Published in final edited form as:
Curr Drug Targets. 2011 March 1; 12(3): 332–347.

Targets of curcumin

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Abstract

Curcumin (diferuloylmethane), an orange-yellow component of turmeric or curry powder, is a polyphenol natural product isolated from the rhizome of the plant *Curcuma longa*. For centuries, curcumin has been used in some medicinal preparation or used as a food-coloring agent. In recent years, extensive *in vitro* and *in vivo* studies suggested curcumin has anticancer, antiviral, antiarthritic, anti-amyloid, antioxidant, and anti-inflammatory properties. The underlying mechanisms of these effects are diverse and appear to involve the regulation of various molecular targets, including transcription factors (such as nuclear factor-κB), growth factors (such as vascular endothelial cell growth factor), inflammatory cytokines (such as tumor necrosis factor, interleukin 1 and interleukin 6), protein kinases (such as mammalian target of rapamycin, mitogen-activated protein kinases, and Akt) and other enzymes (such as cyclooxygenase 2 and 5 lipoxygenase). Thus, due to its efficacy and regulation of multiple targets, as well as its safety for human use, curcumin has received considerable interest as a potential therapeutic agent for the prevention and/or treatment of various malignant diseases, arthritis, allergies, Alzheimer's disease, and other inflammatory illnesses. This review summarizes various *in vitro* and *in vivo* pharmacological aspects of curcumin as well as the underlying action mechanisms. The recently identified molecular targets and signaling pathways modulated by curcumin are also discussed here.

Keywords

Curcumin; molecular targets; transcription factors; growth factors; inflammatory cytokines; protein kinases; enzymes

1. Introduction

Turmeric (the common name for *Curcuma Longa*, known as *haldi* in Hindi) is an Indian spice that belongs to the ginger family [1]. Besides the use as a spice, food preservative and coloring agent, turmeric has been traditionally used in Ayurvedic medicine for the treatment of various ailments such as arthritis, ulcers, jaundice, wounds, fever, trauma as well as skin diseases like psoriasis [2]. Curcumin, a hydrophobic polyphenol, is a principal active constituent of turmeric. In addition to curcumin, turmeric also contains other constituents termed curcuminoids. Curcumin, demethoxycurcumin, bisdemethoxycurcumin, and the recently identified cyclocurcumin are the major curcuminoids isolated from turmeric [3].

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Conflict of interest statement None declared.

Several studies have shown that curcumin is more active than demethoxycurcumin or bisdemethoxycurcumin [4,5]. Commercial available preparations of "curcumin" contain approximately 77% curcumin, 17% demethoxycurcumin and 3% bisdemethoxycurcumin.

Curcumin was first isolated in impure form in 1815 by Vogel and Pelletier, and its chemical structure and synthesis was confirmed by Lampe et al. in 1910 and 1913, respectively [6,7]. Chemically, curcumin is a bis-*α*,*β*-unsaturated *β*-diketone, named (*E*, *E*)-1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5 dione [6] (Fig. **1**). The first study on the use of curcumin in human diseases was published in 1937 [8]. Its antibacterial effect and the ability to decrease blood sugar levels in human subjects was documented in 1949 and 1972, respectively [1]. Over the last 60 years, more than 3000 studies have demonstrated curcumin has antioxidant, antibacterial, antifungal, antiviral, anti-inflammatory, antiproliferative, pro-apoptotic and anti-atherosclerotic effects, exerting medicinal benefits against neurodegenerative diseases, arthritis, allergy, inflammatory bowel disease, nephrotoxicity, AIDS, psoriasis, diabetes, multiple sclerosis, cardiovascular disease, and lung fibrosis [9-12] (Fig. **2**). These effects of curcumin have attracted considerable interests of researchers to uncover its multiple cellular targets and the molecular mechanisms underlying these biological properties. Evidence indicates that the pleiotropic effects of curcumin are dependent on its capacity of interacting and regulation of multiple molecular targets (Table **1**). These targets include transcription factors, growth factors, kinases, inflammatory cytokines, adhesion molecules, apoptosis-related proteins and others. Herein, we present a brief review summarizing the recently identified molecular targets and signaling pathways modulated by curcumin. Various *in vitro* and *in vivo* pharmacological aspects of curcumin as well as the underlying action mechanisms are also discussed here. Because of space limitation, we apologize for not being able to cite all related published studies. The readers who are particularly interested in learning more on curcumin as a therapeutic agent are referred to the excellent review articles [13,14].

2. Molecular targets of curcumin

Modern scientific researches demonstrated curcumin is a highly pleiotropic molecule that interacts with its numerous molecular targets. Curcumin may directly bind and modulate their activity, or indirectly regulate their functions. More than 30 different proteins have been found to interact with curcumin directly, including DNA polymerase [15], focal adhesion kinase (FAK) [16], thioredoxin reductase [17], protein kinase (PK) C [18], lipoxygenase (LOX) [19], and tubulin [20]. It has also been shown that curcumin can bind to certain divalent metal ions such as Fe, Cu, Mn and Zn [21,22].

2.1. Transcription factors

The transcription factors affected by curcumin might be activated or inhibited depending on the particular target. As shown in Table 1, curcumin potently inhibits the activation of some transcription factors including nuclear factor-κB (NF-κB) [23], activated protein-1 (AP-1) [24], signal transducer and activator of transcription (STAT) proteins [25,26], hypoxia-inducible factor-1 (HIF-1) [27], Notch-1 [28], early growth response-1 (Egr-1) [29] and β-catenin [30], but activates other transcription factors such as aryl hydrocarbon receptor (AhR) [31], activating transcription factor (ATF) 3 [32], C/EBP homologous protein (CHOP) [33], electrophile response element (EpRE) [34], peroxisome preoliferator-activated receptor-gamma (PPAR-γ) [35], and NF-E2-related factor (Nrf2) [36].

