

REVIEW

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Curcuma Contra Cancer? Curcumin and Hodgkin's Lymphoma

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Abstract: Curcumin, a phytochemical isolated from curcuma plants which are used as coloring ingredient for the preparation of curry powder, has several activities which suggest that it might be an interesting drug for the treatment or prevention of cancer. Curcumin targets different pathways which are involved in the malignant phenotype of tumor cells, including the nuclear factor kappa B (NFkB) pathway. This pathway is deregulated in multiple tumor entities, including Hodgkin's lymphoma (HL). Indeed, curcumin can inhibit growth of HL cell lines and increases the sensitivity of these cells for cisplatin. In this review we summarize curcumin activities with special focus on possible activities against HL cells.

Keywords: curcumin, cancer, Hodgkin's lymphoma, vitamin D receptor, nuclear factor kappa B

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Introduction

The name curcumin has been used for different unrelated dyestuffs. Today, the name is used more or less exclusively for 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, the yellow dye from *Curcuma longa* (turmeric) and other curcuma plants.^{1,2} The name curcuma is based on the oriental name of the plant, which refers to its similarity with saffron (see the Hebrew word for saffron: כַּרְכֹּמ).³ Approximately 2000 years ago, Plinius described a plant with similar features which is considered to be turmeric (*est et per se Indica herba, quae cypira vocatur; zingiberis effigie; commanducata croci vim reddit*).⁴ [furthermore, an Indian plant exists which is called cypira and which has a similar appearance as ginger; while chewing it constitutes the effect of saffron]). Hybridization of *C. longa* with other species results in marked differences in the curcumin content between different plants.⁵ *C. longa* is a member of the family Zingiberaceae (ginger family). This family contains several plants which are widely used as spices and/or officinal plants, for example *Aframomum spec.* (alligator pepper, false cardamom), *Alpinia officinarum* (Chinese ginger), *Amomum subulatum* (hill cardamom), *Boesenbergia rotunda* (Chinese keys), *C. aromatica* (wild turmeric), *C. xanthorrhiza* (temulawak), *C. zedoaria* (zedoary), *Elettaria cardamomum* (cardamom), *Kaempferia galangal* (galangal), *Zingiber officinale* (ginger), and *Z. mioga* (Japanese ginger).

Recently, the complete transcriptome of *C. longa* rhizomes was analyzed.⁶ For a long time, the lipid-soluble yellow compound which can be isolated from the curcuma plants was used for cooking, cosmetics, and textile dyeing.⁷ In the 13th century, turmeric was introduced into Europe by Arab traders.⁸ Today, turmeric and the isolated curcumin are used as colorant in many food products. Turmeric is one of the important ingredients of curry powder. The color of curcumin depends on the pH and the presence or absence of other substances like boron (Fig. 1). With boron, curcumin forms rosocyanine, a reddish color (Fig. 1) which can be used for the detection and colorimetric quantification of boron.⁹

Multiple biological effects have been documented for curcumin. Curcumin has direct antibacterial¹⁰ and anti-inflammatory¹¹ activity. The anti-inflammatory activity might be mediated in part by the strong antioxidant activity of its caffeic acid moiety.¹² Curcumin

influences multiple signaling pathways.^{13,14} In addition to the anti-cancer related activities described below, curcumin is used for the treatment of a plethora of other diseases including pulmonary, neurological, liver, metabolic, and autoimmune diseases.¹⁵

Anti-Cancer Related Activities of Curcumin

In the last decades, there has been growing interest in curcumin and curcumin derivatives for treatment or prevention of cancer as indicated by the increasing number of curcumin-related publications in the last years (Fig. 2). The basic biological activities of curcumin has been summarized in an excellent review.¹⁶

Early observations suggested that curcumin can inhibit growth of tumor cells,¹⁷ can inhibit chemical carcinogenesis,^{18,19} and can be used for the treatment of patients with cancer.²⁰ Since then, few clinical trials suggest that curcumin might be a drug of interest for treatment of cancer^{21,22} or for the prevention of different forms of cancer.^{23,24}

It has been shown that curcumin and curcumin derivatives alone or in combination with other drugs increase cell death in a wide variety of tumor cells, including brain tumors,^{25–28} sarcoma,^{29–35} breast cancer,^{40–46} ovarian cancer,^{47–49} testicular cancer,⁵⁰ prostate cancer,^{51–53} pancreatic cancer,^{54,55} liver cancer,⁵⁶ biliary cancer,⁵⁷ gastric cancer,^{58,59} colorectal cancer,^{60,61} lung cancer,^{62–65} mesothelioma,⁶⁶ renal cancer,³⁷ bladder cancer,⁶⁷ esophageal cancer,^{68–71} head and neck cancer,^{72–75} and lymphoma/leukemia^{76–86} (Table 1). Curcumin induces death of cancer cells by activation of extrinsic and intrinsic apoptosis pathways. Activation of apoptosis by curcumin is accompanied by modulation of multiple signaling pathways (hedgehog pathway, extracellular signal-regulated kinase (ERK) pathway, wingless (WNT) pathway, Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, Notch pathway, nuclear factor of kappa light polypeptide gene enhancer in B-cells (NFκB) pathway; Table 1). Depending on the cell type investigated, activation or inhibition of certain signaling pathways can occur. The ERK pathway, for example, is activated by curcumin in monocytic leukemia cells⁷⁷ whereas curcumin down-regulates ERK in breast cancer cells.⁴³ In both cases, deregulation of this signaling pathway promotes cell death. Curcumin can up-regulate

