iron and is a key protein in the maintenance of intracellular iron homeostasis [192]. The disparity between ferritin mRNA and protein level suggested that curcumin may selectively inhibit the translation of ferritin mRNA [191]. Since iron chelators act as inhibitors of ferritin translation, these results also implied that curcumin may act as an iron chelator in cells. These results were supported by findings that curcumin activates iron regulatory protein and induces transferrin receptor in normal liver cells, like iron chelators [191]. Since reductions of ferritin protein were also observed in liver tissue obtained from mice that had been exposed to curcumin in the diet, curcumin also has the potential to act as an iron chelator *in vivo* [191]. This may be a consideration in the use of curcumin in the treatment of patients with marginal iron stores or those exhibiting the anemia of cancer and chronic disease.

Curcumin in human clinical trials

Curcumin is under active investigation for its clinical benefit, although clinical trials are still in relatively early phases. Promising initial results were reported in limited subsets of patients treated with curcumin for chronic anterior uveitis [193], idiopathic inflammatory orbital pseudo tumors [194], post-operative inflammation [195], external cancerous lesions [196] and pancreatic cancer [197]. Early trials emphasized safety and pharmacokinetics. While continuing to assess these aspects of curcumin's activity, current trials are also exploring efficacy. Consonant with preclinical demonstrations of curcumin's anti-inflammatory and anti-cancer properties, disease targets include neoplastic and preneoplastic diseases such as multiple myeloma, pancreatic cancer, myelodysplastic syndromes, and colon cancer [198, 199], and conditions linked to inflammation such as psoriasis, and Alzheimer's disease (Table 1).

Safety and pharmacology

Curcumin is remarkably well tolerated, but its bioavailability is poor. It does not appear to be toxic to animals [200] or humans [201] even at high doses. Cheng *et al.* [202] conducted a Phase I trial of curcumin in patients with high risk or premalignant lesions in Taiwan; 24 patients completed the study. Patients included those with resected bladder cancer, oral leukoplakia, stomach metaplasian, cervical intraepithelial neoplasm (CIN) and Bowen's disease. Curcumin was administered as a single daily oral dose ranging from 500 to 8000 mg/day for 3 months. No toxicity was observed at any dose. A planned escalation to 12 000 mg/day was not carried out since the bulky volume of the tablets was not acceptable to patients. Pharmacokinetic studies were performed in patients receiving 4000–8000 mg/day. Serum concentration peaked 1–2 h after oral intake and then gradually declined. Maximum serum concentration ranged from 0.5 ± 0.11 μM at 4000 mg/day to 1.77 ± 1.87 μM at 8000 mg/day. At lower doses, curcumin was not detectable in serum. Pharmacokinetic parameters remained the same after patients had taken curcumin for 1 month. Curcumin was not detected in the urine. Although it was not the primary objective of the study, histological examination of precancerous lesions following curcumin treatment revealed improvement in some cases, including 1 patient with bladder cancer, 2 patients with intestinal metaplasia of the stomach, 1 patient with CIN and 2 patients with Bowen's disease.

An independent dose-escalation study on 15 patients with advanced colorectal cancer was conducted in the UK [203]. Patients consumed a single daily dose of 440–2200 mg curcuma extract, equivalent to 36–180 mg curcumin, for up to 4 months. The treatment was well tolerated and there was no dose-limiting toxicity. Consistent with results reported by Cheng *et al.* [202], neither curcumin nor its metabolites were detected in the plasma, blood cells or blood lipoproteins at up to 29 days of daily treatment. Curcumin was not detected in the urine, but both curcumin and curcumin sulfate were present in feces. Stable disease was observed in 5 patients receiving 2–4 months of therapy. Blood from patients in this trial was also used to explore the utility of leukocyte COX-2 as a biomarker for curcumin; however, measurements of blood levels of PGE2, a product of COX-2, were not significantly different in subjects who did and did not consume curcumin [204].