It has been shown that the nuclear factors, AP-1, NF-κB, STAT-3, β-catenin, Egr-1, HIF-1 and Notch-1, are involved in cell proliferation, cell survival, invasion, angiogenesis, tumorigenesis and inflammation. In most cancers, these transcription factors are upregulated. NF-κB, representing a family of eukaryotic transcription factors, plays an

essential role in regulating the expression of a wide range of genes critical for innate and adaptive immunity, inflammation and cell survival [37,38]. Dysregulated NF-κB activity occurs in a number of diseases, particularly cancer, chronic and acute inflammatory diseases. In non-stimulated cells, NF-κB is constitutively localized in the cytosol as a heterodimer by physical association with an inhibitory protein called inhibitor κB (IκB) [37,39,40]. Various pathogenic stimuli, including bacterial products, carcinogens, tumor promotors, cytokines, radiation, ischemia/reperfusion, and oxidants can activate NF-κB via several signal transduction pathways. Upon activation, NF-κB is translocated to the nucleus, where it induces the expression of more than 200 target genes that have been shown to induce cell proliferation, invasion, metastasis, chemoresistance, and/or inflammation [41]. The expression of constitutively active NF-κB has been reported in most of human cancer cell line and tumors, including breast cancer [42], gynecologic cancer [43], gastrointestinal cancer [44], head and neck squamous cell carcinoma [45], hematological cancer [46], and melanoma [47]. Curcumin prevents NF-κB activation induced by various agents through inhibiting p65 translocation to the nucleus and suppressing IκBα degradation in numerous cell types [48]. By inhibiting NF-κB activation, curcumin suppresses the expression of various cell survival and proliferative genes, including Bcl-2, Bcl-xL, cyclin D1, interleukin (IL)-6, cyclooxygenase 2 (COX-2) and matrix metallopeptidase (MMP)-9, and subsequently arrests cell cycle, inhibits proliferation, and induces apoptosis [49].

It has been identified that significant cross-talk and stimulation occurs between the Notch and NF-κB pathways, both of which are important regulators of cell proliferation and survival, and are key factors in carcinogenesis [28]. The Notch family of genes (Notch-1, -2, -3, -4) encode a group of single-pass transmembrane cell-surface receptors that can be activated by interacting with a family of its ligands [50,51]. Upon activation, Notch is cleaved, generating the nuclear transcriptional co-activator intracellular Notch (ICN). Released ICN translocates into the nucleus where it functions as a transcriptional co-activator by binding the CBF1/RBP-Jκ/Suppressor of Hairless/LAG-1 (CSL) transcription factor. This binding event stimulates further co-activator recruitment and transcriptional activation of Notch target genes that modulate key processes such as cell growth and development, particularly hematopoietic events in cells of the immune system [50]. Curcumin downregulates Notch-1 signaling, which results in the inactivation of NF-κB activity, and contributes to cell growth inhibition and apoptosis in pancreatic cancer cells [28]. Furthermore, silencing expression of Notch-1 by RNA interference inhibits NF-κB DNA binding and sensitizes cells to curcumin inhibition of cell growth, survival and NF-κB activity. On the other hand, overexpression of Notch-1 attenuates curcumin-mediated cell growth suppression, cell death, and NF-κB inhibition [28].

AP-1, which was first known as a 12-*O*-tetradecanoylphorbyl-13-acetate (TPA) inducible transcription factor, is another transcription factor that regulates genes responsible for cell proliferation, survival, differentiation, apoptosis, cell migration, and transformation [52]. AP-1 is a dimeric complex composed of many different proteins belonging to the c-Fos, c-Jun, ATF and Jun dimerization protein families [53]. These AP-1 factors can bind to the TPA-response element sequence and enhance target gene expression [54]. The specific subunit composition of the AP-1 complex determines the diverse cellular responses to AP-1 activity [55]. For example, in mouse fibroblasts c-Jun promotes S-phase entry and proliferation, whereas JunD negatively regulates cell growth [56]. It has been shown that curcumin inhibits the activation of AP-1 induced by tumor promoters via direct interaction with AP-1 binding to its DNA binding motif [57]. Curcumin increases gene expression of glutamate-cysteine ligase (GCL) and other phase II enzymes, which is due to the increased JunD and c-Jun content in AP-1 complexes and decreased MafG/MafK in EpRE complexes [58].

As abovementioned, curcumin can activate some transcription factors such as AhR, ATF3, CHOP, EpRE, and Nrf2. Induction of ATF3 contributes to the proapoptotic effects of this compound [32]. Nrf2 activation by curcumin has been linked to the induction of hemeoxygenase-1 (HO-1), and the increase in the expression and the promoter activity of the aldose reductase [59,60]. In human oral keratinocytes, curcumin initiated nuclear translocation of AhR and formation of the transcriptionally active AhR-aryl hydrocarbon receptor nuclear translocator complex, leading to the upregulation of several AhR-regulated genes [31]. The potential carcinogen bioactivator CYP1A1, one of the AhR-responsive genes, is associated with carcinogen metabolism. Curcumin significantly increased expression and function of CYP1A1, thereby inhibiting CYP1A1-mediated bioactivation of the tobacco-associated carcinogen BP-7, 8-diol in both human oral squamous cell carcinoma keratinocytes and oral mucosal tissues [31].

2.2. Growth factors and protein kinases

Growth factors and their receptors play a critical role in the normal process of growth and differentiation. Unregulated expression of these molecules can lead to abnormal growth and development, resulting in malignant transformation [61]. In addition, increased expression of growth factors, such as transforming growth factor-α (TGF-α), can lead to non-neoplastic disorders like psoriasis [62,63]. Curcumin has been shown to modulate the expression and activity of these growth factors, thereby exhibiting antiproliferative, anti-invasive and antiangiogenic effects (Table **1**).