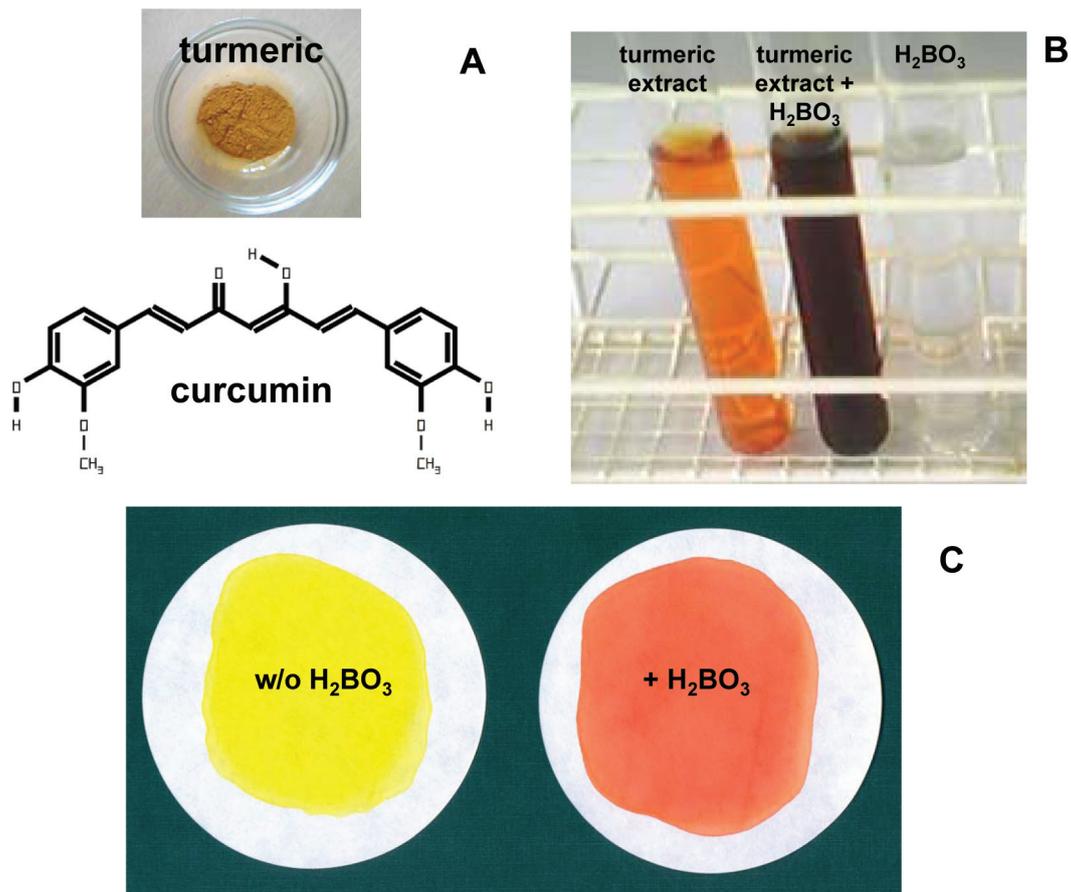


Figure 1. Curcumin and Curcuma. **A)** Curcumin is the yellow dyestuff from turmeric (the structure of curcumin was drawn with C-Design 3.0f; <http://www.ch.tum.de/oc1/EFontain/C-Design/>). **B)** Curcumin forms colored complexes with boron. Turmeric powder (1 g) was extracted with 96% ethanol (10 mL, 37°C, 2 h), centrifuged and steril filtered. In the presence of 0.1 M NaOH, a 1:20 dilution of this extract in water is colored orange. After addition of 0.05 M boric acid the color turns into deep red. **C)** Turmeric powder (1.3 g) was extracted with 96% ethanol (18 mL, 37°C, 4 h) in the absence or presence of boric acid (1 g), centrifuged, steril filtered, and dried on filter paper circles. In the presence of boron, the yellow color changed into red.

pro-apoptotic components of the extrinsic apoptosis pathway (FAS, FAS ligand, Tumor necrosis factor (TNF) receptors or TNF-related apoptosis inducing ligand (TRAIL) receptors).^{30,31} On the other hand, curcumin down-regulates anti-apoptotic factors (B cell leukemia/lymphoma 2 (BCL2), BCL2 like 1 (BCL2L1), X-linked inhibitor of apoptosis (XIAP), survivin).^{25,27,33,41,56,57,58,67,79} In addition, curcumin has been shown to inhibit telomerase which reverses immortalization of cancer cells.²⁵ It seems that curcumin is able to induce apoptosis in cancer cells without pronounced cytotoxic effects on healthy cells. By inhibition of multi-drug resistance transporters, curcumin can overcome chemotherapy resistance of tumor cells.^{64,87} The inhibition of these transporters can explain the depletion of side populations in tumor cells after treatment with curcumin.⁸⁸ If curcumin increases the chemotherapy sensitivity of this

putative stem cell population, a combination with conventional chemotherapy might be able to kill the stem cell population. Antagonistic effects of curcumin and cytotoxic drugs have been observed, however.⁸⁹⁻⁹¹ These observations indicate that the combination of curcumin with other drugs should be carefully evaluated in appropriate models in vitro or in vivo before these combinations are tested in patients.

Another interesting activity of curcumin is the inhibition of tumor cell motility, invasion, and metastasis.^{26,42,92-100} This activity is mediated in part by the down-regulation of matrix-metalloproteinases. A key step in tumor metastasis is the process of epithelial mesenchymal transition (EMT) usually accompanied by loss of epithelial cadherin (CDH1) expression. Inhibition of EMT and up-regulation of CDH1 in tumor cells by curcumin has been described.^{101,102} One inductor of cell motility in cancer

