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# Multiple Molecular Targets in Cancer Chemoprevention by Curcumin

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Rajesh L. Thangapazham,[1,2] Anuj Sharma,[1,2] and Radha K. Maheshwari[1]

[1]Department of Pathology, Uniformed Services University of the Health Sciences, Bethesda, MD
[2]Birla Institute of Technology and Science, Pilani 333031, India

## ABSTRACT

Carcinogenesis encompasses 3 closely associated stages: initiation, progression, and promotion. Phytochemicals are nonnutritive components of plants that are currently being studied in chemoprevention of various diseases for their pleiotropic effects and nontoxicity. Cancer chemoprevention involves the use of either natural or synthetic chemicals to prevent the initiation, promotion, or progression of cancer. Curcumin is the active constituent of turmeric, which is widely used as a spice in Indian cooking. It has been shown to possess anti-inflammatory, antioxidant, and antitumor properties. Curcumin has also been shown to be beneficial in all 3 stages of carcinogenesis. Much of its beneficial effect is found to be due to its inhibition of the transcription factor nuclear factor kappa B (NF-kappaB) and subsequent inhibition of proinflammatory pathways. This review summarizes the inhibition of NF-kappaB by curcumin and describes the recently identified molecular targets of curcumin. It is hoped that continued research will lead to development of curcumin as an anticancer agent.

**KEYWORDS:** Curcumin, NF-kappaB, Nrf2, β-catenin

## INTRODUCTION

Cancer results from a multistage carcinogenesis process that involves 3 distinguishable but closely connected stages: initiation (normal cell → transformed or initiated cell), promotion (initiated cell → preneoplastic cell), and progression (preneoplastic cell → neoplastic cell).[1] Initiation is a result of rather rapid and irreparable assault to the cell. The attack may be due to the initial uptake of a carcinogen and the subsequent stable genotoxic damage caused by its metabolic activation.[2] Other causes of cancer initiation include oxidative stress,[3] chronic inflammation,[3] and hormonal imbalance.[4] The transformed cells undergo many changes to form preneoplastic cells; this promotion process is not as rapid as initiation. Deregulated signal transduction pathways such as the serine threonine kinase, Akt kinase/protein kinase B (Akt[PKB]), activator protein 1 (AP-1), nuclear factor kappa B (NF-kappa B), mitogen-activated protein kinase (MAPK), androgen receptor, estrogen receptor, and Raf/Ras pathways also contribute to carcinogenesis. Inflammation acts as a key regulator in promotion of these initiated cells, possibly by providing them with proliferating signals and by preventing apoptosis.[5] Noninflammatory factors such as hypoxia also regulate carcinogenesis. Hypoxia induces vascular endothelial growth factor (VEGF) in tumor cells and induces matrix metalloproteinase (MMP) expression in endothelial cells, leading to angiogenesis and tumor cell invasion.[6] The role of inflammation in tumor induction and subsequent malignant progression has been well reviewed.[7] Inflammatory responses also produce cytokines, which may be growth and/or angiogenic factors leading transformed cells to proliferate and undergo promotion. Leukocytes produce cytokines, angiogenic factors as well as matrix-degrading proteases that allow the tumor cells to proliferate, invade, and metastasize. Moreover, tumor-infiltrating lymphocytes secrete matrix-degrading proteinases like MMP-9, thereby promoting neoplastic proliferation, angiogenesis, and invasion.[8] These details suggest the role of inflammation in all 3 stages of carcinogenesis. Substantial evidence for the role of inflammation in cancer can be understood by the frequent upregulation of inflammation mediators like NF-kappaB. The pathways activated by NF-kappaB upregulation are implicated not only in tumor growth and progression but also in cancer cell development of resistance to anticancer drugs, radiation, and death cytokines. NF-kappaB is an excellent target for anticancer therapy.[9]

