

Molecular targets of curcumin for cancer therapy: an updated review

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Abstract In recent years, natural edible products have been found to be important therapeutic agents for the treatment of chronic human diseases including cancer, cardiovascular disease, and neurodegeneration. Curcumin is a well-known diarylheptanoid constituent of turmeric which possesses anticancer effects under both pre-clinical and clinical conditions. Moreover, it is well known that the anticancer effects of curcumin are primarily due to the activation of apoptotic pathways in the cancer cells as well as inhibition of tumor micro-environments like inflammation, angiogenesis, and tumor metastasis. In particular, extensive studies have demonstrated that curcumin targets numerous therapeutically important cancer signaling pathways such as p53, Ras, PI3K, AKT, Wnt- β catenin, mTOR and so on. Clinical studies also suggested that either curcumin alone or as combination with other drugs possess promising anticancer effect in cancer patients without

causing any adverse effects. In this article, we critically review the available scientific evidence on the molecular targets of curcumin for the treatment of different types of cancer. In addition, we also discuss its chemistry, sources, bioavailability, and future research directions.

Keywords Anticancer · Curcumin · Polyphenol · Turmeric

Introduction

The term cancer is defined as a group of diseases caused by abnormal cell growth with the potential to invade to different body organs [1, 2]. Statistically, cancer occurs in 14.1 million people in the world annually [3, 4]. A wide range of scientific evidence shows that 90–95 % of cancer cases have been induced by epigenetic factors, with remaining cases due to genetic factors [5–7]. It is well known that tobacco smoking, diet, infections, radiation, and environmental pollutants are the most important and common causes of cancer worldwide [8–10].

Current therapeutic strategies for cancer (such as surgery, chemotherapy, phototherapy, and radiotherapy) have been associated with numerous limitations, including drug resistance, a high risk of relapse, unavailability of treatment, and poor outcomes. In view of these, recent research has been focused on the molecular mechanisms at the basis of the uncontrolled cell proliferation of cancer cells and the presence of genetic alterations in their cell cycle. Numerous molecular mechanisms have been found to lead to uncontrolled growth of cancer cells. For instance, overexpression of cyclin-dependent kinases (CDK 4, 6, 1, and 2) and underexpression of tumor suppressor proteins (p53) have been commonly observed in cancerous tissues [11]. In addition, several cell cycle regulatory proteins, such as CDK inhibitors (CKIs) p21, p27, and

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p57, are also deregulated in malignant conditions. Hence, targeting the key molecules in a cancer cell cycle is an effective approach in cancer therapy [12]. In addition, over the last few years, research has been focused on natural anticancer agents due to their high therapeutic potential and negligible adverse effects [13–19].

Plants are rich sources of bioactive natural compounds [20–24] like polyphenolic compounds, which are known as one of the most important classes of natural products with multiple therapeutic effects [25–29]. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) (Fig. 1) is a naturally occurring polyphenolic phytochemical isolated from the powdered rhizome of the *Curcuma longa* L. (Zingiberaceae) [30]. It was discovered in 1815 by Vogel and Pelletier as a yellow pigment [31]. This yellow-colored hydrophobic compound has been traditionally consumed for over 2000 years in Asian countries due to its various medicinal properties against human pathological diseases, such as cancer and neurodegenerative diseases [32–35]. Moreover, in the last few decades, more than 10,200 research publications and 258 clinical studies have been performed on curcumin and cancer (PubMed report). Numerous molecular targets have been proposed concerning the chemotherapeutical effect of curcumin against different types of cancer. Extensive studies indicate that it can modulate all kinds of cancer hallmarks, including uncontrolled cell proliferation, cancer-associated inflammation, cancer cell death, signaling pathways, cancer angiogenesis, and metastasis [36]. During the past two decades, several studies have been reviewed in the literature regarding molecular targets underlying the anticancer effects of curcumin [37–42]. Shehzad et al. [37] showed that curcumin inhibits several cell signaling proteins such as nuclear factor-kappa B (NF- κ B), activator protein 1 (AP-1), cyclooxygenase-2 (COX-2), matrix metalloproteinases (MMPs), cyclin D1, epidermal growth factor receptor (EGFR), Akt, β -catenin, as well as tumor necrosis factor (TNF). They also showed that caspase family proteins and

anti-apoptotic genes such as Bcl-2 and Bcl-XL were other molecular targets of curcumin in the cancer cells. Oyagbemi et al. [38] showed that curcumin possesses inhibitory effects against cytochrome P450, as well as COX-2, lipooxygenase, ornithine decarboxylase (ODC), NF- κ B, c-Jun N-terminal kinase, and protein kinase C. In another review by Goel et al. [39], COX-2, HER2, TNF, EGFR, Bcr-abl, proteasome, and vascular endothelial cell growth factor are reported as molecular targets of anticancer effects of curcumin. Thangapazham et al. [40] also showed that anticancer effects of curcumin are mainly due to its inhibition of the transcription factor NF- κ B. Studies by Shehzad and Lee [41] showed that the chemoprevention effects of curcumin are mainly due to regulation of different molecular pathways in cell signaling, such as NF- κ B, Akt, MAPK, p53, Nrf2, Notch-1, JAK/STAT, β -catenin, and AMPK. In a recent study carried out by Tuorkey et al. [42], it has been reported that the anticancer effects of curcumin are due to modulation of cell cycle, apoptotic signals, anti-apoptotic proteins, miRNAs, Wnt/beta-catenin signaling, protein kinases, NF- κ B, proteasome activation, epigenetic regulation including DNA methylation and histone modification. In the present article, we critically review the molecular targets of curcumin and its benefits as a drug for cancer therapy. We also discuss its chemistry, sources, bioavailability, and future research directions.

