# Chapter 17
# Curcumin: Structure, Biology and Clinical Applications

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**Abstract** Curcumin, the principal polyphenolic curcuminoid derived from the rhizome *Curcuma longa*, is present in an Indian spice, turmeric. Curcumin possesses antitumor, antioxidant, and anti-inflammatory properties, and has been studied as a cancer chemopreventive agent. Curcumin is extensively studied, evaluated and accepted for its wide range of medicinal properties. The therapeutic activities of curcumin for a wide variety of diseases such as diabetes, allergies, arthritis and other chronic and inflammatory diseases have been known for a long time. The mechanisms of therapeutic action of curcumin include inhibition of several cell signaling pathways at multiple levels, immune-modulation, effects on cellular enzymes such as cyclooxygenase and glutathione S-transferases and effects on angiogenesis and metastasis. It has ability to affect gene transcription and induce cell cycle arrest and apoptosis. Although curcumin is a highly pleiotropic molecule with an excellent safety profile targeting multiple diseases, it could not achieve its optimum therapeutic outcome in clinical trials, largely due to its low solubility and poor bioavailability. Based on the results of the clinical trials, curcumin can be developed as a therapeutic drug through improvement in formulations or delivery systems, enabling its enhanced absorption and cellular uptake. In this review article, we provide a comprehensive outlook for the therapeutic potential of curcumin, and discuss future strategies and potential challenges involved in the use of curcumin.

## Introduction

Epidemiological data support the concept that naturally occurring compounds in the human diet are devoid of toxicity and have numerous long lasting beneficial effects on human health. Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-hepatadiene-3,5-dione; diferulolylmethane], a major constituent of turmeric derived from the rhizomes of *Curcuma spp*., has been reported to have several pharmacological effects including antitumor, anti-inflammatory and antioxidant properties (Piper et al. 1998; Plummer et al. 2001; Susan and Rao 1992). It increases the level of glutathione-S-transferase and, thus, upregulates the synthesis of glutathione (Piper et al. 1998; Sharma et al. 2001). Recent studies have also suggested that it can inhibit tumor metastasis, invasion and angiogenesis (Aggarwal et al. 2006c; Bae et al. 2006; Lin et al. 2007; Singh and Khar 2006; Yoysungnoen et al. 2006). Other beneficial effects of curcumin include wound-healing, antiviral, anti-infectious, and antiamyloidogenic properties. It is used as a flavoring and coloring agent, as a food

preservative, and also has been used in Ayurvedic medicine for over 6,000 years. Crude curcumin has a natural yellow hue and its components include curcumin, demethoxycurcumin, and bisdemethoxycurcumin. Oral administration of curcumin has been shown to inhibit leukemia and solid tumors including breast, prostate, skin, colon, stomach, duodenum, head and neck, and soft palate, through induction of apoptosis (Dikshit et al. 2006; Khor et al. 2006; Okunieff et al. 2006; Parodi et al. 2006; Sharma et al. 2006; Valentine et al. 2006; Yoysungnoen et al. 2006). However, the molecular mechanisms by which it inhibits growth and induces apoptosis in cancer cells are not well understood.

Curcumin induces apoptosis in cancer cells by inhibiting Akt activity, and inducing Bax and Bak genes upstream of mitochondria (Shankar and Srivastava 2007a, b). Furthermore, curcumin inhibits NFκB activity in cancer cells (Divya and Pillai 2006; Singh and Khar 2006) and sensitizes cancer cells to chemotherapy and radiotherapy (Aggarwal et al. 2006a; Chirnomas et al. 2006; Du et al. 2006; HemaIswarya and Doble 2006; Kamat et al. 2007; Kunnumakkara et al. 2007; Wahl et al. 2007).

The process of malignant transformation involves the sequential acquisition of a number of genetic and epigenetic alterations as a result of increasing genomic instability caused by defects in checkpoint controls (Hahn and Weinberg 2002; Nowak et al. 2002). These alterations allow cancer cells to acquire the capabilities to become self-sufficient in mitogenic signals, deregulate the control of cell cycle, escape from apoptosis, and obtain unlimited replication potential via the reactivation of telomerase (Artandi and DePinho 2000; Blasco 2002; Hanahan and Weinberg 2000). Within a growing tumor mass, the genetic changes during tumor progression also enable cancer cells to gain the ability to induce angiogenesis, invade neighboring tissues, and metastasize to distinct organs (Folkman 2003). The new chemopreventive agents or therapeutic strategies that inhibit angiogenesis, metastasis and invasion can be considered for future clinical development.

## Derivatives and Analogues

In recent years, several analogs of curcumin have been prepared. However, some of them are more potent and exhibit better pharmacokinetic and pharmacodynamic properties than others. There are three main analogs of curcumin: (I) Diferuloylmethane/Curcumin (II) Demethoxycurcumin and (III) Bisdemethoxycurcumin (Fig. 17.1). New analogs appear to be better than curcumin in terms of solubility, stability, half-life and bioavailability. Furthermore, curcumin and its analogs are being conjugated with nanoparticles to improve their delivery and bioavailability.

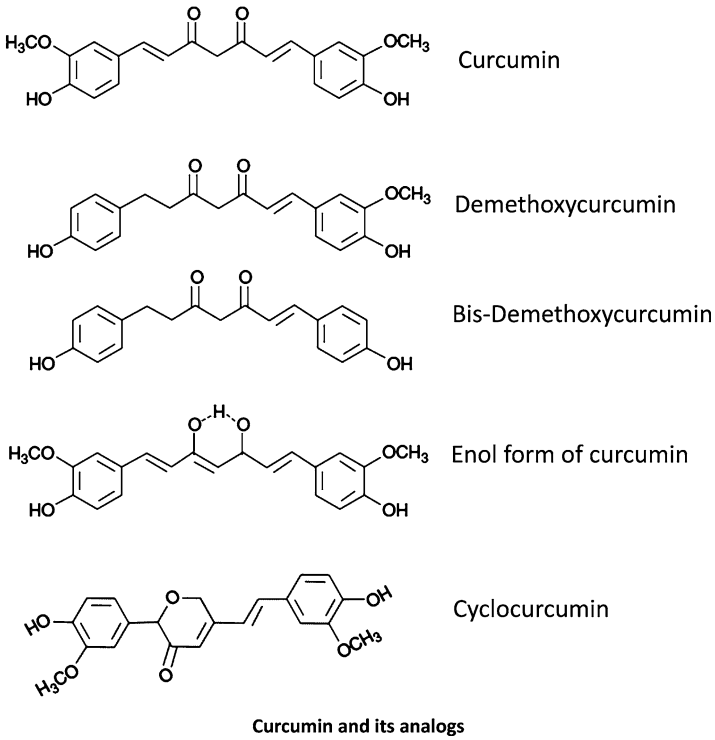


**Fig. 17.1** Structures of curcumin and its analogs. Curcumin, demethoxycurcumin, bis-demethoxycurcumin, enol form of curcumin, and cyclocurcumin

## Mechanism of Action

### *Bcl-2 Family Members*

The Bcl-2 family of proteins plays a key role in regulating apoptosis at the level of mitochondrial cytochrome c release (Srivastava et al. 1999a, b). Once released from mitochondria, cytochrome c interacts with Apaf-1, leading to caspase-9 activation and subsequent cleavage and activation of caspase-3, spurring the demise of the cell. Antiapoptotic Bcl-2 proteins, such as Bcl-2 and Bcl-$X_L$, function to prevent cytochrome c release by counteracting the effects of proapoptotic members, which are divided into two subgroups based on the presence of Bcl-2 homology (BH) domains: the BH3-only family (e.g. Bid and Bim) and the BH123 multidomain proteins (e.g. Bax and Bak). The BH3-only family activates the multidomain proteins, mainly Bax and Bak, either directly or indirectly by engaging the antiapoptotic proteins (Kandasamy et al. 2003; Kuwana and Newmeyer 2003; Willis et al. 2003). The exact mechanism of direct activation remains unclear, but

it appears that Bax and Bak interact with certain BH3-only molecules, such as Bid, inducing them to undergo conformational changes, oligomerize, and permeabilize membranes which causes release of apoptogenic molecules from mitochondria to cytosol (Kuwana and Newmeyer 2003; Wei et al. 2000). Previous studies including those from our laboratories, indicated that curcumin-induced apoptosis in different cellular systems was associated with induction of Bax and Bak protein expression. Alternatively, the indirect mechanism involves BH3-only-family members binding to and occupying the antiapoptotic proteins, thereby derepressing Bax and Bak (Kuwana and Newmeyer 2003; Willis et al. 2003). Neutralization or removal of antiapoptotic proteins may be necessary to initiate proapoptotic signals and, ultimately, Bax or Bak activation. However, release from antiapoptotic molecules may not be sufficient to activate Bax or Bak without an additional activation step. These findings lead to an emerging model, where not only do apoptotic signals often converge on the multidomain proteins, but the activation of these proteins is regulated on multiple levels to determine precisely when to engage an apoptotic program and commit a cell to die.

