

## Potential Anticancer Properties and Mechanisms of Action of Curcumin

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**Abstract.** *Curcumin, a yellow substance belonging to the polyphenols superfamily, is the active component of turmeric, a common Indian spice, which is derived from the dried rhizome of the Curcuma longa plant. Numerous studies have demonstrated that curcumin possesses anti-oxidant, anti-inflammatory and anticancerous properties. The purpose of this review is to focus on the anti-tumor effects of curcumin. Curcumin inhibits the STAT3 and NF-κB signaling pathways, which play key-roles in cancer development and progression. Also, inhibition of Sp-1 and its housekeeping gene expressions may serve as an important hypothesis to prevent cancer formation, migration, and invasion. Recent data have suggested that curcumin may act by suppressing the Sp-1 activation and its downstream genes, including ADEM10, calmodulin, EPHB2, HDAC4, and SEPP1 in a concentration-dependent manner in colorectal cancer cell lines; these results are consistent with other studies, which have reported that curcumin could suppress the Sp-1 activity in bladder cancer and could decrease DNA binding activity of Sp-1 in non-small cell lung carcinoma cells. Recent data advocate that ER stress and autophagy may as well play a role in the apoptosis process, which is induced by the curcumin analogue B19 in an epithelial ovarian tumor cell line and that autophagy inhibition could increase curcumin analogue-induced apoptosis by inducing severe ER stress. The ability of curcumin to induce apoptosis in tumor cells and its anti-angiogenic potential will be discussed in this review.*

Curcumin, a yellow substance belonging to the polyphenols superfamily, is the active component of turmeric, a common

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Indian spice, which is derived from the dried rhizome of the *Curcuma longa* plant (1-2). Turmeric contains three principal components, curcumin, demethoxycurcumin and bisdemethoxycurcumin, of which curcumin is the most abundant and potent (3-6). Curcumin comprises approximately 2%-5% of turmeric (7).

Numerous studies have demonstrated that curcumin possesses anti-oxidant, anti-inflammatory and anticancer properties (8-18). Its ability to induce apoptosis in tumor cells and anti-angiogenic potential will be discussed in this review.

### Curcumin's Mechanisms of Action: The Role of STAT3 and NF-κB

The nuclear factor (NF)-κB, is a ubiquitous transcription factor that regulates many genes implicated in growth regulation, inflammation, carcinogenesis, and apoptosis (19-20). *In vitro* and *in vivo* studies have documented that constitutive activation of NF-κB results in inhibition of chemotherapy-induced apoptosis in a number of cancer cells (21-23). Signal transducer and activator of transcription 3 (STAT3) is a ubiquitously expressed member of the STAT family of transcription factors that is activated by tyrosine phosphorylation *via* upstream receptors, such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF) and cytokines, such as interleukin-6 (IL-6) (24). Recent studies have demonstrated that STAT3 may confer cancer resistance to chemotherapeutic agents (25-28).

STAT3 is one of the major mediators of carcinogenesis (29-30). The oncogenic significance of activated STAT3 molecules is due to their effects on various parameters, such as apoptosis, cell proliferation, angiogenesis, and immune system evasion (31, 32). Constitutively active STAT3 has been involved in the induction of resistance to apoptosis, probably through the expression of Bcl-xL and cyclin D1 (33-35). Its role in tumorigenesis is mediated through the expression of genes that suppress apoptosis, mediate proliferation, invasion, and angiogenesis. Constitutive activation of STAT3 has been implicated in a variety of

cancers, including breast cancer, prostate cancer, head and neck squamous cell carcinoma, multiple myeloma, lymphomas and leukemia, brain cancer, colon, gastric, esophageal, ovarian, nasopharyngeal and pancreatic cancer (36-47). Nevertheless, it is not completely understood why STAT3 is constitutively active in cancer cells.

Curcumin inhibits the STAT3 and NF- $\kappa$ B signaling pathways, which -as it has already been mentioned- play key-roles in cancer development and progression (48). Constitutive activation of the STAT3 and NF- $\kappa$ B signaling pathways has been demonstrated in prostate cancer cell lines and clinical samples of prostate cancer (49-52).

