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Recent Advances of Curcumin and its Analogues in Breast Cancer Prevention and Treatment

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Abstract

More than 230,000 diagnosed cases of invasive breast cancer in women was estimated in 2014 and an expected 40,000 deaths attributed to the aggressive carcinoma. An effective approach to diminish the morbidity and mortality of breast cancer is the development of chemopreventive and chemotherapeutic agents. Nutraceuticals have demonstrated their ability to proficiently halt carcinogenesis. The administration of natural compounds able to effectively serve as chemoprevention and chemotherapeutics without causing harm or adverse effects is imperative. Curcumin derived from the rhizome of *Curcuma longa L.*, is a common spice of India, used for centuries because of its medicinal properties. The main component of curcumin possesses a wide range of biological activities; anti-proliferative, anti-inflammatory, and apoptotic characteristics modulated through the inactivation of pathways such as EGK and Akt/mTOR. In addition, curcumin alters the expression of cytokines, transcription factors, and enzymes involved in cell vitality. The *in vivo* application of curcumin in breast cancer is hindered by its limited bioavailability. The synthesis of curcumin analogues and delivery via nanoparticles has demonstrated enhanced bioavailability of curcumin in the malignancy. This review focuses on recent developments in the use of curcumin, curcumin analogues, and novel delivery systems as a preventive and therapeutic method for breast cancer.

Introduction

A single therapeutic approach to breast cancer is not sufficient to address its heterogeneous nature. Breast cancer is comprised of a plethora of subtypes which express distinct biological features and as a result limits a 'one-way' therapeutic solution.¹ In 2010, nearly 1.7 million women worldwide were diagnosed with the aggressive disease² and 1 out of 9 cases were characterized as metastatic.³ In the United States an estimated diagnosis of 232,670 cases of female invasive breast cancer was expected for 2014 and 62,570 new cases of *in situ* breast cancer. The estimated death attributed to the disease for 2014, was 40,000 second only to lung cancer.⁴

The classification of breast cancer is based upon its wide array of unique biological markers and signalling pathways. Targeted therapeutic approaches focus on proteins and pathways such as MAPK, HER2/EKBB2, p13K/Akt/mTOR, PAPP, TGF- α , EGF, and p53 identified in

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the malignancy.^{5,6} Terlikowska et al.⁷ have identified approximately twenty-six curcumin mediated signalling pathways such as PPAR, COX-2, EGFR and NF- κ B. *In vivo* studies are often performed in three established adenocarcinoma and invasive ductal carcinoma cell lines; MDA-MB-231, MDA-MB-468, SkBr3 and MDA-MB-435, MCF-7, T47D respectively.⁸

In 2003, 70% of new drugs developed were derived from natural compounds. During the years 1983 through 1994 more than 62% of approved therapies for cancer were designed from natural products or their analogues.⁹ The most effective method to combat cancer with natural compounds is to implement an attractive strategy that will target pathways and enzymes leading to anti-proliferation and cytotoxicity. The therapeutic design should also effectively minimize or halt the carcinogenesis and increase cytoprotectivity of healthy cells and organs. Curcumin (1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a polyphenolic compound isolated from *Curcuma longa*, that has demonstrated a wide range of biological activities; anti-inflammatory,^{10–14} anti-oxidative,^{15–19} antibacterial,^{20–26} rheumatoid arthritis,^{27–30,12,31–33} Alzheimer's,^{34–42} psoriasis,^{43,44} and diabetes.^{45–53} Curcumin has been investigated for its anti-cancer properties for cancers such as lung,^{54–58} ovarian,^{59–65} colorectal,^{66–73} and pancreatic.^{74–81}

Therapeutic applications of curcumin are limited because of its reduced bioavailability.⁸² The polyphenolic compound, curcumin is only slightly soluble in an aqueous environment, experiences degradation at alkaline pH, rapidly metabolized and conjugated in the liver (curcumin sulfate and curcumin glucuronide), undergoes rapid systemic elimination, is excreted in feces, demonstrates poor tissue absorption, and characterized as a Class II drug^{83–85}. *In vitro* application as a pharmaceutical agent is challenged by curcumin's degradation and *in vivo* administration results in decreased efficacy because of metabolic changes.⁸⁶ Enhancement of curcumin's activity and bioavailability can be achieved through modifications of its chemical structure. Curcumin binds to various biological enzymes/proteins such as COX1 and COX 2, TNF- α , MMP3 and MMP13, tyrosine kinase, protein kinase c (PKC), and reductases such as thioredozin reductase.

The Effect of Curcumin on Various Breast Cancer Signaling Pathways

Curcumin's anti-proliferative, apoptotic, and anti-tumour actions occurs by the modulation of various pathways and directly bind to or modulating the activity of molecular targets in breast cancer cell lines; MDA-MB-231, MDA-MB-468, MCF-7, and SkBr3 (Table 1). Curcumin acts as an adjuvant chemotherapeutic agent in breast cancer and inhibits transcriptional co-factor p300⁸⁷. The decreased expression of hTERT occurs through a synergistic administration of curcumin and silibinin⁸⁸. Kakarala et al.⁸⁹ determined curcumin is able to target and regulate cancer stem cells in breast cancer cells when exposed to 5–10 μ M of curcumin for 12h. The effect of curcumin on MMP-9 and exogenous TGF- β stimulated expression in MDA-MB-231 breast cancer cell line demonstrates its value as a therapeutic agent. Curcumin performs as an inhibitor of TGF- β in a dose-dependent manner and modulates protein expression of MMP-9 by the induction of TGF- β in a time and concentration manner.⁹⁰ Hassan and Dahestani⁹¹ performed an investigation of curcumin's chemopreventive and anti-metastatic nature in MDA-MB-231 cancer cell line. The study