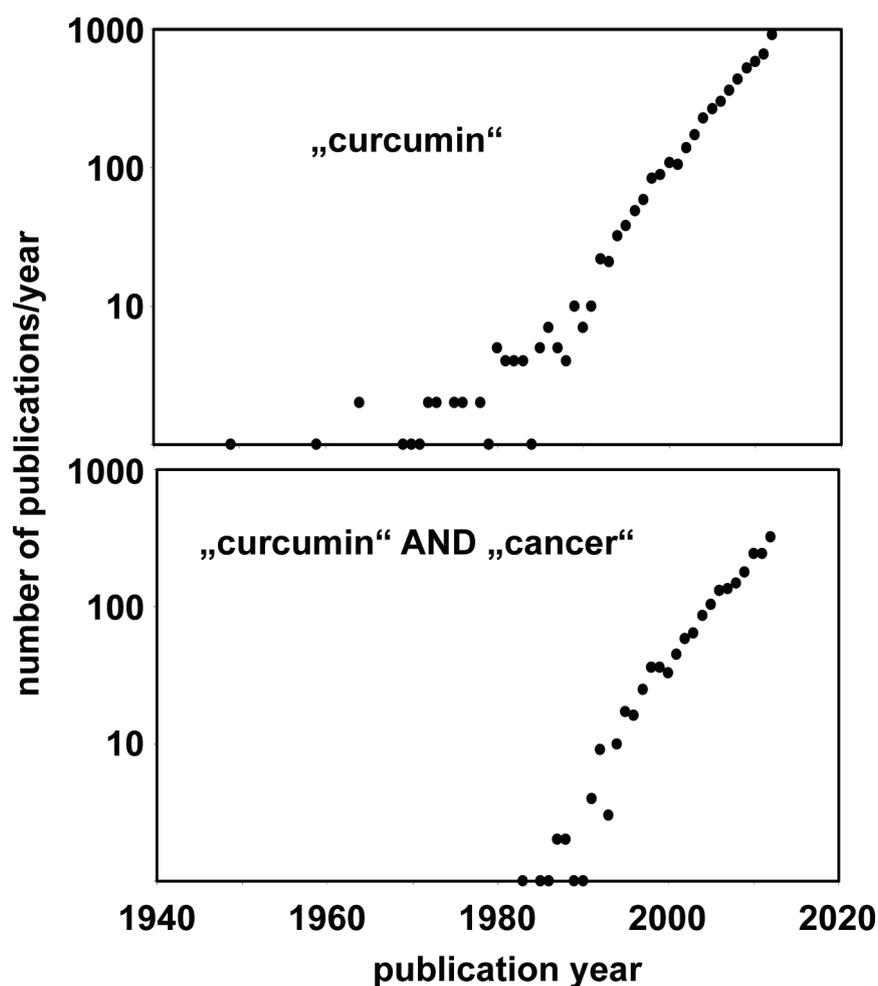


Figure 2. Increasing number of publications about curcumin and cancer. The PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed/>) was searched with the queries “curcumin” or “curcumin cancer”. Presented are the absolute numbers of found publications per publication year.

Table 1. Examples for growth inhibitory activities of curcumin and curcumin derivatives on tumor cells.

Tumor types ¹	Substances ²	Important observations ³	Ref.
brain tumors (glioblastoma, medulloblastoma)	curcumin; curcumin + paclitaxel	cell cycle inhibition; apoptosis; inhibition of telomerase; inhibition of migration; inhibition of hedgehog signaling	25–28
MPNST	curcumin + TRAIL	enhanced TRAIL sensitivity; increased production of ROS	29
sarcoma (chondrosarcoma, liposarcoma, osteosarcoma, Ewing sarcoma)	curcumin; curcumin + JCTH-4; FLLL32	up-regulation of FAS, FAS ligand, and TRAILR2; enhanced JCTH-4 sensitivity; cell cycle inhibition; inhibition of ATP2A2; apoptosis; down-regulation of MMP2	30–35
melanoma	curcumin; FLLL32; FLLL62; DM-1 + dacarbazine; D6	cell cycle inhibition; up-regulation of TNF receptor 1; apoptosis; inhibition of STAT3 signaling	36–39
neuroblastoma	curcumin; D6	apoptosis; inhibition of TNF induced NFKB signaling	39

(Continued)



Table 1. (Continued)

Tumor types ¹	Substances ²	Important observations ³	Ref.
breast cancer	curcumin; curcumin + fluoruracil; curcumin + tamoxifen; curcumin + vinblastin; RL66; RL71	cell cycle inhibition; inhibition of multiple signaling pathways; apoptosis; inhibition of ERK signaling; down-regulation of EZH2; inhibition of migration of endothelial cells; depolymerization of microtubules	40–46
ovarian cancer	curcumin + cisplatin; curcumin + oxaliplatin; B19; HO-3867 + cisplatin;	inhibition of STAT3 signaling; apoptosis; up-regulation of TP53; increased production of ROS	47–49
testicular cancer	curcumin + bleomycin	apoptosis	50
prostate cancer	curcumin; dimethoxycurcumin	cell cycle inhibition; apoptosis; inhibition of MMP2, inhibition of wingless signaling	51–53
pancreatic cancer	curcumin; curcumin + sulforaphane + aspirin	cell cycle inhibition; apoptosis; inhibition of NFKB signaling	54,55
liver cancer	curcumin + adriamycin	apoptosis	56
biliary cancer	curcumin	apoptosis; inhibition of NFKB signaling; inhibition of STAT3 signaling; up-regulation of TRAIL receptors	57
gastric cancer	curcumin; curcumin + doxorubicin; curcumin + etoposide	apoptosis; inhibition of NFKB signaling	58,59
colon cancer	bisdehydroxycurcumin	apoptosis; autophagy	60,61
lung cancer	curcumin; curcumin + cisplatin B63; T63;	cell cycle arrest; apoptosis; enhanced production of ROS; down-regulation of MDR transporters; enhanced degradation of HIF1A	62–65
mesothelioma	curcumin; curcumin + cisplatin	apoptosis	66
renal cell carcinoma	curcumin; FLLL32; FLLL62	apoptosis; inhibition of STAT3 signaling	37
bladder cancer	curcumin + BCG	inhibition of NFKB signaling; up-regulation of TRAIL receptors; apoptosis	67
esophageal cancer	curcumin; curcumin + fluoruracil curcumin + cisplatin	cell cycle inhibition; inhibition of NFKB signaling; apoptosis; non-apoptotic cell death; inhibition of Notch signaling;	68–71
head and neck cancer	curcumin; FLLL32 + cisplatin	cell cycle inhibition; apoptosis; inhibition of STAT3 signaling; increased production of ROS	72–75
leukemia and lymphoma	curcumin; curcumin + daunorubicin; curcumin + IR; CA#12 + bortezomib	cell cycle inhibition; increased production of ROS; apoptosis; inhibition of NFKB signaling; activation of ERK pathway; down-regulation of cyclin D1, down-regulation of MYC	76–85

¹MPNST, malignant peripheral nerve sheath tumors.

