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Anticancer Properties of Curcumin

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1. Introduction

Curcumin is a major biological active compound from turmeric or *Curcuma longa*. This non-toxic natural compound has been reported to possess several biological activities that are therapeutically beneficial to cancer treatment. It has been reported to increase the efficacy of other chemotherapeutic agents and to reduce their toxic side effects which are the major drawback of most chemotherapeutic agents. Curcumin is also well known for its anti-inflammatory activity (Amanda and Robert, 2008). Since cancer often develops under chronic inflammatory conditions, curcumin has the potential to be a preventive treatment agent against cancer. Furthermore, unlike most chemotherapeutic agents which act on a specific process of cancer development, i.e., cell growth or apoptosis, curcumin exerts its effect on various stages of cancer development, i.e., oncogene activation (Singh and Singh, 2009), cancer cell proliferation (Simon et al., 1998), apoptosis evasion (Han et al., 1999), anoikis resistance (Pongrakhananon et al., 2010), and metastasis (Chen et al., 2008) (Figure 1). Therefore, curcumin has the potential to overcome chemoresistance which is a major problem in cancer chemotherapy. This chapter will provide an overview of the anticancer activities of curcumin and present pre-clinical and clinical evidence supporting the use of curcumin as an anticancer agent.

Cancer is known to be associated with genetic instability in which *c-myc* serves as a major modifier of many targeted genes (Mai and Mushinski, 2003). Likewise, the mutation of proto-oncogene *ras* has been identified in many types of tumor (Rajalingam et al., 2007). The dysregulation of these oncogenes is well recognized as an initial step in the development of tumorigenesis. Interestingly, curcumin has been reported to have a suppressive effect on the oncogenes and inhibit their downstream effectors such as cell cycle promoting and proapoptotic proteins (Singh and Singh, 2009). Curcumin also exhibits anticancer properties through its ability to inhibit cell proliferation and induce apoptosis. The anti-proliferative effect of curcumin is dependent on its concentration, duration of treatment, and specific cell type. At low doses, curcumin causes cell cycle arrest, while at higher doses it induces apoptosis. Cell proliferation is controlled by several cell cycle regulating proteins, notably the family of cyclin and cyclin-dependent kinases (Kastan and Bartek, 2004) whose expression is tightly associated with tumorigenesis (Diehl, 2002). Curcumin inhibits cell cycle progression by downregulating cyclin D1 and the transition from G1 to S phase in

human head and neck squamous carcinoma cells (Aggarwal et al., 2004). It also inhibits bladder cancer cell proliferation through the downregulation of cyclin A and upregulation of p21 (Park et al., 2006).

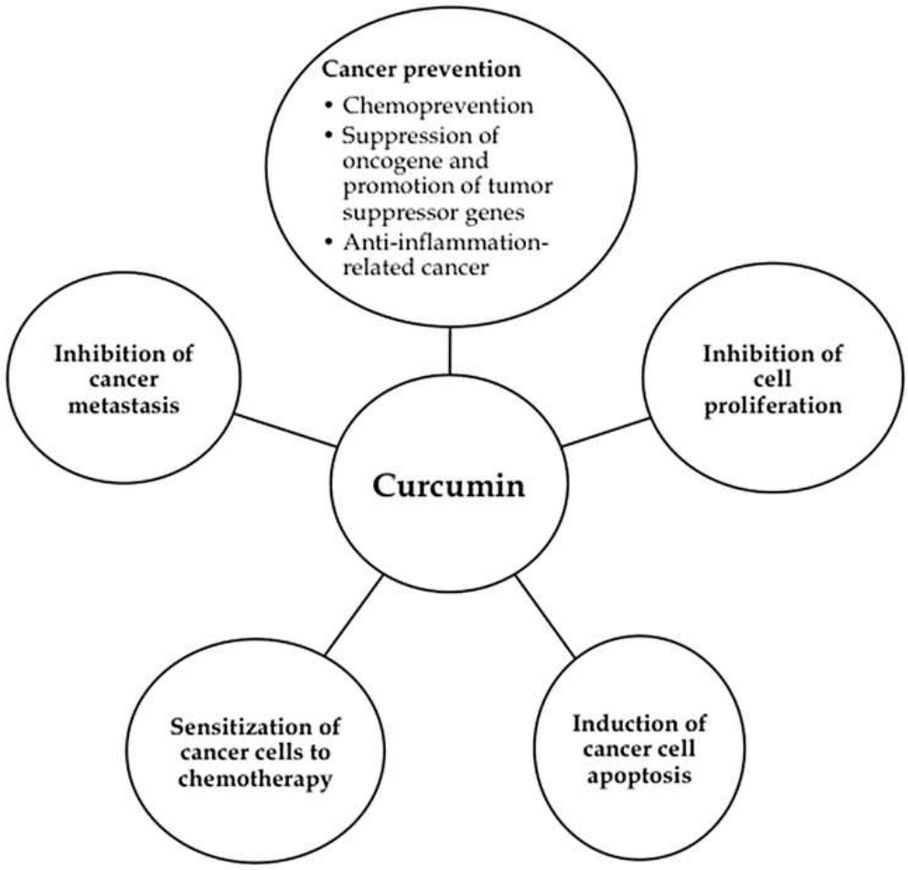

Fig. 1. Anticancer properties of curcumin

Curcumin possesses apoptosis-inducing activity causing cancer cell death primarily through the mitochondrial death pathway. It induces an upregulation of the proapoptotic protein Bax and downregulation of the antiapoptotic protein Bcl-2 in breast cancer cells (Chiu and Su, 2009), resulting in the loss of mitochondrial function, release of cytochrome c, and activation of caspase-9 and -3 (Chen et al., 2010). Curcumin also potentiates the cytotoxic effect of chemotherapeutic agents such as cisplatin (Chanvorachote et al., 2009), doxorubicin (Notarbartolo et al., 2005), tamoxifen (Chuang et al., 2002), and placitaxel (Genta and Amiji, 2009). The use of curcumin as a chemo-sensitizing agent in combination therapy has the potential to overcome chemoresistance which is common in advance staged cancers and is a major cause of cancer-related death.