### Curcumin and Other Transcription Factors

Curcumin has also been suggested to induce apoptosis and cause down-regulation of EGFR, Akt, cMET cyclin D1, in CL-5 xenograft tumors (53). In addition, it has been documented to inhibit lung cell invasion and metastasis through up-regulation of HLJ1 expression in cancer cells (54). Apart from its action on STAT3 and NF- $\kappa$ B pathways, curcumin has been shown to inhibit cell proliferation, cell cycle arrest and stimulate apoptosis *via* modulation of other transcription factors, such as AP-1, Erg-1, p53,  $\beta$ -catenin, Notch-1, Hif-1, and PPAR- $\alpha$  (55).

### Curcumin and Sp-1

Sp-1, a transcription factor highly expressed in breast, gastric and thyroid tumor cells compared to normal cells, has been demonstrated to interact with co-activators and co-repressors and, thereby, activate multiple biological functions, including cell cycle and carcinogenesis. It has also been implicated in nuclear factors, protein-protein interaction, and sequence-specific DNA binding (56). Sp-1 has been related to housekeeping gene expression, such as vascular epithelial growth factors (*VEGF*), urokinase plasminogen activator (*uPA*), urokinase plasminogen activator receptor (*uPAR*) and epithelial growth factor receptor (*EGFR*), which are known to be involved in cell differentiation, tumor angiogenesis and metastasis (57-59). Hence, inhibition of Sp-1 and its housekeeping gene expressions may serve as an important hypothesis to prevent cancer formation, migration, and invasion (60-61). Recent data have suggested that curcumin may act by suppressing the Sp-1 activation and its downstream genes, including *ADEM10*, calmodulin (*CALM*), *EPHB2*, *HDAC4*, and *SEPP1* in a concentration-dependent manner in colorectal cancer cell lines; these results are consistent with other studies, which have reported that curcumin could suppress the Sp-1 activity in bladder cancer and could decrease DNA binding activity of Sp-1 in non-small cell lung carcinoma (NSCLC) cells (62, 63). In addition, curcumin has significantly reduced colony

formation in colorectal cancer cells. These results are in agreement with other studies, which have documented that down-regulation of Sp-1 prevents the colony formation in a patient-derived fibrocarcinoma cell line (64).

### Curcumin and Adhesion Molecules

Curcumin has been demonstrated to inhibit focal adhesion kinase (FAK) phosphorylation and enhance the expression of several extracellular matrix components, which play a pivotal role in invasion and metastasis. Curcumin has been shown to enhance cell adhesion ability, through induction of extracellular matrix components collagen I, collagen III, collagen IV, collagen IX, laminin, and fibronectin in a concentration-dependent manner. Taken together, these results have suggested that curcumin suppresses FAK activity by means of inhibition of its phosphorylation sites and also induces extra-cellular matrix components to enhance cell adhesion ability, thus, preventing detachment of cancer cells and cell migration. Inhibition of FAK expression leads to increased cell adhesion, which may be the potential mechanism of the anti-invasive effect of curcumin (65).

Curcumin has been shown to reduce CD24 expression in a dose-dependent manner in colorectal cancer cells. Moreover, E-cadherin expression has been documented to be up-regulated by curcumin and serve as an inhibitor of epithelial mesenchymal transition. These results suggest that curcumin could exert its function against metastasis, through down-regulation of Sp-1, FAK, and CD24 and by promoting E-cadherin expression in colorectal cancer cells (65). Also, Zhou *et al.* have evaluated eleven curcumin-related compounds, containing a benzyl piperidone moiety in various cancer cell lines and have found that some of them have been associated with a decrease in phospho-Akt and phospho-extracellular signal-regulated kinase (Erk)1/2 (65).

### Curcumin, Endoplasmic Reticulum Stress and Autophagy

Endoplasmic reticulum (ER) is an essential cellular compartment for protein synthesis and maturation. Various pathological conditions may affect ER homeostasis and interfere with protein folding, thus, resulting in an imbalance between ER protein folding load and capacity, leading to the accumulation of un-folded or mis-folded proteins in the ER (66). This cellular condition is widely known as ER stress. Autophagy is an evolutionarily conserved protein degradation pathway in eukaryotes, which plays a key-role in regulating protein homeostasis and which is essential for cell survival under metabolic stress. Ubiquitinated proteins are degraded by the proteasome through the ER-associated degradation pathway and by autophagy through the ER-activated autophagy pathway (67).