Metabolism

One of the drawbacks in the use of curcumin as a therapeutic agent is its rapid metabolism. After adsorption, reduction of the double bonds in the heptadienedione chain takes place, leading to the production of a series of active metabolites [43]. Alcohol dehydrogenase reduces curcumin to tetra- and hexahydrocurcumin in the liver, and an unidentified microsomal enzyme leads to the formation of di- and octahydrocurcumin [30, 31]. Curcumin and the reduced metabolites undergo glucuronidation and are converted into curcumin glucuronide and curcumin sulfate [30, 31]. A cleavage of heptadienedione resulting in vanillin, ferulic acid, and feruloylmethane is also possible; however, it is only a minor pathway [44].

Bioavailability

Curcumin has very low water solubility (<0.005 % w/v) and a high oil–water partition coefficient ($\log P = 3.1$), which presents another problem in its use as a therapeutic agent [45]. The water solubility is low at both acidic and neutral pH; however, curcumin is soluble at pHs above neutral. Tønnesen and Karlsen [46] determined the pKa values for the dissociation of the three acid protons in curcumin to be

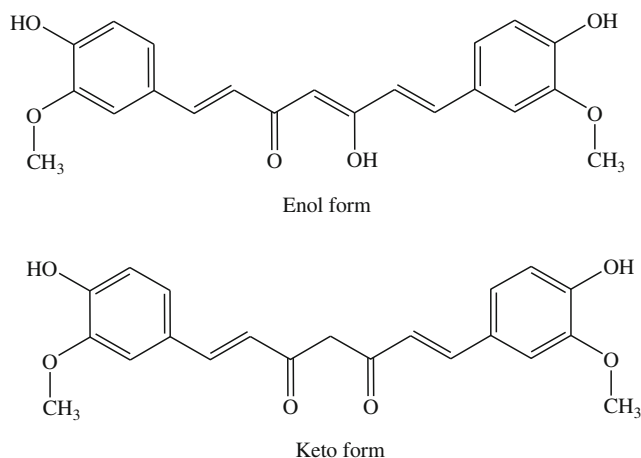


Fig. 1 Chemical structure of curcumin

7.8, 8.5, and 9.0. The compound undergoes rapid decomposition in alkaline media, with a half-life in the range of few minutes. Additionally, photodegradation takes place in organic solvents. These facts limit the applications of curcumin as a bioactive agent [47].

Many techniques have been attempted in order to overcome limitations caused by poor solubility. More than 1500 papers have been published prior to 2015 to find the suitable techniques to improve the bioavailability of curcumin. Recently, nanoformulation-based approaches have been attempted. The water solubility of curcumin is significantly improved when it is present in a complex with cyclodextrins. This also improves the stability of curcumin under alkaline conditions but decreases photostability [47]. Stability of curcumin against alkaline hydrolysis can be improved by encapsulation in micelles composed of cationic surfactants like cetyl trimethylammonium bromide and dodecyl trimethylammonium bromide [47]. Oral administration to rats of a phospholipid complex of curcumin significantly increases bioavailability (maximum plasma drug concentration improving from 266.70 ng/ml with $T_{max} = 1.62$ h to 600.93 ng/ml with $T_{max} = 2.33$ h) [48], as the curcumin-phospholipid complex has better solubility and absorption. It also acts better as an antioxidant and thus has improved effects, such as better hepatoprotective activity [49]. Emulsion-based delivery systems are one of the vehicles that are being increasingly used to protect active ingredients against extreme conditions, to enhance their stability, and to deliver lipophilic bioactive compounds in order to increase bioavailability [44, 50]. Ahmed et al. [44] designed a study, where *in vitro* digestion model was used to evaluate the influence of oil droplet size and lipid phase composition to measure lipid digestion. This model was used to investigate curcumin bioaccessibility. A 0.15 % *w/v* curcumin in the lipid phase was used to prepare either emulsions or nanoemulsions. Long, medium, and short chain triacylglycerols were used as a lipid phase. Results demonstrated that the bioaccessibility of curcumin is highest when medium chain triacylglycerols are used and is slightly better in conventional emulsions than in nanoemulsions.

In the mouse ear inflammation model, it was shown that the anti-inflammatory activity is strongly dependent on the size of droplets of oil-in-water (o/w) nanoemulsions [50]. In the range of 618.6 to 79.5 nm of 1 % curcumin, there was a 43 or 85 % inhibition effect, respectively. Yu and Huang [51] managed to encapsulate curcumin in hydrophobically modified starch, increasing solubility to about 1670-fold. A nanoemulsion composed of 20 % soybean oil, 10 % Tween 80, and 20 % glycerol was used to encapsulate 0.07 % of curcumin. After 60 days, 70 % of the initial amount of curcumin was found to remain in the resulting nanoemulsion [52]. Li et al. [53] used a simple solution mixing method in order to disperse curcumin in the matrix of a cationic polyelectrolyte EUDRAGIT® E PO composed of dimethylaminoethyl methacrylate, butyl

methacrylate, and methyl methacrylate with a molar ratio of 2:1:1. In this way, the water solubility of curcumin was significantly increased to at least 3 mg/ml which is similar to that in conventional organic solvents. Curcumin was also effectively protected from hydrolysis under all pH values examined (5–8), as well as from ultraviolet (UV) degradation. Curcumin loaded into mixed polymeric micelles showed significant improvement in oral bioavailability (around 55-fold) compared to curcumin alone [54].