Studies in healthy human volunteers consuming a single dose of curcumin ranging from 500 to 12 000 mg gave a similar overall picture [198]. No dose-limiting toxicities were observed, and low levels of curcumin were only detected in the serum receiving the highest doses of curcumin (10 000 or 12 000 mg/day). Interestingly, curcumin was only detected in 2 of these 6 patients, perhaps indicating the existence of genetic modifiers of curcumin metabolism. These authors also discovered a greater than twofold variation in the curcumin content of different preparations of commercially procured curcumin, which may partially account for low serum levels despite apparently high consumption.

This points to one of the difficulties associated with interpreting the literature on curcumin, which is the infrequency with which curcumin content is measured and reported. Curcumin is particularly abundant in *Curcuma longa* (3.9–12.3 %), but curcumin and curcuminoids have also been isolated from a variety of other plant species, including *Curcuma aromatica* (0.11 %), and *Curcuma phaeocalis* (0.89 %) [205]. Curcumin content varies among the many commercially available blends of turmeric and curry powders [206]. For example, one study estimated the percentage of curcumin to be between 1.06 % and 5.70 % in four different "commercially available" turmeric samples [207]. Pure turmeric was found to have the highest concentration of curcumin with an average of 3.14 % by weight, while curry powders contained relatively low amounts of curcumin (for comprehensive listing of curcumin content, refer to [206]). In addition, curcumin itself exists in several forms (Fig. 3) that exhibit different potencies as antioxidants and anti-tumor agents [145, 148]. Thus, the actual amount of curcumin used in various studies is often unclear.

Curcumin has also been measured in human tissue, *e.g.*, in the liver and portal blood of 12 patients

Table 1. Clinical trials of curcumin.

Trial	Status of trial	Site	Disease target	Objective	Clinical Trials.gov Identifier* or reference
Curcumin with or without bioperine	Ongoing	MD Anderson, USA	Multiple myeloma	Tolerance and safety of curcumin vs curcumin plus bioperine	NCT00113841
Pharmacokinetics of curcumin in healthy volunteers	Ongoing	MGH, USA	None	Curcumin pharmacology with piperine or silybin	NCT00181662
Gemcitabine with curcumin for pancreatic cancer	Ongoing	Rambam Medical Center Haifa Israel	Pancreatic cancer	Clinical benefit of gemcitabine plus curcumin in pancreatic cancer, Phase II trial	NCT00192842
Trial of curcumin in advanced pancreatic cancer	Ongoing	MD Anderson, USA	Pancreatic cancer	Response rate and pharmacokinetics in pancreatic cancer, Phase II trial	NCT00094445
Efficacy of coenzyme Q10 and curcumin in patients with MDS	Not yet open	Hadassah Medical Organization, Jerusalem Israel	Myelodysplasia	Hematological improvement in patients with MDS	NCT00247026
Curcumin in patients with mild to moderate Alzheimer's disease	Ongoing	UCLA Medical Center, USA	Alzheimer's disease	Safety, biodistribution, efficacy	NCT00099710
Phase III trial of gemcitabine, curcumin and celebrex in patients with metastatic colon cancer	Not yet open	Tel-Aviv Sourasky Medical Center, Israel	Colon cancer	Efficacy (time to progression) Phase III	NCT00295035
Curcumin in preventing colon cancer in smokers with ACF	Ongoing	Multicenter, USA (Meyskens PI)	Colon cancer	Prevention-change in prostaglandin E2 in ACF	NCT00365209
Use of curcumin in the lower GI tract in familial adenomatous polyposis patients	Ongoing	Johns Hopkins, USA	Colon cancer	Regression of colorectal adenomatous polyps in patients with familial adenomatous polyposis	NCT00248053
Curcumin for the chemoprevention of colorectal cancer	Ongoing	University of Pennsylvania, USA	Colon cancer	Prevention- effect on cell proliferation, apoptosis and COX2 in the colonic mucosa of patients with sporadic adenomatous polyps	NCT00118989
Curcuminoids for the treatment of chronic psoriasis vulgaris	Ongoing	University of Pennsylvania, USA	Psoriasis	Safety, efficacy	NCT00235625

