Molecular targets of curcumin in breast cancer (Review)

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Abstract. Curcumin (diferuloylmethane), an orange-yellow component of turmeric or curry powder, is a polyphenol natural product isolated from the rhizome of *Curcuma longa*. For centuries, curcumin has been used in medicinal preparations and as a food colorant. In recent years, extensive *in vitro* and *in vivo* studies have suggested that curcumin possesses activity against cancer, viral infection, arthritis, amyloid aggregation, oxidation and inflammation. Curcumin exerts anticancer effects primarily by activating apoptotic pathways in cancer cells and inhibiting pro-cancer processes, including inflammation, angiogenesis and metastasis. Curcumin targets numerous signaling pathways associated with cancer therapy, including pathways mediated by p53, Ras, phosphatidylinositol-3-kinase, protein kinase B, Wnt-β catenin and mammalian target of rapamycin. Clinical studies have demonstrated that curcumin alone or combined with other drugs exhibits promising anticancer activity in patients with breast cancer without adverse effects. In the present review, the chemistry and bioavailability of curcumin and its molecular targets in breast cancer are discussed. Future research directions are discussed to further understand this promising natural product.

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Abbreviations: Bcl-xL, B-cell lymphoma-extra large; CDK, cyclin-dependent kinase; CXCL, chemokine (C-X-C motif) ligand; GSK3β, glycogen synthase kinase-3β; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; OPN, osteopontin; ODC, ornithine decarboxylase; PI3K, phosphatidylinositol-3-kinase; TNBC, triple-negative breast cancer; uPA, urinary plasminogen activator; VEGF, vascular endothelial growth factor

Key words: breast cancer, curcumin, molecular targets, metabolism, bioavailability, transcription factors, signaling pathway

Contents

1. Introduction

Breast cancer is the most common cancer in women worldwide; it accounts for ~25% of all female malignancies and its prevalence is higher in developed countries (1). Breast cancer is the second leading cause of cancer-associated mortality among women in the world (1,2). Current therapeutic strategies for breast cancer, which include surgery, chemotherapy and radiotherapy, may lack efficacy due to a high risk of relapse, poor patient response and the emergence of drug resistance (3). This supports the requirement to understand the genetic and biochemical factors underlying the uncontrolled cell proliferation in breast cancer, in order to develop novel therapies.

In breast cancer tissues, the overexpression of cyclin-dependent kinases (CDKs) and underexpression of tumor suppressor protein p53 is frequently observed (4). Simultaneously, a number of cell cycle regulatory proteins are downregulated, including the CDK inhibitors, p21, p27 and p57 (5-8). Targeting these molecules may be effective in breast cancer therapy (5), and natural products that target these molecules are particularly attractive as they are likely to have high therapeutic potential and less likely to induce adverse effects (9,10). Plants are an excellent source of bioactive natural compounds (7,11-13), and polyphenolic compounds from plants frequently exert multiple therapeutic effects (14-16). The polyphenolic phytochemical curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione; Fig. 1], isolated from the powdered rhizome of *Curcuma longa* L. (Zingiberaceae) (17,18), interacts with numerous biological targets, including inflammatory mediators, growth factors, enzymes, carrier proteins, metal

ions, tumor suppressors, transcription factors, oncoproteins and cellular nucleic acids (19-21). Discovered in 1815 by Vogel and Pelletier as a yellow pigment (4), curcumin has been consumed for >2,000 years in Asian countries, due to its various medicinal properties against human diseases, including cancer and auto-immune diseases (10,17,22-29).

In the present report, the molecular targets of curcumin and its potential benefits as a drug for breast cancer therapy are critically reviewed.

2. Metabolism

One of the limitations in the use of curcumin as a therapeutic agent is its rapid metabolism. Following absorption, the double bonds in the heptadienedione chain are reduced, leading to the production of a series of active metabolites (30).

Alcohol dehydrogenase reduces curcumin to tetra- and hexahydrocurcumin in the liver, and an unidentified microsomal enzyme leads to the formation of di- and octa-hydrocurcumin (31). Hexahydrocurcuminol, hexahydrocurcumin, tetrahydrocurcumin, dihydrocurcumin and their glucuronide and sulfate conjugates have been detected in hepatocytes (31). Curcumin and its reduced metabolites undergo glucuronidation and are converted into curcumin glucuronide and curcumin sulfate (32).