Molecular targets of curcumin for cancer therapy

Effect of curcumin on CDK/cyclin complexes and CDK inhibitors

CDKs are serine/threonine kinases that control cell cycle progression by forming a complex with their respective cyclin partner [55]. In malignant cells, altered expressions of CDKs, over-expression of cyclins, and loss of expression of CDK inhibitors have been commonly observed. The deregulated CDK activity provides a selective growth advantage for cancer cells. Several studies have documented that curcumin targets the CDK activity and represses the tumor progression. A recent study suggests that curcumin directly targets the overexpression of CDK2 protein function in colon cancer cells [56]. *In vitro* data reveals that curcumin inhibits the proliferation of HCT116 colon cancer cells by causing G₁ cell cycle arrest and reduces expression of phosphorylation of retinoblastoma (Rb) protein. *Ex vivo* results show that curcumin has a strong affinity for the adenosine triphosphate (ATP) pocket of CDK2 protein. Moreover, curcumin shows reduced anticancer potential on CDK2 knockout HCT116 colon cancer cells [56]. This study clearly depicts that curcumin could be a potent cell cycle modulatory agent against CDK2 overexpressed colon cancer cells. In addition, curcumin also promotes the expression of several cyclin-dependent kinase inhibitors (CKIs), including p21, p27, and ING4, in tumor cells. For instance, curcumin-treated prostate cancer cells show apoptosis induction and G₁/S phase arrest. The molecular mechanism has been revealed as an increased expression of CDK inhibitors, such as CDK inhibitor 2A (p16/INK4a), CDK inhibitor 1 (p21/WAF1/CIP1) and CDK inhibitor 1B (p27/KIP1) and an inhibition of the expression of cyclin E and cyclin D1, and hyperphosphorylation of Rb protein [57]. It was further confirmed by proteasome inhibitor lactacystin, which inhibits curcumin-induced suppression of both cyclin E and cyclin D1. Besides, curcumin-induced apoptosis is inhibited upon addition of p21-specific siRNA. Furthermore, curcumin-treated U-87MG human glioblastoma cells show reduced cell proliferation and higher expression of p21WAF1/CIP1. Choi and colleagues [58] investigated a novel mechanism of curcumin-induced p21WAF1/CIP1

expression in U-87MG human glioblastoma cells. Early growth response protein 1 (Egr-1) is a nuclear protein which performs a wide range of functions involved in transcriptional regulation, tumor suppression, cell differentiation, and mitogenesis [59, 60]. Curcumin induces the expression of Egr-1 through extracellular signal-regulated kinase (ERK) and c-Jun NH2-terminal kinase (JNK), but this effect is abrogated on addition of Egr-1-specific small interfering RNA (siRNA) and knock-downed Egr-1U-87MG cells [58]. In summary, these studies confirm that curcumin could be a selective anticancer drug for cancer chemotherapy.

Cyclin E is a nuclear protein which plays an important role in G₁/S progression by interacting with their catalytic partner, the CDK2, and Rb [61]. Moreover, the deregulated expression of cyclin E has also been correlated with malignant transformation of various tumor cells including breast, head and neck, prostate, lung, and leukemic cell lines [62]. Curcumin-treated MCF-7 breast cancer cells showed reduced cell proliferation and arrested growth at the G₁ phase. The growth inhibitory mechanism of curcumin has been revealed as downregulation of cyclin E by promoting proteasomal degradation and upregulation of the CDK inhibitors p53, p21, and p27. Additionally, the effect is suppressed, and cyclin E is upregulated by addition of specific proteasomal inhibitors. Overall, the study suggests that proteasome-mediated downregulation of cyclin E and upregulation of CDK inhibitors may contribute to the antiproliferative effects of curcumin [63]. Similarly, curcumin causes G₁/S block in human osteosarcoma cells. Both flow cytometry and Western blot analysis show that reduction of expression pattern of cdc2/cyclin B complex formation is an essential step in the entry of the cell to S phase [64]. In addition, curcumin-treated ECV304 human umbilical vein endothelial cells induce G₀/G₁ and/or G₂/M phase cell cycle arrest. Microarray analysis results show increased expression of CDKIs, p21WAF1/CIP1, p27KIP1, and p53 and downregulation of cyclin B1 and CDC2 in ECV304 cells [65]. Furthermore, curcumin selectively targets CDK2 overexpressed cancer cells without affecting the normal cells. The study suggests that curcumin induces the p53-dependent apoptosis and causes G₂ phase arrest in mammary carcinoma cells. In contrast, this effect is different in curcumin-treated normal human mammary cells. It causes G₀ cell cycle arrest by blocking the association of Cdk4/Cdk6, as well as by inhibiting phosphorylation of retinoblastoma and preventing the entry of p53-mediated apoptosis. The p53-mediated apoptosis occurs only in G₂ phase-arrested cells [66].