determined curcumin's regulatory role in cell metastasis is accomplished by the inhibition of MMP 2 and 9 and the upregulation of TIMP gene expression that occurs in a time and concentration dependent manner. The downregulation of MMP9 is modulated by the inhibition of NF- κ B and AP1 binding to the DNA promoter region. A significant reduction of MMP2 and MMP9 expression at curcumin concentrations of 20 and 40 μ M after 48 and 72 h of incubation was observed in the study. TIMP 1 and 4 gene expression was significantly upregulated when treated with 20 and 40 μ M of curcumin and incubated for 48 and 72 h. The *in vivo* treatment of aggressive, triple negative breast cancer (TNBC) cells MDA-MB-231 with various concentrations of curcumin reveals inhibited cell proliferation and induced apoptosis.⁹² The suppression of the EGFR signalling pathway modulates anticancer properties in the MDA-MB-213 cell line. The preventive and therapeutic ability of curcumin on highly invasive MDA-MB-231 cells is expressed in its ability to downregulate the EGFR signalling cascade and decreased expression of EGR1 gene when administered *in vitro* for 24 h in the presence of 20 μ M of curcumin.⁹³ Hendrayani et al.⁹⁴ determined curcumin suppresses the activation of cancer associated fibroblasts (CAF) in MDA-MB-231 cancer cells in a dose dependent manner that leads to an induction of p16-dependent senescence, DNA free of damage, and inactivation of JAK2/STAT3 pathway.

Jiang et al.,⁹⁵ performed a study to discover the mechanisms responsible for curcumin's cytotoxicity. The study investigated curcumin's ability to resensitize anti-estrogen-resistant MCF-7/LCC2 and MCF-7/LCC9 breast cancer cell lines to tamoxifen. It was revealed that curcumin induces cell cycle arrest at G2/M and the inactivation of NF- κ B and Akt/mTOR signalling pathways, possesses anti-proliferative and pro-apoptotic characteristics, and down regulates EZH2 proteins. The modulation of miR-19/PTEN/Akt p53 pathway by curcumin leads to anti-proliferation of MCF-7 cancer cells exposed to Bisphenol A (BPA), an endocrine disrupter that increases cell proliferation.⁹⁶ The downregulation of Flap Endonuclease 1 (Fen1) expression is mediated by Nrf2 in an anti-proliferation pathway in the MCF-7 cell line.⁹⁷

MCF-7 and MDA-MB-231 breast cancer cells respond differently to curcumin. There is a significant deregulated expression of SKP2 in curcumin sensitive MDA-MB-231 cells. The suppression of SKP2 in the MCF-7 cell line occurs at higher concentrations and extended incubations (30 or 40 μ M / 12 or 24h). Curcumin inhibits the phosphorylation of Akt at SER-473 in MDA-MB-231 cell lines. However, curcumin treatment in MCF-7 cells results in a substantial increase in Akt phosphorylation. There is a difference in the function of the p13k/Akt-SKP2 pathway of the two cell lines in response to curcumin, highlighting the differential susceptibility of the breast cancer cells to curcumin's cytotoxic effects.⁹⁸ A study of the effectiveness of curcumin's anti-invasive ability to inhibit morphological changes triggered by lipopolysaccharide (LPS) in MCF-7 and MDA-MB-231 cells revealed NF- κ B-Snail pathway inactivation mediates suppression and increase of LPS-induced EMT markers vimentin and E-cadherin respectively.⁹⁹ Sood et al.,¹⁰⁰ performed an investigation of human breast cell carcinogenesis induced by trichloro-carban (TCC) and the use of curcumin as a preventive agent in MCF10A and MCF-7 breast cancer cell lines. TCC, an antimicrobial component in household and personal care products, has the ability to induce progressive human breast cancer carcinogenesis in non-cancerous breast cells to a pre-malignant stage. A significant decrease in cell viability was observed at 10 and 20 μ M curcumin

concentrations. Curcumin also demonstrated decreases in Erk-Nox pathway activation and ROS accumulation. The administration of curcumin as a preventive therapeutic agent suggests its ability to effectively suppress sporadic breast cancer induced by TCC exposure.

Vaughan et al.,¹⁰¹ investigated the ability of curcumin to reverse altered energy homeostasis of cancer, aerobic glycolysis and mitochondrial metabolism in breast epithelial cell lines MCF-10A and MCF-7. The study concluded curcumin can prevent reduction in mitochondrial cell content that is induced by TNF- α in a dose dependent manner. Curcumin is able to restore retinoic acid (RA) sensitivity to RA-resistant TNBC cells MDA-MB-231, MDA-MB-468, SKBr3, and MCF-7. Curcumin modulates the inhibition of growth in the breast cancer cell lines through the suppression of FABP5/PPAR β/δ pathway.¹⁰² An investigation of curcumin's role in the enhancement of TNF-related apoptosis ligand (TRAIL) activity in MCF-7, SKBR3, and T47D breast cancer cell lines revealed a curcumin-TRAIL synergistic relationship that selectively suppresses TRAIL resistance based on the breast cancer cell line. The combination induces down regulation of IAP proteins and induces ROS production leading to enhancement of the mobilization of DR5.¹⁰³ A time and dose response observation of the metastatic characteristics of estrogen receptor negative cell lines SK-BR3, MDA-MB-231, and MDA-MB-468 in the presence of curcumin concluded the reduction of circulating tumor cells (CTCs) may lower or prevent metastasis. The dose response study observed the effects of curcumin at 24, 48, and 72 h demonstrating a 40 and 47% decrease in adhesion propensity for SKBr3 and MDA-MB-231. A curcumin concentration of 10 μ M and 24 h incubation yielded a 20% increase in rolling velocity for all three cell lines.¹⁰⁴

Breast cancer studies exploring curcumin's anticancer activities have reported varied signalling pathways and molecular targets in the compound's mechanism of action; enhanced TRAIL activity, induction of cell cycle arrest at the G2/M phase, apoptosis, E-Cadherin, ROS accumulation, p16, p21, and p53, caspase8, 3, & 7, and PGC1, the upregulation of TIMP 1 & 4 expression, downregulation of Flap Endonuclease 1 (FEN1), SKP2 expression and inhibition of cell proliferation, MMP2, MMP9, NF- κ B, TGF- β 1, ERK $\frac{1}{2}$, P38 MAPK, PERK $\frac{1}{2}$, PEGFR, EGFR signaling pathway, EGR1 gene expression, SKP2, vinmentin, eRK-Nox, JAK2/STAT3 and Akt/mTOR pathway inactivation, and suppression of FABP5/PPAR β/δ pathway.