Chemoprevention is the use of a chemical substance of either natural or synthetic origin to prevent, hamper, arrest, or reverse a disease. The term *chemoprevention* was coined by Michael Sporn in the mid-1970s. His work on retinoids against chemical carcinogenesis[10] showed the time that cancer takes to develop in humans through the initiation, promotion, and progression stages. Phytochemicals are bioactive nonnutrient components of various plant parts, such as seeds, leaves, and rhizomes. Recent epidemiological and preclinical testing has revealed the great potential of phytochemicals in combating cancer and other chronic

**Corresponding Author:** Radha K. Maheshwari, Department of Pathology, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814. Tel: (301) 295-3394; Fax: (301) 295-1640; E-mail: rmaheshwari@usuhs.mil

diseases that result from oxidative stress induced by free radicals.[11] Epidemiological studies indicating a low incidence of large and small bowel adenomas in East Indians and the striking increase in bowel cancer in immigrants to Western countries suggest the protective role of natural antioxidants such as curcumin in Indian cooking.[12] Curcumin (diferuloylmethane) (Figure 1), a major active component of turmeric (Curcuma longa Linn), is a crystalline compound that has been traditionally used in medicine and cooking in India.[13] Preclinical studies have revealed the chemopreventive potential of curcumin in several different animal tumor bioassay systems, including colon,[14,15] duodenal,[16] stomach,[17] prostate,[18] and breast[19] carcinogenesis, both in vitro and in vivo. The absence of dose-limiting toxicity, even when curcumin is administered up to 8 g/day in human clinical trials, reveals the possibility of using curcumin in the prevention and treatment of cancer.[20,21] In this review, we describe the molecular targets of cancer that are modulated by curcumin as a consequence of its effect on NF-kappaB and other prominent transcription factors.

## Curcumin Blocks Tumor Initiation

One of the methods by which inflammation paves the way for tumor initiation is the production of reactive oxygen species (ROS) and reactive nitrogen species by activated neutrophils and macrophages, leading to lethal cancer-causing mutations in epithelial cells.[22] Curcumin inhibits the induction of nitric oxide synthase in activated macrophages and has been shown to be a potent scavenger of free radicals like nitric oxide.[23] In RAW 264.7 macrophages activated with lipopolysaccharide and the interferon-gamma system, curcumin treatment showed antitumorigenic potential by significantly reducing the levels of inducible nitric oxide synthase (iNOS).[24] NF-kappaB has been implicated in the induction of iNOS, which causes oxidative stress, one of the causes of tumor initiation. Curcumin prevents phosphorylation and degradation of inhibitor kappaBalpha, thereby blocking NF-kappaB activation, which results in downregulation of iNOS gene transcription.[25]

Antigens present in early neoplastic lesions can trigger an adaptive immune response. A deregulated balance between adaptive and innate immunity results in chronic inflammation, which is well associated with epithelial tumorigenesis, the prominent mechanism being NF-kappaB activation.[26] Curcumin was found to inhibit cell proliferation and cytokine production by inhibiting NF-kappaB target genes involved in the mitogen induction of T-cell proliferation, interleukin-2 production, and nitric oxide generation.[27] Radiation-induced overexpression of cytokines such as interleukin-10 (IL-10), IL-6, and IL-18 was accompanied by NF-kappaB induction, which was controlled and inhibited in a dose-dependent manner by curcumin in keratinocytes.[28]

