

## ANTICANCER ACTIVITIES OF CURCUMIN

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### Abstract

*Curcumin, an active constituent of Curcuma longa, is responsible for the anticarcinogenic activities which is mediated through multiple mechanisms. Curcumin affects the major transcription factors such as nuclear factor  $\kappa$ -light chain-enhancer of activated B cell (NF- $\kappa$ B) and activator protein-1 (AP-1). These factors regulate inflammation and are responsible for cell proliferation, differentiation and apoptosis.*

**Key Words:** Apoptosis, Antiinflammatory, Anticarcinogenic, Curcumin.

Turmeric (*Curcuma longa*) commonly known as Halad in Marathi and Haldi in Hindi is an Indian spice and medicinal plant belonging to Zingiberaceae family and is extensively used in Ayurveda, Unani and Siddha medicine as home remedy for various diseases.<sup>[1]</sup> The active constituent of turmeric is Curcumin, a flavonoid, responsible for the yellow color and volatile oils like tumerone, atantone and zingiberone. In this short review the potential role of Curcumin in apoptosis and carcinogenesis is summarized.

Apoptosis, a form of programmed cell death, is required to maintain the integrity and homeostasis of multicellular organisms. It is an important biological process, impairment of which may lead to cancer. Recent research has elucidated two biochemical signals that appear to be central to regulation of apoptosis: the cysteine proteases or caspases and the  $\beta$  cell lymphoma protein (bcl-2) related family members. The caspases are executor of cell death: they cause systematic disassembly of the apoptic cell by cleaving some key target proteins. The bcl-2 proteins modulate cell survival by suppressing the caspases activity. Over

expression of bcl-2 genes decrease apoptosis, thereby leading to cancer.

The ability of curcumin to induce apoptosis in cancer cells without cytotoxic effects on healthy cells contributes to the understanding of the anti-cancer potential of curcumin. Curcumin efficiently induces apoptosis in various cell lines like HL-60, K562, MCF-7 and HeLa.<sup>[2]</sup> Curcumin also leads to apoptosis in scleroderma lung fibroblasts (SLF) without affecting normal lung fibroblasts (NLF).<sup>[3]</sup> This effect seems to be due to the weak level of protein kinase (PK) C3 in SLF, generating low levels of glutathione S-transferase (GST). Induction of Caki (human kidney carcinoma cells) programmed cell death is activated by Akt dephosphorylation, bcl-2, bcl-XL and inhibitor of apoptosis (IAP) protein inhibition, as well as cytochrome c release and caspase 3 activation.<sup>[4]</sup> It was reported that in melanoma and HL-60 cells<sup>[5]</sup> described that curcumin induces caspases 8 and 9, although p53 remains unchanged. Nevertheless, the death receptor pathway is activated through Fas in a Fas-Ligand independent way.<sup>[5]</sup> The role of Bcl-2 and bcl-XL inhibition by preventing curcumin-induced apoptosis after over expressing these two key proteins was confirmed.<sup>[6,7]</sup> Inhibition of proteasome activity in mice, potentially leading to induction of apoptosis through caspase 9 activation was inhibited by curcumin.<sup>[8]</sup>

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Carcinogenesis is a complex process but may be broadly considered to be comprised of three main phases: initiation, promotion, and progression. These closely related steps: going from a normal cell to a transformed initiated cell (initiation); from initiated to pre-neoplastic cell (promotion); and from pre-neoplastic to neoplastic (progression); may lend them to curcumin intervention. There is suggestive evidence that inflammation may have a role in the three phases of carcinogenesis.<sup>[9]</sup>

Cancer initiation has been produced by oxidative stress and chronic inflammation.<sup>[10]</sup> Inflammation acts a key regulator in promotion of these initiated cells, possibly by providing them with proliferating signals and by preventing apoptosis.<sup>[11]</sup> The role of inflammation in tumor induction and subsequent malignant progression has been investigated.<sup>[12]</sup> Inflammatory response produces cytokines which act as 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. Tumor-infiltrating lymphocytes secrete matrix-degrading proteinases like matrix metalloproteinase 9 (MMP-9), thus promoting neoplastic proliferation, angiogenesis, and invasion.<sup>[12]</sup> The role of inflammation in cancer may be seen by the frequent up regulation of inflammatory mediators like NF- $\kappa$ B. The pathways activated by NF- $\kappa$ B up regulators are implicated in tumor growth and progression and also in cancer cell development of resistance to anti-cancer drugs and radiation. NF- $\kappa$ B is an excellent target for anti-cancer therapy.<sup>[13]</sup> The effect of curcumin on carcinogenesis is thought to be through inhibition of NF- $\kappa$ B as well as other molecular targets.