Defect in apoptosis may contribute to tumor progression and treatment resistance. Apoptosis signaling may be disrupted by deregulated expression and/or function of antiapoptotic or proapoptotic molecules. Bcl-2 family members are important regulators of apoptosis that include antiapoptotic (Bcl-2, Bcl-$X_L$ and Mcl-1), proapoptotic (Bax and Bak) and the BH-3-domain-only (Bim, Bid, and Bik) proteins. Bax and Bak are multidomain proteins that function as an obligate gateway for the activation of apoptosis via the mitochondrial and endoplasmic reticulum pathway (Kandasamy et al. 2003; Oakes et al. 2005; Wei et al. 2001). In contrast to the BH-3-only proteins, which function as transducers of the apoptotic signals upstream of mitochondria, Bax and Bak also contain BH-1 and BH-2 domains and function at the mitochondrial outer membrane to release holocytochrome c in response to diverse stimuli (Scorrano and Korsmeyer 2003). Consequently, we and others have shown that mouse embryonic fibroblasts (MEFs) lacking both Bax and Bak exhibited marked resistance to diverse pro-apoptotic insults, and loss of either Bax and Bak alone exerts no measurable protective effects (Kandasamy et al. 2003; Wei et al. 2001). Furthermore, mice deleted for either bax or bak alone are viable, showing either defects in only a few discrete lineage (in the case of Bax) or no defects (in the case of Bak) (Lindsten et al. 2000). In contrast, mice lacking both Bax and Bak die in early embryogenesis due to failure of apoptosis in multiple developing tissues (Lindsten et al. 2000). Overall, these findings suggest that Bax and Bak are critical for apoptosis induction.

We have recently demonstrated that curcumin downregulated the expression of Bcl-2, and Bcl-$X_L$ and upregulated the expression of p53, Bax, Bak, PUMA, Noxa, and Bim at mRNA and protein levels in prostate cancer cells (Shankar and Srivastava 2007b). Curcumin upregulated the expression, phosphorylation, and acetylation of p53 in androgen-dependent LNCaP cells (Shankar and Srivastava 2007b). The ability of curcumin to regulate gene transcription was also evident as it caused acetylation of histone H3 and H4 in LNCaP cells (Shankar and Srivastava 2007b). Furthermore, treatment of LNCaP cells with curcumin resulted

in translocation of Bax and p53 to mitochondria, production of reactive oxygen species, drop in mitochondrial membrane potential, release of mitochondrial proteins (cytochrome c, Smac/DIABLO and Omi/HtrA2), and activation of caspase-3 leading to apoptosis (Shankar and Srivastava 2007b). In another study, we have demonstrated that deletion of Bax and Bak genes completely inhibited curcumin-induced cytochrome c and Smac/DIABLO release in mouse embryonic fibroblasts (Shankar and Srivastava 2007a). Tumor tissues derived from curcumin treated mice showed that curcumin inhibited the expression of Bcl-2 and Bcl-$X_L$, and induced the expression of Bax and Bak. The combination of curcumin and TRAIL was more effective in regulating Bcl-2 family members than single agent alone. These studies suggest that curcumin can engage cell-intrinsic pathway of apoptosis by regulating the expression of Bcl-2 family of proteins.

## *Matrix Metalloproteinases*

Matrix metalloproteinases (MMPs) are a family of neutral endopeptidases that require $Zn + 2$ or $Ca + 2$ for their degradation of most or all of the constituent macromolecules of the extracellular matrix. The MMPs gene family consists of 20 structurally related members. MMPs are divided into subgroups including gelatinases, collagenases, stromelysins, membrane type MMPs and others (Decock et al. 2011; Deryugina and Quigley 2010; Hua et al. 2011; Raffo et al. 2011). MMPs are known to be involved in both physiological and pathological processes such as differentiation, inflammation, wound healing, rheumatoid arthritis, tumor invasion and other fibrotic manifestations. MMP9 (gelatinase B) has been implicated in both angiogenesis and potentiation of the invasive character of the producer cells (Raffo et al. 2011). Analysis of the 5'-flanking sequence of its encoding gene revealed the binding sites for transcription factors including AP-1 and NF-kB. Curcumin has been demonstrated to inhibit angiogenesis as well as tumor invasion through inhibition of MMPs in various cancers (Swarnakar et al. 2005). FGF-2, as an angiogenic factor, can induce MMP9 expression that is dependent on AP-1, but not NF-kB activation. In the presence of curcumin, the FGF-2 induced limbal vessel dilatation and corneal anginogenesis was not observed in corneal micropocket assay. These studies suggest that curcumin can inhibit tumor growth by inhibiting angiogenesis and metastasis.

## *MAP Kinases*

MAPK pathway has received increasing attention as a target molecule for cancer therapy. The MAPK cascades include extracellular signal-regulated protein kinases (ERKs), c-Jun N-terminal kinases/stress-activated protein kinases (JNKs/ SAPKs), and p38 kinases. ERKs are believed to play a critical role in transmitting signals

initiated by growth-inducing tumor promoters, including 12- O-tetradecanoyl-phorbol-13-acetate (TPA), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF) (Huang et al. 2010; Katz et al. 2007; Min et al. 2011). On the other hand, stress-related tumor promoters, such as ultraviolet (UV) irradiation and arsenic, potently activate JNKs/SAPKs and p38 kinases. The MAPK pathway consists of a cascade in which a MAP3K activates a MAP2K that activates a MAPK (ERK, JNK, and p38), resulting in the activation of NF-kB, cell growth, and cell survival (Keshet and Seger 2010). The curcumin have been shown to modulate the MAP kinases. The ability of curcumin to modulate the MAPK signaling pathway might contribute to the inhibition of inflammation by curcumin. Curcumin is reported to attenuate experimental colitis through a reduction in the activity of p38 MAPK (Salh et al. 2003). It is also found that curcumin inhibits JNK activation induced by various agonists including PMA plus ionomycin, anisomycin, UV-C, gamma radiation, TNFα, and sodium orthovanadate (Chen and Tan 1998).

### *PI3 Kinase/Akt*

Phosphatidylinositol-3 kinase (PI3K) is a heterodimeric enzyme composed of one 110-kDa catalytic subunit and another 85-kDa regulatory subunit and serves as a major signaling component downstream of growth factor receptor tyrosine kinases (Cantley 2002; Luo et al. 2003). PI3K catalyzes the production of the lipid secondary messenger phosphatidylinositol-3,4,5-triphosphate, which in turn activates a wide range of downstream targets, including the serine/threonine kinase AKT (Luo et al. 2003). Full activation of AKT/PKB is PI3K dependent and requires both recruitment to the plasma membrane and phosphorylation on two key residues, $Thr^{308}$ and $Ser^{473}$ (Cantley 2002; Lawlor and Alessi 2001). The PI3K/AKT pathway regulates multiple cellular processes, including cell proliferation, differentiation, survival, growth, motility and angiogenesis. We and others have shown that the activated PI3K/AKT pathway provides major survival signals to prostate and many other cancer cells (Chen et al. 2001; Datta et al. 1999; Downward 2004; Kandasamy and Srivastava 2002). Constitutive activation of AKT is frequently described in many types of human cancers (Khwaja 1999). Furthermore, the ectopic expression of AKT induces cell survival and malignant transformation, whereas the inhibition of AKT activity stimulates apoptosis in a range of mammalian cells (Beresford et al. 2001, Chen et al. 2001; Kandasamy and Srivastava 2002; Lei et al. 2005; Michl and Downward 2005; Yuan and Whang 2002). Recent studies have identified the substrates of AKT that are involved in the pro-cell survival effects, which thus far include glycogen synthase kinase-3, mTOR, FKHR, MDM2, p21, HIF-1, IKK, Bad, and caspase-9 (Datta et al. 1997; Khwaja 1999; Lentzsch et al. 2004; Schmidt et al. 2002). Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) is a phospholipid phosphatase that dephosphorylates phosphatidylinositol 3,4,5-triphosphate (Maehama and Dixon 1999; Myers et al. 1998) and inhibits PI3K-dependent activation of AKT. The mutation or loss of PTEN leads to

constitutively activated AKT. Overexpression of PTEN into PTEN-deficient breast, prostate, lung and glial cancer cells resulted in a decrease in activated AKT (Davies et al. 1998; Li et al. 1997; Wu et al. 1998). These observations establish AKT as an attractive target for cancer therapy, both alone and in conjunction with standard cancer chemotherapies, as a means of reducing the apoptotic threshold and preferentially killing cancer cells.

Although AKT has been shown to affect nuclear p53 function, the current study provides strong evidence that AKT may serve a more antiapoptotic role by interfering with the mitochondrial accumulation of p53. We have shown that AKT activation by constitutively active AKT inhibits mitochondrial p53 accumulation whereas inhibition of AKT function by PTEN, dominant negative AKT or inhibitors of PI3K (LY294002 and Wortmannin) and AKT promotes curcumin-induced mitochondrial import of p53. This suggests that AKT may regulate Smac release and apoptosis by attenuating the mitochondrial actions of p53. Because mitochondrial p53 accumulation is correlated with p53-induced apoptosis and not cell cycle arrest (Mihara et al. 2003), this strongly suggests that prevention of mitochondrial accumulation of p53 by AKT may be a critical intermediary step in the process of curcumin-induced apoptosis.