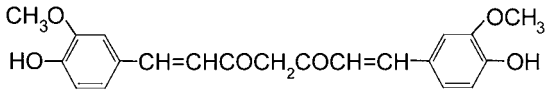


**Figure 1.** Chemical structure of curcumin (diferuloylmethane).

Carcinogens from dietary and environmental sources are subjected to metabolism. Microsomal phase I enzymes primarily oxidize, reduce, or hydrolyze the substrate to a more polar product. The product of the phase I reaction can be either excreted or activated into toxic metabolite. The toxic metabolite is conjugated to substrates in the diet by phase II conjugating enzymes such as sulfotransferase and glutathione-s-transferase and then excreted. Dietary factors like chlorogenic acid have also been found to protect against environmental carcinogen–induced carcinogenesis by their upregulation of phase II conjugating enzymes and suppression of ROS-mediated NF-kappaB, AP-1, and MAPK activation.[29] Curcumin has been found to increase expression of conjugation enzymes and has been shown to be one of the most potent inhibitors of NF-kappaB, thereby exerting anti-inflammatory effects.[30] When unmodified, carcinogens can form a covalent adduct with DNA, resulting in DNA damage. Irreparable damage leads to mutations in critical genes involved in growth, proliferation, and apoptosis, resulting in initiation and subsequent development of cancer. By modulating cytochrome P450 function, curcumin reduces the aflatoxin B1-DNA adduct formation, thereby showing its potential to inhibit chemical carcinogenesis.[31] Dietary supplementation of curcumin induced phase II detoxifying enzymes, suggesting that curcumin has chemopreventive efficacy in inhibiting chemical carcinogenesis and other forms of electrophilic toxicity.[32] A recently published study showed the protective effect of curcumin against a well-known renal carcinogen, ferric nitrilotriacetate, which generates ROS in vivo. Curcumin counteracted the ROS by increasing ornithine decarboxylase, glutathione, antioxidant enzymes, and phase II metabolizing enzymes and therefore protected the kidney from oxidative damage.[33] Curcumin was found to be a superior chemopreventive agent in both initiation and postinitiation stages of 4-nitroquinoline 1-oxide–induced oral carcinogenesis when compared with beta-carotene and hesperidin.[34] Heme oxygenase-1 (HO-1), the rate-limiting enzyme of heme catabolism, has been found to counteract oxidative stress,[35] modulate apoptosis, and inhibit proliferation in rat and human breast cancer cells.[36] Curcumin has been found to induce HO-1 expression by signaling through (NF-E2)-related factor 2 (Nrf-2) and NF-kappaB and thereby has the potential to reduce oxidative stress.[37,38] Nrf2 is a transcription factor that regulates the expression of conjugating enzymes like glutathione S-transferase (GST) via an

antioxidant response element (ARE).[39] Nrf2 activity is regulated by Nrf2's sequestration in the cytoplasm by the kelch-domain-containing protein Keap1 (Kelch-like ECH-associated protein 1). Keap1 releases Nrf2 in the presence of oxidants and chemoprotective agents, thereby leading to the activation of ARE and the expression of phase II enzymes.[40] In renal epithelial cells, curcumin has been shown to promote dislodging of Nrf2 from Nrf2-Keap1 complex, leading to increased Nrf2 binding to the resident HO-1 AREs, resulting in upregulation of HO-1 expression.[38] Curcumin prevents initiation of tumors either by curtailing the proinflammatory pathways or by inducing phase II enzymes (Figure 2).

## Curcumin Suppresses Tumor Proliferation and Progression

The activated NF-kappaB signaling pathway plays a major role in tumorigenesis. Experimental evidence has suggested that NF-kappaB has an important role in not just cancer initiation but cancer promotion and progression. The key protein NF-kappaB binds to DNA and results in transcription of genes that contribute to tumorigenesis, such as inflammatory, antiapoptotic, and positive regulators of cell proliferation and angiogenesis.[41] Activation of NF-kappaB occurs mainly via I-kappaB kinase (IKK)–mediated phosphorylation of inhibitory molecules.[42] Reduced production of tumor-promoting paracrine factors was found to be involved in decreased tumor growth in IKK beta deleted myeloid cells.[43] Curcumin blocks the NF-kappaB signaling and inhibits IKK activation, thereby suppressing proliferation of head and neck squamous cell carcinoma.[44] In addition to suppressing various cell survival and cell proliferative genes, including Bcl-2, cyclin D1, IL-6, cyclooxygenase-2 (COX-2), and MMP-9, curcumin induced apoptosis, as pointed out by caspase activation and poly(ADP-ribose) polymerase (PARP) cleavage.[44]