3. Bioavailability

Curcumin has very low water solubility and a high oil-water partition coefficient. Its water solubility is low at acidic and neutral pH; whereas, curcumin is soluble at an alkaline pH (33). However, the compound decomposes rapidly in alkaline media, with a half-life in the range of a few min. Curcumin photodegrades in organic solvents (33). In total, ~80% of a typical oral dose of curcumin passes unaltered through the gastrointestinal tract, and the majority of the absorbed compound ends up metabolized in the intestinal mucosa and liver (33). These properties limit the applications of curcumin as a bioactive agent.

To overcome the limitations of poor solubility, researchers have examined various strategies. Creating complexes of curcumin with cyclodextrins may significantly improve its water solubility and its stability under alkaline conditions, although such complexation decreases the photostability of curcumin (33,34). Stability of curcumin against alkaline hydrolysis may additionally be improved by encapsulating it in micelles composed of cationic surfactants, including cetyl trimethylammonium bromide and dodecyl trimethylammonium bromide (33,34).

Emulsion-based delivery systems have been demonstrated to stabilize active ingredients and increase their bioavailability (35), and the same is true for curcumin; conjugating it with phosphatidylcholine increases its bioavailability five-fold. Mono-polyethylene glycolylation of curcumin produces pro-drugs that are stable in buffer at a physiological pH and readily release curcumin into human plasma (36).

Curcumin derivatization has additionally led to promising drug compounds. Based on structure-activity studies of the tautomeric forms of curcumin, the diketone system was modified to generate two curcumin analogs, benzyloxime and isoxazole (37). These analogs have demonstrated much greater antitumor potency against MCF-7 breast cancer cells and multidrug-resistant transfected MCF-7 cells (37). Furthermore, these curcumin analogs potently reduce expression of B-cell lymphoma-extra large (Bcl-xL), B cell lymphoma 2 (Bcl-2) and cyclooxygenase-2 in the two cell lines (38).

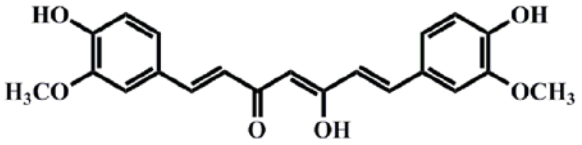

Figure 1. Chemical structure of curcumin.

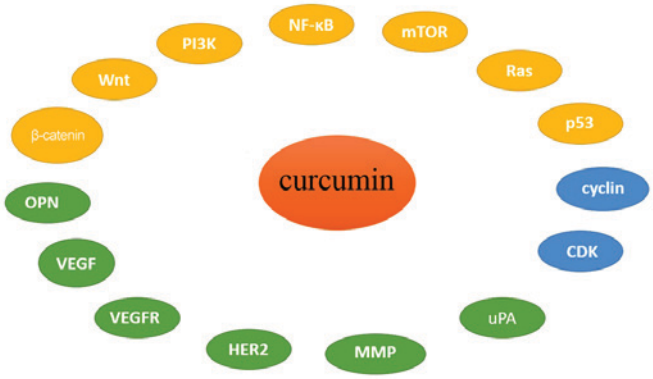

Figure 2. Molecular targets of curcumin. PI3K, phosphatidylinositol-3-kinase; NF-κB, nuclear factor-κB; mTOR, mammalian target or rapamycin; CDK, cyclin-dependent kinase; uPA, urinary plasminogen activator; MMP, matrix metalloproteinase; human epidermal growth factor receptor 2; VEGFR, vascular endothelial growth factor receptor; VEGF, vascular endothelial growth factor; OPN, osteopontin. Yellow indicates transcription factors and signaling molecules; green indicates tumor angiogenesis and growth-associated proteins; blue indicates molecules associated with tumor proliferation.

Curcumin polymers (polycurcumins) have high drug loading efficiency and may be used as backbone-type conjugates to stabilize and solubilize curcumin in water (39). Tang *et al* (39) prepared high-molecular-weight curcumin polycurcumins through condensation polymerization of curcumin. Polyacetal-based polycurcumin is highly cytotoxic to MCF-7 breast cancer cell lines and to SKOV-3 intraperitoneal xenograft tumors (40,41). This condensation approach protected curcumin from hydrolysis at all pH values examined, and from ultraviolet degradation. Loading curcumin into mixed polymeric micelles improved its oral bioavailability ~55-fold (42).