Curcumin Analogues

There are more than 720 natural, semisynthetic, and synthetic curcumin analogues reported in the literature. Some of the analogues have displayed tumor growth suppression in skin, stomach, duodenal, liver, prostate, and colon malignancies¹⁰⁵. Curcumin analogues have been explored to enhance curcumin's efficacy in chemoprevention and therapeutics of breast cancer by improving its low systemic bioavailability and poor pharmacokinetics. A few of the analogues have displayed efficacious anti-breast cancer characteristics; DMC, BDMC, RL66, PAC, PGV-1, and GO-YO30 (Table 2). A study performed by Shieh et al.¹⁰⁶ observed the effects of three curcuminoids found in commercial curcumin powder (Fig 1); curcumin (55–70%), demethoxycurcumin (DMC) a structural analogue of curcumin (15–20%), and bisdemethoxycurcumin (BDMC) (3–5%).

The results of the study concluded DMC as the most cytotoxic against MDA-MB-231 cells and potent cell proliferation suppression of TNBC cells. BDMC has demonstrated potent inhibition of cell proliferation and vitality by the induction of ROS accumulation.¹⁰⁷ Kumaravel et al.,¹⁰⁸ performed a comparative study of curcumin and curcumin analogue BDMC-A (an analogue with greater aqueous solubility) which revealed the analogue's cytotoxic and antiproliferative properties are similar to curcumin. Like curcumin, BDMC-A induces cell cycle arrest at the G2/M phase and inhibits the expression of cyclin D. Another study of BDMC-A conducted *in vitro* observed the induction of apoptosis in MCF-7 breast cancer cells. It was determined that BDMC-A's potency is attributed to the ortho-hydroxy group present. In addition, its effectiveness in the induction of apoptosis occurs by both intrinsic and extrinsic pathways.¹⁰⁹

Tetrahydrocurcumin, a Phase I metabolite of curcumin, effectively induces G2/M cell cycle arrest and apoptosis as well as induces antitumor activities via the p38 MAPK pathway when co-administered with SB203580.¹¹⁰ RL66, L-methyl-3,5-bis[(E)-4-pyridyl)methylidene]-4-piperidone, a second generation curcumin analogue, has high levels of cytotoxicity for ER negative breast cancer cells SKBr3, MDA-MB-231, and MDA-MB-468 both *in vivo* and *in vitro*. *In vitro* studies revealed the induction of apoptosis, cell cycle arrest, JNK ½ and MAPK p38 as well as suppression in Akt and HER2 phosphorylation in a mouse xenograft tumor growth model.¹¹¹ The co-therapeutic potential of curcumin analogues PGV-0 and PGV-1 administered with doxorubicin on MCF-7 and MCF-7/Dox cells has demonstrated PGV-1 enhances the cytotoxic effect of doxorubicin. PGV-1 and curcumin inhibit HER2 and NFκB activation.¹¹²

Hutzen and team synthesized GO-Y030, an active agent in the suppression of cell growth at a magnitude 8 to 40 times greater than free curcumin while still able to retain a similar safety profile. The analogue efficiently induces apoptosis, decreases cell viability, inhibits STAT3 and cell colony formation in MDA-MB-231.¹¹³ Al-Hujaily et al.¹¹⁴ compared the bioavailability and distribution of curcumin and 5-Bis(4-hydroxy-3-methoxybenzylidene)-N-methyl-4-piperdione (PAC) *in vitro* and in a nude mouse model. The study revealed PAC upregulates p21^{WAF1}, is more efficient than curcumin in apoptosis induction and as an inhibitor of cell survival, NF-κB, cyclin D1, and Bcl-2. *In vivo* analogue observations revealed better bioavailability and distribution.

Curcumin analogues (natural, semi-synthetic, and synthetic) DMC, BDMC, BDMC-A, RL66, PAC, PGV-1, and GO-Y030 have displayed cytotoxicity, apoptotic, anti-proliferative, arrest of the cell cycle, p53, p21^{waf1}, cytochrome c and ROS accumulation induction, upregulation of AMPK activity and the reduction of FASN expression, Bcl-2, NF-κB, survivin, cyclin D1, HER2, acetyl CoA carboxylase, PSTAT3, and PAKt/Akt and pathway activity.

Synergistic Curcumin Combinations

The administration of therapeutic cancer agents with a natural compound such as curcumin creates an effective synergistic combination against breast cancer (Table 3). Siddiqui et al.¹¹⁵ studied *in vitro* and *in vivo* synergistic anti-cancer effects of docosahexaenoic acid (DHA) and curcumin in breast cancer.