Table 1 *(Continued)*

Trial	Status of trial	Site	Disease target	Objective	Clinical Trials.gov Identifier* or reference
Effects of curcuminoids on ACF in the human colon	Ongoing	University of Medicine and Dentistry New Jersey USA	Colon	Prevention-effect of curcumin or sulindac on number of ACF in colon	NCT00176618
Pilot study of curcumin and ginkgo for treating Alzheimer's disease	Closed	Chinese University of Hong Kong	Alzheimer's disease	Effect on isoprostanes, amyloid beta protein, cognitive function	NCT00164749
Curcumin for the prevention of colon cancer	Closed (completed)	University of Michigan	None	Pharmacokinetics, MTD, Phase I trial in healthy subjects	NCT00027495;[198]
Sulindac and plant compounds in preventing colon cancer	Closed (suspended)	Rockefeller University	Colon cancer	Prevention-effect of curcumin on biomarkers of colon epithelial cell turnover	NCT00003365
Phase I trial in patients with pre-malignant lesions	Completed	National Taiwan University college of Medicine	Various	Pharmacokinetics and MTD	[166]
Phase I trial: biomarkers	Completed	University of Leicester and University of Liverpool, UK	Colorectal cancer	Pharmacokinetics, MTD, biomarkers	[163]
Phase III trial of gemcitabine, curcumin and celebrex in patients with advance or inoperable pancreatic cancer	Ongoing	Tel-Aviv Sourasky Medical Center, Israel	Pancreatic cancer	Clinical benefit of gemcitabine plus curcumin and Celebrex in pancreatic cancer, Phase III	NCT00486460
Bio-availability of a new liquid tumeric extract	Not yet open	Hadassah Medical Organization, Jerusalem, Israel	Healthy	Pharmacokinetics	NCT00542711
Epilepsy	?	AIIMS, Delhi, India	Epilepsy	Phase 1	Charak International, India www/charakainternational.com/ pdfs/clinic_trial.pdf
Advanced HNSCC	?	Himalayan Institute of Medical Sciences	Advanced HNSCC	Phase II (1-8 g/ day; 56 d)	Charak International, India www/charakainternational.com/ pdfs/clinic_trial.pdf
HNSCC	?	AIIMS, Delhi, India	HNSCC	Phase II/III DBRPC (3.6 g/day, bid)	Charak International, India www/charakainternational.com/ pdfs/clinic_trial.pdf
Cervical cancer (Stage IIb, IIIb)	?	AIIMS, Delhi, India	Cervical cancer	Phase II/III DBRPC (2 g/day, bid, 1 year)	Charak International, India www/charakainternational.com/ pdfs/clinic_trial.pdf
Oral premalignant lesions	?	Tata Memorial Cancer Ctr, India	Oral cancer	Phase II/III DBRPC (4 g/day, bidx 28 d)	Charak International, India www/charakainternational.com/ pdfs/clinic_trial.pdf
Oral premalignant lesions	?	Amrita Institute, Kochi, India	Oral cancer	Phase II/III DBRPC (3.6 g/ day, bid)	Charak International, India www/charakainternational.com/ pdfs/clinic_trial.pdf
Oral leukoplakia	?	Regional cancer center, Thriven, India	Oral leukoplakia	Phase II (curcumin gel, 3x/day, 6 months)	Charak International, India www/charakainternational.com/ pdfs/clinic_trial.pdf
Gall bladder cancer	?	BHU, India	Gall bladder cancer	Phase II (2–8 g/ day)	Charak International, India www/charakainternational.com/ pdfs/clinic_trial.pdf