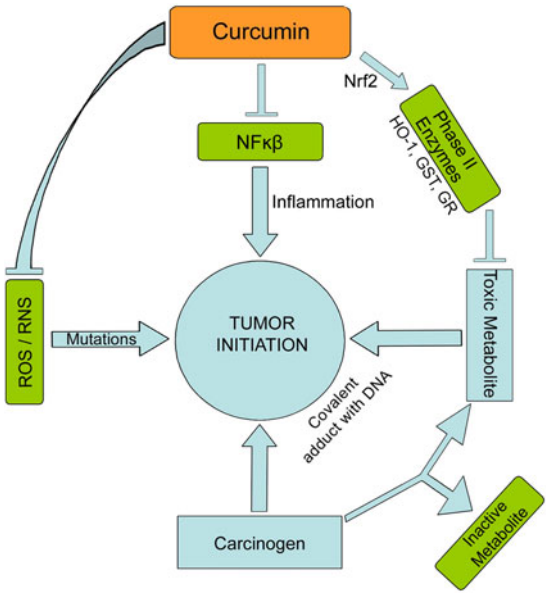


**Figure 2.** Schematic representation of chemopreventive targets of curcumin in inhibiting tumor initiation. ROS indicates reactive oxygen species; RNS, reactive nitrogen species; NFκB, nuclear factor kappa B; Nrf2, (NF-E2)-related factor 2; HO-1, heme oxygenase-1; GST, glutathione S-transferase; GR, glutathione reductase.

Biphasic changes in the regulation of NF-kappaB with curcumin resulted in apoptosis of hepatic cancer cells via activation of caspase 3 and 9, decreasing Bcl-X(L) messenger RNA (mRNA) and increasing Bcl-X(S) and c-IAP-2 mRNAs.[45] Overexpression of cyclin D1 is a characteristic feature of human mantle cell lymphoma (MCL), an aggressive B cell non-Hodgkin's lymphoma. Curcumin effectively inhibits the survival and proliferation of MCL by inducing cell cycle arrest and initiating apoptosis by downregulating NF-kappaB.[46] COX-2, the inducible form of cyclooxygenase that catalyzes the rate-limiting step in prostaglandin synthesis from arachidonic acid, plays an important role in cancer. Several lines of evidence indicate the critical role of COX-2 in carcinogenesis as a well-established tumor promoter.[47,48] Overexpression of COX-2 leads to malignant cell proliferation and invasion, and this effect is reversed by nonsteroidal anti-inflammatory agents, elucidating the importance of COX-2 inhibitors in cancer chemoprevention.[49] It has been suggested that COX-2 induction is mediated by the NF-kappaB intracellular signaling pathway.[50] Curcumin has been shown to decrease the proliferation of various cancer cells of the colon, the blood, the submandibular gland, and the liver[45,51,52] by downregulating COX-2. Curcumin inhibits COX-2 but not COX-1 in colon cancer cells; hence, side effects attributed to nonselective COX inhibitors can be alleviated.[53] Curcumin has been shown to inhibit COX-2 expression by repressing degradation of the inhibitory unit I-kappaB alpha and hindering the nuclear translocation of the functionally active subunit of NF-kappaB, thereby blocking improper NF-kappa B activation.[54]

