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Review Article

Cancer-linked targets modulated by curcumin

Noor Hasima[1,2], Bharat B Aggarwal[1]

[1]*Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas, 77030, United States;* [2]*Institute Science Biology, Faculty of Science, University of Malaya, 50603 Kuala Lumpur, Malaysia*

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Abstract: In spite of major advances in oncology, the World Health Organization predicts that cancer incidence will double within the next two decades. Although it is well understood that cancer is a hyperproliferative disorder mediated through dysregulation of multiple cell signaling pathways, most cancer drug development remains focused on modulation of specific targets, mostly one at a time, with agents referred to as "targeted therapies," "smart drugs," or "magic bullets." How many cancer targets there are is not known, and how many targets must be attacked to control cancer growth is not well understood. Although more than 90% of cancer-linked deaths are due to metastasis of the tumor to vital organs, most drug targeting is focused on killing the primary tumor. Besides lacking specificity, the targeted drugs induce toxicity and side effects that sometimes are greater problems than the disease itself. Furthermore, the cost of some of these drugs is so high that most people cannot afford them. The present report describes the potential anticancer properties of curcumin, a component of the Indian spice turmeric (*Curcuma longa*), known for its safety and low cost. Curcumin can selectively modulate multiple cell signaling pathways linked to inflammation and to survival, growth, invasion, angiogenesis, and metastasis of cancer cells. More clinical trials of curcumin are needed to prove its usefulness in the cancer setting.

Keywords: Curcumin, cancer targets

Introduction

Cancer is a group of over 200 neoplastic diseases, all of which are caused by the dysregulation of multiple cell signaling pathways [1]. A cancer may have as many as 500 different dysregulated genes. The dysregulation of various genes may occur over a period as long as 20-30 years before a given cancer begins to manifest its symptoms. Therefore, targeting or inhibiting a single gene product or cell signaling pathway is unlikely to prevent or destroy cancer. Chemotherapy and specific targeted drugs have been developed to disrupt these gene products or pathways, thereby inducing cell death and impeding progression of malignant changes in cells. However, problems such as ineffective targeting and drug resistance have plagued these agents, necessitating changes in the approach to systemic cancer therapy.

The current paradigm of cancer chemotherapy is either combinations of several drugs or a drug that modulates multiple targets. The combination chemotherapy approach uses drugs with different mechanisms of action to increase cancer killing [2]. Various drugs that modulate multiple targets, have been approved by the U.S. Food and Drug Administration (FDA) for treatment of various cancer types (**Table 1**). However, these drugs are costly, have a long list of undesirable side effects, and are still not effective enough to have a significant effect on the course of the disease. Before the modern chemotherapy era, drugs derived from natural sources were used for centuries for both cancer prevention and treatment. According to some estimates, as many as 80% of all anticancer drugs today have their roots in natural products. The molecular targets of these natural compounds and their true potential against cancer, however, are not fully understood.

One of the most important of these natural compounds is curcumin (diferuloylmethane), a yellow dye that was identified more than a cen-

Table 1. FDA-approved anticancer drugs and their targets

Year	Drug	Trade Name	Target	Cancer type
1952	Leucovorin	Wellcovorin	Thymidylate synthase	Colorectal
1957	Chlorambucil	Leukeran	DNA	CLL, Hodgkin lymphoma, NHL
1963	Vincristine	Oncovin, Vincasar PFS	β-tubulin	ALL, Hodgkin lymphoma, NHL, Rhabdomyo-sarcoma, Wilm tumor
1964	Vinblastine	Velban	Mitotic spindle;	Breast, Head and neck, Hodgkin lymphoma, Lung
1969	Cytarabine	Cytosar, Tarabine PFS	DNA	ALL, AML, CML, Meningeal leukemia
	Procarbazine	Matulane	DNA	Hodgkin lymphoma
1973	Bleomycin	Blenoxane	DNA; RNA	Cervical, Hodgkin lymphoma, Lung, MPE, NHL, Testicular, Vulvar
1975	Dacarbazine	DTIC-Dome	DNA	Hodgkin lymphoma, Metastatic melanoma
1977	Tamoxifen citrate	Soltamox	ER	Breast
1978	Cisplatin	Platinol, Platinol-AQ	DNA	Lung, Mesothelioma, Ovarian
1979	Daunorubicin	Cerubidine	DNA	AML, ALL
1988	Ifosfamide	Ifex	DNA	Breast, Lung, Lymphoma, Osteosarcoma, Ovarian, Testicular
	Methotrexate	Trexall	Folic acid reductase	ALL, Breast, GTD, Hodgkin lymphoma, Osteosarcoma
1991	Fludarabine	Fludara, Oforta	DNA	CLL
1993	Paclitaxel	Onxol, Taxol	Microtubule	Ovarian, AIDS-related Kaposi sarcoma*, Breast**
1994	Etoposide	VePesid,Toposar,Etopophos	DNA topoisomerase II	Ewing sarcoma, Lung, Testicular
	Pegaspargase	Oncaspar	Asparagine	ALL
1996	Anastrozole	Arimidex	Aromatase	Breast
	Docetaxel	Taxotere, Docefrez	β-tubulin	Breast, Gastric, Head and neck, Lung, Prostate
	Gemcitabine	Gemzar	DNA	Breast, Lung, Ovarian, Pancreatic
1997	Rituximab	Rituxan	CD20	CLL, NHL
	Toremifene	Fareston	ER	Breast
	Letrozole	Femara	Aromatase	Breast
1998	Aldesleukin	Proleukin	IL-2R	Melanoma, Renal
	Irinotecan	Camptosar	DNA topoisomerase I	Colorectal
	Trastuzumab	Herceptin	HER-2	Metastatic breast, Gastric*
	Infliximab	Remicade	TNF-α	Crohn disease, Colorectal cancer
1999	Denileukin diftitox	Ontak	IL-2R	Cutaneous T-cell lymphoma
	Doxorubicin	Adriamycin	DNA topoisomerase II	ALL, AML, Bone, Bladder, Breast, Gastric, Hodgkin lymphoma, Neuroblastoma, NHL, Ovarian, Thyroid, Wilm tumor
	Epirubicin	Ellence, Pharmorubicin	DNA topoisomerase II	Breast
	Exemestane	Aromasin	Aromatase	Breast
2000	Arsenic trioxide	Trisenox	DNA	AML
	Bexarotene	Targretin	Retinoid X receptor	Cutaneous T-cell lymphoma
	Gemtuzumab ozagamicin	Mylotarg	CD33	AML
	Leuprolide acetate	Eligard, Lupron	GNRH receptor	Prostate
	Temozolomide	Temodar	DNA	Anaplastic astrocytoma, Glioblastoma multiforme
2001	Alemtuzumab	Campath	CD52	CLL
	Capecitabine	Xeloda	DNA	Breast, Colorectal
	Imatinib	Gleevec	Bcr-Abl,	CML, Gastrointestinal*
2002	5-Fluorouracil	Adrucil,Carac, Efudex	DNA	Basal cell carcinoma, Breast, Colorectal, Gastric, Pancreatic
	Fulvestrant	Faslodex	ER	Breast
	Ibritumomab tiuxetan	Zevalin	CD20	NHL
	Oxaliplatin	Eloxatin	DNA	Colorectal
2003	Abarelix	Plenaxis	GNRH receptor	Advanced Prostate
	Bortezomib	Velcade	Proteasome, NF-κB	Multiple myeloma