Inhibitor of growth protein 4 (ING4) is a tumor suppressor protein involved in cell cycle arrest and apoptosis induction in the case of DNA damage [67]. Suppressed expression of ING4 protein is observed in numerous cancer tissues and transformed cancer cell lines [68]. In addition, increased expression of pro-inflammatory mediators has been correlated with suppressed expression of ING4 in human brain tumor

cells. Curcumin-treated human glioma cells U251 show reduced cell proliferation and G₂/M phase of cell cycle arrest. Moreover, Western blot analysis shows that curcumin-treated cells exhibit increased expression of p53, p21, and ING4 in a dose-dependent manner. It suggests that curcumin upregulates the expression of p21 and p53 through ING4, which negatively impairs the growth of human glioma cells [69]. These promising facts show that curcumin could be a potent cell cycle modulator in cancer cells.

Effect of curcumin on p53 pathway

p53 is one of the most important tumor suppressor proteins, governing a wide range of cellular processes, including cell proliferation, DNA damage, apoptosis, and so on. p53 is encoded by the *TP53* gene which is often mutated in many types of human cancers [70]. This mutation leads to the loss of wild-type activity of p53 which results in loss of cell proliferative control, DNA check points, DNA repair mechanisms, cell death and so on. These characteristic features support the immortal properties of cancer cells. Hence, recovery of the function of p53 is an attractive therapeutic opportunity in cancer therapy [71]. Curcumin induces apoptosis in various cancer cells by p53-dependent and p53-independent pathways. For instance, curcumin-treated breast cancer cells (MCF-7) showed cell cycle arrest and p53-dependent apoptosis. Furthermore, the chemopreventive mechanism of curcumin reveals that curcumin has no effect on null p53 MDAH041 cells and low p53-expressing TR9 cells. Conversely, its effect is higher in p53 expressing cells, such as TR-7 and MCF-7. In addition, the expression of pro-apoptotic protein Bax is also higher in curcumin-treated MCF-7 cells. Altogether, these results suggest that curcumin mediates its chemopreventive property through a p53-dependent pathway [72].

Targeting the DNA to promote wild-type p53 function in cancer cells is an attractive strategy in cancer drug development. An earlier study demonstrated that curcumin induces apoptosis in basal cell carcinoma (BCC) cells, accompanied by an increase in p53, p21CIP1/WAF1, and DNA damage-inducible 45 (Gadd45) protein levels. Notably, curcumin causes apoptotic cell death in BCC cells without causing cell cycle blockage. These responses are due to p53-DNA binding activity as well as the expression of two p53 downstream targets, p21CIP1/WAF1 and Gadd45, in BCC cells after curcumin treatment. This study concludes that curcumin could be an effective drug for the therapy or prevention of skin cancer [73]. Similar results have been reported for S6 myeloid leukemia cells and HepG2 hepatoma cells, where the induction of wild-type p53 fails to arrest cell growth during apoptosis [74]. In addition, curcumin promotes p53-independent apoptosis in HT-29 colon cancer cells by generating superoxide anions. The effect of curcumin-mediated apoptosis is independent of the status of p53. For instance, the apoptotic effect is

similar in p53 (+/+) and p53 (−/−) HCT-116 cells. It is clear that the effect of curcumin on colon cancer cells is a p53-independent mechanism [75].

Targets of curcumin on cancer signaling pathway

Cell signaling pathways are interconnected with each other and perform a wide range of functions in the human body. These signaling mechanisms are evolutionary, well controlled, and occur only when needed, unless they are suppressed by anti-growth signals. In contrast, cancer cells are self-sufficient; they do not need any external signals or stimuli for their growth and function. Altered expression of signaling proteins has often been reported for controlled proliferation of cancer cells. For example, proteins, such as Ras, phosphoinositide 3-kinase (PI3K), EGFR, mammalian target of rapamycin (mTOR), Akt, NF- κ B, Wntless and INT-1 (Wnt), and mitogen-activated protein kinases (MAPK), are commonly deregulated in cancerous tissues. Hence, targeting key molecules in cancer signaling pathways may provide a therapeutic outcome in cancer therapy [76].

Effect of curcumin in Ras signaling

Ras is a small transmembrane protein belonging to the family of GTPase (a huge family of hydrolase enzymes that hydrolyze guanosine triphosphate), a family involved in many cellular functions by transducing signals inside the cell. Mammalian cells have three distinct Ras proteins, namely K-, H-, and N-Ras, each playing a different function. Ras is a well-known oncoprotein, which is constitutively active in several tumor cells. For instance, K-Ras mutation is frequently observed in NSCLC tumors, H-Ras is common in bladder and thyroid cancer, and N-Ras is common in melanoma cancer cells [77]. Blocking the oncogenic Ras signaling is an attractive strategy in cancer therapy. Curcumin has been extensively studied for its role in Ras oncogenic signaling pathways. For instance, curcumin-treated gastric cancer cells show G₂/M cell cycle arrest, accompanied by decreased expression of cyclin D1 and increased expression of cyclin B. Moreover, the molecular mechanism of curcumin leads to the downregulation of Ras protein and upregulation of ERK. Overall, the study suggested that curcumin inhibits the proliferation of AGS gastric cancer cells by abolishing the RAS-ERK signaling mechanism [78]. A similar kind of mechanism has been proposed in Ras-transfected HAG-1 human adenocarcinoma cells. In brief, the curcumin-treated HAG-1 cells (Ras overexpressed) showed G₂/M cell cycle arrest through predominant expression of Erk1/2 and Bax and reduced expression of Bcl-xL. The study suggested that curcumin could be a potent therapeutic agent against Ras-overexpressed cancer conditions [79]. In addition, curcumin treated H-Ras transformed MCF10A human breast epithelial cells induce reactive

