Review Article

ERA'S JOURNAL OF MEDICAL RESEARCH VOL.6 NO.2

DOI:10.24041/ejmr2019.142

CURCUMA LONGA: THE GOLDEN SPICE, POWERFUL ANTICANCER AGENT IN BREAST CANCER TREATMENT

Esha Sarkar, Aparna Misra, Rumana Ahmad, Abbas Ali Mahdi*

Department of Biochemistry

Era's Lucknow Medical College & Hospital, Sarfarazganj Lucknow, U.P., India-226003

King George's Medical University, Lucknow, U.P., India-226003

Received on : 18-11-2019
Accepted on : 19-11-2019

Address for correspondence

Dr. Aparna Misra
Department of Biochemistry
Era's Lucknow Medical College & Hospital, Lucknow
Email: draparnamisra@gmail.com
Contact no:9452242158

ABSTRACT

Various experiments have proved that *Curcuma longa* (CL), the Golden Spice of our kitchen, exibits anticancer effects to inhibit the uncontrolled cell division and metastasis of carcinoma cells, by the cell cycle arrest and finally promote to programmed cell death. In particular, CL exhibits the most powerful phytocompound to affect human breast cancer, the most prevalent type of cancer among the women, throughout the world. The main compounds present in CL can be classified as Curcuminoids and Non-curcuminoids, which shows the anticancer, anti-inflamatory functions for cancer cells. It helps in powerful inhibition in low concentration on breast cancer cell lines that exhibit the estrogen receptor negative(ER^-) and sensitizes the cells towards the anticancer drugs in low dose. Above all, it promotes the cells towards apoptosis, which does not have hormone receptor expression. Curcuminoids and non curcuminoids inhibit the excessive cell division of breast cancer stem cells (BCSC). Prevention of BCSC proliferation is performed by suppressing metastasis and adherence of the cells with one another, ultimately limiting tumor formation. The main powerful phyto-compound present in CL, curcumin, causes the yellow coloration of it, has drawn the main interest as the chemosensitizing agent also. Different mode of cancer cell targeting and apoptosis is discussed.

KEYWORDS: Curcuminoids, Non-curcuminoids, Curcumin, ER receptor, Breast Cancer Stem Cell (BCSC), Chemosensitizer.

INTRODUCTION

Cancer is an excessively-proliferative disorder which involves deregulation of different signaling pathways in the body like proliferation, angiogenesis, metastasis and apoptosis (1). Breast carcinoma is considered as the most prevalent carcinoma among female, affecting almost 2.1 million of females annually, results the highest number of deaths of women due to cancer. According to WHO, in 2018, it is statistically calculated that 627,000 females died because of breast carcinoma that is almost 15% of all cancer deaths among females (2). According to American Cancer Society, depending on mortality trend, it is estimated that near about 42,260 breast cancer deaths (41,760 female, 500 male) may be occured in 2019 (3). Breast malignant growth is the most well-known disease in ladies in India also, according to records, 14% tumors are breast tumors in ladies. On the bases of Globocan 2018 data, new cases registered on breast cancer is 1, 62,468 and estimated deaths is 87,090. Breast cancer is malignant and spreads to different parts of the body. It happens generally both in men and women, but female breast disease is more common (4). Almost 70% of breast carcinoma cells were characterized to be ER positive and would be treated with anti-estrogenic compounds (5,6). Recently, the exponentially growing results of cancer has depicted that applying a single molecule can rarely prevent the complex negative feedback loop formation in cancer cell-metastasis (7). That is why, the drug combinations are performed to target different cell-signaling pathways, considered as the most important chemotherapeutic drug designing to destroy endocrine-resistant breast cancer cells (8). Though, chemotherapeutic drug has been the most effective one for prevention of breast carcinoma and others as well, however, some of the normal cells are also destroyed during this method of treatment. Comprising a huge range of biological activities and less toxic to the healthy neighboring cells, some plant products started being applied as alternative treatments for various carcinomas, including breast one (9)