Apart from causing cancer cell death, curcumin has been found to reduce the invasion and subsequent metastasis of cancer cells. Curcumin suppressed the MMP expression and curtailed the 12-O-tetradecanoylphorbol-13-acetate (TPA)–induced invasiveness of breast cancer cells. Moreover, curcumin blocked the TPA-induced activation of extracellular signal-regulated protein kinase and the transcriptional activity of NF-kappaB.[55] MMP's expression is believed to play a major role in mediating neovascularization and is significantly increased during tumor progression. MMPs are important to endothelial cell migration and tube formation, 2 determinants of neovascularization that help in the process of forming new capillaries from preexisting blood vessels. MMPs, especially MMP-2 and MMP-9, are known to

be involved in tumor angiogenesis, mainly through their matrix-degrading capacity.[56] MMP-9 is also implicated in the growth and invasiveness of brain tumors. Curcumin downregulates MMP-9 expression by inhibiting NF-kappaB and AP-1 binding to the DNA promoter region.[57] Curcumin also inhibits paclitaxel-induced COX-2 and MMP-9 expression.[58] The paclitaxel-induced NF-kappaB pathway is effectively counteracted and inhibited by curcumin in breast cancer cells, and lung metastasis of human breast cancer in nude mice is inhibited in this way.[58] Adhesion molecules such as vascular cell adhesion molecules (VCAM) are implicated in cancer progression, and they are elevated in patients with advanced disease, making them markers of prognostic significance.[59] In human tracheal smooth muscle cells, curcumin treatment resulted in significant inhibition of tumor necrosis factor-alpha (TNF-alpha)–induced VCAM-1 expression, which is related to the activation of the MAPK NF-kappaB pathway.[60] Curcumin also inhibited the proliferation of androgen-independent prostate cancer Du-145 and PC-3 cells by inducing p21 (WAF1/CIP1) as well as inhibiting both constitutive and TNF-alpha-induced NF-kappaB activation in a time-dependent manner.[61] Curcumin has been shown to reduce cell migration and invasion induced by osteopontin (OPN), an extracellular matrix protein, through the NF-kappaB pathway.[62] OPN's viability as a target candidate for cancer treatment was further confirmed by the association between high OPN expression and poor survival of patients with non–small cell lung cancer therapy.[63] Curcumin inhibits OPN-induced MT1-MMP gene expression by blocking signals leading to IKK activation.[62] Elevated expression of proangiogenic cytokines like VEGF and IL-8 is observed in aggressive tumor growth and decreased survival of patients with breast cancer.[64] Curcumin blocked the NF-kappaB activation induced by glutamine deprivation, which leads to the expression of proangiogenic and prometastatic factors like VEGF and IL-8 by breast carcinoma cells.[65] Curcumin also inhibited pancreatic cancer cell growth and viability by downregulating IL-1 expression, which was correlated with NF-kappaB activation, cell growth activity, and inhibition of IL-8–induced receptor internalization.[66] We have reported that curcumin treatment resulted in inhibition of growth, angiogenic differentiation of human umbilical vein endothelial cells on Matrigel and endothelial cell infiltration, and vessel formation in Matrigel plug, indicating antiangiogenic activity.[67,68] Hence, curcumin curtails cancer progression by either blocking its growth or inhibiting its invasive and aggressive potential. Most of the effects in either case are exerted by curcumin-induced NF-kappaB inhibition.

One of the novel molecular targets of curcumin's chemopreventive action is β-catenin. β-catenin/T-cell factor (TCF)/lymphoid enhancer factor (LEF) signaling is disrupted in many cancer cells, such as those of colorectal cancer, hepatocellular carcinoma, and gastric carcinoma.[69-71] Dysregulated β-catenin/TCF is implicated in cancer progression and poor prognosis. β-catenin in the cytoplasmic pool is phosphorylated by the Axin–adenomatous polyposis coli–glycogen synthase kinase 3β complex and subjected to degradation by the ubiquitin-proteasome pathway.[72] Nondegraded β-catenin either enters the nucleus to transactivate the TCF/LEF transcription factor, leading to upregulation of many genes responsible for cell proliferation, or binds to the E-cadherin adhesion complex. Reduction or loss of E-cadherin and/or increased localization of catenin in the nucleus is associated with invasive metastatic cancer progression and poor prognosis.[73,74] Curcumin has been found to decrease nuclear β-catenin and TCF-4 and hence inhibit β-catenin/TCF signaling in various cancer cell lines.[75] Curcumin