oxygen species (ROS)-mediated downregulation of matrix metalloproteinase-2 (MMP-2) and B cell lymphoma 2 (Bcl-2) expression and upregulation of Bax and caspase-3 [80]. A further *in vivo* study also suggested that curcumin inhibits two oncogenes, such as ras-p21 and c-fos, in 7,12-dimethylbenz(a)anthracene (DMBA) and 12-O-tetradecanoylphorbol-13-acetate (TPA) induced skin cancer in Swiss albino mice [81]. Overall, these studies confirm that curcumin plays a therapeutic role in the Ras oncogenic pathway. Animal studies and clinical experiments are needed to clarify the therapeutic effect of curcumin in Ras-induced cancer systems.

Effect of curcumin in PI3K/AKT/mTOR signaling

PI3Ks are family of lipid kinases which phosphorylate inositol phospholipids and generate the secondary messenger phosphatidylinositol-3,4,5-trisphosphate in the plasma membrane. PI3K can interact with AKT molecules causing translocation of AKT inside the cytoplasm. Activated AKT performs numerous functions in cell survival, cell cycle progression, and cellular growth by interacting with many substrates [82]. The above mechanisms occur during external stimuli or signals; otherwise, these pathways are strictly antagonized by various factors such as phosphatase and tensin homolog (PTEN), serine/threonine protein kinase beta (GSK3 β) and (HB9) [83]. Moreover, constituted expression of PI3K/AKT and silenced functions of PTEN and GSK3 β have been commonly observed in many human malignant conditions. Hence, PI3K/AKT is an attractive target in cancer chemotherapy [84]. Curcumin has been shown to inhibit the PI3K/AKT signal transduction pathway in several tumor models. For instance, curcumin enhances radiation-induced apoptosis in three human Burkitt's lymphoma cell lines by inhibiting the radiation-induced activation of the PI3K/AKT pathway. Furthermore, it also downregulates the expression of NF- κ B protein, which is one of the downstream targets for the PI3K/AKT pathway. In addition, the efficiency of curcumin is also confirmed by using PI3K- and AKT-specific inhibitors, such as LY294002 for PI3K or SH-5 for AKT. The activity of curcumin is equivalent to these known inhibitors, and the combined effect of curcumin and radiation does not produce any synergetic effect on human Burkitt's lymphoma cells [85]. In another study, Yu et al. [86] observed the inhibitory effect of curcumin-against activated Akt/mTOR signaling in PC-3 prostate cancer cells. Moreover, the activity of curcumin was similar in siRNA and gene knockout AKT cells, which confirms that AKT is not a direct target for its anticancer properties. Additionally, curcumin also recruits the AMPK and MAPKs, but inhibition of these kinase enzymes also shows similar activity in curcumin-treated PC-3 cells. However, under the addition of protein phosphatase (a kinase enzyme which removes the phosphate group from a protein) inhibitor calyculin A, the anticancer property of curcumin was

abrogated. Finally, the study concluded that curcumin inhibits Akt/mTOR signaling in PC-3 cells by directly targeting PP2A enzyme [86].

Cancer cells survive for a prolonged time by overexpressing survival (PI3K/Akt/mTOR) and anti-apoptotic pathways (Bcl-2). It was found that targeting both survival and apoptosis pathways will be a key strategy in breast cancer therapy in highly metastatic breast cancer cells. The apoptotic potential of curcumin is low in breast cancer cells, but the addition of PI3K-specific inhibitor LY294002 showed increased apoptotic potential. The study hypothesized that the blockade of the PI3K signaling pathway in breast cancer cells by curcumin overcomes the oncogenic expression of Bcl-2 protein [87]. Collectively, these studies suggest that curcumin could be a potent PI3K/AKT/mTOR inhibitor in malignant cells; however, more clinical studies are needed to demonstrate the efficacy of curcumin for cancer therapy.