	Gefitinib	Iressa	EGFR	NSCLC
	Tositumomab and I 131	Bexxar	CD20	NHL
2004	Azacitidine	Vidaza	DNA; RNA	Myelodysplastic syndrome
	Bevacizumab	Avastin	VEGF;VEGFR	Colorectal, Glioblastoma, Lung, Renal*
	Cetuximab	Erbitux	EGFR	Colorectal, Head and neck
	Clofarabine	Clolar	DNA	ALL
	Erlotinib	Tarceva	EGFR	Lung, Prostate
2005	Lenalidomide	Revlimid	NF-κB	Multiple myeloma, Myelodysplastic syndrome
	Nelarabine	Arranon	DNA	ALL
	Sorafenib tosylate	Nexavar	B-RAF; VEGFR; PDGFR	Liver, Renal
2006	Dasatinib	Sprycel	Bcr-Abl; PDGFR; Src	ALL, CML
	Decitabine	Dacogen	DNA	Myelodysplastic syndrome
	Panitumumab	Vectibix	EGFR	Colorectal
	Sunitinib malate	Sutent	PDGFR; VEGFR	Gastrointestinal, Renal, Pancreatic neuroendocrine tumors*
	Vorinostat	Zolinza	HDAC	Cutaneous T-cell lymphoma
2007	Ixabepilone	Ixempra	β-tubulins	Breast
	Lapatinib ditosylate	Tykerb	HER-2; EGFR	Breast
	Nilotinib	Tasigna	Bcr-Abl	CML
	Raloxifene	Evista	ER	Breast
	Temsirolimus	Torisel	mTOR; HIF-1; VEGF	Renal
	Topotecan	Hycamtin	DNA topoisomerase I	Cervical, Lung, Ovarian
2008	Bendamustine	Treanda	DNA	CLL, Hodgkin lymphoma, Lung, Multiple myeloma, NHL
	Plerixafor	Mozobil	CXCR4	MM, NHL
	Adalimumab	Humira	TNF-α	Crohn disease, Colorectal cancer
2009	Degarelix	Firmagon	GNRH receptor	Prostate
	Everolimus	Afinitor, Zortress	mTOR, mTORC1, TSC	Renal, Astrocytoma, Advanced pancreatic neuroendocrine tumors*, Renal angiomyolipoma**
	Ofatumumab	Arzerra	CD20	CLL
	Pazopanib	Votrient	VEGFR; PDGFR	Renal, Soft tissue sarcoma*
	Pemetrexed	Alimta	Folate-dependent metabolic processes	Mesothelioma, Lung
	Pralatrexate	Folotyn	Folate carrier type 1	Peripheral T-cell lymphoma
	Romidepsin	Istodax	HDAC	Cutaneous T-cell lymphoma
2010	Cabazitaxel	Jevtana	Microtubule	Prostate
	Denosumab	Prolia, Xgeva	RANKL	Multiple myeloma, Bone
	Eribulin mesylate	Halaven	Microtubule	Breast
2011	Ipilimumab	Yervoy	CTLA-4	Melanoma, Metastatic melanoma
	Vandetanib	Caprelsa	EGFR	Thyroid cancer
	Brentuximab	Adcetris	CD30	Hodgkin lymphoma, Anaplastic large cell lymphoma
	Peginterferon	Pegintron	α-2b interferon receptors	Melanoma
	Crizotinib	Xalkori	ALK, ROS1	NSCLC
	Vemurafenib	Zelboraf	B-RAF	B-RAF–positive melanoma
2012	Vismodegib	Erivedge	GLI1	Basal cell carcinoma
	Axitinib	Inlyta	VEGFR; PDGFR	Advanced renal cell carcinoma
	Pertuzumab	Perjeta	HER-2	HER-2–positive metastatic breast cancer
	Tofacitinib	Jakafi, Ruxolitinib	JAK2	Myelofibrosis

Cancer types: ALK, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; GTD, gestational trophoblastic disease; MPE, malignant pleural effusion; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung carcinoma. Targets: B-RAF, oncogenic protein encoded by *B-Raf* gene; Bcr-Abl, fusion protein of ABL part of chromosome 9 breaks and BCR part of chromosome 22; CD20, B-lymphocyte antigen; CD30, anaplastic large cell lymphoma–associated marker; CD33, myeloid-associated marker; CD52, mature lymphocytes antigen; COX-2, cyclooxygenase-2; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; CXCR4, chemokine receptor 4; EGFR, epidermal growth factor receptor; ER, estrogen receptor; GLI-1, Hedgehog Pathway Transcription Factor; GNRH, gonadotropin-releasing hormone; HDAC, histone deacetylases; HER-2, human epidermal growth factor receptor 2 (also known as Neu and ErbB-2), HIF-1, hypoxia-inducible factor 1; IκBα, inhibitor of NF-κB transcription factor; IL-2R, interleukin-2 receptor; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PDGFR, platelet-derived growth factor receptor; RANKL, receptor activator of NF-κB ligand; ROS1, c-ros oncogene1, receptor tyrosine kinase; Src, oncoprotein; TSC, tuberous sclerosis complex; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. FDA approved drugs against another cancer type, Bevacizumab approved in 2009*; Everolimus approved in 2011* & 2012**; Imatinib approved in 2002*; Paclitaxel approved in 1997* & 2005**; Pazopanib approved in 2012*; Sunitinib malate approved in 2011*; Trastuzumab approved in 2010*.

tury ago. Curcumin is found in turmeric, a yellow-colored spice of the perennial herb *Curcuma longa*, which has been used widely for centuries not only in cooking but in traditional therapies for various diseases, especially as an anti-inflammatory agent. Curcumin and its metabolite, tetrahydrocurcumin have been extensively investigated as anti-inflammatory and anti-cancer molecules [3, 4].

The wide variety of medicinal effects of curcumin is a result of its ability to interact with a diverse range of molecular targets (**Table 2**), acting upon numerous biochemical and molecular cascades [5]. This polyphenol modulates various targets through either direct interaction or modulation of gene expression, which includes inflammatory biomarkers, growth factors and their cell signaling pathways, protein kinases and protein phosphatases, tumor suppressor genes, transcription factors, proapoptotic pathways, and oncoproteins (**Table 2**). Curcumin can also bind directly to DNA and RNA. Direct binding to its β-diketone moiety is facilitiated, while interaction with other macromolecules is mediated through the α, β-unsaturated β-diketone moiety, carbonyl and enolic groups of the β-diketone moiety, methoxy and phenolic hydroxyl groups, and phenyl rings [6]. As a result of these interactions, curcumin can inhibit tumor proliferation, growth, metastasis, invasion, and angiogenesis. Curcumin has been shown to induce cell death mainly through apoptosis, but in cells that are apoptosis resistant, it has been shown to induce mitotic catastrophe [7] and autophagy [8].

This review examines curcumin's interactions with a diverse range of major anticancer targets in multiple cancer types (**Table 2**) and compares its actions with those of FDA-approved anticancer drugs.

Cancer targets

A desirable anticancer drug must be selective for and cytotoxic to cancer cells, have minimal side effects, and be cost-effective. Since 1952, 89 drugs have been approved by the FDA for the treatment of various cancer types (**Table 1**). The targets for these drugs have been identified in phenotypic or correlative studies as causal factors in the initiation and/or progression of a cancer type [9, 10]. Agents that selectively target cancer-specific mutations are effective because they can discriminate between normal and malignant forms [11]. However, most targets are not cancer specific; for example, CD20 is a normal B-cell differentiation protein, and epidermal growth factor receptor (EGFR) is also expressed on normal cells [12].

Targets with FDA-approved drugs

All the anticancer drugs approved by the FDA (**Table 1**) can be subdivided into three groups: semiselective, cytotoxic, and tissue-selective. The drugs that target growth factor signaling and oncoproteins such as EGFR and Bcr-Abl are semiselective; those that target cellular components such as DNA, DNA topoisomerase, or microtubules are cytotoxic; and those that target cell-surface proteins such as CD20 and CD52 are tissue-selective [12]. Semiselective agents are typically combined with a cytotoxic agent, since semiselective agents are not effective alone and cytotoxic agents are too toxic alone [12]. For example, trastuzumab inhibits ErbB2/HER-2, whose overexpression blocks paclitaxel-induced apoptosis. Yu *et al*. were able to restore the apoptotic response to paclitaxel by administering trastuzumab with it [13]. The targets of the semiselective agents (growth factors and oncoproteins) and the cytotoxic agents (cellular components) are all targets of curcumin (**Figure 1**). Therefore curcumin can be classified as both a semiselective and a cytotoxic agent.

This section highlights cancer-related targets that are modulated by curcumin as well as one or more FDA-approved drugs.

Inflammatory biomarkers

Various inflammatory biomarkers are modulated through suppression of a major inflammatory transcription factor, nuclear factor–kappaB (NF-κB), which is constitutively expressed in almost all cancer types. Bortezomib and lenalidomide, two drugs approved by the FDA for the treatment of multiple myeloma and myelodysplastic syndrome, inhibit the activation of NF-κB, thereby disrupting the cell cycle and inducing apoptosis in cancer cells. Bortezomib kills cancer cells by interfering with the action of a large cellular structure called the proteasome, which degrades proteins that regulate cell proliferation. Resistance against bortezomib prompted clinical trials of various