4. Molecular targets of curcumin for breast cancer therapy

Curcumin inhibits breast cancer cell proliferation by the following mechanisms: i) Inducing cell cycle arrest and p53-dependent apoptosis; ii) altering expression of signaling proteins, including Ras, phosphatidylinositol-3-kinase (PI3K), protein kinase B (Akt), mammalian target of rapamycin (mTOR) and Wnt/β-catenin; iii) downregulating transcription factors; and iv) inhibiting tumor growth and angiogenesis (Fig. 2).

Effects of curcumin on CDK/cyclin complexes. CDKs are serine/threonine kinases that control cell cycle progression by forming a complex with their respective cyclin partners (43,44). Altered expression of CDKs, overexpression of cyclins and

loss of expression of CDK inhibitors are frequently observed in malignant cells (44). Dysregulated CDK activity provides cancer cells with a selective growth advantage. In this way, dysregulated overexpression of cyclin D1 triggers progression of aggressive breast cancer (45). Previous studies in mammary epithelial carcinoma cells suggest that curcumin inhibits cell cycle progression by blocking the association of cyclin D1 with CDK4, thus reducing cyclin D1 activity (46,47). In MCF-7 breast cancer cells, curcumin reduces cell proliferation by arresting cells in G_1 phase. The drug achieves this arrest by stimulating the proteosomal degradation of cyclin E and upregulating CDK inhibitors, p53, p21 and p27; the addition of specific proteosomal inhibitors suppresses these effects of curcumin (48). Cyclin E is a nuclear protein that serves an important role in G_1/S progression by interacting with its catalytic partner, CDK2, and by interacting with the retinoblastoma (Rb) protein (49,50). It appears likely that the anti-proliferative effects of curcumin are due to proteasome-mediated downregulation of cyclin E and upregulation of CDK inhibitors (51).

The anti-proliferative effects of curcumin appear to be selective to cells overexpressing CDK 2. In mammary carcinoma cells, curcumin induces p53-dependent apoptosis and causes G_2 phase arrest. However, in normal human mammary cells, curcumin causes G_0 cell cycle arrest by blocking the association between CDK 4 and CDK 6, and inhibiting the phosphorylation of Rb (52). In this way, curcumin also prevents the initiation of p53-mediated apoptosis, which occurs only in cells arrested in G_2 phase (52).

Effects of curcumin on the p53 pathway. The p53 protein is one of the most important tumor suppressor proteins, regulating a wide range of cellular processes, including cell proliferation, DNA damage and apoptosis (53). It is encoded by the *tumor protein p53* gene, which is frequently mutated in numerous types of human cancer (53), leading to loss of cell proliferative control, DNA check points and DNA repair mechanisms. As a result, cancer cells become immortal. Restoring the function of p53 is an attractive therapeutic strategy in cancer therapy (54).

Curcumin induces apoptosis in breast cancer cells via p53-dependent and -independent pathways. For instance, curcumin arrests the cell cycle and induces p53-dependent apoptosis in MCF-7 breast cancer cells (55). Notably, curcumin exerts no anti-proliferative effects on MDAH041 cells lacking p53 or on TR9-7 cells that express p53 at low levels; rather, its effects are most notable in p53-expressing TR9-7 and MCF-7 cells. Expression of the pro-apoptotic protein apoptosis regulator Bax (Bax) is also higher in curcumin-treated MCF-7 cells. These results suggest that curcumin exerts its anti-proliferative effects via p53-dependent and p53-independent pathways (55,56).

Targets of curcumin in Ras signaling. Ras is a small transmembrane protein belonging to the large GTPase family of enzymes that hydrolyze guanosine triphosphate in order to transduce signals inside the cell (57). Mammalian cells have three Ras proteins (K-, H- and N-Ras), each of which serves a different function (57). Blocking oncogenic Ras signaling is an attractive strategy in cancer therapy.

Curcumin has been extensively studied for its effects on oncogenic Ras signaling pathways. In MCF-10A human breast epithelial cells transformed using H-Ras, curcumin induces reactive oxygen species production, which downregulates activity of matrix metalloproteinase (MMP)-2 and Bcl-2 and upregulates the activity of Bax and caspase-3 (58).