The *in vitro* analysis of SkBr3 (ER+/ HER-2+) breast cancer cells treated with a combination of DHA and curcumin demonstrated an alteration in “PAM50” genes. The *in vivo* study of induced DMBA breast cancer cells in SENCAR mice revealed the synergistic combination effective in decreasing the incidence of breast cancer, decreased tumor growth progression, decreased expression of survivin and increased expression of maspin. A combination of curcumin with silibinin (milk thistle) has greater effectiveness in cytotoxicity and reduction of cell viability than when curcumin is administered alone. The combination inhibits reverse transcriptase and has cytotoxic effects in T47D cells in a time and dose dependent manner.⁸⁸ Curcumin, alone or in combination with docetaxel modifies metabolic properties such as glutathione and lipid/phospholipid metabolism and glucose utilization in MCF7 and MDA-MB-231 breast cancer cells.¹¹⁶ Catania et al.¹¹⁷ conducted a comparison of the effectiveness of free curcumin, liposome loaded with curcumin, and immunoliposome loaded with curcumin bearing herceptin, a HER2 antibody, on JIMT1 and MCF-7 breast cancer cell lines. Greater cytotoxic activities were observed in JIMT1 cells. A decrease in IC₅₀ values of 50% to 33% versus free curcumin was recorded and the immunoliposome decreased the value further than the curcumin loaded liposome. When curcumin was combined with resveratrol and loaded into an immunoliposome, the nano-formulation exhibited improved efficacy in the HER2 positive JIMT1 cell line by 7% and IC₅₀ decrease compared to the liposome form. Paclitaxel, a traditional anti-cancer drug, administered with curcumin has shown a synergistic inhibitory effect in MCF-7 breast cancer cells and female Kunming mouse model. The combination results in an increase of anti-proliferation, apoptosis, and Bax expression *in vitro*. A reduction in the EGFR signalling blockade and a decrease in Bcl-2 expression in MCF-7 breast cancer cell line are modulated by the paclitaxel-curcumin combination. The synergistic combination also demonstrates an increase in anti-tumour efficacy in the *in vivo* model.¹¹⁸ Newjati-Koshki et al.,¹¹⁹ created a curcumin-silibinin combination that demonstrated an ability to inhibit the growth of T47D cells in a dose dependent manner as well as an inhibition of leptin expression and secretion. The ability of 5-fluorouracil (5-FU) to effectively initiate apoptosis and inhibit cancer cell growth is modulated by direct targeting of thymidylate synthase (TS). Overexpression of TS leads to 5-FU resistance in cancerous cells. The administration of curcumin chemosensitizes SKBR3, MCF-7, and MDA-MB-231 breast cancer cells that demonstrated 5-FU resistance. The co-administration of 5-FU and curcumin results in inhibition of DNA synthesis in MDA-MB-231 cells and enhanced LD₅₀.¹²⁰ A synergistic administration of EGCG and curcumin results in inhibition on cell growth and induced apoptosis in MCF-7 cells that are both doxorubicin (DOX) sensitive and resistant. Qian-Mei et al.,¹²¹ studied the combination of curcumin and mitomycin C (MMC) on a MCF-7 xenograft mouse model and observed an increase in apoptosis and inhibition of tumour growth via the ERK pathway. The group also recognized the alteration of more than twenty signalling pathways of twenty-five expressed genes. Curcumin administered with carnosol in SKOV-3 and MDA-MB-231 cell lines results in a synergistic reduction of cell vitality and increased anti-proliferation.¹²²

Synergistic relationships of curcumin with established therapeutic agents used in the treatment of breast cancer have demonstrated enhanced efficacy. Curcumin administered with agents such as docosahexanoic acid, silibinin, docetaxel, resveratrol, paclitaxel, 5-FU, mitomycin c, and carnosol have yielded promising results in the induction in cytotoxicity,

apoptosis, Bax and maspin expression, EGFR signaling blockade activity, and tumoriadial effects, and the reduction of tumor initiation, growth, and progression, Bcl2, survivin and hERT expression, leptin secretion, cell vitality, and DNA synthesis.

Curcumin Drug Delivery Systems

Oral administration of curcumin is rapidly metabolized in the intestine and hepatic system, resulting in approximately 60 to 70% of the compound eliminated in the feces.¹²³ The design and implementation of an efficient drug delivery system of curcumin as a lysosome, micelle, colloidal or nanoparticle results in the improvement in the administration and effectiveness of curcumin (Table 4). Studies of nanoparticles encapsulated with curcumin on MCF-7 breast cancer cells have observed increased efficacy compared to curcumin administered alone. Transferrin-mediated solid lipid nanoparticles (Tf-C-SLN) containing curcumin demonstrates significant increases in apoptosis, cytotoxicity, ROS, and cellular uptake compared to a curcumin solubilized surfactant solution (CSSS) and curcumin-loaded solid lipid nanoparticles (C-SLN).¹²⁴ Enhanced cytotoxic effect in MCF-7 cells and increased solubility, bioavailability, and anti-tumour activities were observed in a complex composed of a curcumin derivative, Diacetylcurcumin (DAC), and a micellular nanoparticle β -casein.¹²⁵ Francis et al.¹²⁶ created an optimized protocol to produce bis-demethoxy curcumin analogue nanoparticles (BDMCA-NP) that exhibit good anti-cancer therapeutic activities against MCF-7 cells. BDMCA-NPs effectively demonstrated anti-cancer activity by increased apoptosis, G2/M cell cycle arrest, cell death induction through the mitochondrial pathway, and the disassembly of the mitotic spindle of breast cancer cells. A nanocomposite of chitosan-starch loaded with BDMCA, (BDMCA-CS), an enhanced drug delivery system capable of inducing cytotoxicity in breast cancer cells has a very slow, sustained, and controlled diffused release of BDMCA in MCF-7 cancer cell line.¹²⁷ Breast cancer HER2-positive MCF-7 cell growth is inhibited in the presence of curcumin loaded PLGA nanoparticles. In the delivery system, curcumin can be released in a time and dose dependent manner intracellularly at low drug concentration yielding cell proliferation inhibition by G2/M cell arrest.¹²⁸ A comparison of nanocapsules determined that poly-(allylamine hydrochloride) (PAH) and poly-(sodium 4-styrenesulfonate) (PSS) nanocapsules of chitosan loaded with curcumin fabricated by solid core/mesoporus (SC/MS) results in higher cytotoxicity in MCF-7 cells than nanocapsules composed in a layer by layer (LbL) synthesis. The SC/MS capsule system is effective for drug delivery with higher curcumin loading and low particle aggregation.¹²⁹ β -cyclodextrin-curcumin (CD-CUR) nanoparticle is reported to inhibit telomerase gene expression in breast cancer cells. A comparison of free curcumin and CD-CUR demonstrated CD-CUR lowers the gene expression of telomerase more than free curcumin in T47D cells in a time and dose dependent manner.¹³⁰