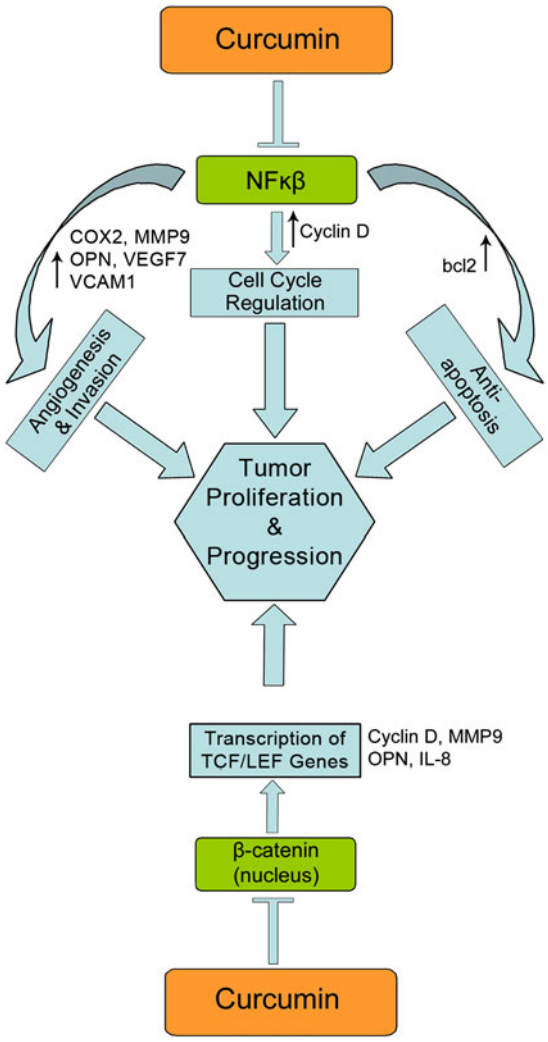


**Figure 3.** Schematic representation of chemopreventive targets of curcumin in curtailing tumor proliferation and progression. COX indicates cyclooxygenase; MMP, matrix metalloproteinase; OPN, osteopontin; VEGF, vascular endothelial growth factor; VCAM, vascular cell adhesion molecules; NFκB, nuclear factor kappa B; TCF/LEF, T-cell factor/lymphoid enhancer factor; IL, interleukin.

induced G(2)/M phase arrest and apoptosis in colon cancer cells by impairing Wnt signaling and decreasing transactivation of β-catenin/TCF/LEF,[76] subsequently attenuating tumor progression. The antitumor effect of curcumin was evidenced by its ability to decrease intestinal tumors in an animal model of familial adenomatous polyposis by reducing the expression of the oncoprotein β-catenin.[77] Some human β-catenin/TCF target genes—including cyclin D, MMP 7, OPN, IL-8, and matrilysin—play a role in tumor promotion and progression.[78] NF-kappaB repression and decreased β-catenin signaling are some of the mechanisms by which curcumin suppresses the promotion and progression of cancer (Figure 3).

## CONCLUSION

The chemopreventive potential of curcumin has been studied for the past few decades, with encouraging outcomes. Curcumin's chemopreventive efficacy in almost all stages of carcinogenesis has received even more attention because of curcumin's nontoxic nature. As NF-kappaB activation has been implicated in all the stages of carcinogenesis, it has been studied as a major intervention target of various chemopreventives, including curcumin. Curcumin has been found to suppress NF-kappaB activation providing beneficial effect by killing and preventing tumor growth as well as inhibiting metastatic progression. The effect of curcumin on other molecular targets, such as the Nrf-2 and β-catenin pathways, has also been discussed to a limited extent. Although preclinical studies in animal and cell cultures have established the chemopreventive potential of curcumin, solid evidence compiled from epidemiological studies and results of clinical trials will be needed to spur the development of curcumin as cancer preventive and therapeutic.

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