An increasing number of reports have described the inhibitory effect of curcumin on cancer metastasis. Metastasis is a multi-step process involving tumor vascularization, cancer cell detachment, avoidance of anoikis, and increased cell invasion. The vascularization induced by tumor is an essential step providing nutrients, oxygen, and removing waste products for tumor growth and metastasis. A key mechanism that cancer cells utilize during metastasis is the acquisition of anoikis resistance. Anoikis or detachment-induced apoptosis is recognized as an important mechanism preventing cancer cell dissemination and invasion to form

secondary tumors. A recent study by our group has shown that curcumin is able to sensitize lung cancer cells to undergo anoikis through a mechanism that involves post-translational modification of Bcl-2 via the ubiquitin-proteasome pathway (Pongrakhananon et al., 2010). Curcumin also acts as a negative regulator of cancer cell migration and invasion through diverse signaling pathways including MMP-9, MMP-2 and COX-2 (Philip et al., 2004, Lee et al., 2005; Hong et al., 2006; Lin et al., 2009).

Animal and clinical studies of curcumin have been well investigated. In mice, curcumin markedly inhibits DMBA and TPA-induced skin tumor formation (Azuine et al., 1992). In a xenograft model, curcumin administration significantly decreases the incidence of breast cancer metastasis to the lung (Aggarwal et al., 2005). In phase 1 clinical studies, oral administration of curcumin was shown to be well tolerated with no dose-limiting toxicity (Sharma et al., 2004; Lao et al., 2006). In patients with intestinal metaplasia, curcumin treatment showed a significant improvement in the precancerous lesion (Cheng et al., 2001), supporting the clinical use of curcumin as a preventive treatment agent against cancer. Although curcumin has demonstrated promising pharmacological effects and safety both *in vitro* and *in vivo*, poor bioavailability and tissue accumulation have been observed with the compound. Further studies on proper drug delivery, dose optimization, and biodistribution are needed.

2. Chemistry of curcumin

For thousands of years, plants and some parts of animal have been used as dietary agents which have been identified to be biologically active. These natural compounds have gained considerable interest for their potential as treatment and preventive agents for human diseases. Curcumin (diferuloylmethane) is a major biologically active compound extracted from the dried rhizome of turmeric or *Curcuma longa*. It has been widely used for centuries as medicinal plant and food additive due to its yellow color. Its medicinal properties are attributed to curcuminoids, which include curcumin (curcumin I), demethoxycurcumin (curcumin II), and bisdemethoxycurcumin (curcumin III) (Figure 2). Curcumin I (77%) is a

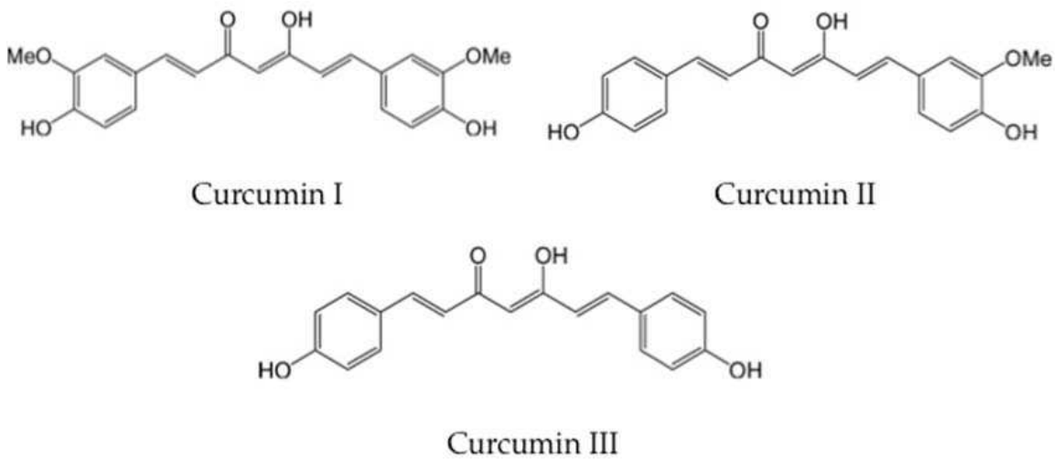

Fig. 2. Chemical structure of curcuminoids

major component found in commercial curcumin, while curcumin II and III constitute approximately 17% and 3% respectively. Cucumin is a water-insoluble compound, but

dissolves well in ethanol, dimethylsulfoxide, and other organic solvents. The molecular weight of curcumin is 368.37 and melting point is 183 °C. It shows a spectrophotometric maximum absorption (λmax) at 450 nm in methanol (Prasad and Sarasija, 1997). Fluorescence of curcumin occurs at 524 nm in acetonitrile and 549 nm in ethanol (Chignell et al., 1994). Curcumin undergoes rapid degradation in phosphate buffer and serum-free media, i.e., 90% within 30 minutes (Wang et al., 1997). In serum-containing (10%) media and human blood, curcumin is more stable with less than 20% degradation in 1 hour, and about 50% after 8 hours. Its degradation products are *trans*-6-(4′-hydroxy-3′-methoxyphenyl)-2,4-dioxo-5-hexenal (major) and vanillin, ferulic acid, and feruloyl methane (minor) (Wang et al., 1997).