Effect of curcumin on Wnt/ β -catenin signaling pathway

Wnts is a family of secreted glycoproteins that regulate the multiple signaling pathways through β -catenin-dependent and -independent mechanisms. It plays a crucial role in the development, survival, and fate of cell metabolism. Inappropriate regulation and hyperactivation of Wnt/ β -catenin signaling have been implicated in numerous human malignancies. β -Catenin is a key player in this pathway, acting as a signal transducer for several Wnt-targeted genes. Overexpression of β -catenin leads to constitutive activation of cell proliferation [88]. On the other hand, GSK3 β is a tumor suppressor protein which controls the activity of β -catenin through ubiquitin-mediated proteosomal degradation. However, its expression is suppressed in tumor cells [89]. Therefore, targeting the Wnt/ β -catenin signaling pathway is an attractive approach in cancer therapy. Curcumin causes cell cycle arrest of G₂/M cells in a human medulloblastoma cell line by modulating the Wnt/ β -catenin signaling pathway. The expression pattern of curcumin-treated medulloblastoma cell line shows increased expression of tumor suppressor protein GSK3 β and the loss of nuclear β -catenin protein. In addition, the loss of nuclear β -catenin protein leads to the loss of its downstream target cyclin D1. Overall, it seems that the anti-tumor mechanism of curcumin in human medulloblastoma cells could be due to abrogation of Wnt/ β -catenin signaling [90].

Osteosarcoma is common in young people with aggressive metastatic potential and poor prognosis rates. The role of curcumin and its analogs was demonstrated in osteosarcoma cells. A total of 43 curcumin analogs were screened, of which six showed 60-fold more potent activity than curcumin in inhibiting Wnt activity. Moreover, curcumin analogs disrupted the β -catenin protein nuclear translocation in osteosarcoma cells. These results suggest that synthesized

curcumin analogs may be more potent than natural curcumin and that these analogs need to be tested in various Wnt-overexpressed cells and in animal models [91]. 12-*O*-tetradecanoylphorbol-13-acetate (TPA) is a tumor promoter which acts by activating protein kinase (PKC) and altering cell signaling pathways [91]. Curcumin inhibits the proliferation and migration of Hep3B hepatocarcinoma cells by activating the GSK3 β protein and inhibiting the β -catenin function. Moreover, curcumin also inhibits the TPA-induced Wnt signaling pathway in xenograft mice model [92]. Overall, curcumin and its analogs could be potent modulators of Wnt/ β -catenin signaling pathway, and this should be further validated in human cancer patients.

Target of curcumin on cancer transcription factors

Transcription factors are proteins which play a crucial role in controlling the expression of several genes. Many of these transcription factors are tightly regulated and inactive under normal physiological conditions. Deregulated expression of several transcription factors have been identified in numerous cancer tissues. Both activation and inactivation of transcription factors can promote cancer development, cell survival, cell proliferation, and tumor angiogenesis. Libermann and Zerbini [93] suggest three important families of transcription factors that play key roles in tumor development, which are validated for drug discovery. They are NF- κ B and AP-1 families, signal transducers and activators of transcription (STAT) family members and steroid receptors.

Effect of curcumin in NF- κ B and AP-1 families of transcription factors

NF- κ B is a family of transcription factors which are involved in immune response and inflammation. A growing body of evidence suggests that it is also involved in human cancer. In cancerous conditions, aberrant and hyperactivated NF- κ B has been observed. NF- κ B has been considered as an emerging target in cancer chemotherapy, and many drugs have been screened against NF- κ B protein function [94]. Curcumin blocks the HPV16-induced viral oncogenesis in an oral cancer cell line. The preventive mechanism of curcumin is that it blocks the DNA-binding capacity of NF- κ B by altering its subunits from p50/p50 to p50/p65. Western blot analysis confirmed the downregulation of the protein expression of AP-1 members: c-Jun, JunD, and JunB, along with NF- κ B members, namely p50 and p65. This study confirms that curcumin has therapeutic potential for the suppression of HPV16-mediated oral oncogenesis by blocking the NF- κ B and AP-1 families of transcription factors [95]. In another study, Singh and Aggarwal [96] demonstrated that curcumin inhibited the NF- κ B/AP-1 pathway in chemically induced conditions. Tumor necrosis factor (TNF), phorbol ester-, and hydrogen

peroxide rapidly promote the NF- κ B function in human myeloid ML-1a cells, an effect which is abrogated during curcumin treatment. It also downregulates NF- κ B-mediated AP-1 function [96]. Likewise, the selective inhibition of NF- κ B by curcumin has also been demonstrated using novel mouse melanoma cells. The study utilized two different melanoma cells, normal human melanocytes and cells which constitutively expressed NF- κ B. Curcumin-treated melanoma cells showed apoptosis induction by caspase-3 activation and dose-dependent inhibition of NF- κ B activity and downstream effect of its target genes, such as COX-2 and cyclin D1. However, curcumin did not produce any apoptotic effect in normal human melanocytes [97].

On the other hand, curcumin showed a differential effect in curcumin-sensitive and -resistant liver cancer cell line. The curcumin-sensitive hepatoma cells showed inhibition of NF- κ B and downstream signaling, such as JNK, cyclin D1, and STAT3, but conversely, the curcumin-resistant hepatoma cells retained their NF- κ B function and tumorigenicity even at a higher concentration of curcumin. The resistance mechanism of curcumin-treated liver cancer cells showed overexpression of histone deacetylases (HDAC) protein. Co-administration of HDAC inhibitor trichostatine reverts the curcumin-resistant cells into sensitive cells. This study suggests that the combination of curcumin and HDAC inhibitor could be a novel therapy in treatment of liver cancer [98].