Table 1 *(Continued)*

Trial	Status of trial	Site	Disease target	Objective	Clinical Trials.gov Identifier* or reference
Pancreatic cancer	Ongoing	Kyoto University, Japan	Pancreatic cancer	Phase II (8 g/day)	[228]
Primary sclerosing cholangitis	Ongoing	Amsterdam Medical Center, The Netherlands	Primary sclerosing cholangitis	Phase I (8 g/day)	[228]
Ulcerative colitis	Ongoing	Amsterdam Medical Center, The Netherlands	Ulcerative colitis	Phase I (8 g/day)	[228]
Barretts Metaplasia	Ongoing	Amsterdam Medical Center, The Netherlands	Barretts Metaplasia	Phase I (8 g/day)	[228]
Monoclonal gammopathy of unknown significance (MGUS)	Ongoing	St. George Hospital, Australia	MGUS	Phase I (3.4 g/day)	[228]

*source: www.clinicaltrials.gov
ACF, aberrant crypt foci; GI, gastrointestinal; MDS, myelodysplastic syndromes.

undergoing resection of hepatic metastases of colorectal cancer who took 450–3600 mg curcumin daily for 1 week prior to surgery [208]. Low nanomolar levels of curcumin and its metabolites, curcumin glucuronide and curcumin sulfate, were detected in portal serum of all 3 patients who received 3600 mg of curcumin. Metabolic reduction products of curcumin (hexahydrocurcumin and hexahydrocurcuminol) were found in the liver of 1 patient. The authors concluded that the bioavailability of curcumin is poor in tissues remote from the gastrointestinal tract, including the liver.

What's wrong with this picture?

Given these and other [155, 156] demonstrations of curcumin's limited bioavailability, one would expect that curcumin would have a spectrum of activity primarily limited to the gastrointestinal tract. However, this is clearly not the case.

Curcumin exerts a number of effects at sites distal from the gastrointestinal tract at doses less than or equivalent to the 12 g/day maximum dose administered in Phase I human clinical trials (to enable rough comparisons, we calculate that 12 g/day is approximately equivalent to 2% curcumin when administered in the diet (12 g/500 g diet); when administered by weight, it is approximately equivalent to 200 mg/kg body weight). For example, immunomodulatory effects of curcumin (*e.g.*, release of ROS [13] and eicosinoids [209] from peritoneal macrophages, antibody response) were observed following treatment with 40 mg/kg curcumin in the diet [210] or by 30 mg/kg introduced by gavage [13, 209]. Dietary curcumin at 160 ppm also lowered oxidized proteins and IL-1β in the brains of a transgenic mouse model of Alzheimer's disease [211]. Oral curcumin, 10–40 mg/kg, attenuated allergen-induced airway hyperresponsiveness in guinea pigs [212], and 200 mg/kg curcumin protected against acute liver damage induced by carbon tetrachloride [213] by blocking NF-κB activation and release of inflammatory cytokines. Diethylnitrosamine-induced hepatocarcinogenesis was inhibited by 0.2% dietary curcumin [214]. Consumption of 0.2% curcumin in the mouse diet exerted a genoprotective effect against DNA damage induced by high concentrations of copper [215]. Dietary curcumin (0.2%) also significantly countered the hypercholesterolemia brought about by high cholesterol feeding. Curcumin lowered hepatic and blood lipid peroxides in hypercholesterolemic rats [216]. In male Wistar rats, curcumin (200 mg/kg/day orally) significantly attenuated the gentamicin-mediated increase in urinary protein and glucose, BUN (blood urea), serum creatinine and decrease in creatinine clearance as well as the activity of γ-glutamyl transferase [217]. Furthermore, data from this study indicated that curcumin reduced malondialdehyde (MDA) and lipid hydroperoxide (LOOH) formation in plasma and kidney induced by gentamicin, indicating the renoprotective effect of this compound against oxidative damage to these membranes [217]. In humans, a single oral dose of 20 mg curcumin induced contraction of the gall bladder as assessed by ultrasound scanning in human volunteers [218].