²B19, (1E, 4E)-1, 5-bis(2-methoxyphenyl)penta-1,4-dien-3-one; B63, 1,5-bis(2-methoxyphenyl)penta-1,4-dien-3-one; DM-1, sodium 4-[5-(4-hydroxy-3-methoxyphenyl)-3-oxo-penta-1,4-dienyl]-2-methoxy-phenolate; BCG, Bacillus Calmette-Guerin; CA#12, (1E,6E)-1,7-Bis(4-valinoyl-3-methoxyphenyl)hepta-1,6-diene-3,5-dione hydrochloride; D6, (3E,3'E)-4,4'-(5,5',6,6'-tetramethoxy-[1,1'-biphenyl]-3,3'-diyl)bis(but-3-en-2-one); FLLL32, (2E,2'E)-1,1'-(cyclohexane-1,1-diyl)bis(3-(3,4-dimethoxyphenyl)prop-2-en-1-one); FLLL62, (2E,2'E)-1,1'-(tetrahydropyran-4,4-diyl)bis(3-(3,4-dimethoxyphenyl)prop-2-en-1-one); HO-3867, 1-[(1-Oxyl-2,2,5,5-tetramethyl-2,5-dihydro-1H-pyrrol-3-yl)methyl]-(3E,5E)-3,5-Bis(4-fluorobenzylidene)piperidin-4-one; IR, ionizing radiation; JCTH-4, synthetic pancratistatin analog; TRAIL, tumor necrosis factor-related apoptosis inducing ligand; RL66, 1-Methyl-3,5-bis[(E)-4-pyridyl)methylidene]-4-piperidone; RL71, 3,5-bis(3,4,5-trimethoxybenzylidene)-1-methylpiperidine-4-one; T63, (1E,6E)-1,7-Bis(3,4-dimethoxyphenyl)-4-(4-hydroxy-3-methoxybenzylidene)hepta-1,6-diene-3,5-dione.

³ATP2A2, sarcoplasmic/endoplasmic reticulum calcium ATPase; ERK, extracellular signal-regulated kinase; EZH2, enhancer of zeste homolog 2; HIF1A, hypoxia inducible factor 1, alpha subunit; NFKB, nuclear factor of kappa light polypeptide gene enhancer in B-cells; TNF, tumor necrosis factor; TP53, tumor protein 53; TRAILR2, TRAIL receptor 2 (death receptor 5); MDR, multi-drug resistance; MMP2, matrix metalloproteinase 2; MYC, myelocytomatosis viral oncogene homolog; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3.



cells is lysophosphatidic acid (LPA). LPA receptors are often expressed in tumor cells and co-expression of LPA receptors and LPA-producing phospholipases in tumor cells have been observed.¹⁰³ Curcumin can also inhibit LPA-induced cancer cell motility.¹⁰¹ Taken together, these observations indicate that curcumin does not only inhibit tumor growth but also metastasis formation. However, enhanced metastasis has been described in a Lewis lung carcinoma model.¹⁰⁴

In addition to the death inducing activities of curcumin on established tumor cells, curcumin and curcumin derivatives can inhibit or delay tumor formation in different tumor models.^{92,105–113} Curcumin significantly inhibited the formation of preneoplastic lesions in animal models for chemical colon carcinogenesis.^{92,102} The combination with fluorouracil or carnitine enhanced this effect. Curcumin inhibited ultraviolet radiation-induced or chemically induced skin carcinogenesis in mice.^{106,107} Furthermore, curcumin inhibited the development of gastrointestinal tumors,^{108,109} mammary tumors,¹¹⁰ and hepatocellular tumors^{111,112} in models for chemical carcinogenesis. The anti-inflammatory activity of curcumin seems to be responsible at least partially for such cancer preventive activities.¹¹³ In addition to the direct activities on tumor cells and pre-malignant cells, the inhibition of the growth of carcinogenic microorganisms such as *Helicobacter pylori* may partially account for tumor prevention by curcumin.¹¹⁴ Very infrequently, enhanced tumor formation in experimental models has been described.¹¹⁵ Such observations indicate that the biology of the used experimental models has not been fully elucidated and that further investigations are required in order to understand the effects of curcumin in the different models.

The Nuclear Factor Kappa B (NFκB) Pathway as Target for Curcumin

Avian reticuloendotheliosis defines a group of diseases that are observed in turkeys, broiler chickens, ducks, among other birds. One of the interesting features of reticuloendotheliosis is the development of lymphoid malignancies. The causative agent of reticuloendotheliosis is a gamma-retrovirus that transforms diverse avian cells. Analysis of the T strain of this virus (reticuloendotheliosis virus strain T; REV-T) led to the identification of the REL oncogene.^{116–118}

Thereafter, the human REL homologue was found on chromosome 2.¹¹⁹ REL is a member of a gene family that includes in the human genome at least 5 members: REL, RELA,^{120,121} RELB,¹²² nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (NFκB1),¹²³ and NFκB2 (Fig. 3).¹²⁴ This family can be divided into two sub-families (Fig. 3) and usually one member of the NFκB1/2 subfamily forms a heterodimer with a member of the REL subfamily. The NFκB pathway is a highly conserved signaling pathway in eukaryotes. Members of the NFκB family are involved in chromosomal rearrangements that have been detected in cancer cells and gene fusions involving REL^{125,126} or NFκB2^{124,127} have been described.

The NFκB pathway is often deregulated in cancer cells. One example is Hodgkin's lymphoma (HL), one of the most frequent lymphomas in Western countries.¹²⁸ The etiology of HL is unclear, but immunological and molecular properties suggest that in most cases HL cells are derived from B cells.^{129–131} HL cells have a characteristic gene expression profile that discriminates these cells from other normal and transformed hematopoietic cells.¹³² With the combination of radio- and chemotherapy the majority of patients, with HL can be cured. However, the established therapy is associated with the induction of secondary malignancies, cardiac toxicities, and treatment-related infertility.^{133–135} In addition, up to 10% of patients still cannot be cured with current therapy regimes, which represent a significant number.^{136,137} Thus, there is a clear demand to search for new treatment options and also for optimization of current treatment strategies by identifying potential treatment resistance mechanisms.

An involvement of the NFκB pathway in HL has been suggested by the high expression of NFκB family members in HL.¹³⁸ Mutations in the NFκB inhibitors NFκB inhibitor alpha (NFκBIA) and tumor necrosis factor alpha-induced protein 3 (TNFAIP3) have been observed in a high percentage of HL.^{139,140} Curcumin inhibits NFκB activity in different cell types (Table 1) and the inhibition of the NFκB pathway can be seen by decreased expression of NFκB. The activity of NFκB is regulated by inhibitors that bind NFκB and release NFκB only after degradation. Curcumin can inhibit NFκB activity indirectly by stabilization of NFκBIA.⁴⁰