The epidermal growth factor receptor (EGFR; ErbB-1; HER1 in humans) is an integral plasma membrane protein kinase that is composed of a cysteine-rich extracellular ligand-binding domain, a hydrophobic transmembrane domain, and intracellular C-terminal tails containing tyrosine kinase function and several tyrosine autophosphorylation sites [64,65]. It is a member of the ErbB family of receptors, which is a subfamily of four closely related receptor tyrosine kinases: EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her3 (ErbB-3) and Her4 (ErbB-4) [65]. The activation of EGFR occurs primarily through ligand-dependent mechanisms, but can also occur through ligand-independent events as well as through receptor overexpression [65]. EGFR and its family members are stimulated by several distinct ligands, including epidermal growth factor (EGF), TGF-α, amphiregulin, betacellulin, epigen, epiregulin, and heparin binding EGF-like growth factor [65,66]. Ligand binding to the extracellular domain of the receptor, induces the formation of receptor homo- or heterodimers [67]. The formation of this receptor-dimer complex stimulates the auto- and/or cross-phosphorylation of key tyrosine residues in the C-terminal tails of the receptor, which can function to initiate phosphorylation/signaling cascades via interaction with SH2- and phosphotyrosine-binding domain containing proteins [65]. It has also been shown that the EGFR can translocate to the nucleus, where it can act as a transcription factor for cyclin D1 [65,68] and as a co-activator for STAT3 [69] and E2F1 [70]. Dysregulated EGFR signaling has been implicated as a major contributing factor to many types of cancers, such as breast [71], lung [72], colorectal [72], and head/neck cancer [72]. Specifically, the EGFR pathway plays critical roles in cancer cell proliferation, migration, survival, angiogenesis, and invasion [67,73].

The EGFR has been reported as a potential target of curcumin [74,75]. Curcumin blocks EGFR signaling by preventing EGFR tyrosine phosphorylation and suppressing EGFR gene expression that is mediated by activation of PPAR-γ [35]. Curcumin significantly inhibited the proliferation and survival of lung adenocarcinoma PC-14 and pancreatic adenocarcinoma p34 cells, which was associated with inhibition of phosphorylation of extracellular receptor kinase (ERK) 1/2, and reduction of protein expression of COX-2 and the EGFR [76]. In addition, curcumin has been shown to inhibit the tyrosine kinase activity of the HER2/neu receptor, and deplete the protein itself [77]. Take together, suppression of

HER2/neu and EGFR activity represents one of the mechanisms by which curcumin suppresses the growth of breast cancer cells.

Angiogenesis is a physiological process involving the growth of new blood vessels from pre-existing vessels. In cancer, angiogenesis is generally considered to be a critical step in tumor growth and metastasis [78]. Growth factors produced by tumors can stimulate vasculature formation. Curcumin may directly inhibit angiogenesis and also downregulate expression of various pro-angiogenic growth factors like vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and EGF [79].

Estrogen and its receptors α and β (ERα and ERβ) play important roles in the genesis and tumor progression of breast cancer [80]. As most of breast cancers express these functional receptors, modulation of ER function is a promising tool for controlling breast cancer. Curcumin has been shown to inhibit the growth of both ER-positive MCF-7 and T47D cells, as well as ER-negative MDA-MB231 cells, suggesting that curcumin may exert its chemopreventive effects independent of the expression of estrogen receptors [81].

In prostate cancer, androgens are believed to be essential at all stages of prostate cancer development [82]. It is known that the ligand-activated androgen receptor (AR) may stimulate or repress androgen-regulated genes. However, several studies suggested that AR can also be transformed in the absence of androgen [83-85]. Some cofactors or proteins, such as AP-1 and NF-κB, have been reported to be interacting with AR [86-88]. One study on AP-1 and AR interference suggested that the mutual transcriptional inhibition was because of direct protein-protein interactions between AR and AP-1, whereas another recent study showed that the cross-talk between AR and AP-1 was largely dependent on the expression of cAMP response element-binding protein (CREB)-binding protein [86,87]. The effects of curcumin on cell growth, signal transduction, and transforming activities of both androgen-dependent and-independent prostate cancer cell lines have been evaluated [89]. It appears that curcumin has potential as an anticancer agent against prostate cancer through downregulation of AR and AR-related cofactors (AP-1, NF-κB and CBP) [89].

Chemokine (C-X-C motif) receptor 4 (CXCR4), also called fusin, is an alpha-chemokine receptor specific for chemokine (C-X-C motif) ligand (CXCL) 12 (stromal-derived-factor-1, SDF-1). It has been shown that the CXCL12-CXCR4 axis is involved in several problematic diseases, including cancer cell metastasis [90], leukemia cell progression [91] and rheumatoid arthritis [92]. Thus, CXCR4 is thought to be one of the greatest therapeutic targets to overcome the above diseases. It has been shown that curcumin inhibited human retinal endothelial cell migration by downregulation of SDF-1α-induced expression of CXCR4 [93]. In follicular lymphoma cells, curcumin also exhibited inhibitory effect on CXCR4 expression, suggesting that curcumin has great potential in anti-metastatic treatment of cancer [94].

The effects of curcumin are also apparently mediated through its inhibition of other protein kinases, including autophosphorylation-activated protein kinase (AK) [18], Ca^{2+}-dependent protein kinase (CDPK) [95], FAK [16], IL-1 receptor-associated kinase (IRAK) [96], Janus kinase (JAK) [25], mitogen-activated protein kinases (MAPKs) [97,98], the mammalian target of rapamycin (mTOR) [99,100], phosphorylase kinase (PhK) [18], cytosolic protamine kinase (cPK) [18], PKA [18], PKB/Akt [101], PKC [98], $pp60^{c\text{-}src}$ [18], and spleen tyrosine kinase (Syk) [102] (Table. **1**). Since these protein kinases are important for cell growth, proliferation, survival, migration and other cellular events, inhibition of their functions is undoubtedly one of the action mechanisms of curcumin. Below we will further briefly discuss effects of curcumin on mTOR and MAPKs.

