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REVIEW

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Curcumin: A Modulator of Mammary Malignancies

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Breast cancer is one of the leading causes of cancer-related deaths among females and accounts for around 25% of all female melanomas worldwide with increasing incidence every day. Among various natural phytochemicals studied against breast cancer, curcumin has been found to possess antioxidative properties with established safety record. Curcumin is a pleiotropic molecule possessing chemopreventive and chemotherapeutic properties. Curcumin arrests cancer formation at various stages ranging from transformation, proliferation as well as invasion. Transformation is arrested by constitutive de-activation of transcription factors like STAT 3, AP-1, NF-kB. Curcumin controls the expressions of oncogenes, growth factor like EGF, PGDF, FGF, decoy receptors, cyclin D1, survival factors that are important for tumoral cell proliferation. Curcumin successfully inhibits tumor metastasis by supressing the expression of matrix metalloproteinase, COX 2, adhesion molecules, Chemokines and TNF.

Curcumin has revealed anticancerous effects in synergism with various compounds like piperine, genistein, mitomycin C, phosphatidicholine, monomethoxy polyethylene glycol, epigallocatechin gallate and metformin. Recent studies have attempted to study the efficacy of curcumin loaded nanoparticles as drug delivery system.

This paper attempts to review the work on antitumoral effects of curcumin against breast cancer, underlying mechanisms and proposes further investigations that are needed for rational cancer therapy.

Key words: Curcumin, Breast cancer, anti-inflammatory, chemotherapeutic, chemopreventive, synergistic

Breast cancer is the most common invasive cancer and a major cause of death in women worldwide. Various therapeutic modalities have been examined and explored by researchers and clinicians for the inhibition of mammary malignancies for years. Recently, various natural phytochemicals have been studied to check their effectiveness to inhibit breast tumors and suppress their promoting factors.

Curcumin, a dietary polyphenol, has been extensively examined to serve as a chemopreventive agent and an inhibitor of metastasis in various tumours ranging from breast, haematological, gastrointestinal, colorectal, liver and prostate cancers (Liu and Chen, 2012). Curcumin is a major curcuminoid extracted from the roots of *Curcuma Longa.* Chemically, diferuloylmethane ($C_{21}H_{20}O_6$), it is an orange yellow phenolic compound, insoluble and unstable in water known to possess antioxidative, chemotherapeutic and chemopreventive properties.

Among curcumin polymers, polyacetal-based polycurcumin (PCurc 8) is found to be highly cytotoxic to tumor cells in various cell lines including MCF-7 breast cancer cells and injected PCurc 8 showed remarkable anticancerous results in xenograft tumour models (Tang *et al.*, 2010).

Studies have revealed that curcumin modulates various targets such as transcription factors, growth factors, enzymes, protein kinases & gene expressions regulating apoptosis.

Inhibition of transformation

Effect of curcumin on NF-kB transcription factor

NF-kB is a nuclear transcription factor essential for the genes expressions involving in cell proliferation, cell invasion, metastasis, angiogenesis, and resistance to chemotherapy. Curcumin can suppress the activation of NF-kB and can cease many reactions in which NF-kB plays a major role as reported in various studies (Chung *et al.*, 2015; Aggarwal *et al.*, 2006).

BB Aggarwal *et al.* demonstrated curcumin as a suppressor of Paclitaxel activated Nuclear factor- kB in breast carcinogenesis through inhibition of IκBα kinase activity and degradation & phosphorylation of IκBα. Curcumin has been reported to enhance the effects of chemotherapy in advance breast carcinogenesis. Oral intake of Curcumin showed remarkable results in reducing breast cancer incidence and it also suppressed the lung metastasis in human breast cancer Xenograft model (Kakarala *et al.*, 2010).

Mehta Kapil *et al.* (1997)concluded that curcumin can show remarkable results in reducing the rapid growth of breast cancer cells in vivo. It can suppress the activation of C-jun/AD-1 and NF- [Kappa] B and Type1 of immunodeficiency virus long- terminal repeat – directed gene expression in vitro. Inhibition of proliferation was measured by [3H] thymidine incorporation, crystal violet dye uptake, Trypan Blue Exclusion and flow cytometry and tumour cells were found to be arrested in G2/S cell cycle phase. It was reported that several breast tumour cell lines such as hormone dependent and independent, Multi Drug resistant (MDR) lines were found highly sensitive to curcumin. Antiproliferation, time and dose dependent effect of curcumin was found to have a mutual relationship with inhibition of ornithine decarboxylase activity. It was reported that cell death is purely caused by Curcumin rather than apoptosis and its related genes including BCL-2, P53, Cyclin B and Transglutaminase.