3. Anticancer properties of curcumin

Curcumin has long been used as a dietary ingredient with known health benefits. Extensive research over the last decade has shown that curcumin possesses anticancer activities and could be used as a preventive or treatment agent against cancers, either as a single or combination therapy with chemotherapeutic agents. Curcumin exhibits biological activities in various stages of carcinogenesis including inhibition of oncogene activation, prevention of cancer-related inflammation, inhibition of cancer cell proliferation, induction of apoptosis and anoikis, prevention of metastasis, and sensitization of cancer cells to chemotherapy.

3.1 Cancer prevention

3.1.1 Chemopreventive properties

Carcinogenesis is a multistep process driven by genetic instability. Continuous exposure to environmental and endogenous genotoxic agents can cause substantial DNA damage. The damaged molecules can be transmitted during cell division producing mutated clones that can give rise to the expansion of premalignant cell population possessing uncontrolled proliferative and invasive properties. Curcumin has been established as a chemopreventive agent that has the ability to suppress or retard the carcinogenic process induced by various chemical carcinogens (Table 1). In animal models of gastric and colon cancer, curcumin inhibits the development of cancerous and precancerous lesions induced by N-methyl-N'-nitro-N-nitrosoguanosine (MNNG), a known mutagenic agent causing DNA methylation (Ikesaka et al., 2001). In the study, MNNG was given in drinking water at the concentration of 100 ppm for 8 weeks, and then 0.2% or 0.5% of curcumin was fed to the rats for 55 weeks. The results showed that the number of atypical hyperplasia in curcumin-treated rats was significantly less than that in the control group. Similarly, the curcumin analog bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione was shown to inhibit the tumorigenic effect of 1,2-dimethylhydrazine in rats (Devasena et al., 2003). Furthermore, natural and synthetic curcuminoids exhibit an inhibitory effect on mutagenesis induced by 2-acetamidofluorene (2-AAF) (Anto et al., 1996). In the study, up to 87% of 2-AAF-induced papilloma was inhibited by bis-(p-hydroxycinnamoyl)methane (curcuminoid III), while 70% and 68% of the papilloma were inhibited by feruloyl-p-hydroxycinnamoylmethane (curcuminiod II) and diferuloylmethane (curcuminoid I), respectively. The most potent curcuminoid was salicylcurcuminoid which completely inhibited the papilloma formation.

3.1.2 Suppression of oncogenes and upregulation of tumor suppressor genes

As mentioned earlier, genetic instability is linked to the initiation of carcinogenesis. This irreversible process involves several molecular events that either promote the activity of

oncogenes such as myc and ras or impede the function of tumor suppressor genes such as p53 (Vogelstein and Kinzler, 2004). Curcumin has been shown to suppress oncogenes and activate tumor suppressor genes in various cancer cell types (Table 1). In an *in vivo* study, curcumin suppresses c-fos and c-Ha-ras activation induced by environmental mutagenic agents (Limtrakul et al., 2001). Dietary administration of curcumin (0.1-0.2%) prevents 2-dimethylbenz(α)anthracene (DMBA) and 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced skin tumor in mice. There is an increase in the oncogene (c-fos and ras) expression in this tumor model, which is suppressed by the dietary curcumin. Similarly, c-myc is also a target oncogene attenuated by curcumin in the TPA-induced tumor model (Kakar and Roy, 1994).

Chemopreventive properties			
Cancer	Carcinogen	Animal	References
Stomach cancer	MNNG	Rat	Ikesaki et al., 2001
Colon cancer	DMH	Rat	Devasena et al., 2003
Papilloma	2-AAF	-	Anto et al., 1996
Mammary tumor	DMBA	Rat	Pereira et al., 1996
Skin tumor	TPA	Mouse	Lu et al., 1993
Liver cancer	Diethylnitrosamine	Mouse	Chuang et al., 2000
Oncogene suppression and tumor suppressor gene activation			
Cancer	Mechanism		References
Skin tumor	Suppress c-fos and c-Ha-ras-activation by DMBA		Limtrakul et al., 2001
B cell lymphoma	Suppress c-myc		Han et al., 1999
Mouse skin cancer	Suppress c-myc activated by TPA		Kakar & Roy, 1994
Human colon adenocarcinoma	Enhance p53 activity		Song et al., 2005
Human breast cancer	Enhance p53 activity		Choudhuri et al., 2002
Human glioma	Enhance p53 activity		Liu et al., 2007
Anti-inflammation -related cancer			
Cancer	Mechanism		References
-	Inhibit NO synthase in macrophages		Brouet & Ohshima, 1995
Human mantle cell lymphoma	Inhibit constitutive NF-κB activation		Shishodia et al., 2005
Mouse melanoma	Inhibit constitutive NF-κB activation		Marin et al., 2007
Human oral cancer	Inhibit constitutive NF-κB activation		Sharma et al., 2006
Non-small cell lung carcinoma	Inhibit constitutive NF-κB activation and COX expression		Shishodia et al., 2003