Yallapu et al.¹³¹ synthesized NANO-Cur6, a curcumin encapsulated PLGA nanoparticle, by using a nano-precipitation technique which resulted in a six-fold cellular uptake and sustained release, decreased cell proliferation, and increased apoptosis in MDA-MB-231 cells. The nanoparticle also has the ability to halt the circulation of MDA-MB-231 cells in the number of adhering tumour cells and vascular adhesion by 70 and 50% respectively.¹³² Microtentacles (McTNs) are plasma membrane protrusions of tubulin-like material that form detached or suspended cells and assist in cell reattachment. Targeting McTNs containing

curcumin leads to rapid elimination of McTN cancer-stem-like cells (CSC) found in MDA-MB-231 and results in the inhibition of cell reattachment.¹³³ Xin Wei et al.¹³⁴ synthesized cholesteryl-hyaluronic acid (CHA) nanogel conjugates to address CD44 (+) and drug resistant tumours in MDA-MB-231 and MFC-7 breast cancer cell lines. The CHAs displayed fast penetration, high therapeutic activity, sustained drug release, and 2 to 7 times higher cytotoxicity in CD44 (+) breast cancer.

Studies of 4T1.2, an aggressive metastatic breast cancer model, with curcumin encapsulated nanoparticles have revealed enhanced activity. Cur-M, a water based formula, has a slower, sustained release that can last a week, maintains cytotoxicity, effective in tumour growth inhibition, apoptosis, and decreased cell proliferation in a 4T1 breast tumour model.¹³⁵ Chen et al.¹³⁶ observed the potent and sustained synergistic inhibition of curcumin and S-trans, trans-farrenslthiosalicyclic acid (FST) in a nanomicelle system on a 4T1.2 cancer mouse model. The nanomicelle demonstrated enhanced anti-tumour activity. Leg-HC-NPs, a legumain-targeting liposomal nanoparticle encapsulated with hydrazinocurcumin, in 4T1 breast cancer cell line and murine mouse model suppresses STAT3 *in vitro* and induces apoptosis, migration, angiogenesis, tumour growth inhibition, and prolonged life span *in vivo*.¹³⁷

Drug delivery studies have identified solid lipid nanoparticles, PLGA encapsulation, microtentacles, nanogels, and polymeric micelles as effective administration techniques to address the pharmacokinetic problems of curcumin/curcumin analogues and improve its anti-cancer activity.

***In Vivo* Studies**

The application of curcumin as a chemopreventive and chemotherapeutic agent is evidenced in the volume of studies performed that reveals its anticancer activity over various cancer cell lines. Efforts to combat curcumin's *in vivo* limitations have generated the study of curcumin analogues (natural, semi-synthetic, and synthetic) and novel delivery systems (nanoparticles) to increase its aqueous solubility, stability, and bioavailability. Animal studies administering curcumin showed synergistic relationships with established breast cancer chemotherapeutic agents, curcumin analogues, and novel delivery systems have demonstrated reduced incidence of breast tumours and decreased tumour size.

RL66, has demonstrated the ability to suppress tumour volume and weight in a time dependent manner in a xenograft mouse model. When treated with 8.5 mg/Kg of RL66 for 4 weeks, tumour volume and growth suppression was apparent and continued until the conclusion of the 10 week study.¹¹¹ Al Hujaily et al.¹¹⁴ investigated the effectiveness of a curcumin analogue, PAC on breast cancer cell line MDA-MB-231 in a nude mouse xenograft model. The 14 day study of 100 mg/Kg/day revealed tumour size reduction, inhibitory effects on onco-proteins, and greater biodistribution and bioavailability than curcumin alone. A synergistic combination of curcumin and docosahexaenoic acid decreased the incidence of and progression of breast tumours as well as reduced the initiation of the tumours in SENCAR mice. Breast tumours were induced in the mouse model by DMBA, a potent carcinogen that affects many sites including the mammary glands. A treatment of 0–20 μ M of curcumin and 10–100 μ M of DMBA for 133 days

showed the synergistic effects of DHA and curcumin were effective on the SK-Br-3 phenotype that possessed ER – and Her- 2+ characteristics.¹¹⁵

Zhan et al.¹¹⁸ studied curcumin's ability to potentiate paclitaxel in breast cancer cells. Female Kunming mice with S180 cells transplanted were treated with paclitaxel, curcumin, and paclitaxel-curcumin combination for 10 days at 25–225 mg/Kg of curcumin and 5mg/kg of paclitaxel. When administered alone, paclitaxel demonstrated significant growth suppression.

However, the synergistic relationship revealed efficient tumour growth inhibition in a dose-dependent manner. Curcumin loaded, self-assembled polymeric micelles have shown increase in apoptotic cells and significant inhibition of tumour growth and spontaneous pulmonary metastatic in a subcutaneous 4T1 breast tumour model.¹³⁵ Chen et al.¹³⁶ investigated the synergistic cytotoxicity of curcumin and FTS in a micellar system targeting breast cancer in 4T1.2 breast cancer model. The study revealed significant efficacy in inhibiting tumour growth without loss of body weight and abnormal appearance. Nanoparticle encapsulation with hydrazinocurcumin has demonstrated tumour weight inhibition and prolonged life span of tumour bearing mice in a 4T1 BALB/c model for 15 days.¹³⁷

Clinical Studies

Since the 1980's, curcumin preclinical trials have demonstrated its therapeutic efficacy in an array of diseases. More than 40 clinical trials have been completed, 40 more are scheduled, and of the nearly 80 curcumin clinical trials, less than 5 have explored curcumin's chemotherapeutic applications in breast cancer. A one-year Phase I trial performed by Bayet-Robert et al.¹³⁸ explored the use of docetaxel in combination with curcumin in patients diagnosed with advanced and metastatic breast cancer. The trial revealed the docetaxel (100 mg/m²) - curcumin (8000 mg/day) combination administered every three weeks operated as an anti-tumour agent. A pilot study lead by Lisa Yee, Ohio State University Comprehensive Cancer Center, in the recruiting stage, will explore curcumin's ability to reduce inflammatory changes in the breast tissue of high risk obese patients and a Phase II study, also recruiting, will investigate if curcumin reduces NF-κB in patients who have completed chemotherapy and receiving radiotherapy.^{139–140}