Curcumin induces apoptosis in MDA- MB- 231 cells by reducing activation of survival pathway NFkB as is evident from the reduced IkB & P65 phosphorylation. Carcinogenesis was silenced in the majority of curcumin treated immunodeficient mice as a result of downregulation of NFkB/ AP-1 dependent MMP expression & direct apoptotic effects on circulating tumor cells but not on established metastasis (Bachmeier *et al.*, 2007). Zong *et al.* (2012) studied the molecular mechanisms of antitumour effects of curcumin on MCF-7 breast cancer cell line. Effectiveness of curcumin, cell invasion and effect of curcumin of uPA expression were assessed by MTT assay, Transwell assay and Western blot respectively. Trans- AM NF-kB Elisa kit in nuclear extracts was used to investigate the binding activity of NF-kB to DNA. Results suggested that dose dependant treatment with curcumin inhibits propagation of MCF-7 cells, expressions of uPA & NF-kB DNA binding activity were significantly reduced. Furthermore, adhesion and

invasion ability of MCF was found to be sharply inhibited through downregulating the protein expression uPA via of NF-kB activation (Zong *et al.*, 2012).

Reports also suggested that curcumin enhances the ability of chemotherapy by tailoring p65NF-κB-p300 cross-talk in favour of p53-p300 for breast carcinogenesis (Sen *et al.*, 2011).

Effect of curcumin on STAT 3 and STAT 5

STAT 3 is a cell signalling protein that is induced by interleukin-6 (IL-6) signalling and by other cytokines as well (de la Iglesia *et al.*, 2008). It is reported to promote oncogenesis by being constitutively active in various pathways (Lee *et al.*, 2012; Musteanu *et al.*, 2010; Aggarwal *et al.*, 2009; Marrogi *et al.*, 2000).

Studies revealed that CD-24+ breast cancer stem cells had preferential activation of STAT 3, reporting STAT 3 as potential therapeutic target in human breast cancer cells. STAT 3 expression has been found to be downregulated by curcumin in MD-MB-231 and MCF-7-HER2 cell lines. Zhang *et al.* (2007) reported that tumours produce exosomes and multivesicular bodies containing a discrete set of proteins that combine with cells of circulating immune system. Instead of non exosomal fraction, purified exosomes secreted by TS/A breast tumor cells inhibits cell cytotoxicity of Natural Killer (NK) induced by IL-2. Dietary curcumin is reported to reverse the inhibition of tumour exosome mediated action of NK cells through impairment of ubinquitin-proteasome system. In curcumin treated mouse breast cancer cells, a dose dependent increase in ubinquinated exosomal proteins was found in contrast to the untreated ones. Moreover, the much attenuated inhibition of IL-2 mediated NK cell activation in the exosomes secreted by tumour cells was evaluated when pretreated with curcumin. Jak3-mediated activation of Stat5 is required for tumour cytotoxicity of IL-2 stimulated NK cells. TS/A tumour exosomes strongly inhibit activation of Stat5, whereas the tumour exosomes isolated from curcumin-pretreated tumour cells have a lowered potency for inhibition of IL-2 stimulated NK cell cytotoxicity.

Effect of curcumin on AP-1

Increased expression of AP-1 transcriptional factor is found to be associated with breast cancers of certain origin (Zhou *et al.*, 2007). Curcumin is found to decrease this expression and thus inhibits transformation (Divya *et al.*, 2006).

Reduction in anchorage-independent growth

The effect of curcumin is evaluated by Calaf GM *et al.* in a breast cancer model which consisted of human breast epithelial cells at different transformation phases: i) Immortalize MCF-10F; ii) Estrogen cell line; iii) a malignant Alpha3 cell line; iv) a malignant and tumorigenic, Alpha5 cell line; and v) a cell line derived from Alpha5 injected into the nude mice that gave rise to Tumor2 cell line. Anchorage-independent growth was found to be reduced by curcumin in transformed breast tumour cell lines as compared to their counterparts and rise in the cell percentage from G_0/G_1 with associated increase in G_2/M phases was reported and decrease in PCNA and Rho-A protein expressions were found as well (Calaf *et al.*, 2012).