Table 1. Cancer preventive properties of curcumin

3.1.3 Anti-inflammatory activity

Epidemiological studies have supported the concept that cancers frequently originate at the site of chronic inflammation. This event has increasingly been accepted as the seventh hallmark of cancer (Colotta et al., 2009). Inflammation is a vital physiological process in response to injury, which leads to the mediation of inflammatory cells in the presence of enzymes and cytokines for repairing tissue damage. The linkage between cancer and inflammation is generally characterized as being intrinsic or extrinsic (Mantovani et al., 2008). The extrinsic pathway is induced by inflammation that facilitates cancer development, while the intrinsic pathway is driven by genetic instability causing inflammatory environment-related cancer. Both processes mediate the transcription factors involved in cell proliferative function and persistent activation of this event can lead to cancer. A considerable number of reports have described the linkage between cancer preventive properties and anti-inflammatory action of curcumin (Table 1). Mechanistically, curcumin inhibits the induction of nitric oxide synthase (NOS) by activated macrophages (Brouet and Ohshima, 1995). Nitric oxide (NO) and its derivatives such as peroxynitrite play a critical role in the inflammation process causing fibroblast proliferation and fibrosis (Romanska et al., 2002). Treatment of macrophages with lipopolysaccharide (LPS) and IFN-γ induces an inflammatory response that leads to the release of NO, which is inhibited by curcumin. Curcumin also suppresses the transcription of inducible NOS which is activated by LPS and IFN-γ. Since NO is implicated in tumor promotion, the attenuation of NO by curcumin hence suppresses tumor development.

Numerous studies have suggested that NF-κB plays a key role in promoting cancer development during chronic inflammation. NF-κB regulates the expression of several genes involved in the immune and inflammatory responses as well as in cell proliferation and apoptosis (Karin et al., 2002). It is required for the expression of a wide range of inflammatory cytokines and adhesion molecules, and is important in the cellular proliferative function by activating growth factor genes, proto-oncogenes and cell cycle regulators that contribute to carcinogenesis. In a study using human mantle cell lymphoma (MCL), curcumin inhibits constitutive NF-κB activation leading to the suppression of NF-κB regulated genes (Shishodia et al., 2005). MCL expresses a high level of cyclin D1, a cell cycle promoting factor and target transcription of NF-κB, which is a key survival factor of this cancer type. Curcumin treatment causes downregulation of constitutive NF-κB activation, inhibits IκBα kinase (IKK) and phosphorylated IκBα and p65, leading to cell cycle arrest and apoptosis. NF-κB is overexpressed in various tumors and cancer cell lines including melanoma cells. Electrophoretic mobility shift and gene reporter assays have demonstrated that curcumin suppresses constitutive NF-κB activation in melanoma cells and increases the number of cells in the sub G1 phase of cell cycle (Marin et al., 2007). Interestingly, curcumin shows selectivity in inducing apoptosis of melanoma cells but not melanocytes.

Other mechanisms of the anti-inflammatory-related cancer effect of curcumin have been proposed including suppression of cyclooxygenase 2 (COX-2). A wide range of stimuli mediates COX-2 expression and overexpression of this molecule is found in various cancer types in association with accelerated cell growth, antiapoptotic activity, angiogenesis, and metastasis (Prescott and Fitzpatrick, 2000). In a cigarette-smoking (CS) study using non-small cell lung cancer model, CS exposure activates NF-κB and subsequently induces COX-2 expression, which is inhibited by pre-treatment with curcumin (Shishodia et al., 2003). This chemopreventive property of curcumin is also observed in smokeless-tobacco mediated

activation of NF-κB and its downstream target COX-2 (Sharma et al., 2006). Since inflammation contributes to tumor initiation, and curcumin possesses anti-inflammatory activity, curcumin could be beneficial in cancer prevention.

3.2 Inhibition of tumor growth and cell proliferation

Excessive proliferation is a hallmark of cancer (Hanahan and Weinberg, 2000). Aberrational cell division is an important basis of cancer development allowing formation and expansion of tumor growth. In normal cells, cell proliferation requires the growth signal that is generated by cell-cell interaction, neighbour cells and extracellular matrix. Cancer cells can further generate their own growth signals, upregulate growth receptors, and be desensitized to antigrowth factors. Upon transmitting the growth signals to their receptors, downstream mediators are activated which drive the quiescent cells to proliferative cycle (Evan and Vousden, 2001). Curcumin has been shown to modulate the expression and activity of growth factors, including epidermal growth factor (EGF) and insulin-like growth factor (IGF) (Table 2). Overexpression of EGF and its receptor, EGFR, was found in human prostate cancer cells undergoing rapid growth expansion (Cai et al., 2008). It has been demonstrated that curcumin blocks the EGF pathway through downregulation of EGFR, suppression of intrinsic EGFR tyrosine kinase activity, and inhibition of ligand-induced EGFR activity in both androgen-dependent and androgen-independent prostate cancer cells (Dorai et al., 2000).

Inhibition of cancer proliferation and tumor growth		
Cancer	Mechanism	References
Prostate cancer cells	Downregulation of EGFR, suppression of intrinsic EGFR tyrosine kinase activity, and inhibition ligand-induced EGFR activity	Dorai et al., 2000
Prostate and breast cancer cells	Downregulation of cyclin D1	Mukhopadhyay et al., 2002
Breast cancer cells	Suppression IGF system	Xia et al., 2007
Breast cancer cells	Induction of cell cycle arrest at S, G2/M phase by upregulation of p21	Chiu & Su, 2009
Human epidermoid carcinoma cells	Inhibit EGFR activity	Korutla & Kumar, 1994
Colon carcinoma cells	Induction of cell cycle arrest at S, G2/M phase	Chen et al., 1999
Human head and neck squamous carcinoma cells	Downregulation of cyclin D1	Aggarwal et al., 2004
Human biliary cancer cells	Downregulation of cyclin D1	Prakobwong et al., 2011
Human hepatocarcinoma cells	Induction of cell cycle arrest at S, G2/M phase	Cheng et al., 2010