Table 2. Modulation of cancer-linked cell-signaling pathways by curcumin

Inflammatory biomarkers:	
Inhibited carrageenan-induced rat paw edema and cotton pellet granuloma	[139]
Inhibition of 5-HETE formation in intact human neutrophils	[51]
Inhibited lipoxygenase and cyclooxygenase in mouse epidermis	[52]
Inhibited activation of NF-κB induced by TNF-α in human leukemia cells	[16]
Inhibited production of TNF-α in a human monocytic macrophage cell line	[22]
Inhibited MMP-9 in human hepatocellular carcinoma cell line	[58]
Inhibited transcription of COX-2 in gastrointestinal cancer cell lines	[56]
Inhibited IL-6 in human osteoblast and osteosarcoma cell lines	[55]
Blocked PYK2 phosphorylation in smooth muscle cells	[64]
Inhibited MMP-2 in H-ras MCF10A cells	[59]
Inhibited DUBs in various colon cancer cells	[19]
Inhibited STAT3 phosphorylation in multiple myeloma	[53]
Inhibited FAK in melanoma cells	[62]
Inhibited p300/CBP-HAT activity in HeLa cells	[60]
Inhibited the catalytic activities of 5-LOX in HT-29 human colon cancer cells	[140]
Inhibited inducible and constitutive iNOS expression in melanoma cells	[141]
Downregulated EZH2 expression in breast cancer cell line	[66]
Reduced HDAC expression in B-non-Hodgkin lymphoma cell line	[28]
Modulation of growth factors and their cell signaling pathway:	
Induced cell cycle inhibitor p21 in human basal cell carcinoma cells	[72]
Inhibited TGF-β expression in transformed keratinocyte	[68]
Inhibited induction of VEGF in osteoblastic cells	[35]
Upregulated p27 in immortalized human umbilical vein endothelial cells	[142]
Inhibited CDK4 activation in various carcinoma cell lines	[71]
Inhibited PDGFR-induced proliferation of human hepatic myofibroblasts	[34]
Inhibited constitutive activation of EGFR in colon cancer cells	[29]
Down-regulated CDK2 in A549 cells	[70]
Abrogated IGF-1R activation in MCF-7 cells	[30]
Decreased expression of VEGFR1 in bladder cancer cells	[36]
Reduced activation of p185/neu/HER-2 in cancer cells	[31, 32]
Modulation of protein kinases and protein phosphatases:	
Suppressed PKC activity in NIH 3T3 cells	[73]
Inhibited PKA which inhibited growth of various cancer cells	[75]
Inhibition of cyclic AMP-dependent protein kinase	[76]
Blocked JNK activation in fibroblast cells	[83]
Inhibited PI3-K activation in breast cancer cells	[78]
Inhibited AKT activation in LNCaP and PC-3 but not in DU-145 cells	[79]
Activated Src homology 2 domain-containing tyrosine phosphatase 2 in brain microglia	[85]
Inhibited activation of p38 MAPK in keratinocyte cells	[80]
Dephosphorylated GSK3 in T-cell acute lymphoblastic leukemia cells	[84]
Inhibited mTOR in various cancer cells	[39]
Downregulated B-RAF in fibroblast cells	[38]
Downregulated p-ERK1/2 levels in pancreatic adenocarcinoma cell lines	[81]
Upregulates MAPK phosphatase-5 in prostate cells	[87]
Activated AMPK to inhibit growth in ovarian cancer cells	[77]
Inhibited Akt/mTOR signaling through stimulation of calyculin A-sensitive PTPase	[86]
Activated mitogen-activated protein kinase phosphatase-1 in hippocampal cells	[88]
Upregulation of tumor suppressor genes:	
Induced apoptosis in human basal cell carcinoma cells by upregulation of *p53*	[72]
Upregulated *PTEN* expression	[91]

Inhibited COP9 signalosome-specific phosphorylation linked to p53 degradation by UPS	[89]
Inhibited CDK4-mediated phosphorylation of retinoblastoma protein in cancer cells	[71]
Modulation of various transcription factors:	
Downregulated AP-1 activation in mouse fibroblast cells	[93]
Downregulated ER expression in breast cancer cells	[42]
Downregulated transactivation and expression of AR in prostate cancer cells	[94]
Decreased activation of β-catenin in colon cancer cells	[95]
Blocked induction of GADD45 in colon cancer cells	[96]
Increased GADD153 in colon cancer cells	[97]
Inhibited STAT1 phosphorylation in multiple myeloma	[53]
Destabilized HIF-1β (ARNT) in various cancer cells	[100]
Inactivated constitutively active FOXO in T-cell acute lymphoblastic leukemia cells	[84]
Downregulated the expression of PPARδ in HT-29 colon cells	[101]
Downregulated HIF-1α in vascular endothelial cells	[99]
Activated Nrf2 in epithelial cells	[102]
Modulation of proapoptotic pathways:	
Decreased Bcl-2 levels in leukemia and colon adenocarcinoma cells	[104]
Downregulated Bcl-xL in B-cell lymphoma	[105]
Upregulated Bax in breast carcinoma cell lines	[110]
Suppressed XIAP to human melanoma cell lines	[106]
Stimulated the activity of caspase-8 in gastric and colon cancer cells	[112]
Activated caspase-8, BID cleavage and cytochrome c release	[111]
Upregulated Bak in acute myelogenous leukemia	[96]
Downregulated c-FLIP in natural killer/T-cell lymphoma cells	[107]
Suppressed expression of IAP-1 in breast cancer cells	[108]
Inhibited IAP-2 in human hepatic cancer cells	[109]
Downregulated survivin in apoptosis-resistant Bcr-Abl–expressing cells	[7]
Induced expression of PUMA, Bim and Noxa in prostate cancer cells	[90]
Activated cysteine proteases for apoptosis in tumor cells	[143]
Modulation of oncoproteins:	
Inhibited c-Myc mRNA expression in smooth muscle cells	[115]
Inhibited induction of endogenous c-*Met* gene in hepatocellular carcinoma cells	[118]
Decreased expression of *Ras* and *Fos* proto-oncogenes in tumorous skin	[120]
Abrogated of Src activity in fibroblast cells	[45]
Downregulated *Bcr-Abl* fusion gene in human chronic myelogenous cells	[46]
Downregulated Mdm2 in various cancer cells	[144]
Downregulated N-Myc in medulloblastoma cells	[116]

Targets: 5-HETE, 5-hydroxy-eicosatetraenoic acid; 5-LOX, 5-lipoxygenase; AKT, AKT8 virus oncogene cellular homolog; AMPK, AMP- activated protein kinase; AP-1, activator protein 1; AR, androgen receptor; ARNT, aryl hydrocarbon receptor nuclear translocator; Bak, B-cell lymphoma 2 homologous antagonist/killer; Bax, B-cell lymphoma 2-associated X protein; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; BID, BH3 interacting-domain death agonist; Bim, BH3-only proapoptotic protein; B-RAF, oncogenic protein encoded by B-RAF gene; CDK2, cyclin-dependent kinase 2; CDK4, cyclin-dependent kinase 4; c-FLIP, cellular FLICE-inhibitory protein; COX-2, cyclooxygenase-2; DUBs, deubiquitinating enzymes; EGFR, epidermal growth factor receptor; ER, estrogen receptor; EZH2, enhancer of zeste homolog 2; FAK, focal adhesion kinase; FOXO, forkhead box O; GADD 45, growth arrest and DNA damage gene 45; GADD153, growth arrest and DNA damage-inducible gene 153; GSK3, glycogen synthase kinase 3; HAT, histone acetyltransferases; HDAC, histone deacetylase; HER-2, human epidermal growth factor receptor 2 (also known as Neu and ErbB-2); HIF-1α, hypoxia-inducible factor-1alpha; IAP-1, inhibitor of apoptosis protein 1; IAP-2, inhibitor of apoptosis protein 2; IGF-1R, insulin-like growth factor-1 receptor; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; JNK, cJun N-terminal kinase; MAPK, mitogen-activated protein kinase; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Noxa, phorbol-12-myristate-13-acetate-induced protein 1; Nrf2, NF-E2 related factor 2; PDGFR, platelet-derived growth factor receptor; p-ERK 1/2, phosphorylated extracellular signal-regulated protein kinases 1 and 2; PI3-K, phosphotidylinositol-3-kinase; PKA, protein kinase A; PKC, protein kinase C; PPARδ, peroxisome proliferator-activated receptorδ; PTEN, phosphatase and tensin homolog; PUMA, p53 upregulated modulator of apoptosis; PYK2, proline-rich tyrosine kinase 2; STAT1, signal transducer and activator or transcription 1; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; VEGFR1, vascular endothelial growth factor receptor 1; XIAP, X-linked inhibitor of apoptosis protein.