Effect of curcumin in STAT family of transcription factors

STAT is a cytoplasmic transcription factor which plays a vital role in inflammation and the immune system. It is activated by phosphorylation through receptor-associated tyrosine kinases and non-receptor protein kinases. The phosphorylated STAT forms homo- or hetero-dimerization, migrates into the nucleus, and controls gene expression [99]. In cancer cells, STAT is consistently activated and contributes to the development and survival of the cells [100, 101]. However, studies have demonstrated that inhibition of STAT function causes growth arrest in several cancer cell lines, which suggests that disruption of STAT is a promising target in cancer therapy. Curcumin has been shown to suppress STAT expression in K562 cells. Low levels of nuclear STAT3 and the truncated forms of STAT-5a and 5b isoforms were also observed, which suggests the cleavage of STAT5 protein under exposure to curcumin. Additionally, curcumin also downregulates Janus Kinase 2 (JAK2) mRNA expression as well as cyclin D1 and v-src gene expression in K562 chronic leukemia cells under interferon γ (IFN- γ) induced conditions. It is clear that curcumin could be used as a potent therapeutic drug against leukemia [102]. STAT is key factor in many inflammation-mediated cancers, including ovarian and endometrial malignancies. Curcumin causes decreased cell viability and increased cleavage of caspase-3 in ovarian and endometrial cancer cells. This

mechanism of action has been revealed to be reversible inhibition of phosphorylation of STAT-3 and decreased expression of suppressors of cytokine signaling proteins (SOCS-1 and SOCS-3). Moreover, on removal of curcumin after 24 h of treatment, phosphorylated STAT-3 levels returned to normal. In addition, protein inhibitor of activated STAT (PIAS-3), a protein involved in the negative regulation of STAT-3 function and suppressive effect of PIA-3, has been observed in endometrial cancer cells. Curcumin-exposed endometrial cells show upregulation of PIA-3 function. Overall, the report concluded that curcumin exhibits its antineoplastic effects on ovarian and endometrial cancer cells by suppressing JAK-STAT signaling mechanisms via activation of PIAS-3, thus leading to the attenuation of STAT-3 phosphorylation and tumor cell growth [103]. Collectively, the above reports clearly show that curcumin could be a potent inhibitor of STAT function in cancer therapy.

Target of curcumin in tumor angiogenesis and metastasis

Angiogenesis is the normal physiological mechanism through which new blood vessels are formed from preexisting blood vessels. It occurs during embryogenesis, menstruation, and wound healing. The role of angiogenesis in tumor has been extensively studied. Tumor cells procure nutrients for their uncontrolled growth through the tumor angiogenesis process. Tumor cells are capable of forming new blood vessels by constitutively producing pro-angiogenic factors, such as the VEGF and basic fibroblast growth factor. In the mammalian system, angiogenesis is strictly controlled by anti-angiogenic molecules. Several reports suggest that curcumin is able to modulate the tumor angiogenesis process by inhibiting angiogenic stimulators [104].

Curcumin inhibits the tumor growth and angiogenesis in breast cancer cell implanted nude mice. Downregulated expression of several VEGF isomers such as VEGF-A, VEGF-C, and VEGFR2 and decreased levels of micro-vessel density are observed during curcumin treatment. The suppression of VEGF function leads to the inhibition of breast tumor growth [105]. Furthermore, a study by Chakraborty et al. [106] showed the anti-angiogenic potential of curcumin in chemically induced tumor angiogenic conditions. Osteopontin (OPN) (a secreted phosphoprotein 1) was able to induce VEGF function through a NF- κ B/ATF-4-dependent pathway. Curcumin inhibits the tumor growth of MDA-MB-231 cells (OPN-induced cells) implanted nude mice by abrogating the binding activity of NF- κ B/ATF-4 and inhibiting the VEGF expression. This clearly suggests that curcumin acts as a potent anti-angiogenic agent in regulating OPN-induced tumor angiogenesis in breast cancer [106]. Similarly, curcumin and its analog tetrahydrocurcumin inhibit the tumor growth of HepG2-implanted nude mice by inhibiting the expression of COX-2, VEGF, and matrix metalloproteinase-9 (MMP-9)