Table 2. Inhibition of cancer proliferation and tumor growth

Likewise, insulin-like growth factor has been implicated in the regulation of normal cell growth, in which its atypical expression is found in human cancer cells (Samani et al., 2007). Curcumin abrogates IGF-1 system in MCF-7 human breast carcinoma cells (Xia et al., 2007). It decreases IGF-1 secretion in concomitant with the increasing IGF binding protein IGFBP-3 in a dose-dependent fashion. Furthermore, it abolishes IGF-1-stimulated MCF-7 growth through the suppression of IGF-1 mediated receptor activity and downregulation of IGF receptor mRNA expression.

Deregulation of cell cycle causes limitless replicative potential of cancer. Curcumin exhibits antiproliferative activity via the regulation of cell cycle (Table 2). It disrupts the progression of cell cycle by increasing the number of cancer cells at S, G2/M phase, hence preventing cell entering next cycle (Chen et al., 1999). Additional mechanistic studies indicate that curcumin downregulates cyclin D1 expression through inhibition of its promoter activity and enhanced degradation (Mukhopadhyay et al., 2002). Cyclin D1 is a subunit of cyclin-dependent kinase (Cdk)-4 and Cdk-6 which plays a key role in determining the cell cycle progression from G1 to S phase (Baldin et al., 1993) and overexpression of this gene is a common event in several forms of cancer (Knudsen et al., 2006). Similarly, in the presence of curcumin, cyclin D1 is suppressed as a result of NF-κB inhibition as observed in human head carcinoma, neck squamous carcinoma, and biliary cancer cells (Aggarwal et al., 2004; Prakobwong et al., 2011).

3.3 Induction of cancer cell apoptosis

Apoptosis plays an essential role in various physiological and pathological processes (Hengartner, 2000). Tissue homeostasis maintains the balance of cell proliferation and cell death as part of normal tissue development. Dysregulation of this process can lead to several diseases including cancer. Avoidance of apoptotic cell death is a major characteristic of malignant cells in response to stress conditions, which is achieved by activating the antiapoptotic signals or inhibiting proapoptotic signals (Hanahan and Weinberg, 2000). Several strategies have been developed to overcome this defective mechanism in cancers and curcumin has shown promising activities that modulate this mechanism in favor of cancer cell apoptosis.

Apoptosis generally occurs through two main pathways, intrinsic and extrinsic (Lavrik et al., 2005). The intrinsic pathway is initiated by several cellular stresses such as DNA damage which activates proapoptotic proteins, notably the Bcl-2 family proteins, causing mitochondrial membrane permeabilization and subsequent activation of the caspase cascade. In the extrinsic pathway, the interaction between death ligands and death receptors results in the assembly of death-inducing signaling complex (DISC) and the activation of initiator caspases. Curcumin is known to overcome the apoptosis resistance of cancer cells through both pathways (Table 3). In human acute myelogenous leukemia HL-60 cells, curcumin induces apoptosis by suppressing the expression of antiapoptotic Bcl-2 and Bcl-xL, causing cytochrome c release, caspase-3 activation, and PARP cleavage (Anto et al., 2002). Curcumin also stimulates the death receptor pathway through caspase-8 activation but overexpression of the DISC protein FADD cannot protect the cells from apoptosis in response to curcumin. In A549 lung adenocarcinoma cells, curcumin treatment up-regulates the mitochondrial Bax protein expression, suggesting the intrinsic pathway as a major pathway of curcumin-induced apoptosis in this cell type (Chen et al., 2010).

Molecular mechanisms of curcumin-induced apoptosis		
Cancer	Mechanism	References
Human acute myelogenous leukemia cells	Downregulation of Bcl-2 and Bcl-xL	Anto et al., 2002
Lung adenocarcinoma cells	Upregulation of Bax and Downregulation of Bcl-2	Chen et al., 2010
Rat histocytoma cells	Induction of ROS production	Bhaumik et al., 1999
Human gingival fibroblasts and human submandibular gland carcinoma cells	Induction of ROS production	Atsumi et al., 2006
Human breast cancer cells	Downregulation of anti-apoptotic and upregulation of proapoptotic proteins in a p53-dependent manner	Choudhuri et al., 2002
Human breast cancer cells	Inhibition of PI3K/Akt pathway	Squires et al., 2003
Human breast and hepatic cancers cells	Glutathione depletion and ROS production	Syng-Ai et al., 2004
Human ovarian cancer cells	Upregulation of caspase-3 and downregulation of NF-κB expression	Zheng et al., 2002
Human colon cancer cells	Induction of ROS production and deactivation of JNK pathway	Moussavi et al., 2006
Human colon adenocarcinoma cells	Downregulation of anti-apoptotic and upregulation of proapoptotic proteins in a p53-dependent manner	Song et al., 2005
Human melanoma cells	Activation of caspase-3, and -8, Fas receptor aggregation, suppression of NF-κB activation, and downregulation of XIAP expression	Bush et al., 2001
T cell leukemia cells	Inhibition of PI3K/Akt pathway	Hussain et al., 2006
Prostate cancer cells	Inhibition of PI3K/Akt pathway	Shankar & Srivastava, 2007
Human glioblastoma cells	Increasing Bax:Bcl-2 ratio, activation of caspase-8, -9, and -3, downregulation of NF-κB	Karmakar et al., 2006
Breast cancer cells	Inhibition of MAPK and PI3K/Akt pathway	Squires et al., 2003

Table 3. Molecular mechanisms of curcumin-induced apoptosis

In human melanoma cells, curcumin induces apoptosis through the extrinsic pathway by activating caspase-8 (Bush et al, 2001). Inhibition of caspase-8 by specific caspase-8 inhibitor or pan-caspase inhibitor prevents cancer cell apoptosis, whereas specific caspase-9 inhibitor lacks this ability. The underlying apoptosis mechanism involves the induction of Fas receptor oligomerization independent of Fas ligand, supporting the role of death receptor modification in curcumin-induced apoptosis. In some cancers such as human glioblastoma T98G cells, curcumin induces apoptosis through both pathways (Karmakar et al., 2006).