Potentially acting through a similar mechanism, curcumin arrests Ras-transfected HAG-1 human adenocarcinoma cells in G_2/M phase by inducing expression of extracellular signal-regulated kinase 1/2 and Bax, and reducing expression of Bcl-xL. These results suggest that curcumin may be a potent therapy against Ras-overexpressing cancer (59). Preclinical studies in animals, and ultimately clinical trials, are required to clarify the therapeutic effect of curcumin in Ras-induced cancer.

Targets of curcumin in PI3K/Akt/mTOR signaling. PI3Ks are a family of lipid kinases that phosphorylate inositol phospholipids and generate the secondary messenger phosphatidylinositol-3,4,5-trisphosphate in the plasma membrane (60). PI3K interacts with Akt to trigger the latter's translocation inside the cytoplasm. Activated Akt interacts with a number of substrates to perform numerous functions in cell survival, cell cycle progression and cell growth (60). Constitutive expression of PI3K and Akt, in addition to silencing of phosphatase and tensin homolog and glycogen synthase kinase 3β (GSK3β), are frequently observed in a number of human malignancies. Therefore, PI3K/Akt-mediated signaling is an attractive target in cancer chemotherapy (61,62).

Cancer cells survive for a prolonged time by activating survival pathways involving PI3K, Akt and mTOR, in addition to anti-apoptotic pathways involving Bcl-2. Targeting survival and apoptosis pathways is likely to be essential for controlling highly metastatic breast cancer. Curcumin on its own weakly stimulates apoptosis in breast cancer cells; however, combining it with the PI3K-specific inhibitor LY294002 stimulates apoptosis more strongly (63,64). The authors of these previous studies hypothesized that the PI3K obstruction overcomes the oncogenic expression of Bcl-2. Further studies are required to verify whether curcumin may inhibit PI3K/Akt/mTOR signaling in breast cancer cells and identify the mechanism(s) involved.

Targets of curcumin in Wnt/β-catenin signaling. Wnts are a family of secreted glycoproteins that regulate multiple signaling pathways through β-catenin-dependent and -independent mechanisms (65-67). Wnts serve a crucial role in development, survival and metabolism. Inappropriate regulation and hyperactivation of Wnt/β-catenin signaling have been implicated in numerous human malignancies. Overexpression of β-catenin leads to constitutive activation of cell proliferation (68), and tumor cells downregulate the tumor suppressor GSK3β, which limits the activity of β-catenin by triggering its ubiquitin-mediated proteosomal degradation. Therefore, targeting the Wnt/β-catenin signaling pathway is an attractive approach in cancer therapy (69,70).

In MCF-7 and MDA-MB-231 cells, curcumin arrests the cell cycle in G_2/M cells by modulating Wnt/β-catenin signaling. In these cells, curcumin upregulates GSK3β and causes loss of nuclear β-catenin. Loss of nuclear β-catenin

results in a loss of its downstream target cyclin D1 (71). This suggests that, at least in MCF-7 and MDA-MB-231 cells, the antitumor effects of curcumin are due to abrogation of Wnt/β-catenin signaling (71).

Targets of curcumin among nuclear factor-κB (NF-κB) transcription factors. NF-κB is a family of transcription factors that are involved in the immune response and inflammation. Gene expression profiling studies suggest that the NF-κB pathway is a key regulator in triple-negative breast cancer (TNBC), with activation of NF-κB signaling strongly implicated in the pathogenesis of specific TNBCs (72-74). Cytoplasmic NF-κB is bound to a group of inhibitory proteins known as inhibitors of NF-κB (IκB); accumulation of non-phosphorylated IκB prohibits the translocation of NF-κB from cytoplasm to nucleus, resulting in inactivation of NF-κB and its downstream targets (74). NF-κB promotes the transcription of numerous key regulators of cancer invasion and progression, including cytokines, chemokines, cell adhesion molecules and inducible pro-inflammatory enzymes (74). In addition, NF-κB has been postulated to be a useful marker of the epithelial-mesenchymal transition (EMT) and invasiveness in breast cancer (19).