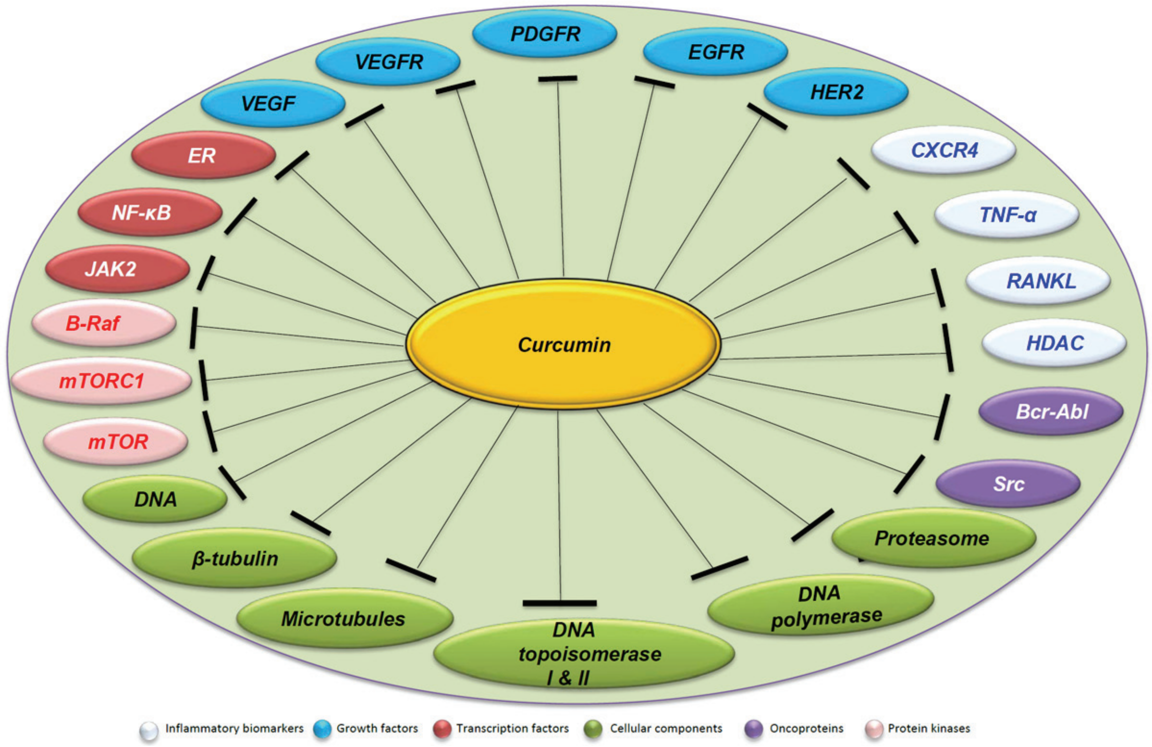

Figure 1. Targets with FDA approved drugs.

second-generation proteasome inhibitors, such as marizomib and carfilzomib [14, 15].

Not only does curcumin inhibit both inducible and constitutive activation of NF-κB in various cancer cells [16], it is also a potent proteasome inhibitor: it directly inhibits the 20S proteasome and induces degradation of IκBα [16, 17]. Curcumin also inhibits the COP9 signalosome kinases and deubiquitinating enzymes, thereby disabling the ubiquitin-proteasome system [18, 19]. The COP9 signalosome has kinase activity that phosphorylates IκBα [18], and curcumin has been identified as an efficient inhibitor of these kinases [20]. Deubiquitinating enzymes are regulators of the ubiquitin-proteasome pathway, and ubiquitin-mediated events play important roles in cell proliferation. In many human cancer types, mutated deubiquitinating enzymes have been seen to function as oncogenes and tumor suppressors [21], implicating curcumin as an effective proteasome inhibitor targeting the ubiquitin-proteasome pathway in multiple ways.

Chronic inflammation is associated with processes that contribute to the onset or progression of cancer. Increased cancer risk is attributed to genetic damage caused by chronic inflammation via production of oxidizing compounds such as reactive oxygen and nitrogen species. Four inflammatory biomarkers, tumor necrosis factor alpha (TNF-α), CXC receptor 4 (CXCR4), receptor activator of NF-kB ligand (RANKL), and histone deacetylase (HDAC), are targets for FDA-approved drugs (**Figure 1**). The inflammatory cytokines have been shown to mediate tumorigenesis, and TNF-α, which controls cell survival and apoptosis, is a vital player in inflammation and cancer. The two FDA-approved drugs that target TNF-α are infliximab and adalimumab. These drugs are similar and work by reducing inflammation induced by TNF-α. Curcumin inhibited production of TNF-α [22] and suppressed the TNF signaling pathways [16].

The chemokine receptor CXCR4 is expressed on multiple cell types, including cancer cells, and when bound by its ligand, CXCL12, is involved in tumor progression, angiogenesis, metastasis, and survival. CXCR4, which helps keep stem cells within the bone marrow, is blocked by the drug plerixafor, causing the

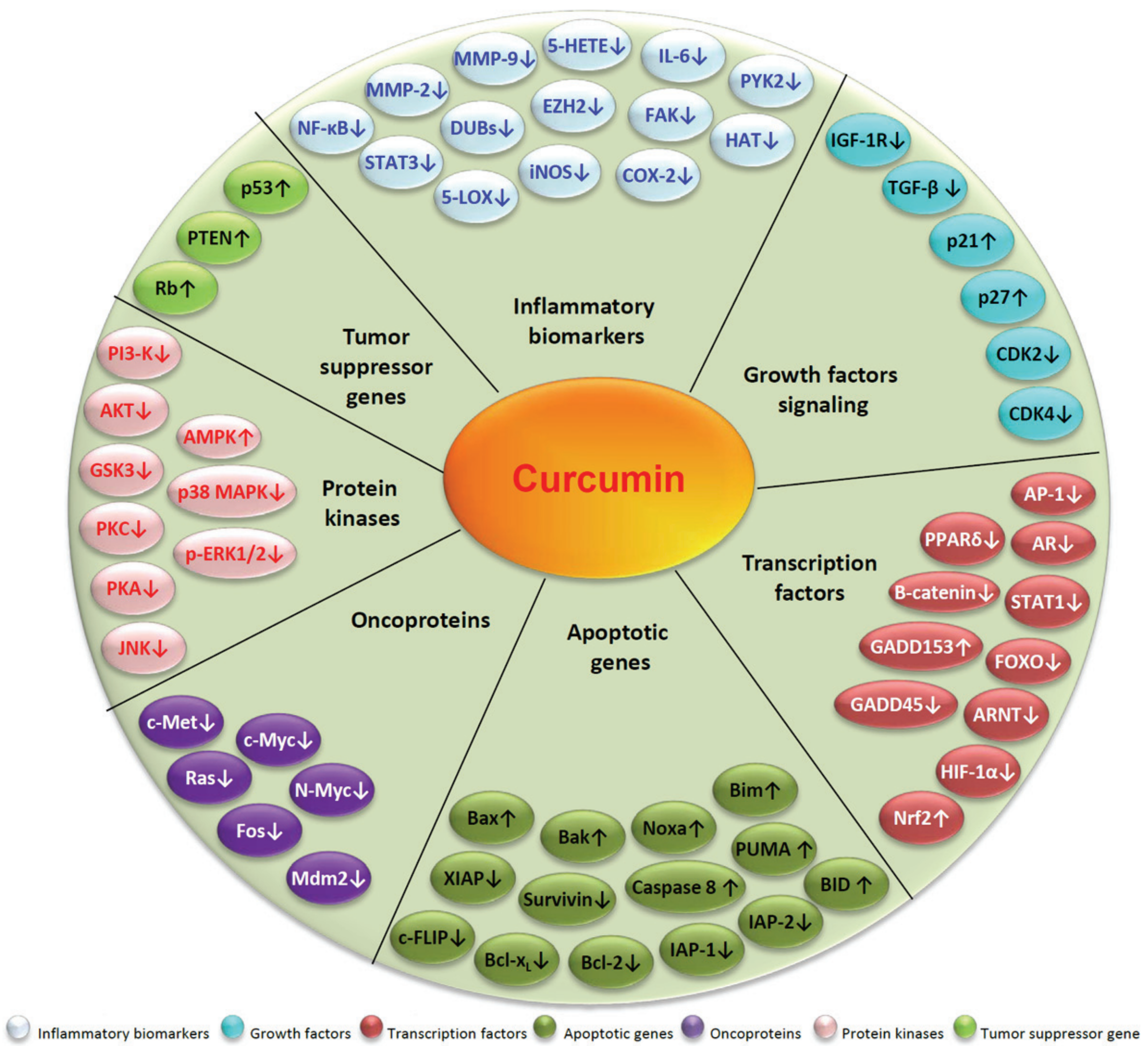

Figure 2. Cancer causing genes targeted by curcumin which are unapproved FDA targets.

stem cells to be dislodged and released into the blood. Xiaoling et al. showed that curcumin could inhibit the invasion and metastasis of human ovarian cancer cells by inhibiting expression of CXCL-12 and CXCR4 [23].

The cytokine RANKL triggers migration of human epithelial cancer cells and melanoma cells that express the receptor RANK. Denosumab, a monoclonal antibody, binds RANKL, blocking it from triggering the migration of these cancer cells. Denosumab also targets osteoclasts to prevent osteoporosis. Curcumin inhibited RANKL activation in osteoclast precursors and suppresses osteoclastogenesis [24].