The activation of apoptotic pathwas by curcumin is regulated by reactive oxygen species (ROS). In various cancer cell types including H460 non-small cell lung cancer cells (Chanvorachote et al., 2009), AK5 rat histocytoma cells (Bhaumik et al., 1999), human gingival fibroblasts (HGF), and human submandibular gland carcinoma (HSG) cells (Atsumi et al., 2006), the induction of apoptosis by curcumin requires ROS generation. Likewise, in MCF-7, MDAMB, and HepG2 cells, apoptosis is mediated through oxidative stress induced by curcumin as a result of glutathione depletion (Syng-Ai et al., 2004). In colon cancer cells, curcumin-induced cell death is associated with ROS generation that converges on JNK activation (Moussavi et al., 2006).

Other mechanisms of curcumin-induced apoptosis have been reported. In human HT-29 colon adenocarcinoma (Song et al., 2005) and breast cancer cells (Choudhuri et al., 2002), curcumin upregulates proapoptotic proteins and downregulates antiapoptotic proteins in the Bcl-2 family through p53-dependent mechanism. In T cell leukemia (Hussain et al., 2006) and breast cancer cells (Squires et al., 2003), apoptosis induced by curcumin involves PI3K/Akt signaling pathway. Curcumin inhibits Akt phosphorylation and upregulates p53 expression which induces the proapoptotic Bcl-2 family proteins facilitating cell apoptosis (Shankar and Srivastava, 2007).

3.4 Sensitization of cancer cells to chemotherapy

In addition to its direct apoptosis-inducing effect, curcumin has been reported to sensitize cancer cells to chemotherapy-induced cell death. The main problem of cancer chemotherapy is the acquisition of apoptosis resistance of cancer cells and the cytotoxicity to normal cells. Combination therapy is an alternative approach that can overcome this problem by potentiating the effects of combination drugs and reducing their cytotoxicity by using optimal dosage regimens. Curcumin is one such agent that has been investigated for its effect in combination therapy (Table 4). In non-small cell lung cancer cells, we have recently shown that cotreatment of the cells with cisplatin and curcumin results in a substantial increase in cancer cell death as compared to cisplatin treatment alone (Chanvorachote et al., 2009). Since cisplatin-based therapy is the first line drug for treatment of lung cancer and the efficacy of this drug is frequently attenuated by the development of drug resistance especially in advanced stage cancer (Chang, 2011), curcumin has the potential to overcome this resistance problem. Curcumin promotes the apoptotic effect of cisplatin by inducing superoxide anion and downregulating the anti-apoptotic Bcl-2 protein which facilitates the cancer cell killing by cisplatin.

In pancreatic cancer cells, the acquisition of apoptosis resistance to the combination therapy of gemcitabine and capecitabine (a prodrug of 5-fluorouracil, 5-FU) is frequently observed. It is thought that overexpression of the multidrug resistance-associated protein 5 (MRP5), which promotes cellular efflux of the drugs (Szakacs et al., 2006), contributes to the

resistance. Curcumin was shown in a recent study to inhibit MRP5 activity and increase the sensitivity of pancreatic cancer cells to 5-FU-induced toxicity in a dose-dependent manner (Li et al., 2010).

Cancer cells	Chemotherapeutic drugs	References
Non-small cell lung cancer cells	Cisplatin	Chanvorachote et al., 2009
Pancreatic cancer cells	5-Fluorouracil	Li et al., 2010
Hela cells	Taxol	Bava et al., 2005
Human hepatic cancer cells	Doxorubicin	Notarbartolo et al., 2005
Hepatocellular carcinoima cells	Doxorubicin	Chuang et al., 2002
Human ovarian adenocarcinoma cells	Paclitaxel	Ganta & Amiji, 2009
Human melanoma cells	Tamoxifen	Chatterjee & Pandey, 2011
Human colorectal cancer cells	Oxaliplatin	Howells et al., 2010
Bladder cancer cells	Gemcitabine	Tharakan et al., 2010

Table 4. Curcumin potentiates chemotherapeutic agent-induced cancer cell death

Curcumin also augments the therapeutic effect of taxol in Hela cells (Bava et al., 2005). The synergistic mechanism involves the inhibition of NF-κB activation and Akt phosphorylation which results in increased apoptosis and decreased DNA synthesis of cancer cells independent of tubulin polymerization. The increased susceptibility of cancer cells to chemotherapeutic agents by curcumin might overcome the drug resistance problem, thus improving the clinical outcomes.