In addition to its role in cellular homeostasis, autophagy has been serving as a form of programmed cell death, as well as a cell-protective role in cases of nutrient deprivation (68-69). Recent studies have suggested that unfolded protein response signaling may also affect interactions within the cancer microenvironment. Unfolded protein response, autophagy and ER stress-induced apoptosis have been documented to regulate cancer cell future. Furthermore, different anti-cancer treatments may activate this signaling in tumor cells, a process that has been proposed to either enhance cancer cell death or to act as a mechanism of resistance to chemotherapy (70-72).

Recent data advocate that ER stress and autophagy may play a role in the apoptosis process, which is induced by the curcumin analogue B19 in an epithelial ovarian tumor cell line and in hepatocellular carcinoma cells and that autophagy inhibition could increase curcumin analogue-induced apoptosis by inducing severe ER stress. In other words, this curcumin analogue may induce ER-stress, autophagy and apoptosis in ovarian cancer cell lines *in vitro* (73-74). Other researchers have demonstrated that autophagy could act as programmed cell death type II and could efficiently suppress the growth of malignant glioma cells after curcumin treatment (75).

### Curcumin Bioavailability

Curcumin lacks toxicity and has lately gained much interest as a potential anticancer agent. Its main disadvantage is its low oral bioavailability due to its extensive first-pass metabolism and its poor aqueous solubility (76-81). It is widely known that the enhanced permeability and retention effect of nanomaterials may improve the accumulation of chemotherapeutic agents at tumor sites. For example, liposomes, carbon nanotubes, dendrimers, and micelles have been used as carriers for SN38, doxorubicin, paclitaxel, and cisplatin to improve drug concentrations in tumors and reduce adverse effects (81-86). Another advantage of using nanomaterials as drug carriers is the enhanced solubility of chemotherapeutic drugs. Self-assembling peptide nanofibers have attracted much attention due to their good biocompatibility, easy modification, and design flexibility through a “bottom-up” approach (87-88). They have been widely used in various cell cultures, as well as drug delivery systems to enhance solubility of a hydrophobic drug, improve accumulation at the tumor site, and reduce adverse effects (89). Hydrophobic antitumor drugs encapsulated into peptide nanofibers, such as paclitaxel, camptothecin and ellipticine, have shown improved anticancer effects (90-92). Some studies have demonstrated that the two-dimensional structure of peptide nanofibers is superior to the three-dimensional structure of nanoparticles for drug carriers. Indeed, Law *et al.* demonstrated that peptide-based

nanofibers have better biocompatibility, better tumor targeting within a shorter time and more rapid elimination compared with spherical nanomaterials (poly[lactic-co-glycolic acid], gold, polystyrene, cadmium and selenium quantum dots), and carbon rods (93).

Nowadays, curcumin has been much explored and various synthetic analogues have been prepared and evaluated for potential pharmacological activities (94-101). Some analogues have shown promising properties in various models and various cancer cell lines. A recent study documented that curcumin-related compounds with a benzyl piperidone have enhanced absorption and biological activities (102-103). Other studies have also demonstrated the potential anticancer properties of curcumin analogues (104-107). The incorporation of curcumin into nano-formulations for enhanced water-solubility has indeed revolutionized the bioavailability of curcumin. Nano-formulations have accomplished improved delivery and better concentrations of curcumin in the cell *in vitro*, while their prolonged release formulas along with their higher degree of compatibility seem to be very promising for their effects *in vivo* (108-110).

### Conclusion

Curcumin and its analogues have been demonstrated to possess various anticancer properties in a series of cancer cell lines, such as pancreatic, lung, ovarian, oral, colorectal, breast carcinoma and even in melanoma cells. In the future, further research will ascertain or not the potential of curcumin analogues as effective chemotherapy agents.

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