Curcuma longa (CL), an Indian household spice comes under the genus in the family- Zingiberaceae, present in

almost about 110 species, cultivated in tropical Asia and the Asia-Pacific regions. The greatest diversity of this genus studied in India, Myanmar and Thailand and extends to Korea, China, Australia, and the South Pacifics. CL has been found to be economically valuable, known as turmeric commercially in daily life (10). The main phyto-compound, Curcumin, a potent flavanoid has started being diversely studied for its anti-inflammatory, anti-cancer, anti-angiogenic, antioxidant and wound repairing activities because of its ayurvedic properties in Indian and Chinese research of medicine(11). Now-a-days, studies have also proved that curcumin, either separately or combined with other commercially used anticancer drugs, can efficiently trigger apoptosis in cancer cells. This has been found by its inhibitory effects to the proliferation of various tumor cells, both *in vitro* and *in vivo* (12).

Classification of Curcuma longa

Fig 1: Turmeric Image courtesy www.en.wikipedia.org

Kingdom:	Plantae
Division:	Tracheophyta
Class:	Lilliopsida
Order:	Zingeberales
Family:	Zingberaceae
Genus:	Curcuma
Species:	Longa

The main active phyto-compound present in CL is curcumin (curcuminoids), which is responsible for yellow coloration of the spice, turmerone, elemene (non-curcuminoids) (13)

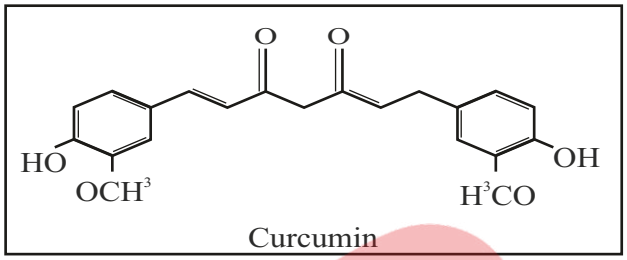

Fig 2 : Curcumin structure Image courtesy www.en.wikepedia.org

Throughout the long periods, Curcumin, of CL has started being applied in ayurvedic medicine for treating several diseases. Now-a-days it is considered as an efficient anticancer agent that helps in regulation of multiple cell signaling pathways, with the help of transcription factors (like NF-κB, STAT3, AP-1), receptors proteins (like HER2, IL-8, CXCR4), kinases enzymes (like JAK, EGFR), cytokines (like IL, TNF, MIP), enzymes (like MMP, GST, iNOS), and growth factors (like EGF, HGF, NGF) and so on (14).

The antiproliferative role of curcumin is attributed by regulating transcription factors, including NF-κB and protein kinases in cell cycle. In a malignant cell line, curcumin has been studied to exhibit an anti-proliferative potential by inhibiting the binding effect of NF-κB (15). Curcumin also exhibit the similar effects on AP-1, EGR, and B-catenin (16).

Proliferation

In case of breast carcinomas, the apoptosis inducing molecule, NF-κB exhibits a major role in cell proliferation (17). A study has reported that curcumin was efficient to decrease NF-κB expression(18) and down-regulate several cell-signaling procedures, triggering inflamatory cytokines, like CXCL1 and CXCL2, and enhances the expression of matrix metalloproteinase9 (MMP-9), urokinase plasminogen activator(uPA), uPA receptor(uPAR) and chemokine receptor 4 (CXCR4) (19). So, curcumin interferes in cell growth of breast cancer and invasion to other part of body through downregulating NF-κB signaling pathways (20). Some hormone regulatory factors can also induce the proliferation as well as the growth of breast cancer cells. Human Epidermal Growth factor receptor2 (HER2) and estrogen receptor (ER) are the members of this group. Another one study has been noted that the combined effect of curcumin and its analogues AS-KTC006 and AS-KTC021 could prevent some particular tyrosine kinase, performing as an antagonist against HER2 (21). Additionally,

curcumin would also be used for the enhancement of doxorubicin activity (chemotherapeutic drug) in low dose to prevent cytotoxicity in breast cancer cells (22).