Inhibition of proliferation

Effect of curcumin on growth factors

In breast cancer cell line MDA-MD-231, BT-483 curcumin exhibited antiproliferation effects in time & dose dependent manner through NFkB inducing genes. In MDA-MB- 231 expression of cyclin D1 had declined & in BT- 483 exp. Of CDK4 had declined, so both results suggests downregulation through NFkB inducing genes (Liu *et al.*, 2009).

Carroll found that when estrogen and progesterone receptor containing T47-D human breast cancer cells was exposed to 10 nM synthetic progestins and various concentrations of curcumin, VEGF Secretion from T47-D cells induced by widely used progestin in HT, medroxyprogesterone acetate (MPA) was reduced in a dose-dependent manner by curcumin, But the VEGF secretion from the cells treated with progesterone or progestins other than MPA was unaffected by curcumin. Reports, therefore revealed that Curcumin may provide a clinically useful tool for the inhibition of MPA-induced elaboration of VEGF by cancer cells (Carroll *et al.*, 2008).

Effect of curcumin on receptors

Studies reported that epidermal growth factor is associated with proliferation and breast cancers. Curumin has been found to downregulate the vascular

endothelial growth factor VEGF in cancer cells. α6β4 signaling receptors such as EGFR, AKt are found to be inhibited by curcumin (Soung, Chung, 2011; Zhen *et al.*, 2014). Furthermore, synergistically epigallocatechin gallate (EGCG) and curcumin in vivo and vitro found to modulate the expression of VEGFR1 (Somers-Edgar *et al.*, 2008). Curcumin's natural ability to compete with aryl hydrocarbon for both the AhR & CYPA1 suggest it to be a natural legend & substrate of Aryl Hydrocarbon Receptor (AhR) pathway in MCF-7 mammary epithelial carcinoma cells (Ciolino *et al.*, 1998).

Effect on oncogenes

Oncogenes such as c-Ha-Ras and Ras homologous A (Rho-A) are important factors in cell signalling for malignant transformation and to reach their active GTP bound state. Ras proteins has to first release GRF (guanine nucleotide releasing factor) mediated bound GDP then RasGRF1 protein expression is reduced by curcumin in malignant cell lines. After curcumin treatment differential expression levels of cleaved (ADP) ribose polymerase 1 (PARP-1) and phosphorylated histone H2AX (γ-H2AX) were observed. As Poly [ADP-ribose] polymerase1 (PARP-1) similar to H2AX is involved in proliferation, differentiation, tumor transformation and DNA repair thus distrupts the curcumin performance, so targeting either PARP-1 or H2AX may provide remarkable results by maximizing the therapeutic value of curcumin for cancer prevention (Calaf *et al.*, 2012).

Inhibition of tumor metastasis

Effect of curcumin on COX2

Cyclooxygenase 2 (COX 2), chemically prostaglandin endoperoxide synthase [PTGS] is a type of enzyme whose expression has been found to be upregulated in various cancers (Aggarwal *et al.*, 2006; Marrogi *et al.*, 2000). COX 2 is reported to suppress apoptosis, thus promote tumours. Various studies revealed that curcumin reduces the expression of COX 2 (Aggarwal *et al.*, 2005; Aggarwal *et al.*, 2006; Marrogi *et al.*, 2000). As reported by Plummer *et al.* curcumin when added to blood from healthy persons in vitro, downregulated the expression of COX2 protein significantly (Plummer *et al.*, 2001).

Bayet et al (2010) show that the maximal tolerance dose of curcumin was raised to 8000 mg/day against recommended dose of 6000 mg/day when used in combination with Docetaxel during phase I chemotherapy trials on patients with advanced and metastatic breast cancer.

Effect of curcumin on chemokines

Effects of curcumin were investigated in MDA-MB-231 breast cancer cells using microarray gene expressions. 62 genes were found to be significantly altered out of which 37 were downregulated and 25 were upregulated. Notable increase in expression has been found in are hemeoxygenase-1 (HMOX1) and GCLM whereas several genes were significantly reduced such EGR1, prostaglandin-endoperoxide synthase and the chemokines CXCL1 and CXCL2. It is suggested that this decreased expression of CXCL1 and CXCL2 is involved in inhibition of metastatis through cytoxine receptor CXCR4 (Bachmeier *et al.*, 2007). In another human breast cancer cell line MDA- MB- 435, curcumin was found to inhibit proliferation via downregulation of expression of E2H2 gene through MAPk pathway (Hua *et al.*, 2010).