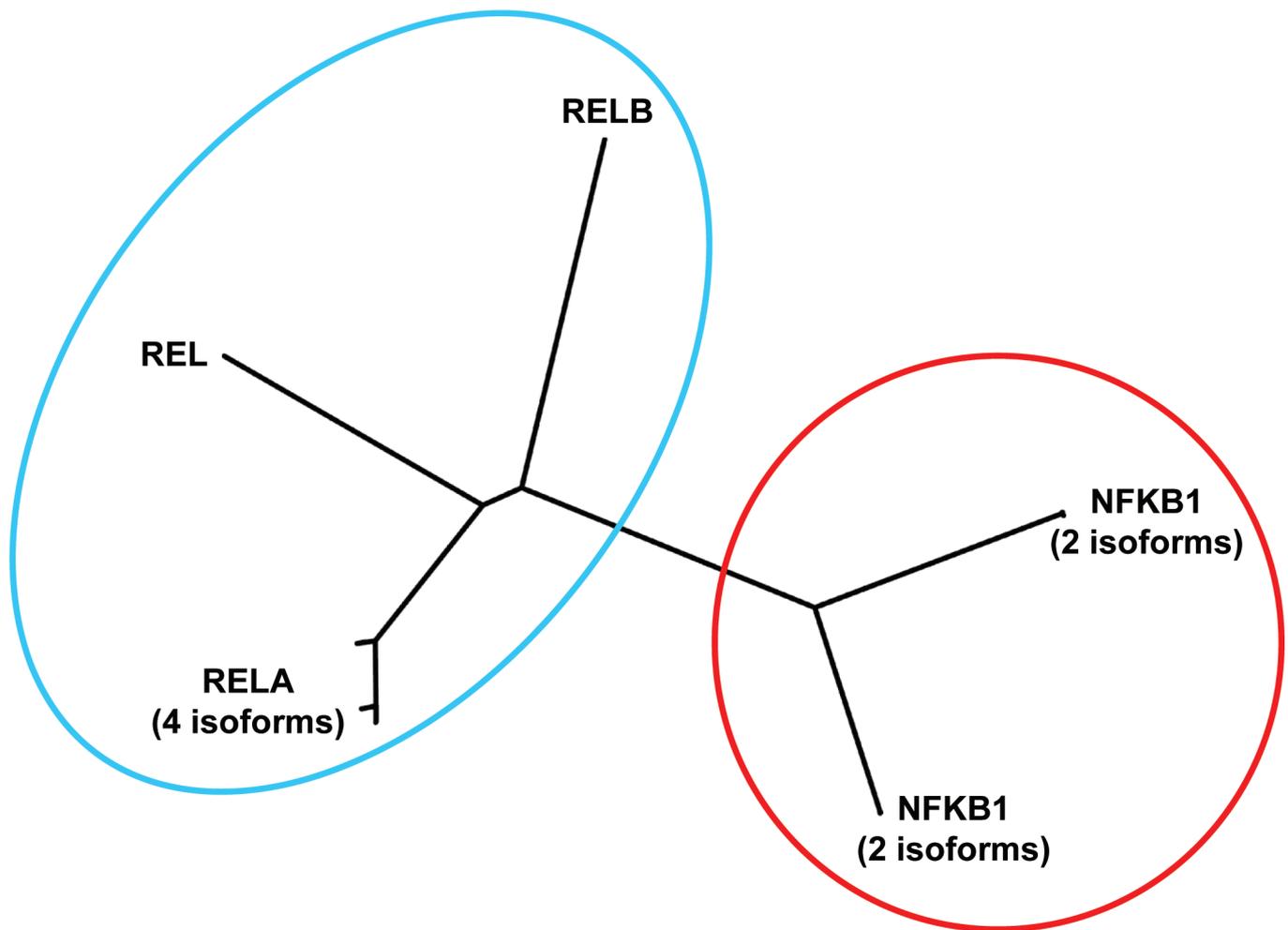


Figure 3. Known human proteins of the REL/NFKB family. Reference sequences of the indicated human proteins were used for a phylogenetic tree analysis using the clustalW algorithm (<http://www.genome.jp/tools/clustalw/>). For human RELA (protein accession numbers NP_001138610, NP_001230913, NP_001230914, and NP_068810), human NFKB1 (NP_001158884, NP_003989) and human NFKB2 (NP_001070962, NP_001248332) different protein isoforms with highly similar sequences have been identified. For REL (NP_002899) and RELB (NP_006500) no additional human isoforms are in the databases. The family can be separated into two sub-families. A complete NFKB transcription factor consists of a heterodimer of a member of the NFKB1/2 subfamily and a member of the REL subfamily.

In addition to constitutive activation of NFKB, in some tumors NFKB expression and activation is induced by treatment with cytotoxic drugs or cytokines.^{40,141,142} Curcumin and curcumin derivatives can prevent such induced activation. Curcumin derivatives, for example, have been shown to decrease the TFR-induced expression of NFKB in melanoma and neuroblastoma cells.⁴⁰ In some cases the anti-NFKB activity of curcumin requires the presence of additional treatment elements. In pancreatic tumor cells, for example, curcumin inhibits DNA binding-activity of NFKB only in combination with aspirin and sufuraphane.⁵⁴ As the final consequence of NFKB inhibition, expression of NFKB target genes is suppressed. These target genes include anti-apoptotic factors and the suppression of

these factors can increase tumor cell death. In addition, the crosstalk between NFKB and other signaling pathways can lead to complex alterations of the phenotype of tumor cells after inhibition of NFKB.

The activation of the NFKB pathway in HL makes curcumin an interesting drug for the treatment of HL. Indeed, curcumin induces cell death in HL cells. As shown in Figure 4A, incubation with curcumin leads to decreased cell viability in all HL cell lines tested whereas normal peripheral blood mononuclear cells (PBMC) are not affected by the used concentration of curcumin. Similar results were found by Mackenzie et al who showed that curcumin leads to cell cycle arrest in G2-M and reduced cell viability in Hodgkin and Reed-Sternberg cells.¹⁴³