## *Wnt/β-Catenin*

Wnt/β-catenin pathway modulates cell proliferation, differentiation, migration, apoptosis and stem cell self-renewal (Barker and Clevers 2000; Clevers 2004; Dodge and Lum 2011; Polakis 2000; Smalley and Dale 1999; Wend et al. 2010). Wnt ligands are lipid-modified secreted glycoproteins that regulate embryonic development, cell fate specification, and the homeostasis of self-renewing adult tissues. Wnt/β-catenin signaling is also implicated in the maintenance of cancer stem cells (CSCs) of leukemia, breast, colon, melanoma, lung and liver cancers. Overexpression of β-catenin in stem cell survival pathway mediates the resistance of mouse mammary stem/progenitor cells to radiation (Woodward et al. 2007). Wnt/β-catenin signaling promoted expansion of the hepatic progenitor cell population when it is overexpressed in transplanted rat oval cells and when it is transiently expressed in adult mice (Yang et al. 2008). Elimination of β-catenin abrogated the chemoresistant cell population endowed with progenitor-like features (Yang et al. 2008). β-Catenin, the essential mediator of canonical Wnt signaling, participates in two distinct functions in the cell, depending on its cellular localization. Membrane-localized β-catenin is sequestered by the epithelial cell–cell adhesion protein E-cadherin to maintain cell–cell adhesion (Nelson and Nusse 2004). On the other hand, cytoplasmic accumulation of β-catenin and its subsequent nuclear translocation, followed by cooperation with the transcription factors T cell factor/lymphoid enhancer factor (TCF/LEF) as a transcription activator, eventually leads to activation of Wnt target genes such as c-Jun, c-Myc, fibronectin and cyclin D1 (Clevers 2006; He et al. 1998; Lin et al. 2000; Liu et al. 2005; Mann et al. 1999; Tetsu

and McCormick 1999). Binding of Wnt proteins, a family of secreted proteins, to Frizzled receptors results in the cytoplasmic accumulation of β-catenin (Schweizer and Varmus 2003). In the absence of Wnt signaling, β-catenin forms a multiprotein complex with glycogen synthase kinase 3β (GSK3β), adenomatous polyposis coli, casein kinase1α and axin (Takahashi-Yanaga and Sasaguri 2008). When β-catenin is phosphorylated at Ser33/Ser37/ Thr41 by GSK3β, it is immediately subject to ubiquitin-proteasome degradation (Liu et al. 2002; Takahashi-Yanaga and Sasaguri 2008). The link between PI3K/Akt and Wnt/β-catenin pathway has been well established. Activated Akt (i.e., phospho-Akt Ser473) phosphorylates Ser9 on GSK3β, which may decrease the activity of GSK3β, thereby stabilizing β-catenin (Cohen 2003; Cohen and Frame 2001; Pap and Cooper 1998). Furthermore, PI3K/Akt pathway is important in regulating the mammary stem/progenitor cells by promoting β-catenin downstream events through phosphorylation of GSK3β (Korkaya et al. 2009).

Curcumin induced caspase-3-mediated cleavage of β-catenin, leading to inactivation of Wnt/β-catenin signaling in HCT116 intestinal cancer cells (Jaiswal et al. 2002). Curcumin decreased β-catenin/TCF transcription activity in all tested cancer cell lines, including gastric, colon and intestinal cancer cells, which was attributed to the reduced amount of nuclear β-catenin and TCF-4 proteins (Park et al. 2005). In a recent study, the expression of Wnt receptor Frizzled-1 was potently suppressed by curcumin (Yan et al. 2005). Curcumin attenuated response of β-catenin to Wnt-3a in colon cancer cells through down-regulation of p300, a positive regulator of Wnt/β-catenin signaling (Ryu et al. 2008).

## *Hedgehog*

The Hedgehog (Hh) pathway is a conserved signalling system essential for embryonic development and for the maintenance of self-renewal pathways in stem cells and progenitor cells (Cerdan and Bhatia 2010; Katoh and Katoh 2009; Kelleher 2011; Merchant and Matsui 2010; Pece et al. 2011; Takebe et al. 2011). The hedgehog pathway plays a crucial role in regulating self-renewal of normal and malignant human mammary, pancreatic and prostate stem cells (Hsieh et al. 2011; Kelleher 2011; Klarmann et al. 2009; Liu et al. 2006; Sarkar et al. 2010; Thayer et al. 2003; Ulasov et al. 2011). Another recent study revealed the essential role of hedgehog-Gli signaling in controlling the self-renewal behavior of human glioma CSCs and tumorigenicity (Katoh and Katoh 2009; Natsume et al. 2011; Zbinden et al. 2010). In the absence of hedgehog ligands (Sonic Hedgehog, Desert Hedgehog and Indian Hedgehog), their transmembrane receptor Patched (Ptch) associates with Smoothened (Smo) and blocks Smo function (Traiffort et al. 2010). When secreted hedgehog ligands bind to Ptch, Smo is released, triggering dissociation of transcription factors, Gli1, Gli2 and Gli3 from Fused (Fu) and suppressor of Fused (SuFu), leading to transcription of an array of genes, such as cyclin D, cyclin E, Myc and elements of EGF pathway (Cohen 2003; Pasca di Magliano and

Hebrok 2003). Sonic hedgehog pathway is also linked to transcription factor NF-κB signaling. It was suggested that overexpression of sonic hedgehog is activated by NF-κB in pancreatic cancer and pancreatic cancer cell proliferation is accelerated by NF-κB in part through sonic hedgehog overexpression (Nakashima et al. 2006). Sonic hedgehog was characterized as a novel NF-κB target gene by mapping the minimal NF-κB consensus site to position +139 of sonic hedgehog promoter (Kasperczyk et al. 2009). Canonical Hh signaling promotes the expression of target genes through the oncogene GLI transcription factors. There is now increasing evidence suggesting that 'non-canonical' Hh signalling mechanisms, some of which are independent of GLI-mediated transcription, may be important in cancer and development.

Curcumin has been shown to inhibit the Shh-Gli1 signaling pathway by downregulating the Shh protein and its downstream targets GLI1 and PTCH1 in various cancers (Elamin et al. 2010; Mimeault and Batra 2011). Furthermore, curcumin reduced the levels of beta-catenin, the activate/phosphorylated form of Akt and NF-kappaB, which led to downregulating the three common key effectors, namely C-myc, N-myc, and Cyclin D1. Consequently, apoptosis was triggered by curcumin through the mitochondrial pathway via downregulation of Bcl-2, a downstream anti-apoptotic effector of the Shh signaling. Importantly, the resistant cells that exhibited no decrease in the levels of Shh and Bcl-2, were sensitized to curcumin by the addition of the Shh antagonist, cyclopamine. Furthermore, curcumin enhances the killing efficiency of nontoxic doses of cisplatin and gamma-rays. In addition, piperine, an enhancer of curcumin bioavailability in humans, potentiates the apoptotic effect of curcumin against several cancer cells (Garg et al. 2005; Li et al. 2011; Manoharan et al. 2009; Shaikh et al. 2009). This effect was mediated through strong downregulation of Bcl-2. Therefore, it can be suggested that curcumin represents great promise as Shh-targeted therapy for cancers.

## *Notch*

Notch receptor or ligand overexpression is associated with Drosophila eye tumors that exhibit hallmarks of mammalian cancers such as uncontrolled overgrowth, invasion, and metastasis (Ferres-Marco et al. 2006; Martinez and Cavalli 2010; Martinez et al. 2009; Palomero et al. 2007), providing a powerful model for the genetic dissection of the regulatory circuits controlling tissue homeostasis, growth and cancer by Notch signalling pathway. The activation of the Notch pathway is an ancient mechanism to control the growth of numerous tissues and organs (Artavanis-Tsakonas et al. 1995; Artavanis-Tsakonas and Muskavitch 2010), and recent evidence indicates this pathway is often recruited to stimulate growth of many solid tumors and leukemic stem cells and to orchestrate angiogenesis and/or the reprogramming of cancer cells via epithelial–mesenchymal transition (EMT) (Bailey et al. 2007; Miele 2006; Miele et al. 2006).

In Drosophila, there is a single Notch receptor and two genes that encode the ligands Delta and Serrate (Ser) (Martinez and Cavalli 2010). Four different Notch receptors (NOTCH1–4) and five canonical ligands of the Delta (DLL1, 2, and 4) and Ser (JAGGED/JAG1, 2) families have been characterized in humans. In all phyla, Notch binding of its ligand triggers receptor activation through a round of two consecutive cleavages, one extracellular and the other intracellular. The latter requires the activity of the ADAM protease family and γ-secretase. Subsequently the intracellular domain of Notch is released, which then translocates to the nucleus to form a transcriptional activator in complex with the DNA binding protein, CSL (CBF1/RBP-J in mammals, Suppressor of Hairless in Drosophila, and LAG-1 in Caenorhabditis elegans), and with the co-activator Mastermind-like proteins (Artavanis-Tsakonas et al. 1995). Timely ligand-receptor activation and signal strength requires not only spatiotemporal regulation of ligand genes but also post-transcriptional regulation of ligand levels via ligand endocytosis, ubiquitination, and endosome sorting (Bray 2006; Kopan and Ilagan 2009). The importance of ligand regulation is highlighted in humans in which the loss of one gene copy or gain of Notch ligand are directly linked to developmental syndromes and age-related diseases including cancer (Kopan and Ilagan 2009). Significantly, high JAG1 protein correlates with the metastasis, shorter survival time, and recurrence in human carcinomas, including prostate (Santagata et al. 2004). High JAG1 has been shown to induce invasion and migration through EMT in breast and prostate cancer cell lines (Chen et al. 2010; Ferrari-Toninelli et al. 2010; Kettunen et al. 2001; Lindner et al. 2001; Noseda et al. 2004; Pang et al. 2010; Santagata et al. 2004; Six et al. 2004; Vallejo et al. 2011; Weller et al. 2006; Yang and Proweller 2011; Yeh et al. 2009; Zhang et al. 2010). However, how the tightly regulated NOTCH pathway activation is subverted in carcinogenesis remains poorly understood, particularly since activating mutations of NOTCH pathway components are rarely detected in solid tumors.