mTOR is a 289 kDa serine/threonine protein kinase that is a member of the PI3K-related kinase family of kinases [103]. mTOR functions as a master regulator of numerous key cellular processes, including cell growth [104], proliferation [105], motility [106], survival [107], autophagy [108], protein synthesis [103], and RNA Polymerase I/II/III-mediated transcription [109,110]. mTOR also functions as a central sensor of cellular nutrient/amino acid levels [104,111,112], cellular energy status [111], cellular redox status [113], and mitogen stimulation, particularly from insulin, IGF-1, and IGF-2 [114,115]. Dysregulation of the mTOR pathway is frequently observed in various human diseases, such as cancer and diabetes. For example, activation of the mTOR pathway was noted in squamous cancers [116], adenocarcinomas [117], bronchioloalveolar carcinomas [118], colorectal cancers [119], astrocytomas [120] and glioblastomas [121]. These findings indicate a crucial role of mTOR signaling in tumorigenesis. mTOR functions as two distinct signaling complexes, mTOR complex 1/2 (mTORC1/2). These two complexes consist of unique mTOR-interacting proteins which determine their substrate specificity. A rapamycin and nutrient-sensitive complex, mTORC1, consists of mTOR, raptor (regulatory associated protein of mTOR), mLST8 (also termed G-protein β-subunit-like protein, GβL, a yeast homolog of LST8), and two negative regulators, PRAS40 (proline-rich Akt substrate 40 kDa) and DEPTOR [122-125]. The main function of mTORC1 is to regulate cell growth, proliferation and survival by sensing mitogen, energy and nutrient signals [126]. mTORC1 functions primarily in the regulation of translation initiation through signaling to its two major targets p70-S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E (eIF4E) binding protein 1 (4E-BP1) [103,104]. Like mTORC1, mTORC2 also includes mTOR and mLST8, but instead of raptor, mTORC2 contains two special subunits, rictor and mSin1 (mammalian stress-activated protein kinase [SAPK]-interacting protein 1) [114,127]. In addition, protor (protein observed with rictor), DEPTOR, PRR5 (proline-rich protein 5) and heat-shock protein 70 (HSP 70) are other novel components of mTORC2 [125,128-130]. mTORC2 regulates the actin cytoskeleton by mediating phosphorylation state of PKCα [127], and modulates cell survival in response to growth factors by phosphorylating its downstream effector Akt at the hydrophobic motif site, S473 [131-133].

Several studies have shown that curcumin inhibited the mTOR pathway and the phosphorylation of S6K, resulting in the inhibition of proliferation and the induction of apoptosis, as well as the induction of autophagy [99,100,115,134]. Our studies demonstrated that curcumin inhibited the IGF-1-stimulated mTORC1-mediated phosphorylation of S6K1 and 4E-BP1, and mTORC2-mediated phosphorylation of Akt in a spectrum of cancer cell lines, including Rh30 (rhabdomyosarcoma), DU145 (prostate cancer), MCF-7 (breast cancer), HeLa (cervical cancer), and HT-29 (colon cancer), suggesting that curcumin inhibition of mTOR signaling was not cell- or cancer-type dependent [115]. Curcumin inhibition of Akt/mTOR/S6K signaling pathway may be related to its induction of autophagy in malignant glioma cells [100]. Most recent studies have further demonstrated that curcumin is able to dissociate raptor from mTOR, thereby inhibiting mTORC1 activity [135].

MAPKs are serine/threonine-specific protein kinases that play key roles in the transmission of extracellular stimuli (mitogens or hormones) and the regulation of various cellular activities, such as gene expression, mitosis, differentiation, cell proliferation, and cell survival/apoptosis [136]. Early studies showed that curcumin was able to inhibit c-jun N-terminal kinase (JNK) activation induced by various agonists, including phorbol 12-myristate 13-acetate (PMA) plus ionomycin, anisomycin, UV-C, gamma radiation, TNF-α, and sodium orthovanadate [137]. In MDA-MB-468 breast cancer cells, curcumin also inhibited anisomycin-induced JNK activation, as well as EGF-induced phosphorylation of ERK1/2 [138]. However, curcumin was able to induce cell apoptosis in cisplatin-resistant ovarian cancer cells, in part by activation of p38 MAPK [139]. In human astroglioma cell

lines, curcumin potently suppressed the phosphorylation of ERK, JNK, and p38 MAP kinase, as well as MMP-9 enzymatic activity and protein expression [140]. The study also demonstrated that AP-1 was under the control of all three MAPKs, while NF-κB was controlled by only two MAPKs, JNK and p38, suggesting that the inhibition of curcumin on PMA-induced MMP-9 expression is mediated through the suppression of MAPKs and subsequent inhibition of NF-κB and AP-1 [140]. The inhibitory effect of curcumin on MAPKs pathway reveals a possible mechanism of AP-1 and NF-κB suppression, and these effects may contribute to the potent anti-inflammatory and anti-cancer effects of this chemical.

2.3. Inflammatory cytokines

During severe infection or after severe injury, excessive synthesis and production of pro-inflammatory cytokines, including TNF-α, IL-1β and IL-6, play an major role in the development of local and systemic inflammation, causing severe pathophysiological derangement or organ failure [141]. Cytokine gene and protein expression are tightly controlled in the producing cells, and one of the most important steps in this regulation is gene transcription. Therefore, inhibition of pro-inflammatory cytokine production by regulation of transcriptional factors, such as NF-κB, is an potential strategy for controlling inflammatory responses [142,143]. Several studies have demonstrated that curcumin was able to modulate the production of various inflammatory cytokines, thereby exhibiting potent anti-inflammatory activity [144-146].

TNF-α plays an important role in the regulation of immune cells and the development of systemic inflammation [147]. Dysregulation of TNF-α production has been implicated in a variety of inflammatory diseases (such as rheumatoid arthritis, Crohn's disease, multiple sclerosis, and psoriasis), as well as cancer [148]. Both *in vitro* and *in vivo* studies showed that curcumin has profound inhibitory effects on the production of TNF-α. In monocytes and alveolar macrophages, curcumin inhibited PMA- or lipopolysaccharide (LPS)- stimulated production of TNF-α [145]. In diabetic rats, chronic treatment with curcumin significantly reduced serum TNF-α level, attenuating cognitive deficit, oxidative stress and inflammation [149]. In the CCl_4 rat model, curcumin protected the rat liver from CCl_4-induced injury and fibrogenesis by reducing inflammatory cytokines levels in the liver and in serum, including interferon-γ (IFN-γ), TNF-α, and IL-6 [150]. In addition, curcumin also showed effects on modulation of TNF-α-induced signaling. Singh et al. firstly reported that curcumin can down-regulate TNF-α-induced activation of NF-κB and AP-1 [48]. In endothelial cells, treatment with curcumin suppressed TNF-induced NF-κB activation and the expression of adhesion molecules, thereby inhibiting the adhesion of monocytes to endothelial cells [151].