This partial list of studies performed in many different laboratories that have examined a variety of experimental pathologies and endpoints in tissues, including immune cells, brain, lung, liver, kidney, gall bladder and blood, suggests that curcumin has substantial biological effects outside the GI tract despite its

relatively poor bioavailability. Whether these are attributable to rare but potent metabolites, retention and concentration of this lipophilic molecule in membranes, local environmental factors that potentiate curcumin's effects, or other factors, remains unknown. The disparity between bioavailability and efficacy is a topic that merits investigation, particularly since clinical trials targeting some of these sites have been initiated.

Cautionary tales

Although it is clear that curcumin has a wide variety of beneficial activities, not all studies are consistent with this rosy picture. Indeed, several studies have suggested that in selected settings, curcumin may not only be ineffective, but may have adverse activities. For example, in chemical studies, curcumin induced DNA fragmentation and base damage in the presence of copper and isozymes of cytochrome p450 (CYP) that are present in lung, lymph, liver, and skin [219]. The authors hypothesized that the damage was the result of CYP-catalyzed *O*-demethylation of curcumin, leading to the formation of an *O*-demethyl curcumin radical, which, in the presence of copper, formed a DNA-damaging Cu(I)-hydroperoxo complex. DNA damage was attenuated when concentrations of curcumin exceeded those of copper, presumably due to the chelation of copper by curcumin [219]. Copper-dependent formation of 8-hydroxy-deoxyguanosine in response to curcumin was also reported by Yoshino *et al.* [220]; they further linked the appearance of DNA damage to apoptotic cell death. Strasser *et al.* [221] observed that exposure of U937 cells to curcumin led to a time- and dose-dependent increase in ROS. Although the increase in ROS was transient, presumably because of a subsequent elevation in glutathione, cell viability was nevertheless decreased. Similarly, curcumin-mediated DNA damage was reported in mouse lymphocytes using a comet assay [222]. In contrast to these studies, Polasa *et al.* [223] reported that curcumin inhibited B(a)P-induced strand breaks in human peripheral blood lymphocytes. The reason for the discrepancy among these studies is unclear; however, since curcumin exhibits a temporal change from pro- to anti-oxidant [221], it is likely that timing of sample collection may strongly influence conclusions.

Findings of curcumin-induced DNA damage *in vitro* have been corroborated by measures of DNA damage *in vivo*. Long-Evans Cinnamon (LEC) rats, a strain that accumulates copper in the liver, were given 0.5 % curcumin in the diet, and DNA damage in the liver measured. A 9–25-fold increase in etheno-DNA adducts (a species proposed to play a causal role in initiation and progression of liver cancer) was observed in nuclear DNA [224]. Consistent with these findings, curcumin did not protect LEC rats from spontaneous tumor formation in the liver, and in fact shortened median life span [224, 225]. Curcumin has also been reported to inhibit p53 function in colon cancer cells by disrupting the conformation of p53 required for its DNA binding and transactivation activity [226]. Since p53 is a critical protein in the protection against genotoxic stress, curcumin-mediated inactivation of this pathway may also contribute to the accumulation of tumor-inducing DNA damage. In addition to its potential to induce DNA damage, curcumin may also inhibit the activity of chemotherapeutic agents. Thus, curcumin inhibited camptothecin-induced death of cultured breast cancer cells, and attenuated cyclophosphamide-induced breast tumor regression in nude mice [227]. The authors of this study recommended that breast cancer patients receiving cytotoxic chemotherapy be excluded from curcumin-based chemoprevention trials.

These studies are useful reminders that the many desirable medicinal effects of curcumin should not obscure the need for caution until the data have been fully assessed. Given the enthusiasm for this natural compound and the number of ongoing clinical trials, such data should be available in the near future.

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