Recent studies have demonstrated that Notch-activated genes and pathways can drive tumor growth through the expansion of CSCs (Bigas et al. 2010; D'Souza et al. 2008; Dikic and Schmidt 2010; Guo et al. 2011; Radtke et al. 2010; Stockhausen et al. 2010). Notch pathway is believed to be dysregulated in CSCs, ultimately leading to uncontrolled CSC self-renewal. For example, Notch pathway was shown to play an important role in the self-renewal function of malignant breast cancer CSCs (Farnie and Clarke 2007; Guo et al. 2011; Harrison et al. 2010; Kakarala and Wicha 2008; Li et al. 2011). NOTCH pathway activates downstream target genes such as c-Myc, cyclin D1, p21, NF-κB (Brennan et al. 2009; Cohen et al. 2010; D'Altri et al. 2011; Das et al. 2010; Ling et al. 2010; Mazumdar et al. 2009; Okuhashi et al. 2010; Ronchini and Capobianco 2001; Sharma et al. 2007; Stahl et al. 2006; Tanaka et al. 2009; Wei et al. 2010). NOTCH1 has been reported to cross-talk with NF-κB pathway in diverse cellular situations (Chen et al. 2007; Jang et al. 2004; Nickoloff et al. 2002; Oswald et al. 1998; Shin et al. 2006; Wang et al. 2001, 2006b). It has also been demonstrated that NOTCH-1 is necessary for expression of several NF-κB subunits (Cheng et al. 2001; Jang et al. 2004) and

stimulates NF-κB promoter activity (Jang et al. 2004). These studies directly link NOTCH pathway with NF-κB to regulate various physiological functions.

Antiproliferative effects of curcumin has been associated with down-regulation of NOTCH-1 and NF-κB in various cancers (Chen et al. 2007; Howells et al. 2010; Li et al. 2011; Sarkar et al. 2009; Wang et al. 2006a, 2008). Curcumin-induced inactivation of NF-κB DNA-binding activity was potentially mediated by Notch-1 signaling pathway (Wang et al. 2006a). Taken together, these studies suggest that the down-regulation of NOTCH-1 and/or NF-κB by curcumin could be an effective approach for inhibiting tumorigenesis.

## *Cyclooxygenases*

Cyclooxygenases are prostaglandin H synthase, which convert arachidonic acid released by membrane phospholipids into prostaglandins (Aggarwal et al. 2006b; Subbaramaiah and Dannenberg 2003). Two isoforms of prostaglandin H synthase, COX-1 and COX-2 are identified. COX-1 is constitutively expressed in many tissues, but the expression of COX-2 is regulated by mitogens, tumor promoters, cytokines, and growth factors. COX-2 is overexpressed in practically all premalignant and malignant condition involving the liver, colon, pancreas, lung, breast, bladder, skin, stomach, head and neck, and esophagus (Subbaramaiah and Dannenberg 2003). Many transcription factors have been shown to stimulate COX-2 transcription. Curcumin was one of the first chemopreventive phytochemicals shown to possess significant COX-2 inhibiting activity through the suppression of NF-kB. COX-2 inhibitors will be particularly useful in the treatment of breast cancers through inhibition of HER-2/neu activity and aromatase activity (Subbaramaiah and Dannenberg 2003). Preclinical studies have shown that curcumin suppresses COX-2 activity through the suppression of NF-kB-inducing kinase (NIK) and IkBa kinase (IKK) enzymes (Plummer et al. 1999).

Recently, it has been observed that difluorinated-curcumin (CDF) together with 5-fluorouracil and oxaliplatin (5-FU + Ox) were more potent than curcumin in reducing CD44 and CD166 in chemo-resistant colon cancer cells, accompanied by inhibition of growth, induction of apoptosis and disintegration of colonospheres (Kanwar et al. 2011). These changes were associated with down-regulation of the membrane transporter ABCG2 and attenuation of EGFR, IGF-1R, and NFκB signaling consistent with inactivation of β-catenin, COX-2, c-Myc and Bcl-$X_L$ and activation of the pro-apoptotic Bax. This study suggests that CDF together with the conventional chemotherapeutics could be an effective treatment strategy for preventing the emergence of chemo-resistant colon cancer cells by eliminating cancer stem cells.

## *Epidermal Growth Factor Receptors*

The epidermal growth factor receptor (EGFR) is a 170 kDa receptor tyrosine kinase. Upon EGF stimulation, EGFR dimerizes and becomes enzymatically active, and these results in a cascade of cellular events, including phosphorylation and activation of its substrates (Dasari and Messersmith 2010; Lo 2010). This enzymatic activation of EGFR is essential to propagate the EGF-induced signaling that culminates in DNA synthesis and cell division. The inhibitory effect of curcumin on the ligand-induced activation of EGFR was observed and this might explain the antiproliferative effect of curcumin on EGF stimulated cells (Korutla et al. 1995; Korutla and Kumar 1994). Furthermore, curcumin inhibited EGFR expression in pancreatic, lung, colon and prostate cancers (Chen et al. 2006; Dorai et al. 2000; Kim et al. 2006; Lee et al. 2011; Lev-Ari et al. 2006). Curcumin potentiates antitumor activity of gefitinib in cell lines and xenograft mice model of NSCLC through inhibition of proliferation, EGFR phosphorylation, and induction EGFR ubiquitination and apoptosis (Lee et al. 2011). In addition, curcumin attenuates gefitinib-induced gastrointestinal adverse effects via altering p38 activation. These findings provide a novel treatment strategy that curcumin as an adjuvant to increase the spectrum of the usage of gefitinib and overcome the gefitinib inefficiency in NSCLC patients.

## *Transcription Factors*

### NFκB

The NFκB family of transcription factors has been shown to be constitutively activated in various human malignancies, including a number of solid tumors and leukemias, lymphomas (Karin 2006b). NFκB is shown to contribute to development and/or progression of malignancy by regulating the expression of genes involved in cell growth and proliferation, anti-apoptosis, angiogenesis, and metastasis (Karin 2006b). Prostate cancer cells have been reported to have constitutive NFκB activity due to increased activity of the IκB kinase complex (Aggarwal et al. 2006c). Furthermore, an inverse correlation between androgen receptor (AR) status and NFκB activity was observed in prostate cancer cell lines (Peant et al. 2007). In prostate cancer cells, NFκB may promote cell growth and proliferation by regulating expression of genes such as c-myc, cyclin D1, and IL-6 (Karin 2006a, b), and inhibit apoptosis through activation of expression of anti-apoptotic genes, such as Bcl-2. NFκB-mediated expression of genes involved in angiogenesis (IL-8, VEGF), and invasion and metastasis (MMP9, uPA, uPA receptor) may further contribute to the progression of prostate cancer. Constitutive NFκB activity has also been demonstrated in primary prostate cancer tissue samples and suggested to have prognostic importance for a subset of primary tumors. We have shown that curcumin inhibits the activation of NFκB and its gene products (e.g. VEGF, Bcl-2,

Bcl-$X_L$, uPA, cyclin D1, MMP-2, MMP-9, COX-2 and IL-8) in xenografted tumors, which play significant roles in invasion, metastasis and angiogenesis (Shankar et al. 2007a, b). All these events will significantly contribute to the anti-proliferative and antitumor activities of curcumin. The inhibitory effect of curcumin on NF-κB signal transduction pathway may be mediated via the various components of the HDACs and p300/Notch 1 signal molecules, and may represent a novel therapeutic option for cancer. These findings suggest that NFκB may play a role in human cancer development and/or progression, and curcumin can inhibit these processes through regulation of NFκB-dependent gene products.

## STAT

STAT proteins are signaling molecules with dual functions that were discovered during studies on interferon (IFN) gamma-dependent gene expression (Darnell et al. 1994). Of the seven STAT proteins identified so far, constitutively activated STAT3 and STAT5 have been implicated in multiple myeloma, lymphomas, and several solid tumors, making these proteins logical targets for cancer therapy. These STAT proteins contribute to cell survival and growth by preventing apoptosis through increased expression of antiapoptotic proteins, such as bcl-2 and bcl-$X_L$. STAT3 was shown to be a direct activator of the *VEGF* gene, which is responsible for increased angiogenesis. Elevated STAT3 activity has been detected in head and neck squamous cell carcinoma, leukemias, lymphomas, multiple myeloma, and pancreatic, prostate and breast cancers (Arthan et al. 2010; Hazan-Halevy et al. 2010; Li et al. 2010; Lin et al. 2010a; Liu et al. 2010; Madoux et al. 2010; Pandey et al. 2010; Ramakrishnan et al. 2010; Sandur et al. 2010; Scuto et al. 2011; Yang et al. 2010).

Curcumin has been shown to inhibit interleukin (IL) 6-induced STAT3 phosphorylation and consequent STAT3 nuclear translocation. It was even more efficient than JAK2 inhibitor AG490. Overall, curcumin is a potent inhibitor of STAT3 phosphorylation and therefore, it suppresses proliferation of cancer cells (Aggarwal et al. 2006a; Glienke et al. 2010; Goel and Aggarwal 2010; Lin et al. 2010a, b; Rezende et al. 2009; Seo et al. 2010; Weissenberger et al. 2010). Curcumin has been shown to inhibit cellular proliferation and the expression of STAT5 mRNA, and to downregulate the activation of STAT5 in chronic myelogenous leukemia cells and solid tumors (Bhattacharyya et al. 2007; Bill et al. 2009; Blasius et al. 2006; Lin et al. 2004; Rajasingh et al. 2006). These studies suggest curcumin exerts its antitumor activity through inhibition of JAK/STAT pathway.

## AP-1

AP-1 is associated with activation of NF-κB and has been closely linked with proliferation and transformation of tumor cells (Karin 2006b). Curcumin suppresses the JNK activation hence suppresses the phosphorylation of c-jun and ultimately suppresses the activation of AP-1 (Huang et al. 1991). It also interacts with the

AP-1-DNA binding motif, thereby inhibiting activation of AP-1 (Haase et al. 2008). It suppresses AP-1-DNA binding and transcriptional activity in an HTLV-1-infected T-cell line. It inhibited the growth of these cells by inducing cell cycle arrest followed by apoptosis. Curcumin has been inhibited hydrogen peroxide induced heparin affin regulatory peptide (*HARP)* and LNCaP cell proliferation and migration (Polytarchou et al. 2005). It is also reported to downregulate AP-1 binding activity in cancer cells (Balasubramanian and Eckert 2007; Balogun et al. 2003b; Cai et al. 2011; Sharma et al. 2010).