Histone deacetylases remove acetyl groups from many different proteins that regulate gene expression, inducing tumor cell differentiation, cell cycle arrest, and apoptosis. Two drugs, vorinostat and romidepsin, inhibits the activity of HDACs. They were approved by the FDA for treatment of cutaneous T-cell lymphoma on the basis of positive phase II trial data [25-27]. Curcumin is a significant HDAC inhibitor, blocking expression of various class I HDACs (HDAC1, HDAC3, and HDAC8) in Raji cells [28].

Growth factors and their cell signaling pathways

Growth factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) are major regulatory molecules that control the growth of cells. Multiple signaling pathways that mediate the normal functions and activities of these growth factors, such as cell division, cell movement, cell responses to certain external stimuli, and cell death, are usually upregulated in cancer. Recent studies provide evidence that curcumin targets these growth factors and the signaling pathways they regulate; these findings increase our understanding of the mechanisms of curcumin's antiproliferative and antigrowth activities.

EGFR is a protein found on the surface of some cells, and its binding to EGF enables cells to divide. It is found at abnormally high levels on some types of tumor cells. The FDA has approved six anti-EGFR drugs: gefitinib, cetuximab, erlotinib, panitumumab, lapatinib ditosylate, and vandetanib. Gefitinib, erlotinib, and lapatinib ditosylate inhibit the tyrosine kinase activity of EGFR. Cetuximab binds to the external portion of EGFR, preventing its activation by growth signals and inhibiting signal transduction and thus proliferation. Panitumumab and vandetanib attach to EGFR and prevent it from sending growth signals. Curcumin inhibited the constitutive activation of both EGFR and insulin growth factor–1 receptor signaling pathways in colon cancer cells [29] and MCF-7 breast cancer cells [30].

HER-2/erbB2/neu/p185, another member of the EGFR superfamily, is overexpressed in breast, gastric, lung, colorectal, and head and neck cancers. The FDA-approved anti-HER-2 drugs are trastuzumab for HER2-neu–positive breast cancer, lapatinib ditosylate, and pertuzumab for HER-2–positive metastatic breast cancer; pertuzumab is expensive and prone to production problems. Trastuzumab is a monoclonal antibody that binds to HER-2, while lapatinib ditosylate inhibits the tyrosine kinase activity of HER-2; pertuzumab is another monoclonal antibody that binds to HER-2 but at a different region than trastuzumab, preventing HER-2 from sending growth-promoting signals. Curcumin targets HER-2 effectively [31, 32], and its combination with any of these drugs could reduce drug dose and cost and circumvent supply problems.

PDGF, through its cell-surface tyrosine kinase receptor (PDGFR), stimulates various cellular functions, including growth, proliferation, and differentiation. PDGF expression as a result of autocrine stimulation of cancer cell growth or paracrine interactions involving adjacent cells has been seen in many types of solid tumors [33]. The FDA has approved five anti-PDGFR drugs: sorafenib tosylate, dasatinib, sunitinib malate, pazopanib, and axitinib, which inhibit the tyrosine kinase activity of PDGFR to block cell growth and proliferation. Curcumin inhibited PDGFR-induced proliferation of human hepatic myofibroblasts [34].

Angiogenic endothelial cells express on their surfaces protein receptors for VEGF, angiopoietins, and various other adhesion molecules. Overexpression of VEGF and its receptor VEGFR has been used widely as a biomarker for angiogenic activity in cancer. The six FDA-approved anti-VEGF and anti-VEGFR drugs are bevacizumab, sorafenib tosylate, sunitinib malate, temsirolimus, pazopanib, and axitinib. Bevacizumab binds to VEGF and prevents it from interacting with receptors on endothelial cells, blocking the step necessary for initiation of new blood vessel growth, while the other five drugs inhibit the tyrosine kinase activity of VEGFR to halt development of new blood vessels. Since curcumin has the ability to inhibit both VEGF and VEGFR in various cancer types, it might be an effective antiangiogenic agent [35, 36].

The growth activation functions of cancer cells are continuously switched on, prompting unregulated growth and proliferation of these cells. Kinase inhibitors attack that problem by preventing cancer cells from binding to phosphates in the bloodstream and thus halting phosphorylation, which is required for cell growth. The current trend of development of kinase inhibitor drugs that modulate multiple growth factors, such as sorafenib tosylate, dasatinib, sunitinib malate, lapitinib ditosylate, pazopanib, and axitinib, has been strongly supported by the FDA. Curcumin also targets all of these potent growth factors and might be an effective antigrowth agent.

Protein kinases and protein phosphatases

Deregulation of cell signaling is a vital part of cancer development. The protein kinases and protein phosphatases are involved in regulating cell signaling pathways that are responsible for cell growth, proliferation, and death, such as RAS-RAF-MAPK/ERK, JNK, cAMP/PKA, PKC, and RTK/PI3K/AKT/mTOR.

B-RAF is a member of the RAF family of serine/threonine kinases that mediate cellular responses to growth signals through the RAS-RAF-MAP kinase pathway. Mutated B-RAF proteins have elevated kinase activity and are transforming in NIH3T3 cells; inhibition of B-RAF's oncogenic activity decreases tumor cell proliferation and increases tumor cell death [37]. Two anti-B-RAF drugs have been approved by the FDA, sorafenib tosylate for liver and renal cancers and vemurafenib for melanoma. Sorafenib tosylate inhibits the threonine kinase activity of B-RAF, while vemurafenib blocks the activity of a permanently activated mutant form of B-RAF, B-RAF V600E. Curcumin induced heme oxygenase-1 (HO-1), an enzyme with antioxidant, antiangiogenic, and antiapoptotic properties mediated by inhibiting B-RAF [38].

mTOR (mammalian target of rapamycin) is a serine/threonine kinase in the receptor tyrosine kinase/phosphoinositide 3 kinase/AKT/mTOR (RTK/PI3K/AKT/mTOR) pathway, through which it plays a prominent role in regulating the growth, proliferation, motility, survival, and angiogenesis of cells. This signaling pathway is highly active in many cancer cells. The two FDA-approved anti-mTOR drugs are temsirolimus and everolimus. Temsirolimus specifically inhibits the serine/threonine kinase mTOR that is activated in tumor cells, halting their growth and proliferation, while everolimus binds to a protein called immunophilin FK binding protein-12 to form a complex that binds to and inhibits the mTOR kinase. mTOR is specifically targeted by curcumin in various cancer cells, suggesting that curcumin would be an efficient anti-mTOR agent [39].

Transcription factors

The transcription factors estrogen receptor (ER) and janus kinase 2 (JAK2) are preferentially active in breast cancer cells compared with other tumor cell types, and inhibition of these transcription factors decreased their number and blocked growth of xenografts [40, 41].

Estrogen can stimulate proliferation of cells with an inherited or induced mutation, because when it binds to the ER on these cells it is able to regulate the activity of many different genes that promote proliferation and uncontrolled growth. The four FDA-approved anti-ER drugs are tamoxifen citrate, toremifene, fulvestrant, and raloxifene, which are also known as selective estrogen receptor modulators. Tamoxifen, toremifene, and raloxifene bind to ER to prevent estrogen binding, while fulvestrant binds to ER to promote its destruction, thereby reducing estrogen levels inside cells. Aromatase inhibitors are another class of FDA-approved drugs that interfere with estrogen's ability to promote the growth of ER-positive breast cancers. The enzyme aromatase is vital for production of estrogen in the body; by blocking its activity, estrogen levels in cells are lowered and the growth of cancer cells that require estrogen is inhibited. Aromatase inhibitors are used mostly in menopausal women; they are ineffective in premenopausal women, whose ovaries can produce enough aromatase to overcome the inhibition. The three aromatase inhibitors approved by the FDA for the treatment of ER-positive breast cancer are anastrozole, letrozole, and exemestane. Curcumin blocks the proliferative action of breast cancer cells by downregulating ER activity and can reduce the toxic effects of the current drugs [42].

Marotta et al. found that the interleukin 6 (IL-6)/JAK2/Stat3 pathway was preferentially active in $CD44^+CD24^-$ breast cancer cells compared with other tumor cell types, and inhibition of JAK2 was able to induce cancer cell death and prevent growth of xenografts. The authors highlighted the differences between distinct breast cancer cell types and identified JAK2 as a more specific and effective breast cancer therapy than existing regimens [41]. JAK2 inhibitor tofacitinib was recently approved by the FDA. Curcumin inhibited *JAK2* mRNA expression in K562 chronic leukemia cells [43].

Oncoproteins

Identification of cancer-specific oncoproteins, such as Src, has been an effective approach to development of new diagnostics and therapeutics [44]. The Src proto-oncoprotein is activated in more than half of human breast and colon cancers but, unlike many other oncoproteins, its gene is not mutated. This suggests that aberrant regulation of Src is involved. Src is predominantly inactive in cells under normal circumstances and is switched on only at specific times. The FDA-approved drug dasatinib, an inhibitor of tyrosine kinase, targets Src family kinases in the treatment of acute lymphocytic leukemia and acute myelocytic leukemia. Curcumin can retard cellular growth and migration via downregulation of Src kinase activity [45].