In further studied, curcumin has been found to prevent the cell division in breast cancer by inhibiting some different trophic signaling processes, by showing the influency on fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC) through AMPK activation pathway (23). It is also found to inhibit breast carcinoma cell proliferation by the decreasing the synthesis of insulin-like growth factor 1 (IGF-1) (24).

Apoptosis

Curcumin has been studied to enhance breast cancer cell death by regulation of the apoptosis related gene expression. Lv *et al.*(25) applied microarray hybridization of total RNA for analyzing and characterizing the genes of human breast cancer cells. In MCF-7 cells, some genes viz.CRAF1, HPRT, HIAP1, MCL-1, BCL2L2, GADD45, NIP1, TRAP3, GSTP1, DAXX, PIG11, RBP2, PIG3, and JNK1 were found to get up-regulated in the study. On the other hand, genes TNFR, AP13, TNFb, TRAIL, SARP3, TRAIL-R2, TNFRSF5, and hTRIP were found to be down-regulated in presence of curcumin. Again it was noticed to influence in the process of apoptosis, by blocking pro-apoptotic pathways, Bcl-2 was found to inhibit the extrinsic apoptosis pathway (26). Induced by curcumin, the antiapoptotic protein Bcl-2 increased, while the pro-apoptotic protein Bax decreased, leading to an elevated Bax/Bcl-2 ratio (27). In a study researchers have found the mode of action of curcumin on triple-negative breast cancer cells (ER^-, PR^- and $HER2^-$) to significantly inhibit the phosphorylation of endothelial growth factor receptor (EGFR) and down-regulate the signaling components, like- ERK1/2 (28). Recent studies have proved that curcumin enhances the TNF-induced apoptosis by activating its ligand (TRAIL) and finally triggers apoptosis also in TRAIL-resistant breast cancer cells (29). Other than that, telomerase activity was also found to get prevented by curcumin by downregulation of the expression of hTERT (telomerase reverse transcriptase) (30).

Cell Cycle Arrest

The cell division process can be divided into four stages- G1, S, G2, and M. Various regulators take part in propagation from one stage to the next one (31). Cyclin B1, a regulator, participating in the cell cycle at M-stage, whose over-expression causes tumor. It helps to propegate from the G2 phase to M phase. And mRNA and protein levels of cyclin B1 are found to get decreased after 24 h of treating with curcumin in cancer cells. A flow cytometry study has shown that small-cell lung cancer (SCLC) cells were arrested after curcumin application (32). Cyclin-dependent kinase2 (CDK2) is the second regulator, which leads cells from G1 to S phase in the cell cycle propagation, is also found to be regulated by curcumin. Curcumin inhibits CDK2 activity *in vitro* process and decreases the rate of cell division in colon cancer cells in dose-dependent manner. Higher concentration of sh-CDK2 has been found to transfect the cells of the colon cancer cell line HCT116 and arrested in the G1 phase in control cells (33).

Curcumin found to work on human breast cancer cells by helping in cell cycle arrest at the G2-M phase and late S phase in MCF-7 cell- lines. Curcumin led to an obvious increment of the G2-M phase duration (34). Ke et al (35) has proven in their study that increasing the doses of curcumin promotes better cells arrest in the G2 phase and late S phase is enhanced with the. Curcumin also acts similarly to Aurora-A SiRNA (small interfering RNA), leads to the formation of monopolar spindles and helps in S and G2-M arrest, thus the cell divisions get reduced in MCF-7 cells (36).