### Nrf2

Transcription factor NrF-2 normally exists in an inactive state as a result of binding to a cytoskeleton-associated protein, Keap1. It can be activated by redox-dependent stimuli. Nrf-2 translocates to the nucleus, bind to the antioxidant-responsive element (ARE), and initiate the transcription of genes coding for detoxifying enzymes and cytoprotective proteins. Nrf-2-ARE signaling pathway plays a key role in activating cellular antioxidant. The same response is also triggered by curcumin. It stimulated concentration and time dependently expression of Nrf-2. This effect is associated with increased Ho-1 protein expression and hemoxygenase activity. The *ho-1* gene expression is stimulated by curcumin through inactivating Nrf-2-Keap1 complex, leading to increased Nrf-2 binding to resident *ho-1* ARE (Balogun et al. 2003a, b). It has been known that curcumin activates ARE-mediated gene expression in human monocytes through PKC delta (Rushworth et al. 2006). It has been also found to exert anti-inflammatory and anticarcinogenic effects by up-regulating the selenoprotein gastrointestinal glutathione peroxidase by activating the Nrf-2/Keap1syatem (Banning et al. 2005).

## Apoptosis

Anticancer drugs or irradiation induce the release of mitochondrial proteins such as cytochrome c, second mitochondria-derived activator of caspases (Smac)/ direct inhibitor of apoptosis protein (IAP) binding protein with low isoelectric point (DIABLO), apoptosis inducing factor (AIF) and endonucleases G. Cytochrome c together with apoptosis protease activating factor (Apaf-1) and procaspase-9 forms the apoptosome complex (Liu et al. 1996). Caspase-9 subsequently activates caspase-3 that can cleave several caspase substrates leading to apoptosis (Zou et al. 1997). Smac/DIABLO contains an $NH_2$-terminal 55-amino-acid mitochondrial import sequence (Du et al. 2000; Verhagen et al. 2001). Once released into the cytosol, Smac docks to IAPs within the baculovirus IAP repeat domains via an $NH_2$-terminal motif, thereby eliminating the inhibitory effects of IAPs on caspase-3, caspase-7, and caspase-9 (Verhagen and Vaux 2002). In addition, the interaction of Smac with IAPs results in a rapid ubiquitination and subsequent degradation of

released Smac, which is mediated by the ubiquitin-protein ligase (E3) function of some IAPs (Du et al. 2000; MacFarlane et al. 2002). Recent studies have shown that mitochondrial Smac release is suppressed by Akt, Bcl-2, and Bcl-$X_L$, but promoted by Bax, Bad, and Bid (Du et al. 2000; Kandasamy et al. 2003; Verhagen et al. 2000).

Binding of TRAIL to its receptors TRAIL-R1/DR4 and TRAIL-R2/DR5, both of which contain a cytoplasmic region of 80 amino acids designated as the "death domain", activated the extrinsic apoptosis pathway. Death receptors DR4 and DR5 can recruit the initiator caspases, caspase-8 and caspase-10, by a homotypic interaction between the death effector domains of the adapter molecule Fas-associated death domain (FADD) protein and the prodomain of the initiator caspase, thereby forming the death-inducing signaling complex (DISC). The formation of active DISC is essential for TRAIL to transmit apoptotic signals. We and others have shown that tumor-selective targeting molecules such as tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) induces apoptosis in prostate cancer cells, both *in vitro* and *in vivo* (Shankar et al. 2004, 2005; Shankar and Srivastava 2004; Srivastava 2001). Data on experimental animals and primates led us to believe that TRAIL has great promise as a selective anticancer agent (Ashkenazi et al. 1999; Shankar et al. 2004, 2005). We have recently demonstrated that TRAIL induces apoptosis in several prostate cancer cells lines, but it was ineffective in inducing apoptosis in LNCaP cells (Chen et al. 2001; Shankar et al. 2004, 2005). Chemopreventive agent curcumin has been shown to sensitize TRAIL-resistant prostate cancer cells *in vitro* (Deeb et al. 2003, 2005; Jung et al. 2006). However, the ability of curcumin to sensitize TRAIL-resistant cells *in vivo* has not yet been demonstrated.

## Cell Cycle

Inappropriate and/or accelerated rates of cell proliferation are hallmark of cancer. The molecular regulatory network of the cell cycle and apoptosis are tightly intertwined (Hahn and Weinberg 2002; Nowak et al. 2002) The known molecular regulatory networks of the cell cycle and apoptosis are quite complex and can overlap. During malignant transformation, a number of genetic and epigenetic alterations occurs as a result of increasing genomic instability caused by defects in checkpoint controls (Hahn and Weinberg 2002; Nowak et al. 2002) These alterations allow cancer cells to acquire the capabilities to become self-sufficient in mitogenic signals, deregulate the control of cell cycle, escape from apoptosis, and obtain unlimited replication potential.

The transition from one cell cycle phase to another occurs in an orderly fashion and is regulated by different cellular proteins. Key regulatory proteins are the cyclin-dependent kinases (CDK), a family of serine/threonine protein kinases that are activated at specific points of the cell cycle. Until now, nine CDK have been identified and, of these, five are active during the cell cycle, i.e. during G1 (CDK4, CDK6 and CDK2), S (CDK2), G2 and M (CDK1). When activated, CDK induce

downstream processes by phosphorylating selected proteins (Morgan 1995; Pines 1995) CDK protein levels remain stable during the cell cycle, in contrast to their activating proteins, the cyclins. Cyclin protein levels rise and fall during the cell cycle and in this way they periodically activate CDK (Evans et al. 1983). Different cyclins are required at different phases of the cell cycle. The three D type cyclins (cyclin D1, cyclin D2, cyclin D3) bind to CDK4 and CDK6, and CDK-cyclin D complexes are essential for entry in G1 (Sherr 1994) Unlike the other cyclins, cyclin D is not expressed periodically, but is synthesized as long as growth factor stimulation persists (Assoian 1997). Another G1 cyclin is cyclin E which associates with CDK2 to regulate progression from G1 into S phase (Ohtsubo et al. 1995). Cyclin A binds with CDK2 and this complex is required during S phase (Girard et al. 1991; Walker and Maller 1991). In late G2 and early M, cyclin A complexes with CDK1 to promote entry into M phase. Mitosis is further regulated by cyclin B in complex with CDK1 (Arellano and Moreno 1997; Azuine and Bhide 1994). Cyclins A and B contain a destruction box and cyclins D and E contain a PEST sequence [segment rich in proline (P), glutamic acid (E), serine (S) and threonine (T) residues]; these are protein sequences required for efficient ubiquitin-mediated cyclin proteolysis at the end of a cell cycle phase (Glotzer et al. 1991).

In addition to cyclin binding, CDK activity is also regulated by phosphorylation on conserved threonine and tyrosine residues. Full activation of CDK1 requires phosphorylation of threonine 161 (threonine 172 in CDK4 and threonine 160 in CDK2), brought about by the CDK7-cyclin H complex, also called CAK. These phosphorylations induce conformational changes and enhance the binding of cyclins (Jeffrey et al. 1995; Paulovich and Hartwell 1995). The Wee1 and Myt1 kinases phosphorylate CDK1 at tyrosine-15 and/or threonine-14, thereby inactivating the kinase. Dephosphorylation at these sites by the enzyme Cdc25 is necessary for activation of CDK1 and further progression through the cell cycle (Lew and Kornbluth 1996). Alterations of CDK molecules in cancer have been reported, although with low frequency. CDK4 overexpression, that occurs as a result of amplification, has been identified in cell lines, melanoma, sarcoma and glioma (Wolfel et al. 1995). CDK1 and CDK2 have been reported to be overexpressed in a subset of colon adenomas, a greater overexpression was seen in focal carcinomas in adenomatous tissue (Kim et al. 1999; Yamamoto et al. 1998).

CDK activity can be counteracted by cell cycle inhibitory proteins, called CDK inhibitors (CKI) which bind to CDK alone or to the CDK-cyclin complex and regulate CDK activity. Two distinct families of CDK inhibitors have been discovered, the INK4 family and CIP/KIP family (Sherr and Roberts 1995) The INK4 family includes p15 (INK4b), p16 (INK4a), p18 (INK4c), p19 (INK4d), which specifically inactivate G1 CDK (CDK4 and CDK6). These CKI form stable complexes with the CDK enzyme before cyclin binding, preventing association with cyclin D (Carnero and Hannon 1998). The second family of inhibitors, the CIP/KIP family, includes p21 (WAF1/CIP1), p27 (KIP1), p57 (KIP2). These inhibitors inactivate CDK-cyclin complexes (Harper et al. 1995; Koff 2006). They inhibit the G1 CDK-cyclin complexes, and to a lesser extent, CDK1-cyclin B complexes (Hengst and Reed 1998). CKI are regulated both by internal and external signals:

the expression of p21/WAF1/CIP1 is under transcriptional control of the *p53* tumour suppressor gene.(el-Deiry et al. 1993). p27/KIP1 binds to CDK2 and cyclin E complexes to prevent cell cycle progression from G1 to S phase (Harper et al. 1995; Koff 2006; Lees 1995). Cell cycle deregulation associated with cancer occurs through mutation of proteins important at different levels of the cell cycle. In cancer, mutations have been observed in genes encoding CDK, cyclins, CDK-activating enzymes, CKI, CDK substrates, and checkpoint proteins (McDonald and El-Deiry 2000; Sherr 1996). Mutations in *CDK4* and *CDK6* genes resulting in loss of CKI binding have also been identified (Easton et al. 1998).