3.5 Inhibition of cancer metastasis

Cancer metastasis is the spread of cancer cells from the initiation site to other parts of the body, and particularly presented in several advanced stage cancers which are difficult to treat (Gubta and Massagué, 2006). Cancer metastasis is a multistep process involving complex interactions between the disseminating cancer cells and their microenvironment. When transformed cells are initiated and continue to grow at the primary site, angiogenic factors are synthesized for vascularization which increases the likelihood of tumor cells to enter in the blood stream or lymphatic system and colonize at distant sites. Once at the new sites, the extravasation of cancer cells allows the formation and growth of secondary tumors which complete the metastatic process (Fidler, 2003). Agents that inhibit metastasis provide a major advantage in treating cancers. Several studies have shown that curcumin inhibits cancer angiogenesis, migration and invasion by interacting with key regulatory molecules as summarized in Table 5.

It is well established that vascular endothelial growth factor (VEGF) and matrix metallo-proteinase family proteins (MMP) are essential factors in the angiogenesis and invasion of cancer cells (Carmeliet, 2005; Helmestin et al., 1994). In non-small cell lung cancer cells, VEGF, MMP-9 and MMP-2 are inhibited by curcumin through MEKK and ERK-dependent pathways, resulting in inhibition of cell migration and invasion (Lin et al., 2009). Similarly, in a human glioblastoma xenograft mouse model, curcumin inhibits tumor growth,

suppresses angiogenesis, and increases animal survival through the inhibition of MMP-9 and neovascularization (Perry et al., 2010). Curcumin also acts as a potent inhibitor of breast cancer cell motility and invasion through the attenuation of MMP-3 which acts as an invasive factor in this cancer cell type (Boonrao et al., 2010).

Cancer	Effects	Mechanism	References
Human non-small cell lung cancer	Inhibition of cell invasion and migration	Inhibition of VEGF, MMP-9, and MMP-2 through MEKK and ERK pathway	Lin et al., 2009
Human glioblastoma	Suppression of angiogenesis	Inhibition of MMP-9	Perry et al., 2010
Human breast cancer	Inhibition of cancer motlity and invasion	Attenuation of MMP-3 activity	Boonrao et al., 2010
Human non-small cell lung cancer	Sensitization of cancer cell anoikis	Downregulation of Bcl-2 through proteasomal degradation	Pongrakhananon et al., 2010
Human lung cancer	Inhibition invasion and metastasis	Activation of tumor suppressor HLJ1 through JNK/JunD pathway	Chen et al., 2008
Human colon cancer	Inhibition of migration	Inhibition of neurotensin-mediated activator protein-1 and NF-κB activation, and suppression of neurotensin-stimulated IL-8 gene induction	Wang et al., 2006
Prostate cancer	Inhibition of invasion	Downregulation of MMP-2 and MMP-9	Hong et al., 2006
Human fribosarcoma	Inhibition of migration and invasion	Downregulation of MMP-2, MMP-9, uPA, MT1-MMP, and TIMP-2	Yodkeeree et al., 2008

Table 5. Antimetastatic properties of curcumin

Several studies have investigated the molecular mechanisms of cancer cell survival during metastasis. Survival of primary cancer cells in the circulation is a key factor determining its metastatic ability. In general, most adherent cells undergo apoptosis when detached due to improper environmental conditions. This detachment-induced apoptosis or anoikis which is often impaired in metastatic cancers (Mehlen and Puisieux, 2006) has increasingly been recognized as an important mechanism for controlling cancer cell dissemination and invasion to secondary sites. A recent study by our group has shown that curcumin can sensitize non-small cell lung cancer cells to anoikis (Pongrakhananon et al., 2010) through a mechanism that involves Bcl-2 downregulation through ubiquitin-proteasomal degradation. This process is dependent on ROS generation, partcularly superoxide anion which mediates the Bcl-2 degradation process, consistent with the previous findings on the pro-oxidant properties of curcumin (Bhaumik et al., 1999; Khar et al., 2001; Wang et al., 2008).

3.6 Animal studies

Several animal studies have been reported on the anticancer and chemopreventive effects of curcumin in various cancer types. Since the *in vivo* chemopreventive effect of curcumin has earlier been described under 3.1.1 and summarized in Table 1, we will focus on the direct *in vivo* anticancer properties of curcumin.

The anticancer property of curcumin in prostate cancer was investigated by using prostate cancer cells implanted into nude mice (Dorai et al., 2001). Dietary curcumin at the concentration of 2% was given to the mice, and after 6 weeks of treatment the animals were examined for tumor growth, apoptosis, and vascularity. The results showed that curcumin was able to decrease tumor volume, increase cancer cell apoptosis, and inhibit vascular angiogenesis as indicated by the reduction in microvessel density. A similar study using a murine xenograft model of human lung carcinoma cells was reported (Su et al., 2010). In this study, NCI-H460 cells were implanted subcutaneously into nude mice, and curcumin (30 and 45 mg/kg of bodyweight) was intraperitoneally injected into the mice every 4 days after the tumor reached 100 mm^3 in size. Curcumin was shown to significantly decrease the tumor size as compared to non-treated control.

The antitumor property of curcumin-encapsulated nanoparticles was investigated in the xenograft mouse model of human pancreatic cancer (Bisht et al., 2010). The nanoparticle formulation was injected twice daily for 3 weeks into the xenografted mice. Plasma concentration of curcumin was sustained in the treated mice at Tmax of 2.75 ± 1.50 h and Cmax of 17,176 ± 5,176 ng/ml. Tumor volume was substantially decreased in curcumin treated group. A greater antitumor effect was observed when curcumin was combined with gemcitabine. Curcumin also exhibited antimetastatic activity which was greatly enhanced by the combination treatment. The underlying mechanism of curcumin action involves NF-κB activation and downregualtion of cyclin D1 and MMP-9.