Effect of curcumin on protein expressions

Studies done on MDA-MB-231 and MCF-7 human breast cancer cells by Lv *et al.* (2014) reported curcumin to show anticancer effects through apoptosis where tumours were established by injecting MDA-MB-231 cancer cells in nude BALB/c mice followed by curcumin administration. The cell viability for cultured cells was assessed by MTT assay, apoptosis detection was done by flow cytometry, acridine orange staining & transmission electron microscopy and protein expression was calculated by western blot analysis. The results revealed significant decrease in BCL-2 protein expression, increase in BAX protein expression and subsequent increase in BAX/BCL-2 ratio. A remarkable decrease in size and weight of tumours were evaluated after curcumin administration.

Studies done by Choudhuri *et al.* (2002) were to investigate the means of apoptosis induction in MCF-7 breast cancer cells by curcumin. Reports suggested that curcumin-induced apoptosis is found to be due to an increase in expression of wild- type p53 and its DNA

binding activity which was followed by an increase in Bax expression at protein level. Other experiments done by using p53-null MDAH041 cell as well as low and high p53-expressing TR9-7 cell, where p-53 was tetracycline dependent conveyed that tumour cell death is through p53-dependent pathway where Bax is the downstream effector of p53 (Choudhuri *et al.*, 2002).

Curcumin has been found to customize expressions and activities of diverse proteins such as inflammatory cytokines & enzymes, cell survival & proliferation linked gene products and transcription factors (Liu and Chen, 2013).

Cytostatic properties of curcumin

Cytostatic properties of curcumin were investigated in MCF- 7 breast cancer cells where G2/M arrest & micronucleation were found to be the major results induced by curcumin. Curcumin executes this effect by creation of aberrant, monopolar spindles that are impaired in their ability to segregate chromosomes (Holy, 2002).

Effect of curcumin on protein kinases

Breast cancer is found to be associated with increased expressions of several protein kinases such as HER2, HER1, EGFR etc. (Witton *et al.*, 2003). Studies revealed that low doses of curcumin can downregulate the HER2, CDK, SkP2 expressions in MD-MB-231 cells and P27 is found to be upregulated in associated case (Sun *et al.*, 2012). Furthermore, Curcumin inhibits generation of reactive oxygen species and -Jun NH_2-terminal kinase (JNK) pathway (Somasundaram *et al.*, 2002).

Antiangiogenic activity of curcumin

Angiogensis i.e. blood vessel formation is essential for tumors and metastatis (Folkman, 2001). Curcumin has been reported to act as anti angiogenic factor by serving as the suppressor of proliferation of human vascular endothelial cells in vitro.

In vitro, Curcumin inhibits the proliferation of human breast carcinoma cells in estrogen dependent manner – positive in MCF–7 cells and the effects are louder in estrogen containing media and also when 17–β estradiol is used exogenously. In ER- positive MCF-7 cells, curcumin prohibits the expression of genes like pS2 and TGF-β in estrogen dependent manner. Reduction of 17–β estradiol induced ERE CAT activities has also been reported. Non estrogen dependent anti invasive effects of curcumin are also observed in ER – negative MDA–MB-231 breast carcinomas and appear to be exerted through effector regulatory molecules of TIMP-1 and MMP-2. Curcumin has been reported to reduce the transcript levels of major angiogenesis factors VEGF and b- FGF in ER- negative MDA-MB-231 cells (Shao *et al.*, 2001).

It is reported in recent studies that curcumin along with metformin inhibit angiogenesis (Farajzadeh *et al.*, 2017).

Synergistic effects of curcumin

Curcumin has been reported to show synergism with various synthetic as well as natural agents for the treatment of different ailments. **C**urcumin and piperine, individually and in combination can show remarkable results in inhibiting breast cancer cells completely at concentration 10 μM and also prevented mammosphere formation and percentage of ALDH+ cells at the same concentration as reported by Madhuri Kakrala et al (2010).

Curcumin derived from Turmeric and genistein from soyabean (both non toxic) shows a synergistic effect leading to total inhibition of proliferation of estrogen positive MCF- 7 cells induced by a mixture of pesticides & 7- estradiol (Verma *et al.*, 1997).