The retinoblastoma tumor suppressor protein (pRB) is a negative regulator of cell proliferation (Classon and Harlow 2002). The antiproliferative activity of pRB is mediated by its ability to inhibit the transcription of genes that are required for cell cycle progression. This transcriptional regulatory function of pRB is achieved through several distinct mechanisms, which are best illustrated by its interaction with the E2F family and the inhibition of E2F-regulated gene expression. The binding of E2F to pRB requires the large pocket of pRB (amino acids 379–870). The ability of pRB to inhibit cellular proliferation is counterbalanced by the action of CDKs (Sherr and Roberts 1999; Taya 1997). pRB is phosphorylated in a cell cycle-dependent manner by CDKs. In quiescent and early G1 cells, pRB exists in a predominantly unphosphorylated state. As cells progress toward S phase, pRB becomes phosphorylated. The initial phosphorylation of pRB is most likely catalyzed by CDK4-cyclin D or CDK6-cyclin D complexes. Subsequently, CDK2-cyclin E and CDK2-cyclin A phosphorylate pRB (Ortega et al. 2002; Sherr 2002). pRB is rapidly dephosphorylated during mitosis (Ludlow et al. 1993). Inactivation of pRB by phosphorylation leads to the dissociation and activation of E2F, allowing the expression of many genes required for cell cycle progression and S phase entry. It has been shown that CDK4-cyclin D1, but not CDK2-cyclin E, specifically phosphorylated Ser780 in pRB, which cannot bind to E2F-1 (Kitagawa et al. 1996).

Proliferation arrest is the main effect of curcumin on cancer cells from different origins. Using different prostate cancer cell lines, it has been suggested that curcumin induces disruption of the G1/S transition of the cell cycle (Aggarwal et al. 2007a; Shenouda et al. 2004). We have recently shown that curcumin caused a growth arrest at G1/S stage in both androgen-sensitive LNCaP and androgen-insensitive PC-3 cells (Srivastava et al. 2007). The G1/S phase arrest by curcumin was associated with the induction of p21/WAF1, p27/KIP1, and p16, and inhibition of cyclin D1, cyclin E, Cdk4 and cdk 6 (Srivastava et al. 2007). The ability of curcumin to induce cdk inhibitors p21 and p27 and inhibit cyclin D1 expression was also confirmed in our xenograft experiment. In support of our data, it has been demonstrated that curcumin induces the degradation of cyclin E expression through ubiquitin-dependent pathway and up-regulates p21 and p27 in several cancer cell lines (Aggarwal et al. 2007a). Moreover, deregulated expression of cyclin E was found to be correlated with chromosome instability (Spruck et al. 1999), malignant transformation (Haas et al. 1997), tumor progression (Rosen et al. 2006), and patient survival (Keyomarsi et al. 2002). Overall, these data suggest that curcumin induces growth arrest at G1/S stage of cell cycle.

Curcumin inhibited hyper-phosphorylation of pRB and enhanced hypo-phosphorylation of pRb in both PC-3 and LNCaP cell lines. Similarly, curcumin induced the expression of p16/INK4a, p21/WAF1/CIP1 and p27/KIP1, and inhibited the expression of cyclin D1 in LNCaP xenografts implanted in nude mice (Shankar et al. 2007). Curcumin also inhibited LNCaP tumor growth, metastasis and angiogenesis *in vivo* (Srivastava et al. 2007), suggesting its clinical utility for anticancer therapy and/or prevention. The G1/S phase arrest by curcumin was associated with the induction of CDK inhibitors p16/INK4a, p21/WAF1/CIP1, and p27/KIP1, and inhibition of hyper-phosphorylated state of pRb protein *in vitro*. The ability of curcumin to induce CDK inhibitors p21/WAF1/CIP1 and p27/KIP1 was also confirmed in our xenograft experiment (Shankar et al. 2007). Most importantly, we have demonstrated a link between cell cycle and apoptosis as CDK inhibitor p21/WAF1/CIP1 blocked curcumin-induced apoptosis.

The p27/KIP1 binds to CDK2 and cyclin E complexes to prevent cell cycle progression from G1 to S phase. p27/KIP1 also acts as a tumor suppressor and its expression is often disrupted in human cancers. Studies in mice have shown that loss of p27/KIP1 increases tumor incidence and tumor growth rate in either specific genetic backgrounds, or when mice are challenged with carcinogens (Fero et al. 1998; Ophascharoensuk et al. 1998). Decreased p27/KIP1 levels have been correlated with tumor aggressiveness and poor patient survival (Loda et al. 1997; Lu et al. 1999; Migita et al. 2002; Mineta et al. 1999; Ponce-Castaneda et al. 1995; Porter et al. 1997). Although p27/KIP1 is characterized as a tumor suppressor, inactivating point mutations with loss of heterozygosity are rarely observed in human cancer. The abundance of p27/KIP1 protein is largely controlled through a variety of post-transcriptional regulatory mechanisms (Alessandrini et al. 1997; Chu et al. 2007; Grimmler et al. 2007; Kardinal et al. 2006), among which are sequestration by cyclin D/CDK4 complexes, accelerated protein destruction and cytoplasmic retention. In certain types of cancers, such as colorectal cancer, high expression levels of Skp2 and Cks1, specific p27/KIP1 ubiquitin ligase subunits, were strongly associated with low p27/KIP1 expression and aggressive tumor behavior (Hershko and Shapira 2006). p27/KIP1 protein level changes during cell cycle progression, accumulating when cells progress through G1 and sharply decreasing just before cells enter S phase (Kaldis 2007). Additionally, p27/KIP1 protein levels rise when cells exit cell cycle to G0, and decreases when cells enter the cell cycle again (Kaldis 2007). These alterations in p27/KIP1 levels are mainly caused by regulation at the protein degradation level (Alessandrini et al. 1997; Chu et al. 2007; Grimmler et al. 2007; Kardinal et al. 2006). However, several studies have indicated that p27/KIP1 can also be regulated at the level of translation (Chiarle et al. 2000; Chilosi et al. 2000; Hengst and Reed 1996; Millard et al. 1997). Similarly, induction of p19(INK4d) expression contributed to cell cycle arrest by vitamin D(3) and retinoids (Tavera-Mendoza et al. 2006).

Cyclins are tightly regulated in different stages of cell cycle. In support of our data, it has been demonstrated that curcumin induces the degradation of cyclin E expression through ubiquitin-dependent pathway (Aggarwal et al. 2007a). Moreover, deregulated expression of cyclin E was found to be correlated with

chromosome instability (Spruck et al. 1999), malignant transformation (Haas et al. 1997), tumor progression (Rosen et al. 2006), and patient survival (Keyomarsi et al. 2002). Cyclin E expression increases with increasing stage and grade of the cancers including breast, head and neck, prostate, colon, and lung cancer, and acute lymphoblastic and acute myeloid leukemias (Gong et al. 1994; Iida et al. 1997; Keyomarsi et al. 2002; Kitahara et al. 1995; Muller-Tidow et al. 2001; Rosen et al. 2006; Scuderi et al. 1996), suggesting its potential use as a prognostic marker. The down-regulation of cyclin E by curcumin correlates with the decrease in the proliferation of human prostate cancer cells. The suppression of cyclin E expression was not cell type dependent as down-regulation occurred in androgen-sensitive LNCaP and -insensitive PC-3 prostate cancer cells. Curcumin-induced down-regulation of cyclin E was reversed by proteasome inhibitor lactacystin, an inhibitor of 26S proteasome, suggesting the role of ubiquitin-dependent proteasomal pathway.

Cyclin D acts as a growth sensor and provides a link between mitogenic stimuli and the cell cycle. Cyclin D1 binds to CDK4 and CDK6 in early G1. Aberrant cyclin D1 expression has been reported in many human cancers. Cyclin *D1* gene amplification occurs in breast, esophageal, bladder, lung and squamous cell carcinomas (Hall and Peters 1996), and parathyroid adenomas (Motokura et al. 1991). Cyclin D2 and cyclin D3 have also been reported to be overexpressed in some tumours (Hunter and Pines 1994; Keyomarsi et al. 1995; Leach et al. 1993). The suppression of cyclin D1 by curcumin led to inhibition of CDK4-mediated phosphorylation of Rb protein. The present study has demonstrated that curcumin-induced down-regulation of cyclin D1 was inhibited by lactacystin, suggesting that curcumin represses cyclin D1 expression by promoting proteolysis. Similarly, recent studies have demonstrated that curcumin can regulate cyclin D1 expression through transcriptional and posttranslational modifications (Aggarwal and Shishodia 2006; Aggarwal et al. 2007b), and this may contribute to the antiproliferative effects of curcumin against various cell types. Overall, these data suggest that downregulation of cyclins may be useful for cancer therapy and prevention.