The *BCR-ABL* oncogene was the first chromosomal translocation shown to be associated with chronic myelogenous leukemia. Three FDA-approved drugs target Bcr-Abl: imatinib, dasatinib, and nilotinib, all tyrosine kinase inhibitors. Imatinib, a potent inhibitor, blocks expression of primary tumor angiogenesis regulators to prevent tumor growth. Curcumin inhibited the proliferation of leukemia cells through downregulation of the abundant Bcr-Abl oncoprotein and the RAS signal transduction pathway in human leukemia cell lines [46].

Cellular components

The FDA-approved cytotoxic anticancer agents recognize and destroy cellular components such as DNA, RNA, DNA polymerase, mitotic spindle/microtubules/β-tubulin, and DNA topoisomerase I and II (**Table 1**).

DNA and RNA are required for growth and multiplication of cells. Anti-DNA/anti-RNA drugs such as cytarabine stop cancer cells from multiplying by inhibiting the production of DNA and RNA, which leads to unbalanced cell growth and death. DNA polymerases are enzymes specialized for replication, repair, or tolerance of damaged DNA. Many point mutations that occur in cancer cells arise from the error-generating activities of DNA polymerases, and these enzymes have become viable anticancer targets [47]. Curcumin binds directly to DNA and RNA and functions as an anti-DNA/anti-RNA drug [6]. It also is a specific inhibitor of DNA polymerase [48].

Microtubules (α-tubulin and β-tubulin) are important in cell growth and division, development, and maintenance of cell shape, motility, and signaling. Loss of their equilibrium dynamics often results in development of cancer. The FDA has approved three drugs that target microtubules, three that target β-tubulin specifically, and one that targets the mitotic spindle. All seven of these drugs have the same effect, inhibition of cell proliferation. The three most widely used of these drugs are vincristine (anti-β-tubulin), vinblastine (anti–mitotic spindle), and paclitaxel (anti-microtubule). They bind to microtubules and prevent the separation of DNA during cell division, inhibiting cell reproduction. They also prevent manufacture of DNA, RNA, and proteins. Curcumin has been identified as an antimicrotubule agent and inhibited cancer cell proliferation by perturbing microtubule assembly dynamics in HeLa and MCF-7 cells [49].

DNA topoisomerases are essential to maintaining the helical structure of DNA. Five FDA-approved anticancer drugs, including irinotecan and etoposide, selectively target DNA topoisomerases I and II. Blocking one of these enzymes leads to breaks in the DNA and thus to cell death. Curcumin induced both topoisomerases I and II to trigger death in K562 cells [50].

FDA-unapproved targets

The previous section discussed molecular targets modulated by curcumin for which FDA-approved targeted drugs are available. There are, however, many curcumin targets for which no FDA-approved drug is available (**Figure 2**).

Inflammatory biomarkers

Although the anti-inflammatory effect of curcumin has been established, its mechanism of action is not clear. Some of the early studies of inflammatory biomarkers targeted by curcumin examined 5-hydroxy-eicosatetraenoic acid (5-HETE), cyclooxygenase (COX), and lipoxygenase (LOX), and curcumin's anti-inflammatory activities were shown to be a result of its inhibition of arachidonic acid metabolism [51, 52]. Efforts toward understanding curcumin's anti-inflammatory and anticancer activities provided evidence for its interaction with as many as 16 potent inflammatory biomarkers, such as NF-κB, signal transducer and activator of transcription 3 (STAT3), histone acetyltransferase (HAT), HDAC, COX2, 5-LOX, inducible nitric oxide synthase (iNOS), TNF-α, IL-6, matrix metalloproteinases (MMP)-2 and -9, focal adhesion kinase (FAK), proline-rich tyrosine kinase 2 (PYK2), deubiquitinating enzymes, 5-HETE, and enhancer of zeste homolog 2 (EZH2) (**Figure 2** and **Table 2**).Curcumin modulates these inflammatory biomarkers through suppression of inflammatory transcription factors such as NF-κB [16] and STAT3 [53]. These transcription factors are constitutively expressed in almost all cancer types, and curcumin has been shown to inhibit both inducible and constitutive activation of both. As a result, curcumin is able to modulate the downstream genes induced by these transcription factors, inhibiting cell proliferation, invasion, metastasis, and angiogenesis and inducing cell death.

Interleukins are inflammatory cytokines that play crucial roles in induction of adhesion molecules, metalloproteinases, and proangiogenic factors that can promote tumor invasion and angiogenesis [54]. Curcumin has successfully inhibited IL-6, which can stimulate development of osteoclasts from their hematopoietic precursors [55].

Cyclooxygenases catalyze the synthesis of prostaglandins from arachidonic acid. COX was identified as one of the targets of curcumin anti-inflammatory activity [51, 52]. There are two isoforms of COX, designated COX1 and COX2. COX1 appears in most normal tissues, while COX2 is induced by oncogenes, growth factors, carcinogens, and tumor promoters. Curcumin had no inhibitory effects on COX1 but directly inhibited the activity of COX2 [56].

Matrix metalloproteinases are involved in tumor metastasis [57]. Curcumin suppressed the expression of MMP-9 in the highly invasive human hepatocellular carcinoma SK-Hep-1 cell line to inhibit cellular migration and invasion [58]. Similarly, curcumin inhibited an H-*ras*–induced invasive phenotype in MCF10A human breast epithelial cells by downregulating MMP-2 [59].

Histone acetyltransferases have critical roles in various cellular processes, including cell cycle control, differentiation, and apoptosis. Curcumin inhibited p300/CBP HAT activity in HeLa cells. p300/CBP HAT is known to acetylate several nonhistone proteins such as p53, and this was confirmed when curcumin inhibited the p300-mediated acetylation of p53 *in vivo*, suppressing its DNA repair activity [60].

Focal adhesion kinase is an important modulator of cell proliferation, survival, and migration and was demonstrated to be involved in liver tumor progression and to have prognostic significance in hepatocellular carcinoma [61]. Curcumin inhibited FAK activity in melanoma cells [62]. Proline-rich tyrosine kinase 2, also known as cell adhesion kinase-β, is a tyrosine kinase that is structurally related to FAK [63]. Pyk2 has been demonstrated to promote migration and invasion and mediate angiogenesis. Curcumin blocked PYK2 phosphorylation in smooth muscle cells [64].

The enhancer of zeste homolog 2 is a transcriptional repressor that has been linked to aggressive cancer types such as prostate and breast [65]. Curcumin decreased proliferation of MDA-MB-435 breast cancer cells by downregulating the expression of EZH2 [66].

Growth factors and their cell signaling pathways

Recent findings suggest that curcumin targets not only EGF, PDGF, and VEGF but also the transforming growth factor (TGF). TGF-β signaling is an important regulator of tumorigenesis, and its signaling pathways are often modified during tumor progression. TGF-β is able to recruit certain cell types that can facilitate angiogenesis [67]. Curcumin inhibited TGF-β in transformed keratinocytes, the major cell type of the epidermis and a primary target of carcinogens [68].

Several proteins that control the cell cycle are tightly regulated to ensure that cells divide only when necessary; loss of this regulation is one of the hallmarks of cancer. Major control switches of the cell cycle are cyclin-dependent kinases (CDKs) and their inhibitors. The CDK inhibitor p21/WAF1 blocks the activity of CDK2, which is required for progression through G1. Another inhibitor, p27/KIP1, regulates the G0 to early G1 phase transition through CDK2 and the G1 to S phase transition through CDK4 and CDK6 [69]. Since curcumin targets CDK2 [70], CDK4 [71], and p21 [72], it might be very efficient in controlling aberrant cell cycling in cancer.

Protein kinases and protein phosphatases

Protein kinase C (PKC) is a family of serine/threonine kinases that regulate a diverse set of cellular processes, including proliferation, apoptosis, survival, and migration. The pattern of expression of PKC is profoundly altered in various types of cancers, reflecting their involvement in disease progression. Curcumin was shown to inhibit 12-O-tetradecanoyl-phorbol-13-acetate–induced tumor promotion through inhibition of PKC activity [73]. Protein kinases A are ubiquitous intracellular cAMP effectors that regulate multiple processes. The cAMP/PKA signaling pathway is altered in various cancers [74]. Curcumin is a selective and noncompetitive inhibitor of PKA [75]. The enzyme 5-AMP-activated protein kinase (AMPK) is activated during metabolic stress, and recent findings suggest that AMPK activation strongly suppresses cell proliferation and induces cell apoptosis in a variety of cancer cells. Strong p38-dependent activation of AMPK induced cytotoxicity in various cancer cells [76, 77].