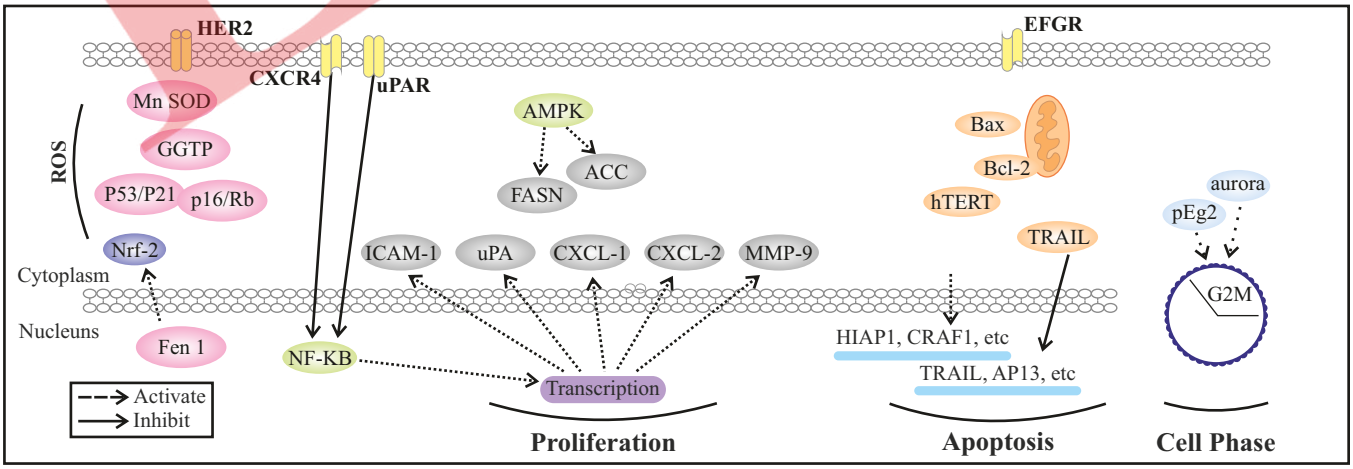

Fig 2: Cell signaling Pathway Regulated by Curcumin on Cell-proliferation, Apoptosis, Cell Phase Arrest, ROS and HER2, Human Epidermal Growth Factor Receptor 2 (image Courtesy: Wang Y. 2016 (63)

Reactive Oxidative Stress

The anticancer effects of drugs are mainly determined by the rate of apoptosis. Sometimes apoptosis can also occur by activating the intrinsic or mitochondrial pathways. It can be regulated either by changing in the membrane potential or protein released into the extracellular matrix. Curcumin can induce apoptosis by interfaring with reactive oxygen species (ROS) (37,38). As an example, curcumin increases the concentration of the ROS and superoxide radicals (SOR) in case of human lung cancer (adenocarcinoma epithelial) cells. Curcumin was found to boost up the formation of ROS, which triggers the activation of apoptotic pathways in cancer cells (39). Curcumin increases the intracellular calcium concentration, which helps in apoptosis by changing cell membrane poetical (40, 41)

Besides that, ROS induces cancer by the mutations of DNA. In some cases ROS was observed to kill tumor cells. Curcumin has been reported to down-regulate the expression of Flap endonuclease 1 (Fen1) (over-expression of which causes breast cancer development, by increasing the concentration of nuclear factor 2–related factor, Nrf-2), prevents breast cancer cell proliferation (42, 43). On the other hand, curcumin has been found to increase the scavenger elements, viz. catalase and manganese superoxide dismutase (MnSOD) (44). Breast cancer can be prevented by increasing ROS in cell. Accumulation of ROS leads to breast cancer inhibition by P53/p21- and p16/Rb-mediated process (45). A study has proven a lower rate of gamma-glutamyl transpeptidase (GGTP) activition also in oxidation-resistant cell line, after curcumin treatment (46).

Metastatic Growth Factor

Curcumin is reported to suppress the breast cancer cell growth through immuno-supression. A recent article has observed curcumin to prevent the loss of T-lymphocyte cells and prevented immuno suppression caused by cytokines, with transforming growth factor beta (TGF-β) and interleukin 10 (IL-10) in case of carcinogenesis (47, 48). Specifically, in presence of Curcumin, exosome-mediated inhibition of NK cells was found to be partially reversed by degradation of ubiquitin–proteasome system (49). Additionally, MEK/ERK signaling pathway was also found to get inhibited in presence of curcumin and finally suppresses TGF-β-induced cell proliferation (50). Curcumin has also been studied to affect metastatic factors in two ways inhibit (Fig. 3). Firstly, by inhibiting the factors participating in angiogenesis, such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), in ER^- breast cancer cells (51, 52). In a study Carroll *et al.* has observed curcumin to suppress the angiogenic factor secretion (like-medroxyprogesterone acetate) Secondly, by affecting metastasis factors through invasion (53).