The transition of the G1 to the S phase of the cell cycle marks an irreversible commitment to DNA synthesis and proliferation and is strictly regulated by positive and negative growth-regulatory signals. The G1-S transition is controlled by the Rb-E2F pathway, which links growth-regulatory pathways to a transcription program required for DNA synthesis, cell cycle progression and cell division (Brugarolas et al. 1999; Dyson 1998; Weinberg 1995). This transcription program is activated by the E2F transcription factors and repressed by E2F-Rb complexes (Nevins et al. 1997). E2F overexpression or Rb inactivation is sufficient to induce S phase entry, whereas Rb overexpression can arrest cycling cells in G1, suggesting that the Rb-E2F pathway is central to the control of the G1-S transition (Dyson 1998; Weinberg 1995). Mitogenic signal causes sequential activation of the CDK-cyclin complexes CDK4/6-cyclin D and CDK2-cyclin E, which hyper-phosphorylate pRb and thereby cause the release of active E2F (Dyson 1998; Weinberg 1995). pRB-deficient cells are hypersensitive to DNA damage-induced apoptosis.(Almasan et al. 1995; Knudsen et al. 2000). On the other hand, E2F-1 has a role distinct from other

E2Fs in the regulation of apoptosis (DeGregori et al. 1997). Loss of E2F-1 reduces tumorigenesis and extends the lifespan of Rb1(+/−) mice (Yamasaki et al. 1998). E2F-1 has been found to induce the expression of many apoptotic genes(Attwooll et al. 2004) and thus mediate the response of chemopreventive agents.

Overall, these studies provide the molecular mechanisms through which curcumin contributes to the antiproliferative and antitumor activities. The down-regulation of cyclin E, cyclin D1, and hyper-phosphorylation of pRb, and up-regulation of CDK inhibitors $p16^{/INK4a}$, $p21^{/WAF1/CIP1}$ and $p27^{/KIP1}$ may contribute to the antiproliferative effects of curcumin against various cancer. These events may be responsible for growth arrest followed by apoptosis in cancer cells. Curcumin chemosensitizes and radiosensitizes the effects by down-regulating the MDM2 oncogene through the PI3K/mTOR/ETS2 pathway (Li et al. 2007). Thus, targeting of cyclins and/or CDKs by curcumin may be considered beneficial for cancer therapy or prevention.

## Metastasis and Angiogenesis

Entry of malignant cells into the vasculature (i.e. intravasation) requires proteolytic remodeling of the extracellular matrix so that tumor cells may pass through the local stroma and penetrate the vessel wall. The circulatory system then provides a means of transporting tumor cells to distant sites where they extravasate and establish metastatic lesions. Matrix metalloproteinase (MMP) is up-regulated in many tumor types and has been implicated in tumor progression and metastasis (Bailey et al. 2007; Dreesen and Brivanlou 2007; Lopez-Otin and Matrisian 2007; Lynch 2011). MMP is critical for pericellular degradation of the extracellular matrix, thereby promoting tumor cell invasion and dissemination. To grow efficiently *in vivo*, tumor cells induce angiogenesis in both primary solid tumors and metastatic foci. Curcumin significantly inhibited the growth of TRAIL-resistant LNCaP xenografts and sensitized these xenografts to undergo apoptosis by TRAIL (Shankar et al. 2007b, 2008). Tumor tissues derived from curcumin treated mice showed that curcumin inhibited proliferation (PCNA and Ki67 staining), induced apoptosis (TUNEL staining), metastasis (uPA, MMP-2 and MMP-9 staining), and angiogenesis (CD31 and VEGF staining). Curcumin also inhibited VEGFR2-positive circulating endothelial cells. Treatment of LNCaP xenografted mice with TRAIL alone had no effect on tumor growth, apoptosis, metastasis and angiogenesis. *In vitro* studies demonstrated the role of ERK MAP kinase on the inhibitory effects of curcumin in capillary tube formation and endothelial cell migration. These data suggest that curcumin can inhibit tumor growth by inhibiting apoptosis, metastasis and angiogenesis.

Activation of death receptor pathway by TRAIL play a major role in apoptosis. The upregulation of death receptors by chemotherapeutic and chemopreventive drugs, irradiation and chemopreventive agents have been shown to enhance or sensitize cancer cells to TRAIL treatment (Srivastava 2001). TRAIL-resistant

LNCaP cells can be sensitized by chemotherapeutic and chemopreventive drugs, and irradiation *in vitro* and *in vivo* through upregulation of death receptors DR4 and/or DR5 (Shankar et al. 2004, 2005). These finding suggest that upregulation of death receptors DR4 and DR5 by curcumin may be one of the mechanisms by which curcumin enhances the therapeutic potential of TRAIL.

## Clinical Significance of Curcumin

Curcumin is known to possess antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, anticancer and antidiabetic activities and is also beneficial in allergies, arthritis, and alzheimer's disease. Here, we present a brief update on the mechanisms of curcumin action in various diseases.

### *Antioxidant Activity of Curcumin*

Oxidative stress plays a major role in the pathogenesis of various diseases including cancer, diabetes, cardiovascular diseases, neuronal cell injury and hypoxia. Curcumin exhibits strong antioxidant activity that is comparable to ascorbic acid and vitamin E. Curcumin is a potent scavenger of a variety of reactive oxygen species including superoxide anion radicals, hydroxyl radicals (Reddy and Lokesh 1994) and nitrogen dioxide radicals (Sreejayan and Rao 1997; Unnikrishnan and Rao 1995a; Unnikrishnan and Rao 1995b). It was also shown to inhibit lipid peroxidation *in vivo* (Reddy and Lokesh 1992; Sreejayan and Rao 1994). It has protected oxidative cell injury of kidney cells (LLC-PK1) by inhibiting lipid degradation, lipid peroxidation and cytolysis (Cohly et al. 1998; Dikshit et al. 1995). Curcumin treatment showed beneficial effects on renal injury by its ability to inhibit the expression of the apoptosis-related genes Fas and Fas-L (Jones et al. 2000; Jones and Shoskes 2000). In short, curcumin appears to have a significant potential in the treatment of multiple diseases that are a result of oxidative stress. These protective effects of curcumin are attributed mainly to its antioxidant properties and should be further exploited to develop novel drugs.

### *Neuroprotective Activity of Curcumin*

Several reports suggest that curcumin has potential against Alzheimer's disease, a disease characterized by the amyloid-induced inflammation in the brain. It is suggested that dietary supplementation with curcumin may be beneficial in neurodegenerative diseases including Alzheimer's disease (Giri et al. 2004; Lim et al. 2001; Yang et al. 2005). The effect of curcumin in Alzheimer's disease is

mediated through the downmodulation of cytokine (i.e., TNF-$\alpha$ and IL-1$\beta$) and chemokine (i.e., MIP-1b, MCP- 1, and IL-8) activity in peripheral blood monocytes and reduces amyloid-$\beta$ plaque formation.

## *Anti-inflammatory Activity of Curcumin*

Curcumin has been known to possess anti-inflammatory activity since thousands of years. It suppresses the activation of NF-kB that regulates pro-inflammatory genes. It down-regulates the expression of COX-2 enzyme and inhibits the expression of pro-inflammatory enzyme 5-LOX. The curcumin induces down-regulation of various inflammatory cytokines viz., TNF, IL-1, IL-6, IL-8 and chemokines (Surh 2002).

## *Curcumin in Cardiovascular Disorders*

With several recent studies focusing on the beneficial effects of polyphenol-based dietary components such as red wine on vascular health, curcumin has been shown to improve several aspects of cardiovascular health. The key findings are: (I) Curcumin has potent cholesterol lowering ability mediated through increased expression of LDL receptors. The increased LDL receptors will result into increased uptake of LDL-cholesterol from plasma and (II) It also reduces triglycerides and inhibits platelet aggregation. Curcumin treatment resulted in a significant decrease in early atherosclerotic lesions (fatty streaks) in rabbits fed high fat and cholesterol diets. Curcumin has established antioxidant and anti-inflammatory activities that offer promise in the treatment of cardiovascular diseases. For example, it can inhibit lipid peroxidation; reduce creatinine kinase and lactate dehydrogenase levels; and restore reduced glutathione, glutathione peroxidase, and superoxide dismutase to normal levels. Curcumin can also downregulate the expression of myocardial TNF-$\alpha$ and MMP-2 and upregulate the expression of eNOS mRNA (Cheng et al. 2005; Dikshit et al. 1995; Nirmala and Puvanakrishnan 1996a; b; Yao et al. 2004).

## *Curcumin in Cancer Therapy*

Anti-cancerous property of curcumin is the also one of the most significant medicinal property of curcumin. The extensive research has been done on these areas and several research papers have been published. The extensive reviews of curcumin and cancer can be found elsewhere (Aggarwal et al. 2006a; Bemis et al. 2006; Bengmark 2006; Bengmark et al. 2009; Kunnumakkara et al. 2008; Shanmugam et al. 2011; Thomasset et al. 2007). Curcumin has been found to inhibit

growth of oral and hepatic cancers. It inhibited polyp formation in rodents and cell death in colon cancers. It has also inhibited the growth of head and neck tumor cells *in vitro*, as well increased cell death. It has been shown to increased sensitivity to a specific chemotherapy (IFN-γ) in non-small cell lung cancer that without curcumin was relatively insensitive. Curcumin was able to target breast stem/progenitor cells, as evidenced by suppressed mammosphere formation along serial passage and by a decrease in the percent of ALDH-positive cells (Kakarala et al. 2010). By comparison, curcumin had little impact on differentiated cells (Kakarala et al. 2010). By utilizing a TCF-LEF reporter assay system in MCF7 cells, it was confirmed that the effect of curcumin on breast cancer stem/progenitor cells was mediated through its potent inhibitory effect on Wnt/β-catenin signaling pathway.