Interleukins are another group of inflammatory cytokines that play critical role in the regulation of inflammation response, as well as signaling pathways such as NF-κB and the STATs that are involved in tumor invasion and angiogenesis [152]. In TNF-α-treated HaCaT cells, curcumin attenuated the expression of IL-1β and IL-6 through inhibition of NF-κB and MAPK pathways [153]. In concanavalin A (Con A), phytohemagglutinin (PHA), and PMA stimulated human lymphocytes, curcumin inhibited IL-2 synthesis and this effect may be mediated via NF-κB inhibition [154]. Other studies reported that curcumin also inhibited IL-5 [155], IL-8 [156,157], IL-12 [158], and IL-18 [159] expression. In addition, curcumin showed inhibitory effect on IL-12-induced STAT4 phosphorylation in human T cells [158]. In human multiple myeloma cells, curcumin inhibited IL-6-induced STAT3 phosphorylation and consequent STAT3 nuclear translocation, as well as the IFN-γ-induced STAT1 phosphorylation [160]. Other inflammatory cytokines regulated by curcumin include CXCL1 and CXCL2 [161], monocyte inflammatory protein-1 alpha (MIP-1α) [145], monocyte chemoattractant protein-1 (MCP-1) [145,162].

2.4. Enzymes

A variety of enzymes that are closely associated with inflammation and cancer were found to be modulated by curcumin. These enzymes include COX-2, inducible nitric oxide synthase (iNOS), 5-LOX, and phospholipases A2 (PLA2).

COX-2, the inducible form of COX, can be selectively induced by mitogenic and inflammatory stimuli, which results in enhanced synthesis of prostaglandins in inflamed and neoplastic tissues [163,164]. Several lines of evidence showed that COX-2 is overexpressed in a wide variety of human cancers, such as colon, liver, pancreas, breast, lung, bladder, skin, stomach, head and neck cancers [163]. Either genetic downregulation of COX-2 or pharmacological inhibition of COX-2 protected against the development of tumors in animals [165-168]. Curcumin can downregulate the expression and the activity of COX-2 both *in vitro* and *in vivo* [169,170]. In TPA-treated mouse skin, curcumin potently inhibited the expression of COX-2 protein, as well as TPA-stimulated NF-κB activation [169]. In hepatocellular carcinoma cell-implanted nude mice, curcumin treatment reduced the tumor-induced overexpression of two angiogenic biomarkers, COX-2 and VEGF, indicating that curcumin could inhibit tumor angiogenesis [171]. In gastrointestinal cell lines (SK-GT-4, SCC450, IEC-18 and HCA-7), curcumin suppressed chenodeoxycholate- or PMA-induced COX-2 protein and mRNA expression [172]. Most recently, AMP-activated protein kinase (AMPK), a master regulator of cellular energy homeostasis, was found to act as a regulator of ERK1/2, p38, and COX-2 in cancer cells [173,174]. Regulation of AMPK-COX-2 cascade played an important role in the inhibitory effect of curcumin on adipocyte differentiation and caner cell proliferation [174]. In HT-29 colon cancer cells, curcumin exhibited a potent apoptotic effect, which was mediated by the decrease in AKT phosphorylation and COX-2 expression, as well as the increase of AMPK phosphorylation [173].

HO-1 is an enzyme that catalyzes the degradation of heme into biliverdin, iron, and carbon monoxide [175]. Induction of HO-1 is implicated in inflammatory responses in the lung [176], liver [177] and kidney [178], as well as the systemic responses to hemorrhagic shock [179]. It has been shown that curcumin inhibited glomerular fibrosis through induction of HO-1 [180]. Mechanistically, curcumin induction of HO-1 was correlated with the generation of reactive oxygen species (ROS), p38 activation and phosphatase inhibition [181].

Inosine monophosphate dehydrogenase (IMPDH) is a rate-limiting enzyme that converts inosine monophosphate to xanthosine monophosphate in the *de novo* biosynthesis [182]. Enhanced IMPDH enzyme expression or activity is correlated with increased cellular proliferation and malignant transformation [183,184]. Therefore, IMPDH is an attractive target of immunosuppressive, anticancer and antiviral agents. A most recent study found that curcumin potently inhibited IMPDH activity and decreased the cellular guanosine triphosphate (GTP) level in HT-29 colon carcinoma cells [185].

Other important enzymes that are downregulated by curcumin include arylamine N-acetyltransferase [186], ATPase [187], desaturase [188], DNA polymerase [15], farnesyl-protein transferase (FPTase) [189], iNOS [140], 5-LOX [190], MMP [191-193], NAD(P)H dehydrogenase quinine [194], ornithine decarboxylase (ODC) [195,196], PLA2 [190], telomerase [197,198], and xanthine oxidase (XO) [199,200]. By contrast, the enzymes that are upregulated by curcumin include GCL [201], and src homology 2 domain-containing tyrosine [202] (Table **1**). Because these enzymes are involved in the regulation of cell growth, proliferation, survival, migration, invasion, and other physiological functions, inhibition of their activities clearly constitutes partial action mechanisms of curcumin.

2.5. Adhesion molecules

Cell adhesion molecules (CAMs) are glycoproteins, which are located on the cell surface and are required for binding with other cells or with the extracellular matrix in the process called cell adhesion [203]. Cell surface expression of various adhesion molecules, such as intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (ELAM-1) plays a critical role in inflammatory and neoplastic diseases [204,205]. It has been reported that inhibition of NF-κB completely blocked TNF-α-induced expression of ICAM-1, VCAM-1, and E-selectin, indicating that the expression of CAMs is regulated in part by NF-κB [206]. In human umbilical vein endothelial cells (HUVEC), curcumin potently inhibited TNF-α-induced expression of ICAM-1, VCAM-1, and ELAM-1 partially through NF-κB inhibition, and finally blocked HUVEC adhesion to monocytes [151]. Most recent studies have also shown that curcumin inhibited the expression of VCAM-1 in human intestinal microvascular endothelial cells through suppression of Akt, p38 MAPK, and NF-κB [207].