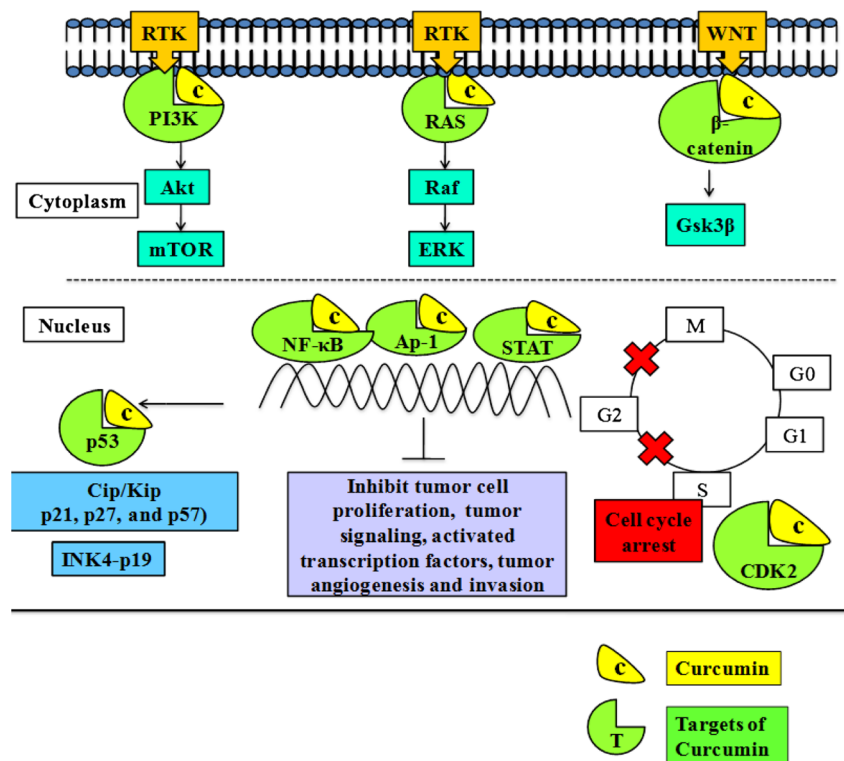
[107]. Basic fibroblast growth factor (bFGF) is another potent angiogenic molecule which stimulates both neovascularization and migration of cancer cells. Curcumin inhibits the neovascularization process of angiogenesis in mouse cornea under bFGF induced conditions. In addition, curcumin has no effect on VEGF expression in transformed human keratinocyte HaCaT cells under TPA induced conditions. It is suggested that curcumin has a direct effect on angiogenesis inhibition, which is relatively specific to endothelial cells and has little effect on tumor cells [108, 109].

Tumor metastasis is a complex cascade and is the final event in the carcinogenesis process. Tumor cells actively migrate from their origin into nearby or distinct organs and ultimately lead to death in cancer patients. This metastasis cascade develops due to specific genetic and epigenetic alteration in tumor cells. Those alterations are degradations of the extracellular matrix (ECM) by MMP, aberrant expression of chemokine receptors, tumor inflammation, angiogenesis, and so on. Hence, inhibition of tumor migration will be a strong therapeutic approach in metastatic tumor therapy [110, 111].

Several studies have shown signs of promise in using curcumin as a possible means of treating cancer metastasis. For instance, curcumin inhibits the migration of colon cancer cells by inhibiting the activity of MMP-9 and suppressing NF- κ B and AP-1 activation [111]. A similar study showed that curcumin inhibits the MMP-9 activity in TPA-induced human astrogloma U87MG and U373MG cells by blocking the PKC/MAPK signaling pathways [112]. Recently, Radhakrishnan et al.

[113] reported a novel mechanism of curcumin on the migration property of colon cancer cells. The study demonstrated that overexpression of the phosphorylated form of cortactin protein (especially in phospho tyrosine 421) is attributed to the migration and motility of colon cancer cells. The tyrosine-protein phosphatase non-receptor type 1 (PTPN1) is the tyrosine phosphatase which controls the phosphorylation status of cortactin protein and negatively regulates its function. However, in HCT116 cells and SW480 colon cancer cells, the complete suppression of PTPN1 was observed. Curcumin-treated HCT116 and SW480 cells show decreased levels of pTyr421-CTTN (CTTN is the gene which encode the cortactin protein) and upregulation of PTPN1 protein. Moreover, the study concludes that curcumin interacts with and activates PTPN1 function, which leads to the dephosphorylation of pTyr421-CTTN and blocks the migration and motility of colon cancer cells. This could be exploited for novel therapeutic approaches in colon cancer therapy based on tumor pTyr421-CTTN expression [113]. In prostate tumor cells, migration has been attributed to the presence of an inflammatory environment. Curcumin inhibits prostate cell migration by abolishing the pro-inflammatory cytokine CXCL1 and -2 in an orthotopic mouse model [114]. These observations suggest that curcumin might target the proteins involved in the metastatic process and could be used as an effective drug for the treatment of metastatic oncologic diseases.

Fig. 2 Molecular targets of curcumin for cancer therapy



Conclusion

Overall, the accumulated data suggests that the anticancer effects of curcumin are multi-targeted in nature (Fig. 2). It can modulate all kinds of cancer hallmarks, including cell proliferation, cancer signaling pathways, transcription factors, tumor angiogenesis, and metastasis. In cell proliferation, it targets the overexpression of CDK2 activity by arresting the cell cycle. Moreover, several studies suggest that curcumin is a potent inducer of cyclin-dependent kinase inhibitors, such as p21WAF1/CIP1, p27KIP1. Additionally, it promotes p53 function in numerous wild and mutant p53 cancer cell lines. Curcumin also modulates several oncoproteins which are involved in tumor signaling pathways. Notably, curcumin represses the growth of numerous cancer cell lines by targeting PI3K, AKT, Ras, and β -catenin pathways. Moreover, curcumin also inhibits several key molecules of tumor angiogenesis and metastasis including VEGF, MMP, PTPN, and CXCL1. Collectively, curcumin could be used as an excellent dietary molecule for the treatment of different types of human cancer. Finally, we recommended that future studies should be focused on:

- Increasing the bioavailability of curcumin by liposomal curcumin, curcumin nanoparticles, curcumin phospholipid complex, and so on.
- Ascertaining the most effective formulation of curcumin for cancer therapy.
- Examination of possible interactions of curcumin with common anticancer drugs.
- Clinical studies to examine the in vivo anticancer effects of curcumin.

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Compliance with ethical standards

Conflicts of interest None.

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