Curcumin is reported to show anticancerous effects synergistically with phosphatidylcholine (meriva) in human breast cancer cells. Phosphatidylcholine is reported to reduce the expression of MMP- 9 in xenograft model in which mammary gland tumor cell line (ENU1564) was introduced into the mammary fat pad of athymic nude mice where curcumin or meriva was administered orally. The cancer and lung metastasis were examined grossly, microscopically, and immunohistochemically (Ibrahim *et al.*, 2010).

Wichitnithad W with coauthors concluded that curcumin when conjugated with monomethoxy polyethylene glycol with carboxylic ester spacers, shows cytotoxicity against four human cell lines including MCF-7 breast cells. Results suggest that prodrugs formed by mono-PEGylation of curcumin are stable in buffer at physiological pH, Curcumin is readily released in human

plasma, and exhibits antitumor activity (Wichitnithad *et al.*, 2011).

Studies done by Zhou QM *et al.* (2009) suggests that Mitomycin C (MMC) when used with curcumin, not only show significant reduction in weight loss, improvement in kidney function and bone marrow suppression but also inhibited DNA cross-linking mediated by glucose regulatory protein (GRP58) and inhibition of GRP58 through the ERK/p38 MAPK pathway was induced by synergistic effect of mitomycin and curcumin. This process fairly reduced the side effects of MMC. Chung *et al.* (2015) reported that curcumin and epigallocatechin gallate together function as anticancer agents for inhibiting breast cancer stem cell phenotypeby downregulating STAT3 and NF-kB signalling on breast cancer cell lines, MDA-MB-231 and MCF-7 transfected with HER2.

Recent studies have reported that combination treatment of metformin and curcumin against EMT6/P mice breast cancer cells, inhibited tumour cell proliferation and growth significantly by reducing VEGF expression, inducing apoptosis without Trp53 & catalyzing Th2 immune responses without showing any toxicity (Farajzadeh *et al.*, 2017).

Curcumin reduced radiation dermatitis severity in breast cancer patients receiving radiotherapy (Ryan *et al.*, 2013).

Curcumin loaded nanoparticles

Yallapu et. al (2012) have formed curcumin loaded magnetic nanoparticles (MNPs) which exhibits potential anti tumour activity in MDA-MB- 231 cells. These nanoparticles have superior imaging & magnetic targeting ability.

Studies also suggested that the careful delivery of nano technology based formulations of curcumin to cancers may enhance the chemopreventive and chemotherapeutic effects (Liu and Zhiwei, 2013).

A recent study revealed that curcumin loaded PLGA-PEG nanoparticles have an inhibitory effect on the MCF-7 human breast cancer cell line to a greater degree than pure curcumin (Tabatabaei *et al.*, 2016).

Inhibition of apoptosis

Tissue culture studies shown that curcumin inhibits camptothecin-, mechlorethamine-, and doxorubicin-induced apoptosis of MCF-7, MDA-MB-231, and BT-474 human breast cancer cells. Cyclophosphamide- induced tumor regression is also significantly inhibited in vivo model (Somasundaram *et al.*, 2002). Ramachandran *et al.* (2002) have shown that curcumin inhibits telomerase activity by downregulating hTERT mRNA expression in breast cancer cells in MCF-7 cell line.

On comparison of MCF-10 A & MCF-7 (TH) cell lines, it was found that although both cell lines accumulated similar amount of curcumin, a higher % age of apoptotic cells was induced in MCF-7 (TH) as compared to very low %age of MCF-10 A. Reduced expression of Ki67, PCNA, and p53 mRNAs was found in MCF-7 cells. MCF-10 A showed downregulation of p21 mRNA & upregulation of BAX mRNA expression. Thereby Ramchandran et. al concluded apoptosis to be the major tumour inhibition pathway for curcumin (Ramachandran and Wei, 1999).

CONCLUSION

The marvellous ways in which curcumin acts as anticancer remedy alone as well as in combination with other synthetic drugs, phytochemicals and therapies makes it a wonder drug (Shao *et al.*, 2002; Siddique *et al.*, 2010; Yu *et al.*, 2007). Curcumin arrests cancer at various stages ranging from transformation, proliferation as well as metastasis. Owing to its ubiquitous abilities, research is on way to improvise the solubilising and stabilising properties of curcumin (Liu and Chen, 2012). Newer techniques of extraction of curcumin in purest form are being developed (Kulkarni *et al.*, 2012). Improved ability of drug delivery through nano particles is being tried to facilitate sufferers of breast cancer and cancers in general.

CONFLICTS OF INTEREST

The authors declare that they have no potential conflicts of interest.

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