Conclusion

Since 1989, a steady decrease in breast cancer mortality in the United States has been observed and attributed to aggressive methods to detect the threat early in its onset. Curcumin holds great promise as a chemopreventive and chemotherapeutic natural compound. Its anti-cancer and anti-tumour nature is broad and has been established effective in ovarian, pancreatic, prostate, liver, and breast cancers. Cytotoxic, cytostatic, and anti-metastatic therapeutic properties are a result of its proficient modulation of essential enzymes, inflammatory and transduction pathways in cancerous cells. Its apoptotic nature, induction of cell cycle arrest, and deterrence of metabolic processes in cancer in concert with its anti-oxidant properties makes it an excellent chemotherapeutic agent and cytoprotective to healthy cells. Curcumin's shortcoming hinders its *in vivo* application in

breast cancer. It undergoes extreme biotransformation when administered orally, has poor aqueous solubility, is chemically instable, and has limited systemic distribution. Therefore, technology must be implemented to address the pharmacokinetic restraints of *in vivo* curcumin application. Synthesis of curcumin analogues, synergistic therapy with established therapeutics, and novel delivery systems may effectively combat the aggressive and metastatic cancer. Curcumin analogues such as RL66 and DMC have demonstrated *in vitro* safety profiles like that of the parent compound and express greater cytotoxicity. Further studies of structurally modified curcumin's effectiveness *in vivo* should be performed to determine pharmacodynamic and toxicity profiles. Synergistic administration of curcumin with established therapeutics such as docetaxel and paclitaxel enhance the chemotherapeutic characteristics and cytotoxicity than when given alone.

Delivery systems that encapsulate curcumin in nanoparticles or liposomes represent a viable alternative to oral administration. Nanoparticles and liposomes carriers may be tumour targeted and release curcumin over time while retaining curcumin's efficacy and cytoprotective nature.

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Curcumin

Demethoxycurcumin (DMC)

Bisdemethoxycurcumin (BDMC)

Fig. 1.
Structures of Natural Curcumins

Fig. 2.
Structures of Semisynthetic and Synthetic Curcumins

Table 1**Biological Activities of Curcumin on Breast Cancer Signalling Pathways**

Biological Effects	Curcumin (con.)	Mechanism of Action	Cell line	Ref
Curcumin inhibits cell migration and invasion via TGF- β /Smad pathway in breast cancer cells	(5–50 μ M)	$\downarrow$ MMP-9 $\downarrow$ TGF- β 1 $\downarrow$ ERK 1/2 $\downarrow$ p38MAPK	MDA-MB-231	90
Curcumin inhibits MMP gene expression activity in breast cancer cells	(10–40 μ m)	$\downarrow$ MMP- 2 & 9 $\uparrow$ TIMP 1 & 4	MDA-MB-231	91
Curcumin inhibits cell proliferation in triple negative breast cancer cells via EGFR-MAPK signalling pathway	(10–30 μ M)	$\downarrow$ pERK $\frac{1}{2}$ $\downarrow$ PEGFR	MDA-MB-231	92
Curcumin inhibits gene expression in breast cancer cells and identifies relevant networks involved in cell growth and development	20 μ M	$\downarrow$ Cell viability $\downarrow$ EGR1 gene expression	MDA-MB-231	93
Curcumin enhance tumour suppression proteins and inhibits pro-carcinogenic expression in breast cancer cells	(10 μ M)	$\uparrow$ p16,21,53 $\downarrow$ MMP-2 $\downarrow$ MMP-9 $\downarrow$ SDF-1 $\downarrow$ IL-6	MDA-MB-231	94
Curcumin induces apoptosis and enhances sensitivity to tamoxifen in breast cancer cells	10–30 μ M	$\downarrow$ Bcl-2 $\downarrow$ Bcl-XL $\downarrow$ IKK $\downarrow$ NF-KB $\downarrow$ Akt/mTOR	MCF-7/LCC2 MCF-7/LCC9	95
Curcumin alone or in combination with Bisphenol A enhances anti-proliferative activity in breast cancer cells	1 μ M	$\downarrow$ P53 $\downarrow$ miR-19a $\downarrow$ miR-19b $\downarrow$ Cell growth	MCF-7 MDA-MB-231	96
Curcumin enhances anti-proliferation via altered expression and activity of proteins in breast cancer cells	10–30 μ M	$\downarrow$ Fen1 $\downarrow$ Cell proliferation	MCF-7	97
Curcumin alters Akt/SKP2 signalling pathway in breast cancer cells for anti-proliferative activity	2–40 μ M	$\downarrow$ SKP2 $\downarrow$ Akt Phosphorylation	MCF-7 MDA-MB-231	98
Curcumin inhibits EMT expression with LPS in breast cancer cells	20–70 μ M	$\downarrow$ Cell invasion $\downarrow$ NF-KB activation $\downarrow$ Cell proliferation $\downarrow$ E-Cadherin $\downarrow$ Vimentin	MCF-7 MDA-MB-231	99
Curcumin inhibits triclocarban cytotoxicity in breast cancer cells	10–20 μ M	$\downarrow$ Cell viability $\uparrow$ ROS $\uparrow$ DNA damage $\downarrow$ ERK-NoX	MCF10A MCF-7	100
Curcumin inhibits expression of TNF- α , induces aerobic glycolysis and mitochondrial metabolism in breast cancer cells	5–10 μ M	$\uparrow$ PGC1 $\downarrow$ GLUT1 RNA expression	MCF10A MCF-7	101
Curcumin inhibits FABP5 expression in triple negative breast cancer cells by enhancing sensitivity to retinoic acid	30–50 μ M	$\downarrow$ Cell proliferation $\downarrow$ PPAR β / expression	MDA-MB-231 MDA-MB-468	102
Curcumin induces apoptotic proteins to restore sensitivity to TRAIL in breast cancer cells	20 μ M	$\uparrow$ ROS $\uparrow$ TRAIL Receptor $\uparrow$ Cellular caspase activity(Cas 8,3,7) $\downarrow$ IAP (Inhibitor apoptosis protease)	MCF-7 T47D SK-Br3	103
Curcumin reduces metastatic activity in estrogen receptor negative breast cancer cells	1–40 μ M	$\downarrow$ Adhesion propensity $\uparrow$ Cell Death	SK-Br3 MDA-MB-231 MDA-MB-468	104