The integrins are a family of heterophilic CAMs that bind immunoglobulin superfamily CAMs or the extracellular matrix. During the last decade, studies on the function of integrins revealed that these molecules regulate an array of cellular processes, including cell death, proliferation, migration and differentiation [208]. It has been described that curcumin-treated B16F10 melanoma cells formed eight-fold fewer lung metastases in C57BL6 mice [209]. This appears to be related to curcumin inhibition of the expression of α5β1 and α5β3 integrin receptors in B16F10 cells, as well as the cell binding to the extracellular matrix proteins, such as fibronectin, vitronectin, and collagen IV [209]. Most recent studies have further shown that curcumin directly inhibited phosphorylation of β4 integrin (Y1494), thereby inhibiting α6β4-mediated breast cancer cell motility and invasion [210].

2.6. Apoptosis-related proteins

Apoptosis or programmed cell death, which is defined as a mechanism of cellular suicide occurring after sufficient cellular damage, is essential for the development and the maintenance of cellular homeostasis in unicellular and multicellular organisms [211]. Deregulation of apoptosis can lead to cancer, autoimmune and degenerative diseases [212]. Therefore, increasing interest has focused on the elucidation of the apoptotic pathways for disease etiology and the identification of compounds that can induce apoptosis. Studies have demonstrated that curcumin can induce apoptosis in a number of human cancer cell lines, and inhibit the tumor initiation and tumor promotion in animals [213-216]. The chemopreventive action of curcumin might be due to its ability to induce apoptosis by several pathways [139,195,217]. A microarray study has characterized apoptotic genes regulated by curcumin in tumor cells [218]. The results showed that the expression of 104 genes was altered by curcumin treatment among the 214 apoptosis-associated genes [218]. The up-regulated genes by curcumin included HIAP1, CRAF1, TRAF6, CASP1, CASP2, CASP3, CASP4, HPRT, GADD45, MCL-1, NIP1, BCL2L2, TRAP3, GSTP1, DAXX, PIG11, UBC, PIG3, PCNA, CDC10, JNK1 and RBP2. The down-regulated genes were TRAIL, TNFR, AP13, IGFBP3, SARP3, PKB, IGFBP, CASP7, CASP9, TNFSF6, TRICK2A, CAS, TRAIL-R2, RATS1, hTRIP, TNFb and TNFRSF5 [218]. In recent years, more and more targets of curcumin have been discovered in the signaling pathways implicated in apoptosis. In both PC-3 and LNCaP prostate cancer cells, curcumin elevated the expression of pro-apoptotic proteins, such as Bax, Bim, Bak, Puma, Noxa, and death receptors (TRAIL-R1/DR4 and TRAIL-R2/DR5), and inhibited the expression of anti-apoptotic proteins, including B-cell lymphoma protein 2 (Bcl-2), Bcl-XL, survivin and inhibitor of apoptosis protein (IAP) [219]. In human leukemia U937 cells, curcumin down-regulated the anti-apoptotic Bcl-XL, and IAP proteins, induced cytochrome c release, activated caspase-3 and acted as a stimulator of intracellular Ca^{2+} uptake into mitochondria

via uniporter pathway [220]. In human acute myelogenous leukemia HL-60 cells, curcumin induced apoptosis through mitochondrial pathway involving poly(ADP)ribose polymerase (PARP) cleavage, BID cleavage, cytochrome c release, caspase-8/3 activation [221]. In mantle cell lymphoma and multiple myeloma cell lines, curcumin activated caspase-7/9, and induced PARP cleavage [222,223]. In melanoma cells, curcumin induced apoptosis, which was dependent on activation of the death receptor Fas-initiated Fas-associated death domain (FADD)/caspase-8-dependent apoptosis pathway, but was independent of p53 and the Bcl-2 family [224]. Taken together, several apoptosis signaling pathways and apoptosis-related proteins have been implicated in curcumin-induced apoptosis. However, due to the cell specificity and the crosstalks between various apoptosis pathways, the precise action mode of curcumin still remains to be elucidated.

2.7. Other targets

It is well known that p53 gene is critical for cell cycle control, tumor suppression and induction of apoptosis [225]. Over half of all human cancers contain a mutation or deletion of the *TP53* gene. As a transcription factor and tumor suppressor, functional p53 directly induces the expression of downstream genes such as Bax and $p21^{WAF1}$, thereby inhibiting the growth of DNA damaged cells and inducing apoptosis [226,227]. In human neuroblastoma, treatment of curcumin decreased cell viability, and induced cell cycle arrest and apoptosis. It was suggested that these effects may be mediated through functional activation of p53 by curcumin, followed by induction of $p21^{WAF1}$ and Bax expression [228]. In addition, several studies showed that p53 were overexpressed during curcumin-induced apoptosis in various cell lines such as glioma cancer, prostate cancer and breast carcinoma cells [229-231]. However, other studies showed downregulation of p53 by curcumin [232,233]. For example, in BKS-2 cells, an immature B cell lymphoma, curcumin decreased the expression of p53, as well as various survival gene products, including Egr-1, the proto-oncogene c-myc and the transmembrane antiapoptotic protein Bcl-XL [232]. In colon cancer cells, curcumin disrupted the conformation of the p53 protein required for its tumor suppression functions, including serine phosphorylation, binding to DNA, transactivation of p53-responsive genes and p53-mediated cell cycle arrest [233]. The finding of reduced p53 activity by curcumin was also observed in normal thymocytes and myeloid leukemic cells, where curcumin induced p53 degradation. Mechanistically, curcumin promoted the dissociation of NAD(P)H:quinone oxidoreductase 1 (NQO1)-p53 complexes by suppressing the activity of NQO1, a flavoenzyme that binds and stabilizes wild type p53 [194]. In terms of these contradictory reports on the effects of curcumin on p53 expression and function in different cells, it has been speculated that the potential chemopreventive effect of curcumin might relate specifically to certain types of cancer. Due to the inhibition of p53-induced apoptosis in some types of cells, curcumin treatment might confer a modest carcinogenic risk. Therefore, these cautions must always be borne in mind while using it in humans.