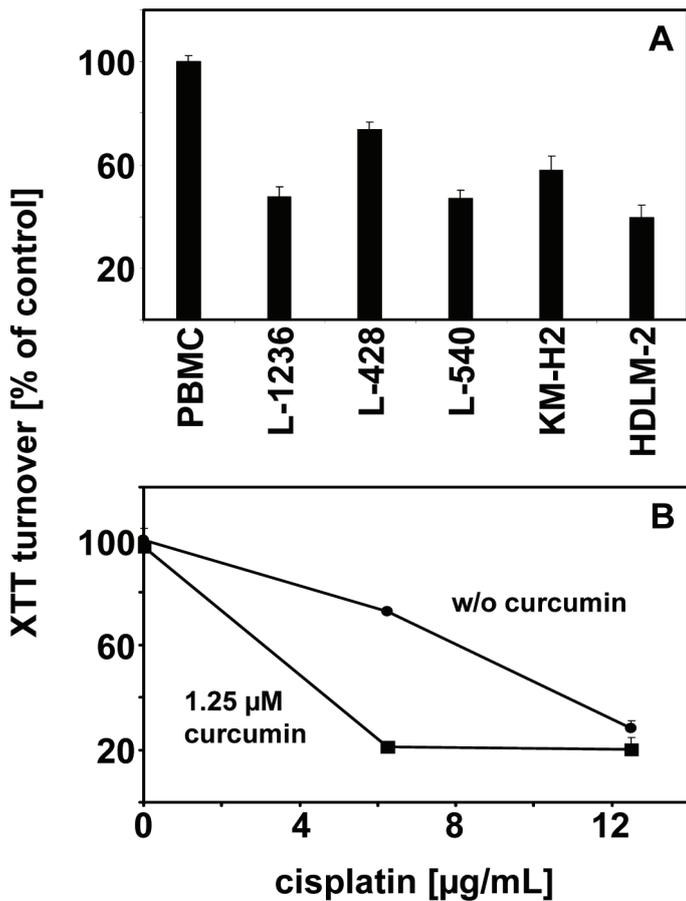


Figure 4. Curcumin inhibits growth of HL cells. A) HL cells from the indicated cell lines and peripheral blood mononuclear cells (PBMC) were incubated for 24 hours with 25 µM curcumin (Sigma, Taufkirchen, Germany). Cell viability was assessed by 2,3-bis-(2-methoxy-4-nitro-5-sulphophenyl)-2H-tetrazolium-5-carboxanilide (XTT) assay (Roche, Mannheim, Germany). Shown are means and standard errors from 4 replicates. **B)** Cells of the HL cell line L-428 were incubated with 1.25 µM curcumin or with carrier. The cells were treated with 6.25 and 12.5 µg/mL cisplatin (Sigma) or with the same concentrations of carrier (dimethylformamide). After 24 hours the cell viability was assessed using XTT assay (Roche). Shown are means and standard errors from triplicates.

In order to determine whether the combination of curcumin with conventional chemotherapy might have synergistic effects, HL cells were incubated either without curcumin or with a low dose (1.25 µM) of curcumin and varying concentration of cisplatin. The results are shown in Figure 4B. With the used concentration of curcumin, only marginal effects on cell viability were observed. In contrast, the combination of curcumin with cisplatin had a strong cytotoxic effect on the cells. However, inhibition of the Fanconi anemia (FA) pathway might be an important factor for the synergistic effect of cisplatin and curcumin on HL cells. Ubiquitination of the FA complementation group D2 (FANCD2) protein in response

to DNA damage is an important step during repair of cross-links in the DNA, caused by cisplatin. Chirnomas et al¹⁴⁴ showed that curcumin inhibits the FA pathway by inhibition of ubiquitination of FANCD2. This inhibition sensitized ovarian and breast tumor cells for cisplatin.¹⁴⁴ It remains to be shown whether similar mechanisms are responsible for increased cisplatin sensitivity of curcumin treated HL cells. The HL cell lines used in our study outlined above were established from patients with refractory disease and are not perfect models for the situation in most patients in vivo. However, the increased cell death of these highly chemotherapy resistant cell lines after treatment with curcumin seems to be encouraging.

Curcumin shares the NFκB-inhibitory activity with another interesting dietary phytochemical: capsaicin.¹⁴⁵ Curcumin can bind the vanilloid receptor TRPV1 (transient receptor potential cation channel, subfamily V, member 1), the same receptor that is activated by capsaicin.¹⁴⁵ However, curcumin binding to TRPV1 did not result in the same signaling. TRPV1 is not the only receptor for curcumin and interestingly, curcumin can bind the aryl hydrocarbon receptor AHR.¹⁴⁶ Many carcinogenic polycyclic aromatic hydrocarbons are carcinogens only after in vivo activation. Cytochrome P450 family member A1 (CYP1A1) is an enzyme which can catalyze this activation. Expression of CYP1A1 is induced after binding of AHR to polycyclic aromatic hydrocarbons. It was shown that curcumin can inhibit the CYP1A1 inducing activity of the AHR.¹⁴⁷ Binding to AHR and competition with aryl hydrocarbon derivatives might explain the chemopreventive activity of curcumin.¹⁴⁷ Probably more important for the cancer cell death inducing activity of curcumin is the third curcumin receptor, the vitamin D receptor.^{148,149}

Vitamin D Receptors (VDR) and Curcumin

Anti-neoplastic activities of vitamin D have been described, but epidemiological data also suggests that for some cancer types sunlight can reduce cancer risk independent from vitamin D.¹⁵⁰ Curcumin increases apoptosis and differentiation of vitamin D-treated tumor cells.^{151,152} Direct binding of curcumin to the vitamin D receptor (VDR) was demonstrated.¹⁴⁸ This binding allows VDRs to heterodimerize with the retinoic X receptor and translocate to the nucleus.

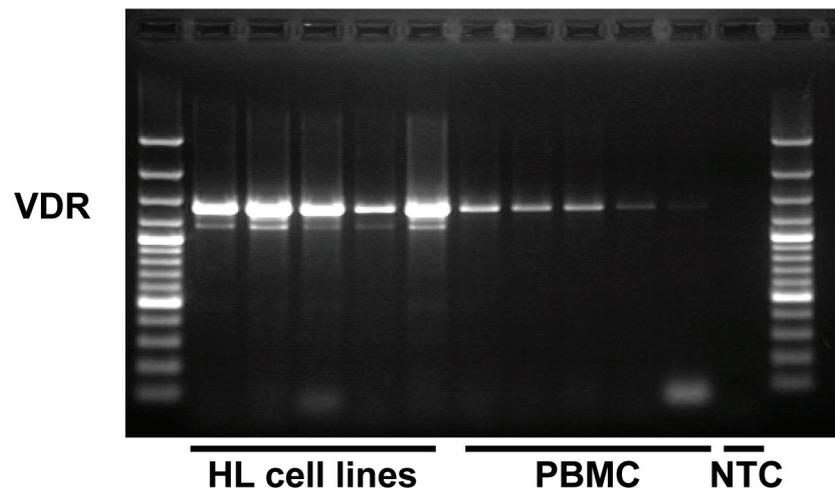


Figure 5. Expression of VDR in HL cell lines. RNA was isolated from HL cell lines and PBMC, reverse transcribed and used as template for polymerase chain reaction with specific primers for VDR (5'-gcc ttg ggg tct gaa gtg tc-3' and 5'-cag gct gtc cta gtc agg aga t-3'). The used primers recognize all three transcript variants of the human VDR (accession numbers NM_000376, NM_001017535, NM_001017536). PCR products were separated by agarose gel electrophoresis in the presence of ethidium bromide. NTC: no template control.