Inflammation may initiate carcinogenesis through the production of reactive oxygen species (ROS) and reactive nitrogen species by activated neutrophils and macrophages that lead to cancer causing mutations.<sup>[14]</sup> Curcumin has demonstrated significant reduction in the levels of inducible nitric oxide synthase (iNOS). Curcumin inhibits the induction of nitric oxide synthase and is a potent scavenger of free radicals like nitric

oxide.<sup>[15]</sup> NF- $\kappa$ B has been implicated in the induction of iNOS which produces oxidative stress, one of the causes of tumor initiation. Curcumin prevents phosphorylation and degradation of inhibitor  $\kappa$  B  $\alpha$ , thereby blocking NF- $\kappa$ B activation which down regulates iNOS gene transcription.<sup>[16]</sup> Deregulatory imbalances between adaptive and innate immunity results in chronic inflammation which is associated with epithelial tumorigenesis, through the NF- $\kappa$ B activation.<sup>[17]</sup> Curcumin was found to inhibit cell proliferation and cytokine production by inhibiting NF- $\kappa$ B target genes involved in this mitogen induction of T-cell proliferation, interleukin and nitric oxide generation.<sup>[16]</sup> Reduction induced over expression of cytokines, such as IL-10, IL-6, and IL-18, is accompanied by NF- $\kappa$ B induction which is controlled by and inhibited by curcumin.<sup>[18]</sup> Curcumin has been demonstrated to increase expression of conjugation enzymes (phase II). These have been shown to suppress ROS-mediated NF- $\kappa$ B, AP-1 and mitogen-activated protein kinases (MAPK) activation.<sup>[19]</sup>

These enzymes, such as sulfotransferase and glutathione-S-transferase, conjugate toxic metabolites (through phase I enzymatic action) and then excrete them as conjugated products.<sup>[19]</sup> In various cancer models, curcumin was reported to counteract ROS by increasing ornithine decarboxylase, glutathione, antioxidant enzymes and phase II metabolizing enzymes.<sup>[20]</sup> Heme oxygenase-1 (HO-1) has been reported to counteract the oxidative stress, modulate apoptosis and inhibit cancer cell proliferation. Curcumin induces HO-1 expression by signaling through nuclear factor (erythroid-derived 2)-related factor 2 (NRF-2) and NF- $\kappa$ B and thereby has the potential to reduce oxidative stress.<sup>[21-25]</sup> Curcumin prevents initiation of tumors either by curtailing the proinflammatory pathway or by inducing phase II enzymes.<sup>[26]</sup>

It has been reported that NF- $\kappa$ B has an important role in cancer initiation, promotion and progression. NF- $\kappa$ B binds to DNA and results in transcription of genes contributory to tumorigenesis: inflammation, anti-apoptosis and positive regulators of cell proliferation and angiogenesis.<sup>[26]</sup> NF- $\kappa$ B activation occur primary *via* inhibitor  $\kappa$  B kinase (IKK)-mediated

phosphorylation of inhibitory molecules.<sup>[27]</sup> Curcumin blocks NF- $\kappa$ B signaling and inhibits IKK activation.<sup>[28]</sup> The anti-tumor effect of curcumin was evidenced by its ability to decrease intestinal tumors in an animal model of FAP by reducing the expression of the oncoprotein  $\beta$ -catenin.<sup>[29]</sup> NF- $\kappa$ B repression and decreased  $\beta$ -catenin signaling are some of the mechanisms by which curcumin suppresses the promotion and progression of cancer.

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