P300/CREB-binding protein (CBP), which is one of the most studied enzymes in the histone acetyltransferase (HAT) family, plays a role in the activation of a wide variety of genes and other cellular events. Dysfunction of HATs contributes to several diseases, including cancer, cardiac hypertrophy, and asthma [234,235]. These enzymes, therefore, represent novel, therapeutically relevant molecular targets for drug development [236]. Curcumin is a selective HAT inhibitor. It was documented that curcumin specifically repressed the P300/CBP activity, resulting in several effects, including attenuation of inflammatory responses in human tracheal smooth muscle cells [237], inhibition of human immunodeficiency virus proliferation [238], and suppression of the proliferation of human B cell lymphoma Raji cells [239].

The other molecular targets that are affected by curcumin include cyclin D1 [240], DNA fragmentation factor 40-kd subunit [241], HSP 70 [242], multi-drug resistance protein

(MRP) [243], urokinase-type plasminogen activator (uPA) [23], and uPA receptor [23]. Since these proteins are also important for cell growth, proliferation, survival, migration, invasion, drug resistance, and many other cellular functions, targeting them contributes to the therapeutic effect of curcumin.

3. Human clinical trials

Over the past years, a number of clinical trails have addressed the pharmacokinetics, safety and efficacy of curcumin in humans. Consistent with the growing *in vitro* and *in vivo* evidence of curcumin's anti-inflammatory and anti-cancer properties, disease targets include rheumatoid arthritis [244], postoperative inflammation [245], idiopathic inflammatory orbital pseudotumors [246], Alzheimer's disease, multiple myeloma [247], pancreatic cancer [247], and colon cancer [248]. The results from several preclinical and clinical trials showed that curcumin is remarkably well tolerated. Even at high doses, curcumin appears nontoxic to animals or humans [249,250]. A Phase I clinical trial of curcumin was conducted in patients with high risk conditions or pre-malignant lesions of the bladder, skin, cervix, stomach or oral mucosa [249]. When curcumin was administered as a single daily oral dose ranging from 500 to 8000 mg/day for 3 months, the treatment was well tolerated [249]. In an independent dose-escalation study of curcuma extract on 15 patients with advanced colorectal cancer, curcumin extract was administered to patients at doses between 440 and 2200 mg/day, equivalent to 36-180 mg of curcumin, for up to 4 months. No treatment-related toxicity was observed at any doses either [251].

Although curcumin is well tolerated, and has a wide variety of beneficial activities, the *in vivo* bioavailability of curcumin is poor, which may be an important obstacle to its utility as a therapeutic agent [252]. In a clinical study, it was shown that serum levels of curcumin were undetectable or very low after 2 g of pure curcumin powder was administered alone to fasting volunteers [253]. A subsequent clinical phase I dose escalation study, which was conducted in 15 patients with advanced colorectal cancer refractory to standard chemotherapies, showed that consumption of 3.6 g of oral curcumin daily for up to 4 months results in levels of drug and conjugates in plasma near the limit of detection of the assays used, indicating the low systemic bioavailability of curcumin after oral dosing [254]. This finding is consistent with other data shown in preclinical models [255-257] and in humans [245,249,251,253]. Several pharmacokinetic studies of curcumin showed that curcumin seems to be metabolized through extensive conjugation and reduction in the gastrointestinal tract [252]. Curcumin undergoes avid glucuronidation and sulfation leading to the formation of curcumin glucuronide and curcumin sulfates, as well as metabolic reduction to tetrahydrocurcumin and hexahydrocurcumin, which were found in intestinal and hepatic microsomes, and cytosol, respectively [252,258]. Based on these results, it was suggested that the low systematic bioavailability of curcumin may be due to the hydrophobic nature of the molecule, poor absorption and the metabolic biotransformation in intestine and liver [10]. Several approaches have been tried to improve the bioavailability of curcumin. These approaches include: the use of adjuvants such as piperine to suppress glucuronidation in the liver [253], the use of liposomal curcumin [259], curcumin nanoparticles [260], the use of curcumin phospholipid complex [261], and the use of structural analogs of curcumin [262]. In addition, curcumin has also been conjugated with other carriers, such as cyclodextrin [263] and phosphatidylcholine [264]. Shoba et al. reported that combined treatment with curcumin and piperine (20 mg/kg) produced higher serum concentration of curcumin from 0.25-1 h post-drug and increased the bioavailability by 2000% [253]. A most recent study conducted to characterize the curcumin nanoparticles showed that the biodegradable curcumin nanoparticulate formulation, which was based on poly (lactide-co-glycolide) (PLGA) and a stabilizer polyethylene glycol (PEG)-5000, exhibited enhanced cellular uptake, increased bioactivity *in vitro*, superior bioavailability *in vivo* and substantially longer

half-life than curcumin [260]. In another study, it was shown that curcumin-phospholipid complex maintained effective concentration of curcumin for a longer time in rat serum and proved better hepatoprotective activity than free curcumin at the same dose level [261]. However, there is still little information available about the *in vivo* efficacy and the safety of those reformulated curcumin. Therefore, more studies are required to address these questions.

4. Conclusions

For thousands of years, curcumin has been used in the Orient as a healing agent for a wide range of inflammatory, neoplastic and other conditions. In recent years, the great therapeutic potential against various human diseases, including cancer, cardiovascular diseases, diabetes, arthritis, neurological diseases, and HIV-disease, has been documented. According to the PubMed, over 3000 studies have been carried out with curcumin. This natural product can modulate multiple cellular signaling pathways and affect numerous molecular targets. Although curcumin is quite safe in humans, its low bioavailability may be a limitation for clinical use. Various approaches are being undertaken to enhance the bioavailability of curcumin. Obviously, more studies are needed to fully evaluate the efficacy and the safety of reformulated curcumin, the structural analogues of curcumin as well as the combination of curcumin with existing therapies. Nevertheless, the low cost, pharmacological safety, proven therapeutic efficacy and multiple targeting potential make curcumin a promising agent for prevention and treatment of various human diseases. Meanwhile, reformulations of curcumin with enhanced bioavailability may also hold great promise in the future.