The complex can then activate gene transcription of vitamin D target genes.¹⁴⁸

Recently, high expression of the VDR has been observed in HL biopsies.¹⁵³ HL cell lines also express high levels of VDR (Fig. 5). Lymphoma cells can synthesize vitamin D¹⁵⁴ and increased vitamin D levels have been repeatedly reported in HL patients.¹⁵⁵ In addition, seasonal fluctuations of the prognosis of HL patients have been observed and discussed as being caused by fluctuations of endogenous vitamin D levels.¹⁵⁶ Vitamin D can probably activate the NF κ B pathway,^{157,158} but in most systems, vitamin D inhibits NF κ B activation.^{159–162} In Jurkat cells with constitutive expression of VDR, no inhibition of NF κ B by vitamin D was observed,¹⁶³ suggesting that some tumor cells have inactivated this pathway. Interestingly, NF κ B can inhibit VDR signaling.¹⁶⁴ This cross-inhibition might explain the simultaneous high constitutive expression of VDR and activated NF κ B in lymphoma cells. Stimulation of VDR by curcumin might shift this balance to the inhibitory activity of VDR.

Indirect Effects of Curcumin: Immunomodulation

Curcumin can reduce the number of myeloid-derived suppressor cells,¹⁶⁵ an important immunosuppressive cell population in tumors. Tumor patients, especially HL patients, often have a tumor-mediated dysfunction of the immune system. Experimental data suggest that curcumin is able to restore the immune

function in tumor-bearing hosts.¹⁶⁶ On the other hand, induction of regulatory T cells might be increased in the presence of curcumin,¹⁶⁷ and the direct induction of apoptosis in activated T cells has been described.¹⁶⁸ As an anti-inflammatory agent, curcumin can suppress T cells.^{169,170}

Such effects, however, might negatively affect anti-cancer immune responses. The balance between immunostimulation and -suppression might be dependent on the concentration of curcumin.¹⁷¹ In the case of HL, the immune system is a double-edged sword. On the one hand, cytotoxic T cells can kill HL cells; on the other hand, T cells can provide survival signals for HL cells. The very low number of tumor cells and the presence of a high background of “normal” cells in HL indicate the importance of the interaction between tumor cells and the stroma. Whether curcumin can shift the balance between tumor promoting activities and anti-tumor activities of T cells in HL into the direction of tumor destruction must be analyzed. HL is a disease with features of chronic inflammation and the accumulation of stroma cells by HL derived cytokines is an important factor for HL biology.^{172,173} The anti-inflammatory activities of curcumin may be able to counteract this inflammatory stimulus.

Other Curcumin Activities Related to HL Biology

Another interesting activity of curcumin is the suppression of histone deacetylases (HDAC).^{174,175} Reports



describe the inhibition of histone acetyltransferases by curcumin without HDAC inhibition.^{176,177} In addition, curcumin has DNA methylation inhibiting activity.¹⁷⁸ Epigenetic regulation of gene expression by DNA methylation or histone deacetylation plays an important role in HL biology. Treatment of HL cells with HDAC inhibitors can increase the sensitivity of HL cells to cytotoxic drugs.¹⁷⁹ Treatment of HL cells with DNA methylation inhibitors can increase the expression of tumor antigens which might increase the recognition by the immune system.^{180,181} However, increased expression of factors involved in chemotherapy resistance might also occur after the treatment of HL cells with such drugs.¹⁸¹

Interestingly, curcumin has been shown to inhibit transcription initiated by human immunodeficiency virus (HIV) type 1 long terminal repeats (LTR).¹⁸² The activation of LTRs from endogenous retroviruses (ERV) in HL has been demonstrated. This activation can lead to the aberrant expression of oncogenes in HL.¹⁸³ Whether curcumin can modulate the activity of ERV promoters in tumor cells is under investigation. If ERV activity is essentially involved in the pathogenesis of HL, such ERV inhibition might reverse the malignant phenotype of the tumor cells.

A high percentage of HL carries copies of the Epstein Barr virus (EBV) in the tumor cells. Activation of the NF κ B pathway by EBV seems to be involved in the pathogenesis of EBV positive HL. Curcumin can inhibit B cell immortalization by EBV.^{184,185} EBV-immortalized B cells undergo pronounced apoptosis in the presence of curcumin which may inhibit the outgrowth of cell lines.¹⁸⁵ In addition, it seems that oxidative stress promotes B cell immortalization by EBV.¹⁸⁶ The anti-oxidant activity of curcumin might inhibit this effect in a similar way as it was shown for vitamin E.¹⁸⁶ Whether this activity can interfere with the EBV driven HL pathogenesis requires further investigations.

Additional HL related activities of curcumin have been described. For example, HL cells express the anti-apoptotic BCL-X_L isoform of the B cell leukemia/lymphoma 2 (BCL2)-like 1 (BCL2L1) oncogene.^{187,188} Recently, a link between expression of BCL-X_L and survival of HL patients has been suggested.¹⁸⁹ Curcumin can down-regulate BCL-X_L.¹⁹⁰ Furthermore, curcumin is a topoisomerase II inhibitor with a similar activity as etoposide, a drug which is used for treatment of HL.¹⁹¹ In addition to the NF κ B pathway, curcumin

inhibits the STAT pathway (Table 1). This pathway is similarly important for HL cell proliferation and survival as the NF κ B pathway and inhibitors of this pathway can induce apoptosis in HL cells.^{143,189,192–200} Constitutive activation of the STAT pathway by rearrangements of the JAK2 have been described in HL.²⁰¹ Taken together, curcumin targets several pathways in HL cells. The scarcity of the tumor cells in the tumors hampers the analysis of larger numbers of ex vivo isolated living cells. The number of established HL cell lines is very low and these cell lines are not perfectly representative for the tumor cells in vivo. Whether curcumin or curcumin derivatives with better bio-availability can be used for the treatment of HL patients requires further investigation.