In recent years, it has been shown that the PI3K/PKB signaling pathway components are frequently altered in human cancers. Curcumin has several different molecular targets within the PI3K/PKB signaling pathway that could contribute to inhibition of proliferation and induction of apoptosis. For example, inhibition of basal activity of Akt/PKB induced apoptosis in breast cells [78] and prostate cancer cells [79].

p38 mitogen-activated protein kinase (p38 MAPK) is known as a stress-activated MAPK able to promote expression of numerous inflammatory agents, such as TNFα, IL-1β, IL-8, COX-2, iNOS, prostaglandin E2, MMPs, and vascular cell adhesion molecule. Curcumin suppressed elevated COX-2 expression by inhibiting p38 MAPK in ultraviolet B–irradiated keratinocytes [80]. Extracellular signal regulated kinase (ERK) has two closely related isoforms, ERK1 (44 kDa) and ERK2 (42 kDa), whose expression is elevated in human cancer and implicated in rapid malignant cell growth and resistance to apoptosis. Curcumin downregulated elevated ERK1/2 protein levels in pancreatic adenocarcinoma cell lines [81]. That the cJun NH2-terminal kinase (JNK) pathway is implicated in tumor development was shown by studies in murine embryo fibroblasts demonstrating that loss of JNK caused major defects in cell proliferation [82]. Curcumin blocked N-methyl-N-nitro-N-nitrosoguanidine–mediated JNK activation in fibroblasts [83].

The serine/threonine protein kinase glycogen synthase kinase 3 (GSK-3) is part of many signaling pathways, including those involved in glycogen production, apoptosis, and stem-cell maintenance. Curcumin dephosphorylated and thus inactivated constitutively active GSK-3 in T-cell acute lymphoblastic leukemia cells [84].

Tyrosine phosphorylation, an important signaling mechanism, is controlled by protein-tyrosine phosphatases (PTPases). Oncogenic activation modulated by PTPase is a common feature in cancer. With increasing understanding of the oncogenic activity of PTPase, PTP inhibitors are considered potential antitumor drugs; curcumin should be further investigated, as it is an effective PTP inhibitor. For example, curcumin activated Src homology 2 domain–containing tyrosine phosphatase 2, a negative regulator of the JAK-STAT pathway, in brain microglia [85]; it inhibited Akt/mTOR signaling through stimulation of calyculin A–sensitive PTPase [86]; it upregulated MAPK phosphatase-5 in prostate cells [87]; and it attenuated ethanol-induced neurotoxicity by activating MAPK phosphatase-1, which acts as the negative regulator of p38 MAPK in hippocampal cells [88]. There are currently no FDA-approved drugs that target tyrosine phosphatases.

Tumor suppressor genes

Tumor suppressor genes, such as retinoblastoma (*Rb*) and *p53*, are defined by their inactivation in human cancer. As a result, their main function in growth regulation and differentiation is altered. A drug that can upregulate these genes is a desirable anticancer agent. Curcumin is able to upregulate three important tumor suppressor genes, *p53*, *Rb*, and *PTEN* (phosphatase and tensin homolog), making it an effective antiproliferation and proapoptosis agent.

p53, an important cell cycle and apoptosis regulator, has a major role in eliminating cancer-prone cells from replicating. Curcumin induced apoptosis in human basal carcinoma cells by upregulation of p53 [72]. Curcumin inhibited the COP9 signalosome-specific phosphorylation linked to p53 degradation by the ubiquitin-proteasome system [89].

PTEN protects cells from growing and dividing too rapidly or in an uncontrolled way by triggering apoptosis. It also inhibits migration, invasion, and angiogenesis. Somatic mutations in the *PTEN* gene are among the most frequent genetic changes in human cancers. In one study, wild-type PTEN enhanced curcumin-induced apoptosis and, in contrast, inactive PTEN inhibited curcumin-induced apoptosis [90]. Upregulation of PTEN expression was to inhibit vascular smooth muscle cell proliferation and arterial restenosis [91].

The Rb protein plays a pivotal role in negative control of cell cycle and tumor progression. Loss of its functions may induce cell cycle deregulation, which would lead to a malignant phenotype. Curcumin inhibited hyperphosphorylation of Rb and cell cycle deregulation in prostate cancer cells [92] and inhibited CDK4-mediated phosphorylation of Rb protein in cancer cells [71].

Transcription factors

The transcription factor activator protein (AP-1), androgen receptor (AR), β-catenin, growth arrest DNA damage (GADD), STATs, hypoxia inducible factor (HIF-1), Forkhead family of transcription factors (FOXO), peroxisome proliferator-activated receptor (PPARδ), and NF-E2-related factor 2 (Nrf2) are important transcription factors that are upregulated in most cancers. They are involved in cell growth and proliferation, apoptosis, invasion, metastasis, angiogenesis, and resistance to cancer therapy.

c-Fos forms a functional heterodimer complex with c-Jun to enable formation of the AP-1 complex, which is responsible for tumor cell proliferation and transformation. Curcumin inhibited tumor progression by decreasing expression of c-Fos, inhibiting AP-1 complex formation in fibroblasts [93].

Androgen binding and acting through its receptor is vital in the normal development and maintenance of the prostate. Mutations of AR and its coregulators play important roles in prostate cancer progression by contributing to differences in AR ligand specificity or transcriptional activity. Curcumin is an effective anti-AR agent that downregulated the transactivation of both AR and AR-related cofactors AP-1, NF-κB, and CREB-binding protein in two prostate cancer cell lines [94].

β-catenin is an important protein in cancer promotion and progression of various malignancies, such as colon cancer, melanoma, hepatocellular carcinoma, ovarian cancer, endometrial cancer, medulloblastoma pilomatricomas, and prostate cancer. Curcumin inhibited cancer promotion by decreasing activation of β-catenin in colon cancer cells [95].

GADD controls two functions: it is a positive regulator of growth inhibition and apoptosis and a negative regulator of cell cycle arrest and apoptosis. Curcumin blocked induction of GADD45 [96] and increased expression of pro-apoptotic GADD153 in colon cancer cells [97].

The STATs, upon binding to a JAK, translocate to the nucleus to induce or modulate expression of target genes. Numerous reports have shown that STATs are constitutively activated in a variety of tumors. Curcumin downregulated expression of Bcl-x_L and cyclinD1 by inhibiting activation of both STAT3 and STAT1 in multiple myeloma [53].

Hypoxia-inducible factor 1 activates the transcription of genes involved in angiogenesis, cell survival, glucose metabolism, and invasion. To date, there is only one drug that targets HIF-1, temsirolimus, which was approved by the FDA for treatment of renal cancer and is highly effective [98]. Curcumin reduced expression of HIF-1 cofactors HIF-1α [99] and ARNT [100] in various cancer cells, suggesting that it would be an effective anti-HIF agent in cancer therapy.

Forkhead box O transcription factors are involved in multiple signaling pathways and play critical roles in promotion and progression of cancer. These factors are important substrates of the protein kinase AKT. Curcumin downregulated constitutively active FOXO, leading to inhibition of proliferation and induction of caspase-dependent apoptosis in T-cell acute lymphoblastic leukemia cells [84].

Peroxisome proliferator-activated receptors are ligand-activated transcription factors that have been implicated in the disease-related processes of inflammation and cancer. Curcumin downregulated VEGF through inhibition of PPARδ in colon cancer cells [101].

Nrf2 is an important regulator of cellular responses to oxidative stress and is regulated by Keap1 for proteasomal degradation. The Nrf2/Keap1 system is dysregulated in lung, head and neck, and breast cancers, and this affects cellular proliferation and response to therapy. Curcumin significantly increased expression of HO-1 (a redox-sensitive inducible protein that provides protection against various forms of stress) through stimulation of Nrf2 [102].

Proapoptotic pathways

Studies in *p53*-null mice show increases in the occurrence of premature tumors, strong evidence that apoptotic genes are critical to tumor development. It is therefore not surprising that most anticancer treatments act through apoptosis [103]. Curcumin induced cell death by modulating a majority of the apoptotic genes; it downregulated antiapoptotic *Bcl-2* [104], *Bcl-x*$_L$ [105], survivin [7], *XIAP* [106], c-*FLIP* [107], *IAP-1* [108], and *IAP-2* [109], while upregulating proapoptotic genes *Bax* [110], *Bak* [96], *BID* [111], *PUMA*, *Bim*, and *Noxa* [90] in various cancer types. Its numerous apoptotic targets hint at curcumin's anticancer potential.

Caspase-8 is a cysteine protease required for induction of apoptosis through proper signaling via the death receptor (extrinsic) pathway. Dysregulation of caspase-8 expression or function contributes to cancer formation and progression. Inactivation of caspase-8 promotes resistance to current treatment approaches that induce apoptosis via the death receptor pathway. Therefore, the restoration of caspase-8 function is important in overcoming this resistance. Curcumin stimulated caspase-8 activity in gastric and colon cancer cells and induced cell death [112]. Curcumin also induced non-apoptotic cell death, such as autophagic cell death, through degradation of Beclin-1 and accumulation of microtubule-associated protein 1 light chain 3 [113].