Acknowledgments

The authors' work cited in this review was supported in part by NIH (CA115414 to S.H.) and American Cancer Society (RSG-08-135-01-CNE to S.H.).

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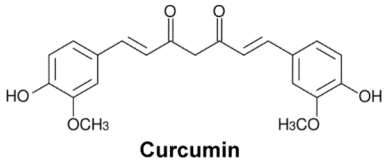

Fig. (1).
Chemical structure of curcumin.

Fig. (2).
Therapeutic potential of curcumin on various human diseases. For more information, see reference [9-12].

Table 1

A list of molecular targets of curcumin.

Transcriptional factors
Aryl hydrocarbon receptor (AhR)↑
Activating protein-1 (AP-1)↓
Activating transcription factor 3 (ATF3)↑
β-Catenin↓
CCAAT/enhancer-binding protein (C/EBP)↓
C/EBP homologous protein (CHOP)↑
CTCF↓
Early growth response -1 (Egr-1)↓
Electrophile response element (EpRE)↑
Heat shock factor-1↓
Hypoxia inducible factor-1 (HIF-1)↓
Notch-1↓
Nuclear factor erythroid 2-related factor 2 (Nrf2)↑
Nuclear factor-kappa B (NF-κB)↓
Peroxisome proliferator-activated receptor-gamma (PPAR-γ)↑
Signal transducers and activators of transcription-1 (STAT-1)↓
Signal transducers and activators of transcription-3 (STAT-3)↓
Signal transducers and activators of transcription-4 (STAT-4)↓
Signal transducers and activators of transcription-5 (STAT-5)↓
Wilms' tumor gene 1 (WT-1)↓
Growth factor and growth factor receptors
Androgen receptor (AR)↓
Chemokine (C-X-C motif) receptor 4 (CXCR 4)↓
Connective tissue growth factor (CTGF)↓
Epidermal growth factor (EGF)↓
EGF-receptor↓
Estrogen receptor-alpha (ER-α)↓
Granulocyte macrophage-colony stimulating factor (GM-CSF)↓
Fibroblast growth factor (FGF)↓
Hepatocyte growth factor (HGF)↓
Human epidermal growth factor receptor-2 (HER-2)↓
Nerve growth factor (NGF)↓
Platelet derived growth factor (PDGF)↓
Tissue factor (TF)↓

Transforming growth factor-α (TGF-α)↓
TGF-β↓
Vascular endothelial growth factor (VEGF)↓
Protein kinases
Autophosphorylation-activated protein kinase (AK)↓
Ca^{2+}-dependent protein kinase (CDPK)↓
EGF receptor-kinase↓
Extracellular receptor kinase (ERK)↓
Focal adhesion kinase (FAK)↓
IL-1 receptor-associated kinase (IRAK)↓
Janus kinase (JAK)↓
c-jun N-terminal kinase (JNK) ↓↑
P38 mitogen-activated protein kinase (p38 MAPK)↓↑
Mammalian target of rapamycin (mTOR)↓
Phosphorylase kinase (PhK)↓
Protamine kinase (cPK)↓
Protein kinase A (PKA)↓
PKB↓
PKC↓
$pp60^{c\text{-}src}$↓
Spleen Tyrosine Kinase (Syk) ↓
Adhesion molecules
Endothelial leukocyte adhesion molecule-1 (ELAM-1)↓
E-selectin↓
Intracellular cell adhesion molecule-1 (ICAM-1)↓
P-selectin↓
Vascular cell adhesion molecule-1 (VCAM-1)↓
Inflammatory cytokines
Chemokine (C-X-C motif) ligand 1 (CXCL1)↓
CXCL2↓
Interleukin-1β (IL-1β)↓
IL-2↓
IL-5↓
IL-6↓
IL-8↓
IL-12↓
IL-18↓
Monocyte chemoattractant protein-1 (MCP-1)↓
Macrophage inflammatory protein-1 alpha

(MIP-1α)↓

Tumor necrosis factor alpha (TNF-α)↓

Enzymes

Arylamine N-acetyltransferases-1↓

ATPase↓

Cyclooxygenase-2 (COX-2)↓

Desaturase↓

DNA polymerase↓

Farnesyl protein transferase (FPTase)↓

Gluthathione-S-transferase (GST) ↓↑

Glutamyl cysteine ligase (GCL)↑

Hemeoxygenase-1 (HO-1)↑

Inducible nitric oxide synthase (iNOS)↓

5-lipoxygenase (5-LOX)↓

Matrix metalloproteinase (MMP)↓

NAD(P)H:quinone oxidoreductase↓

Ornithine decarboxylase (ODC)↓

Phospholipases A2 (PLA2)↓

Src homology 2 domain-containing tyrosine Phosphatase 2↑

Telomerase↓

Xanthine oxidase (XO)↓

Apoptosis-related protein

Bak↑

Bax↑

Bim↑

B-cell lymphoma protein 2 (Bcl-2)↓

Bcl-xL↓

Caspase-3↑

Caspase-7↑

Caspase-8↑

Caspase-9↑

Cellular FLICE inhibitory protein (c-FLIP)↓

Death receptor 4 (DR4)↑

Death receptor 5 (DR5)↑

Fas↑

Fas-associated death domain (FADD)↑

Inhibitor of apoptosis protein (IAP)↓

Noxa↑

Puma↑

Survivin↓

Others
Cyclin D1↓
DNA fragmentation factor 40-kd subunit↑
Heat-shock protein 70 (HSP 70)↑
Multi-drug resistance protein (MRP)↓
P53↓↑
P300/CREB-binding protein (CBP)↓
Urokinase-type plasminogen activator (uPA)↓
uPAR↓