A number of microarray experiments of curcumin treated cells and animals have been published (Table 2). These experiments indicate that the specific effects of curcumin on gene expression are dependent on the investigated model. However, a model-independent common schema of curcumin activities can be seen. These activities include the shift from pro-inflammatory to anti-inflammatory gene expression signatures, the shift from anti-apoptotic to pro-apoptotic signatures, cell cycle inhibition, and down-regulation of pro-invasive factors (e.g., metalloproteinases). Such experiments might help to identify the relevant pathways which are involved in the biological effects of curcumin in the different models and may lead to the identification of new therapeutic targets.

Future Directions

The bio-availability of curcumin is limited by the rapid metabolism and the low water solubility of this phytochemical. Curcumin is rapidly conjugated with sulfate or glucuronic acid in the gut and liver.²³⁰ In addition, reduction to tetrahydrocurcumin and hexahydrocurcumin occurs.²³⁰ The resulting curcumin sulfate, curcumin glucuronide, and reduced curcumin derivatives can be found in the feces of curcumin treated patients.²³¹ The curcumin metabolites have some biologic activities, for example tetrahydrocurcumin can inhibit the activity of multi-drug resistance (MDR) transporters.²³² However, enhanced excretion of curcumin metabolites and the shortening of the half life of curcumin after conjugation are not desired. Inhibition of glucuronidation by piperine

**Table 2.** Examples for DNA microarray experiments investigating the gene expression after treatment of cells or animals with curcumin or curcumin derivatives.

Models	Substances ^{1,2}	Important observations ³	Ref.
head and neck cancer cells	curcumin	decreased expression of MMP10	97
colon cancer cells	curcumin	regulation of cell-cycle-related genes; down-regulation of RELA and MMP2	202,203
bladder cancer ⁴	curcumin	regulation of cell-cycle-related genes	205
endothelial cells	demethoxycurcumin	decreased expression of MMP9 and other angiogenesis-related genes	206
lung cancer cells	curcumin; CLEFMA	decreased expression of MMP14 and other invasion-related genes; down-regulation of microRNA-186* ⁵ ; up-regulation of genes related to cellular redox status	207–209
smooth muscle cells, peritoneal phagocytes	curcumin	up-regulation of pro-apoptotic genes, cell adhesion molecules, and anti-inflammatory factors	210
breast cancer cells	curcumin	up-regulation of cell cycle inhibitors; complex regulation of apoptosis-related genes; down-regulation of pro-inflammatory chemokines; down-regulation of EGF pathway	211–214
hepatic stellate cell line	Curcuma oil	down-regulation of interleukin 6 and TIMP2	215
colon ⁵	curcumin	strain-dependent differences in regulated genes; reduced expression of pro-inflammatory genes	216–218
Ewing sarcoma cells ⁶	curcumin	down-regulation of radiation-induced anti-apoptotic factors	220
pancreatic cancer cells	curcumin	regulation of microRNAs and microRNA-target genes	221
liver ⁷	curcumin	weak peroxisomal proliferator activity (in rats)	222
leukemia cells	curcumin	down-regulation of cell cycle regulators and JAK/STAT signaling	223
heart ⁸	curcumin	down-regulation of pro-inflammatory factors	224
liver cancer cells	curcumin	down-regulation of protein kinase C	225
microglia cell line	curcumin	up-regulation of anti-inflammatory factors	226
retinoblastoma cells	curcumin	regulation of multiple genes involved in apoptosis, cell cycle regulation, and angiogenesis; regulation of microRNAs and microRNA-target genes	227,228
blood cells ⁹	curcumin	down-regulation of pro-inflammatory factors	229

¹CLEFMA, 4-[3,5-bis(2-chlorobenzylidene-4-oxo-piperidine-1-yl)-4-oxo-2-butenoic acid].

²In some investigations curcumin or curcumin derivatives were compared with other substances.

³EGF, epidermal growth factor; JAK/STAT, janus kinase/signal transducer and activator of transcription MMP2, matrix metalloproteinase 2; MMP9, matrix metalloproteinase 9; MMP10, matrix metalloproteinase 10; MMP14, matrix metalloproteinase 14; TIMP2, tissue inhibitor of metalloproteinases 2.

⁴In the cited publication the investigated cell line (ECV304) was used as a model for endothelial cells, but there is evidence that this cell line is identical to the bladder cancer cell line T24.²⁰⁴

⁵In-vivo models for inflammatory bowel diseases.

⁶In the cited publication the investigated cell line (SK-N-MC) was used as a model for neuroblastoma, but there is evidence that this cell line is derived from Ewing sarcoma (Askin tumor).²¹⁹

⁷In-vivo toxicology study.

⁸In-vivo model for myocardial infarction.

⁹In-vivo model for arthritis.

(the alkaloid from black pepper) has been shown to increase the bio-availability of curcumin.²³³

In addition to inhibition of glucuronidation, piperine can inhibit the activity of MDR transporters.²³⁴ On the other hand, increased expression of these transporters after exposure to piperine has been observed.²³⁵ Together with the inhibitory effect of curcumin on MDR transporter expression and function,^{88,236} inhibition of MDR transporter function by piperine might counteract the effect of piperine on

MDR transporter expression. In order to increase the solubility of curcumin, conjugation of curcumin with proteins or cyclodextrins have been tested.^{236,237} In addition, different types of nanoparticles, liposomes, and self-assembling polymers have been used for encapsulation of curcumin.^{238–240} Such formulations might finally overcome the bio-availability problem of curcumin.

Another interesting question that remains to be addressed is whether the effects of turmeric are only



mediated by curcumin or whether additional turmeric ingredients are involved. Early studies suggest that curcumin-free turmeric extracts also have cancer preventing activities.^{241,242} Indeed, differences between turmeric and curcumin in the regulation of pro-inflammatory genes have been described.²⁴³ The characterization of the factors that are responsible for biological activities of curcumin-free turmeric requires further investigations.

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Author Contributions

Conceived and designed the experiments: MSS, SK. Analyzed the data: SK, IV, MSS. Wrote the first draft of the manuscript: SK, MSS. Contributed to the writing of the manuscript: SK, IV, MSS. Agree with manuscript results and conclusions: SK, IV, MSS. Jointly developed the structure and arguments for the paper: SK, IV, MSS. Made critical revisions and approved final version: SK, IV, MSS. All authors reviewed and approved of the final manuscript.

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Competing Interests

Authors disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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