Table 2**Biological Activities of Curcumin Analogues on Breast Cancer Signalling Pathways**

Biological Effects (Chemical Structure Description)	Curcumin analogue (conc)	Mechanism of Action	Cell line	Ref
DMC inhibits eukaryotic initiation factor and mRNA translation in breast cancer cells (curcumin without one methoxyl group)	DMC (20 µM)	↓cell proliferation ↓FASN expression ↑AMPK activity ↓Acetyl CoA Carboxylase	MDA-MB-231	106
BDMC induces apoptosis in MCF cells by mitochondrial membrane potential and ROS alteration (curcumin without two methoxyl groups)	Bisdemethoxy curcumin (10–40µM)	↓cell proliferation ↑ROS ↓G2/M Phase	MCF-7	107
Curcumin analogue BDMC-A inhibits cyclin D1 protein expression in breast cancer cells (positional isomer of BDMC)	BDMC-A (15–75µM)	↓Cell viability	MCF-7	108
Curcumin analogue bis-demethoxy curcumin has an increased efficacy in apoptosis and induction compared to free curcumin. (positional isomer of BDMC)	BDMC-A (15µM)	Regulates P13k/Akt Apoptotic Intrinsic and extrinsic pathways ↑p53 ↑Bax ↑cytochrome c, ↑apoptosis	MCF-7	109
Tetrahydrocurcumin induces intrinsic apoptotic pathway change in breast cancer cells (saturated curcumin analogue)	THC (34–112.5µM)	↓Bcl-2 ↑Bax ↑Cytochrome C ↑G2/M phase ↑Apoptosis	MCF-7	110
Curcumin analogue RL66 induces cytotoxic effects in ER-negative breast cancer cells (synthetic analogue/N-methyl piperidone analogue)	RL66 (12.6 µM)	↓HER2/neu expression ↓pAkt/Akt	MDA-MB-231 MDA-MB-468 SKBr-3	111
Curcumin and its novel analogue PGV-0 and PGV-1 induces cytotoxicity in breast cancer cells resistant to doxorubicin (cyclopentanone)	PGV-0 and PGV-1 (21–82 µM)	↓p65 ↑G-1 population ↑Sub-G-1 population	MCF-7	112
Curcumin analogue GO-Y030 reduces cell viability and induces apoptosis in breast cancer cells (semi-synthetic analogue)	GO-Y030 (05.–5.0 µM)	↓pSTAT3 Cell ↑apoptosis ↓Cell Viability	MDA-MB-231	113
Curcumin analogue, PAC inhibits mitochondrial pathway in breast cancer cells (synthetic analogue/ N-methyl piperidone analogue)	PAC (10–40µM)	↓Bax and Bcl-2 ↓NF-κB ↑P21 ^{waf1} ↑Th2 production IL-4 and IL-10 ↓Survivin and cyclin D1	MCF-7 MDA-MB-231	114

Table 3**Synergistic Effects of Curcumin**

Biological Effects	Synergistic Agent (Curcumin con.)	Mechanism of Action	Cell line	Ref
Curcumin in combination with Docosahexaenoic acid inhibits "PAM50" genes in <i>in-vivo</i> model of DMBA-induced mice	Docosahexaenoic Acid (DHA) (2 gm/ kg)	↑Maspin Expression ↓Survivin expression ↓Tumor progression ↓Tumor Initiation	SkBr3 ER(-) HER-2+ <i>in-vivo</i> model	115
Curcumin, alone or in combination with silibinin inhibits reverse transcriptase activity in breast cancer cells	Silibinin (5–17.5 μM)	↓hTERT expression	T47D	88
Curcumin, alone or in combination with docetaxel inhibits relative metabolic activity in breast cancer cells	Docetaxel (28–70μM)	↑Total Glutathione	MCF-7 MDA-MB-231	116
Curcumin, alone or in combination with resveratrol in immunoliposome inhibits HER2 expression	Resveratrol (0.10- 0.02mM)	↑Cytotoxicity	JIMT1 MCF-7	117
Curcumin, alone or in combination with paclitaxel enhances apoptosis in breast cancer cells	Paclitaxel (12.6 μM)	↑Bax expression ↑EGFR signal blockade ↓Bcl2 expression	MCF-7	118
Curcumin combined with silibinin inhibits leptin receptor in breast cancer cells	Silibinin (20–120μM)	↓Leptin secretion	T47D	119
Curcumin, alone or in combination with 5-FU enhances cytotoxicity in breast cancer cells	5-Fluorouracil (5-FU) (10μM)	↓DNA synthesis	MDA-MB-231	120
Curcumin and mitomycin C (MMC) synergistically inhibits tumour growth and induces apoptosis in breast cancer cells.	100mg/kg Cur 1.5mg/kg MMC (0.5–5.0 μM)	↓ Tumor Growth (MCF-7) ↑ Tumoricidal Effect ↑Apoptosis (MDA-MB-231)	MDA-MB-231 MCF-7	121
Curcumin combined with carnosol increases anti-proliferative activity in breast cancer cells	Carnosol	↓Cell vitality	MDA-MB-231	122