Curcumin also improves the therapeutic activity of paclitaxel in breast cancer (Aggarwal et al., 2005). Since most metastatic breast cancers acquire apoptosis resistance to paclitaxel, which is the first line therapy for breast cancer, a combination therapy with apoptosis-sensitizing agents such as curcumin could be beneficial. In a mouse model of breast cancer metastasis, curcumin was shown to decrease the incidence of breast cancer metastasis to the lung as compared to paclitaxel treatment alone. Tissue sections from treated animals showed that NF-κB, MMP-9, and COX-2 expression were increased in the paclitaxel-treated group but suppressed in the curcumin co-treatment group, supporting the ability of curcumin to abrogate paclitaxel resistance in this metastatic breast cancer model.

3.7 Clinical studies

Several clinical studies are ongoing to investigate the efficacy and safety of curcumin as a preventive treatment agent for a variety of cancers. In prospective phase I clinical trials, curcumin was shown to be safe even at high doses (Cheng et al., 2001). In this study, patients with premalignant lesions caused by oral leukoplakia, intestinal metaplasia, uterine cervical intraepithelial neoplasia, skin Bowen's disease, and bladder cancer were given a curcumin tablet which was taken orally for the period of three months at the daily dose of 500, 1000, 2000, 4000, and 8000 mg. No toxicity was observed in these patients even the highest dose (8000 mg/day). However, this dose was unacceptable by the patients due to its bulky volume. Peak serum concentration of curcumin after the 4000 mg administration was 0.51±0.11 μM, and 0.63±0.06 μM and 1.77±1.87 μM respectively after the 6000 mg and 8000 mg dosing. A similar study showed that a single dose of curcumin up to 12,000 mg had no

dose-limiting toxic effect in healthy volunteers, not even minor adverse effects such as diarrhea (Lao et al., 2006).

Expanding from the above findings, another phase I clinical study was conducted in patients with colon adenocarcinoma to investigate the phamacodynamic of curcumin (Sharma et al., 2004). Curcuminoid, formulated as 500 mg in soft gelatin capsule containing 450 mg of curcumin, 40 mg of desmethoxycurcumin, and 10 mg of bisdesmethoxycurcumin, was taken orally at the dose of 450, 900, 1800, and 3600 mg/day of curcumin for 4 months. Since curcumin is known to induce glutathione S-transferase (GST), suppress prostaglandin E2 (PGE2) production, and inhibit oxidative DNA adduct (M1G) formation, these biomarkers are frequently used to indicate curcumin efficacy. Curcumin and its metabolites were collected from plasma, urine, and feces, and analyzed to assess the pharmacokinetic parameters. The results showed that curcumin was well tolerated by the patients without a dose-limiting toxicity, except in a few cases where patients reported a minor gastrointestinal upset. The result also showed that curcumin at the dose of 3600 mg/day was suitable for phase II evaluation. Curcumin was shown to inhibit PGE2 without affecting GST and M1G, suggesting that GST and M1G may not be useful as indicators for curcumin efficacy. Furthermore, curcumin and its glucuronide and sulfate metabolites were found in the plasma and urine. The presence of these metabolites at all time points indicates that curcumin has poor systemic availability when given orally.

Consistent with the above finding, numerous other studies have demonstrated low systemic bioavailability of curcumin resulting from poor absorption, rapid metabolism, and rapid systemic elimination (Hsu et al., 2007; Ireson et al., 2001; Maiti et al., 2007; Garcea et al., 2004). Glucuronide and sulfate metabolites of curcumin are rapidly detected in the peripheral and portal circulation after curcumin administration (Garcea et al., 2004). In this study, patients with liver metastasis from colorectal adenocarcinoma were administered orally with curcumin at the daily dose of 450, 1800, and 3600 mg for a week. No curcumin or its metabolites was detected in the bile or hepatic tissue, indicating that curcumin is not suitable for treating patients with tumors distant from the absorption site.

In a phase II clinical study conducted in patients with advanced pancreatic cancer, curcumin was administered orally at the dose of 8 g/day for 8 weeks (Dhillon et al., 2008). The treatment was well tolerated by the patients with no systemic side effects, while effectively reducing the tumor size and the activation of NF-κB and COX-2. Mechanistically, curcumin induces cancer cell apoptosis through an upregulation of p53 in the tumor tissues (He et al., 2011).

4. Conclusion

Curcumin has a great potential in cancer therapy and is gaining wide acceptance as a preventive treatment agent due to its safety. It affects multiple steps in the carcinogenic process, which is important in avoiding chemoresistance. Clinical studies have indicated its efficacy as a single agent or in combination therapy; however, more rigorous testing are needed. Furthermore, problems associated with the low bioavailability of curcumin, including poor absorption, rapid metabolism, and limited tissue distribution, must be addressed. Current strategies that have been investigated to overcome these problems include alternative administration routes, chemical modifications, and various drug delivery and formulation strategies. These strategies will likely benefit the development of curcumin as an anticancer agent.

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6. References

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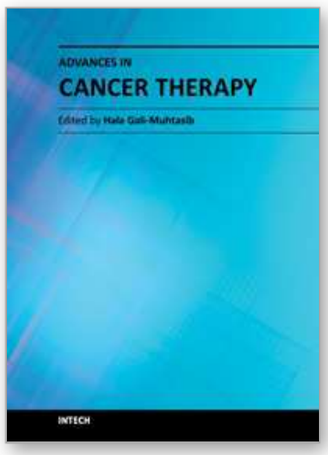

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