Oncoproteins

Oncoproteins are one of the most important contributors to tumorigenesis, and curcumin targets most of the important oncoproteins, such as Mdm2, c-Myc, N-myc, c-Met, Ras, and Fos, that are linked to major cancer types. The three closely related Myc family proteins (c-Myc, N-Myc, and L-Myc) regulate a varied range of gene products, including cell-cycle factors, transcription factors, growth factor receptors, and angiogenesis inhibitors [114]. Curcumin downregulated c-Myc [115] and N-Myc [116] in various cancer types.

c-Met is a family of oncogenes that regulate important cellular processes, such as differentiation, proliferation, cell cycle, motility, and apoptosis. These changes in c-Met have been seen in solid tumors, such as lung cancer, mesothelioma, colon cancer, head and neck cancer, esophageal cancer, gastric cancer, pancreatic cancer, sarcomas, thyroid cancer, ovarian cancer, breast cancer, cervical cancer, brain tumors, and especially hereditary papillary renal cell carcinomas [117]. Curcumin blocked transactivation of the c-*Met* promoter by AP-1 and inhibited induction of endogenous c-Met in hepatocellular carcinoma cells to inhibit cell growth and differentiation [118].

In a study on the development of colorectal cancer, the expression of Ras, Jun, and Fos oncoproteins occurred significantly more often in large tubulovillous adenomas and adenocarcinomas than in normal human colons [119]. Curcumin decreased the expression of two potent proto-oncogenes, *Ras* and *Fos*, in tumorous skin [120].

In many cellular stress pathways, such as DNA damage, hypoxia, telomere shortening, and oncogene activation, there is rapid stabilization of p53 via blockade of its degradation by its specific E3 ubiquitin ligase, Mdm2 [121]. Curcumin downregulated Mdm2, which resulted in p53 stabilization in various cancer cells [122].

Synergistic effects of curcumin with FDA-approved drugs

The current focus in targeted therapies is on combinations with traditional therapies; such combinations are thought to decrease side effects and toxicity without compromising therapeutic efficacy. Navis et al. found that curcumin enhanced the antitumor effects of cisplatin when used in combination against fibrosarcoma [123]. NF-κB has been implicated in the development of cancer cell resistance to drugs such as doxorubicin, 5-FU, cisplatin, and paclitaxel. In a study that pretreated cancer cells with common biologic modulators such as tamoxifen, dexamethasone, or curcumin, doxorubicin-induced NF-κB activation was attenuated significantly. This inhibition may overcome the problem of drug resistance and contribute to sensitization of cancer cells to chemotherapeutic drugs [124]. Synergistic inhibition of proliferation resulted when curcumin was combined with FDA-approved drugs such as cisplatin and 5-FU to treat a variety of human cancer cells [125, 126]. Chirnomas et al. found that curcumin sensitized ovarian and breast tumor cells to cisplatin through apoptotic cell death, while Du et al. demonstrated synergism between curcumin and 5-FU at higher doses against the human colon cancer cell line HT-29; the synergism was associated with decreased expression of COX2 protein. Waly et al. provided evidence that curcumin significantly ameliorated oxidative stress induced by either cisplatin or oxaliplatin in HEK cells by significantly inhibiting the activities of the antioxidant enzymes and reducing the concentrations of glutathione and total antioxidant capacity [127].

Curcumin has been administered in combination with celecoxib, a specific COX2 inhibitor, to treat colorectal cancer [128]. The rationale for combining curcumin and celecoxib was that both drugs inhibit COX2 by different mechanisms: curcumin downregulates COX2 mRNA and protein levels [56, 129], whereas celecoxib inhibits COX2 directly by binding to its active site [130].

In a preclinical study that evaluated the antitumor activity of liposomal curcumin with oxaliplatin in colorectal cancer, there was synergism between these two compounds at a ratio of 4:1 in LoVo cells, and significant tumor growth inhibition was observed in Colo205 and LoVo xenografts [131]. In stand-alone analysis, the growth inhibition by liposomal curcumin was greater than that by oxaliplatin in Colo205 cells. Tumors from animals treated with liposomal curcumin showed an antiangiogenic effect. Therefore this study established that the combination of liposomal curcumin with oxaliplatin had comparable or greater growth-inhibitory and apoptotic effects than either agent alone in colorectal cancer, both *in vitro* and *in vivo*.

At the 2012 Meeting of the American Association for Cancer Research, results of a phase II study of curcumin and docetaxel in castration-resistant prostate cancer were presented; the combination was synergistic and yielded better results than docetaxel alone. Curcumin synergistically enhanced the *in vitro* and *in vivo* antitumor efficacy of docetaxel against lung cancer. Simultaneous administration of curcumin and docetaxel caused little toxicity in normal tissues, including bone marrow and liver, at the therapeutic doses. The authors suggested that introduction of curcumin into traditional chemotherapy regimens is a most promising way to counter the spread of non-small cell lung cancer [132]. Cort et al. found that concurrent use of curcumin with bleomycin induced extensive expression of caspase-3, -8 and -9 in human NTera-2 neural cells, greater than either drug alone. They suggested that the effects of curcumin and bleomycin on apoptotic signaling pathways are synergistic and proposed combination regimens to decrease therapeutic dose and side effects [133]. Duan et al. observed that simultaneous administration of doxorubicin and curcumin achieved the highest reversal efficacy and downregulation of P-glycoprotein in MCF-7/ADR, an MCF-7 breast cancer cell line resistant to doxorubicin [134].

In a combination regimen, curcumin potentiated the therapeutic efficacy of bortezomib in multiple myeloma, as evidenced by inhibition of IL-6/sIL-6R–induced STAT3 and ERK phosphorylation, and synergistically inhibited the growth of multiple myeloma cells co-cultured with bone marrow stromal cells [135]. Mujtaba et al. found therapeutic benefit when a water-soluble analog of curcumin enhanced the proteasome-inhibitory effect of bortezomib in multiple myeloma cells. The sensitivity of the myeloma cells to cytotoxic killing in the presence of otherwise sublethal concentrations of bortezomib was enhanced by incubation with the curcumin analog [136].

Bava et al. observed that curcumin increased sensitivity of tumor cells more efficiently to the therapeutic effect of paclitaxel, as evidenced by increased cytotoxicity and reduced DNA synthesis, activation of caspases, and cytochrome c release in HeLa cells. Evaluation of signaling pathways common to both drugs revealed that this synergism was due to downregulation of NF-κB and serine/threonine kinase Akt pathways. The investigators concluded that paclitaxel in combination with curcumin may provide a superior therapeutic index and advantage in the clinic for the treatment of refractory tumors [137]. In their investigation, Kang et al. looked into whether inactivation of NF-κB by curcumin would enhance the efficacy of paclitaxel for inhibiting breast cancer growth *in vitro* and *in vivo*. They confirmed that curcumin inhibited paclitaxel-induced activation of NF-κB and potentiated the growth-inhibitory effect of paclitaxel in MDA-MB-231 breast cancer cells.

The combination of curcumin with paclitaxel elicited significantly greater inhibition of cell growth and more apoptosis than either agent alone. In the experimental MDA-MB-231 breast cancer murine model, combination therapy with paclitaxel and curcumin significantly reduced tumor size and decreased tumor cell proliferation, increased apoptosis, and decreased the expression of MMP-9 compared with either agent alone [138].

Conclusion

Cancer is not one disease but a combination of many; to effectively halt tumor progression, a drug that can target multiple dysregulated proteins would be ideal. Targeted therapies have their limitations, the most prominent being that cancer cells develop resistance to them. In some patients whose cancer develops resistance to imatinib, for example, a mutation in the *BCR-ABL* gene has changed the protein so that it no longer can bind to this drug. In most such cases, another targeted therapy that could overcome this resistance is not available. Combinations of targeted therapies with either other targeted therapies or more traditional therapies may be the solution to this problem.

Curcumin, a natural polyphenol, appears to possess a blend of anticarcinogenic, proapoptotic, antiangiogenic, antimetastatic, immunomodulatory, and antioxidant activities. The molecular mechanisms underlying the pleotropic activities of curcumin are diverse and involve combinations of cell signaling pathways at multiple levels of tumorigenesis. With the ongoing problems of drug resistance, toxicity, and high treatment cost associated with the current FDA-approved anticancer drugs (**Table 1**), it would be most advantageous to look into curcumin as an anticancer agent, to be administered alone or in combination with available anticancer drugs; such explorations may demonstrate that curcumin offers not only efficacy but also affordability.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Address correspondence to: Bharat B Aggarwal, Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas, 77030, USA. Phone: 713-7941817; E-mail: aggarwal@mdanderson.org

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