A number of previous studies suggest that curcumin inhibits NF-κB expression and therefore additional downstream signaling pathways, ultimately leading to the silencing of inflammatory cytokines, including chemokine (C-X-C motif) ligand (CXCL)1 and CXCL2 (19); and to alterations in the expression of MMP-9, urokinase plasminogen activator (uPA), uPA receptor, intercellular adhesion molecule 1 and chemokine receptor 4 (3,72,75). In this manner, curcumin is likely to inhibit the growth and invasion of breast cancer, in part, by downregulating NF-κB signaling pathways.

Curcumin may modulate the expression of NF-κB target genes (76,77), which include Bcl-2, ornithine decarboxylase (ODC) and c-myc, which are associated with apoptosis or cell survival (78). For example, ODC is the rate-limiting enzyme in polyamine biosynthesis and curcumin has been demonstrated to suppress ODC activity and inhibit cell proliferation (79). Activation of the NF-κB/Bcl-2 pathway is associated with drug resistance in cancer cells (80).

Accumulating evidence suggests that targeting NF-κB to inhibit cell growth and reverse EMT may be a novel therapeutic strategy in breast cancer.

Targets of curcumin in tumor angiogenesis. Angiogenesis is the normal physiological mechanism by which novel blood vessels are formed from pre-existing blood vessels. It occurs during embryogenesis, menstruation and wound healing (81). Angiogenesis in tumors is crucial for cancer progression. Tumor cells procure nutrients for their uncontrolled growth through tumor angiogenesis (81). Tumor cells constitutively produce pro-angiogenic factors, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor, which curcumin may inhibit in order to modulate tumor angiogenesis (81,82).

Curcumin inhibits angiogenesis and growth of breast cancer tumors implanted into nude mice. These effects are associated with downregulated expression of a number of VEGF isomers, including VEGF-A, VEGF-C and VEGF receptor 2, in addition to decreased microvessel density (83). These results are in agreement with other previous studies demonstrating that suppression of VEGF function inhibits breast tumor growth (83,84). In nude mice, which were implanted with MDA-MB-231 tumors and treated with osteopontin (OPN; additionally termed secreted phosphoprotein 1) to stimulate angiogenesis, curcumin blocked NF-κB/cyclic AMP-dependent transcription factor ATF-4 binding and prevented OPN-induced upregulation of VEGF (85). This suggests that curcumin acts as a potent anti-angiogenic agent in regulating OPN-induced tumor angiogenesis in breast cancer.

5. Potential risks and adverse side effects of curcumin

Curcumin causes blood thinning, which may decrease blood flow and increase the risk of ischemic stroke (86). It may also inhibit the ability of chemotherapeutics to induce production of reactive oxygen species and block the c-Jun NH2-terminal kinase pathway. In fact, curcumin may exert pro-oxidant effects, similar to numerous other anti-oxidants (87).

Curcumin significantly inhibits cyclophosphamide-induced regression of human breast cancer xenografts in mice (88,89). In cultures of MCF-7, MDA-MB-231 and BT-474 human breast cancer cells, curcumin may inhibit the ability of camptothecin, mechlorethamine and doxorubicin to induce apoptosis by ≤70% (18,90). Curcumin may also serve as an iron chelator to inhibit hypoxia inducible factor-α prolyl hydroxylase activity (91). Therefore, further research is urgently required to establish whether patients with breast cancer undergoing chemotherapy should limit their intake of curcumin.

6. Conclusion

The available evidence suggests that curcumin, a polyphenolic compound derived from the dietary spice turmeric, is a non-toxic, highly promising natural anti-oxidant that exerts anticancer effects by targeting multiple molecules and pathways. By affecting different targets, curcumin modulates numerous cancer hallmarks, including cell proliferation, cancer signaling pathways, transcription factors and tumor angiogenesis. Curcumin may have applications as a novel drug in the near future to control various diseases, particularly breast cancer.

The clinical use of curcumin is limited by its poor bioavailability; however, specific novel derivatives have been prepared that may improve patient responses. Research is in progress on nanotechnology-based formulations and delivery systems to improve curcumin pharmacokinetics. Possibilities include encapsulating curcumin into polymeric or lipid micelles, or liposomes, and combining or conjugating curcumin to ligands or antibodies that may target cancer cell receptors or other epitopes. Novel curcumin analogs and nanotechnology-based formulations may overcome the limitations of oral administration of curcumin.

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Availability of data and materials

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Authors' contributions

XS conceived and designed the article. MZ and ED read the literature and collated the appropriate information. XS and YL wrote the paper.

Ethics approval and consent to participate

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Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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