Table 4**Curcumin Drug Delivery Systems**

Biological Effects	Delivery vessel (Curcumin con.)	Mechanism of Action	Cell line	Ref
Curcumin in a solid lipid nanoparticle enhances cytotoxicity and apoptosis in breast cancer cells	Transferrin-mediated solid lipid nanoparticles (Tf-C-SLN)	↑Cellular uptake ↓Cell viability ↑ROS	MCF-7	124
Curcumin analogue DAC with β -casein enhances anti-tumour activity in breast cancer cells	Diacetylcurcumin (DAC) (10–40 μ M)	↑Bioavailability ↑Solubility ↑Cytotoxicity ↓Cell survival	MCF-7	125
Bis-demethoxy curcumin analogue nanoparticles enhance cell cycle arrest and increase apoptosis in breast cancer cells.	Bis-demethoxy curcumin analogue nanoparticle (BDMCA-NP)	Fragmentation of PARP and Bax proteins ↑Apoptosis, ↑dispensability ↑Surface volume ratio	MCF-7	126
BDMC-A in chitosan-starch nanocomposite enhances drug delivery system and cytotoxicity in breast cancer cells	Bis-demethoxy curcumin analogue nanoparticle (BDMCA-CS) (1.953–1000 μ g/ml)	Very slow, sustained & diffused controlled release ↑Cell aggregation ↑Membrane shrinkage	MCF-7	127
Curcumin in PLGA encapsulation induces cytotoxicity by G2/M cell cycle arrest in breast cancer cells	Poly(lactic-co-glycolic acid) (100 μ M)	Release by Fickian-Law diffusion over 10 days Increases curcumin intracellularly Improves pharmacokinetics and pharmacodynamics	MCF-7	128
Curcumin by solid core/mesoporous shell synthesis enhances cellular uptake and cytotoxicity in breast cancer cells	PSS nanocapsules (10–140 pg)	↓Cell Proliferation	MCF-7	129
Curcumin loaded β -cyclodextrin nanoparticle inhibits telomerase expression	β -cyclodextrin-curcumin (CD-CUR) 5–100 μ M	↓Telomerase expression	T47D	130
Curcumin PLGA nanoparticle accumulated in breast cancer cells inhibits cell survival and colony formation	Poly(lactic-co-glycolic acid) (10 mg)	6 fold increase in cellular uptake in metastatic cells Sustained Curcumin release	MDA-MB-231	131 & 132
Curcumin halts reattachment of McTNs and decreases metastasis in breast cancer cells.	Microtentacles (McTNs) (5–50 μ M)	↓Cellular Aggregation ↓Reattachment	SKBr3 MDA-MB-231 MDA-MB-436 MDA-MB-468 HMLE Bt549 HS578	133
Curcumin in CHA nanogel enhances cytotoxicity in drug resistant tumours and breast cancer cells	Cholesteryl-Hyaluronic Acid (CHA) (28 mg)	High drug load Fast penetration Sustained drug release Significantly increased bioavailability	MDA-MB 231/F MCF-7	134
Curcumin in polymeric micelles enhances anti-tumour activity in breast cancer models	Curcumin self-assembled polymeric micelles (CUR-M) (15 mg)	Slow and Sustained release ↑Cytotoxicity ↑Cellular Uptake	4T1.2	135

Biological Effects	Delivery vessel (Curcumin con.)	Mechanism of Action	Cell line	Ref
Curcumin and S-trans in a PEG nanomicelle synergistically inhibits tumour growth in breast cancer cells	S-Trans-farnesylthiosalicylic Acid (FTS) (10uM)	Enhanced <i>in vitro</i> and <i>in-vivo</i> anti-tumour activity ↑Cytotoxicity ↓Akt ↓NF-Kb	4T1.2	136
Hydrazinocurcumin in nanoparticle inhibits tumour progression in breast cancer model	Legumain-targeting liposomal nanoparticle (Leg-HC-NP) (100µm)	↑ Tumor sensitivity ↓Tumor growth ↑Apoptosis ↓Cell Proliferation	4T1	137

Table 5**In Vivo Curcumin Breast Cancer Studies**

Compound	Cell Line/Animal Model	Dose/ Time Interval (Days)	Biological Activity	Ref
RL66	MDA-MB-498/ CD-1 mice (female)	8.5 mg/Kg (70d)	Decreased tumour volume and weight in time dependent manner	111
Curcumin & DHA	DMBA Induced (SK-BR-3 phenotype)/ SENCAR Mice (female)	0–20 μ M (Cur) 10–100 μ M(DHA) (133d)	Decreased tumour incident and progression and delayed tumour initiation	114
PAC	MDA-MB-231/ Nude Mice	100 mg/Kg/day (14d)	Greater biodistribution and bioavailability and decreases tumour size	115
Curcumin & Paclitaxel	S180 cell Transplant/ Kunming Mice (female)	25–225 mg/Kg (Cur) 5mg/Kg (PTX) (10d)	Marked growth inhibition of tumour in dose-dependent manner	118
Curcumin-Micelles	4T1 T Tumor Model/ BALB/C Mice	30 mg/Kg (10d)	Inhibits growth and spontaneous pulmonary metastasis. Improved anti-tumour and anti-metastasis activity	135
PEG-FTS Micelles w/ Curcumin	MCF-7/ 4T1 Tumor Model	12.5–50 μ M (4d)	Improved anti-tumour activity	136
Leg-HC-NPs	4T1 Cells/ BALB/C (female)	1mM (15d)	Increased tumour sensitivity and inhibits tumour growth	137

Table 6

Curcumin-Breast Cancer Clinical Trials

ClinicalTrials.gov Identifier No.	Year Started	Phase	Patient Condition	Dose of Curcumin	Purpose
NCT01975363	2015	Pilot/ Recruiting	Atypical Ductal Breast Hyperplasia	100 mg /d for 3 months	Effect of curcumin nanoemulsion formulation in reducing inflammatory changes in breast tissue in obese women at high risk for breast cancer.
Phase I Complete	2010	Completed	Metastatic	8000 mg/d for 18 weeks	Determine optimum dose of docetaxel - curcumin combination
NCT01740323	2015	Phase II/ Recruiting	Breast Cancer	600 mg/ d for 6 weeks	Curcumin vs Placebo for Chemotherapy-Treated Breast Cancer Patients Undergoing Radiotherapy