## *Wound Healing Property of Curcumin*

Tissue repair and wound healing are complex processes that involve inflammation, granulation and tissue remodeling. Injury initiates a complex series of events that involves interactions of multiple cell types, various cytokines, growth factors, their mediators and the extra-cellular matrix proteins (ECM). Many studies have evaluated the effect of curcumin on enhancement of wound healing (Maheshwari et al. 2006). Curcumin treated wound biopsies showed a large number of infiltrating cells such as macrophage, neutrophils and fibroblasts as compared to untreated wound. The presence of myofibroblast in curcumin treated wound demonstrated faster wound contraction (Sidhu et al. 1998). Migration of various cells represents potential sources of growth factors required for the regulation of biological processes during wound healing. Curcumin treatment resulted in enhanced fibronectin (FN) and collagen expression (Sidhu et al. 1998). Furthermore, the treatment led to an increased formation of granulation tissue including greater cellular content, neo-vascularization and a faster re-epithelialization of wound in both diabetic as well as hydrocortisone impaired wounds (Sidhu et al. 1999) by regulating the expression of TGF-β1, its receptors and nitric oxide synthase during wound healing (Mani et al. 2002). Systemic administration of curcumin has shown its beneficial effects by the enhancement of muscle regeneration after trauma in vivo by modulating NF-κB activity (Thaloor et al. 1999). Curcumin incorporated collagen matrix treatment showed increased wound reduction, enhanced cell proliferation and efficient free radical scavenging as compared with control and collagen treated rats (Gopinath et al. 2004). It has also been studied for antiulcer activity in acute ulcer model in rat by preventing glutathione depletion, lipid peroxidation and protein oxidation. Both oral and intraperitoneal administration of curcumin blocked gastric ulceration in a dose dependent manner. It accelerated the healing process and protected gastric ulcer through attenuation of MMP-9 activity and amelioration of MMP-2 activity (Swarnakar et al. 2005). Thus it is well established that curcumin treatment results in faster closure of wounds, better regulation of granulation tissue formation and induction of growth factors.

## *Neuroprotective Property of Curcumin*

Inflammation in Alzheimer's disease (AD) patients is characterized by increased cytokines and activated microglia. Several studies suggest reduced AD risk associates with long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs). Beta-amyloid-induced oxidative toxicity on neuronal cells is a principal route in AD, and its toxicity occurs after fibril formation. Epidemiological studies have raised the possibility that curcumin used by Asian Indian population is involved for the significantly lower prevalence of AD in India compared to United States. 500 ppm dose of curcumin placed in rat diets for 2 months could prevent deficits in memory, as tested with the Morris Water Maze analysis after an intracerebroventricular infusion of the amyloid β peptide. Moreover, the amyloid β peptide deposits in 9 month old female rat were also attenuated (Frautschy and Cole 2010). Curcumin can exist in an equilibrium between keto and enol tautomers, binds to beta-amyloid fibrils/aggregates. The keto-enol tautomerism of curcumin derivatives may be a novel target for the design of amyloid-binding agents that can be used both for therapy and for amyloid detection in Alzheimer's disease. These observations suggest that curcumin has potential to inhibit the amyloid β fibril formation (Kim et al. 2005).

## *Role of Curcumin in Diabetes*

Curcumin has been reported to suppress blood glucose levels, increase the antioxidant status of pancreatic $\beta$- cells, and enhance the activation of PPAR-$\gamma$ in diabetes (Arun and Nalini 2002; Srinivasan 1972). Curcumin has been observed to lower blood sugar levels in diabetic patients (Lin and Chen 2011). Curcumin administration also reduced the serum levels of cholesterol and lipid peroxides in ten healthy human volunteers receiving 500 mg of curcumin daily for 7 days. A significant decrease in the level of serum lipid peroxides (33%), an increase in high-density lipoproteins (HDL) cholesterol (29%), and a decrease in total serum cholesterol (12%) were noted. Daily administration of 10 mg of curcumin for 30 days to eight human subjects increased HDL cholesterol and decreased LDL cholesterol (Ramirez Bosca et al. 2000). The same research group also investigated the effect of curcumin in human subjects with atherosclerosis, in which 10 mg curcumin was administered twice a day for 15 days to 16 men and 14 women. Curcumin significantly lowered the levels of plasma fibrinogen in both men and women. A recent study conducted an interventional, randomized, double-blind, controlled trial to investigate the effects of curcumin administration at escalating doses (low dose three times 15 mg/day, moderate dose three times 30 mg/ day, and high dose three times 60 mg/day) on total cholesterol level, LDL cholesterol level, HDL cholesterol level, and triglyceride level in 75 acute coronary syndrome (ACS) patients (Alwi et al. 2008). Based on 63 patient's results, it is concluded that the

administration of low-dose curcumin showed a trend of reduction in total cholesterol level and LDL cholesterol level in ACS patients (Alwi et al. 2008). Moreover, curcumin in physiological concentration was reported to induce the expression of ABCG1 in the human hepatoma cell line HepG2, thus increasing HDL-dependent lipid efflux and plasma HDL cholesterol levels.

Hyperglycemia leads to increased oxidative stress resulting in endothelial dysfunction. A randomized, parallel-group, placebo-controlled, 8-week study was performed to evaluate the effects of NCB-02 (a standardized preparation of curcuminoids), atorvastatin, and placebo on endothelial function and its biomarkers in patients with type 2 diabetes mellitus. In this study, 72 patients with type 2 diabetes were randomized to receive NCB-02 (two capsules containing curcumin 150 mg twice daily), atorvastatin 10 mg once daily, or placebo for 8 weeks. NCB-02 had a favorable effect, comparable with that of atorvastatin, on endothelial dysfunction in association with reductions in inflammatory cytokines and markers of oxidative stress. Patients receiving NCB-02 showed significant reductions in the levels of malondialdehyde, endothelin-1 (ET-1), IL-6, and TNFα. Recently, the effect of curcumin has been investigated in the activities of drug-metabolizing enzymes such as CYP1A2, CYP2A6, N-acetyltransferase (NAT2), and xanthine oxidase (XO) in 16 healthy male Chinese volunteers, using caffeine as a probe drug. After 14 days, in the curcumin-treated (1,000 mg/day) group, CYP1A2 activity was decreased by 28.6%, while CYP2A6 activity was increased by 48.9%. Curcumin–phosphatidylcholine complex (Meriva / Norflo) was evaluated in 50 patients with osteoarthritis at dosages corresponding to 200 mg of curcumin per diem. After 3 months of treatment, C-reactive protein (CRP) levels significantly decreased in the subpopulation with high CRP, while control group experienced only a modest improvement in these parameters in the CRP plasma concentration. It has been suggested that Meriva is clinically effective in the treatment of osteoarthritis and could be taken into consideration for clinical use. In addition, the same curcumin–phosphatidylcholine complex has been investigated among inflammatory conditions such as chronic anterior uveitis relapses in a 12-month follow-up clinical trial.

Curcumin's ability to lower blood glucose and cholesterol and its antioxidant nature make it a potential therapeutic for the treatment of obesity-related diseases. Recent evidence has shown that curcumin plays a key role in the protection against various obesity-related cancers including pancreatic cancer. Curcumin (8,000 mg/day) in concomitant administration with gemcitibine intravenously (1,000 mg/m/week) was observed in 17 patients of advanced pancreatic cancer for 4 weeks. According to a join report of the Food and Agriculture Organization and the World Health Organization on food additives, the recommended maximum daily intake of curcumin is 0–1 mg/kg body weight, but several clinical studies dealing with its efficacy suggested that it is safe and well tolerated even when intake is as high as 12 g/day. However, high doses of curcumin caused side effects such as gastrointestinal upset, chest tightness, inflamed skin, and skin rashes. The chronic use of curcumin can cause liver toxicity, and individuals with hepatic disease, persons misusing alcohol, and those who take prescription medications that are metabolized by liver should probably avoid curcumin. Curcumin is not

recommended for persons with biliary tract obstruction, because it stimulates bile secretion. Nevertheless, the multifaceted pharmacological nature of curcumin and its pharmacokinetics in obesity remains unknown and additional research is needed to understand it's therapeutic benefits.

## Future Prospects

In recent decades, a rapid increase in the costs of health care has increased the importance of naturally occurring phytochemicals in plants for the prevention and treatment of human diseases, including obesity. The modulation of several cellular transduction pathways by curcumin has recently been extended to elucidate the molecular basis for obesity and obesity-related metabolic diseases. Current knowledge suggests that the potential complementary effect of curcumin may occur through several mechanisms including suppression of inflammatory proteins, uptake of glucose, stimulation of catabolic pathways in adipose tissues, liver, and other tissues, inhibition of angiogenesis in adipose tissues, inhibition of differentiation of adipocytes, stimulation of apoptosis of mature adipocytes, and reduction in chronic inflammation associated with adiposity. Numerous studies confirm its potential role *in vitro* and in animals, yet further human studies, in particular clinical trials, are required to confirm the therapeutic nature of curcumin in obesity and insulin resistance. Expanded use of molecular technologies such as DNA microarrays and proteomics will help to identify newly molecular targets of curcumin and individuals at high risk of obesity-related metabolic diseases. Recent studies have successfully demonstrated the enhanced *in vitro* and *in vivo* anticancer activity of encapsulated curcumin with several types of nanoparticles such as poly(lactic-co-glycolide) (PLGA), β-cyclodextrin, ploy(β-cyclodextrin), cellulose, fibrinogen and hydrogel. Encapsulating hydrophobic drugs on polymer is a promising method for sustained and controlled drug delivery with improved bioavailability of curcumin. Future trials should also include suitably planned pharmacodynamic studies, because the effective dose required for modulating these metabolic responses is unclear at the present. It is important to note that high doses of curcumin in supplement form may have adverse effects. At present, there is not sufficient data to support recommending long-term, safe usage for the prevention and treatment of obesity. Future translational and clinical research overlapping metabolism with the aim to unravel the role of curcumin in obesity-related comorbidities is highly warranted. On behalf of such studies, one might be able to gain insights into curcumin mechanisms at a clinical level and assess, within a short period, the potential success or failure of long-term interventions.

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