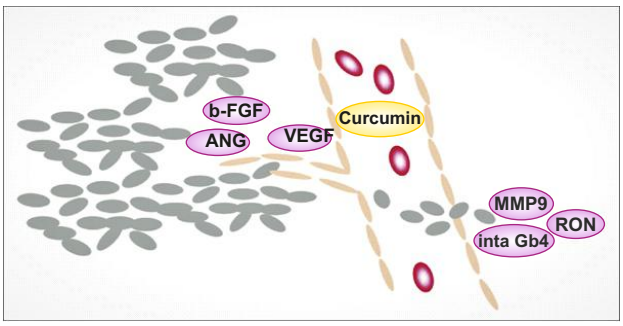

Fig 3: Curcumin Targets VEGF, ANG, b-FGF, MM9 and RON (Image Courtesy: Wang Y. (2016) (63)

Oncogene And Tumor Suppressor Gene

In some unfavorable conditions, proto-oncogene gets transformed to active oncogene and promotes the normal cells to become cancerous. In a study Hong *et al*. has found over-expression of the p185neu tyrosine kinase encoding gene, erbB2/neu (HER2) causes breast cancer. It was also studied that curcumin inhibits the over-expression of this gene (54). Simultaneously, curcumin has also been found to activate tumor suppressor genes (such as maspin and p16 INK4A in invasive ductal carcinoma and cancer-associated myofibroblasts) which prevents the normal cells transforming into cancerous (55)

Telomerase Effect

Cancer cells have a property to regain the ability of the telomeres. Curcumin is found to prevent cancer cells by affecting telomerase. (56) in brain tumor cells (57) and human leukemia cells (58,59) in a dose-dependent and time-dependent manner.

Curcumin As Chemosensitizer For Future

Now-a-days, Curcumin is treated as a chemosensitizing agent with the therapeutic drugs like Doxorubicin and Cisplatin to reduce its toxicity and side effects to the neighborhood healthy cells. It can work as a chemosensitizer with some other anticancer compounds also for treating multi-drug-resistant in breast cancer cells. Limtrakul *et al.* has investigated the effects of tetrahydro-curcumin on P-glycoprotein (ABCB1/P-gp) and ATP-binding cassette (ABC) channel proteins, multidrug resistance protein 1 (ABCC1) and mitoxantrone resistance protein (ABCG2/MXR). Where the binding with these channel proteins lead to the efflux of anticancer drugs and inhibits the drug to the cancer cells to work. Curcumin can work on the cannel proteins and helps to overcome drug resistance in cancer cells (60,61,62,63).Although All the parts of many tree like its bark, flowers, leaves, twigs, fruits, roots, seeds, sap and gum are employed in customary native medication as a source of numerous therapeutic agents are also documented in literature but curcumin is easily available option.(64)

CONCLUSION

That we have already seen the multi-purpose activity of Curcumin (*Curcuma longa*) in breast cancer cells which leads to apoptosis by undergoing several signaling pathways. It is also tested that Curcumin can work as a chemosensitizer with commercial drugs to minimize the huge toxic effect on the healthy cells of the body. So our future purpose of this article would be the application of the different components of CL to increase chemosensitivity towards the cancerous cells with least harm to the non-cancerous ones.

ACKNOWLEDGEMENT

Authors are thankful to the Department of Biochemistry, Era University, Lucknow.

I would also thank to Miss Afreen Khan and Dr. S. M. Shiraz Rizvi for their constant support and encouragement.

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How to cite this article : Sarkar E., Misra A., Ahmad R., Mahdi A. A. Curcuma Longa: The Golden Spice, Powerful Anticancer Agent In Breast Cancer Treatment. Era J. Med. Res. 2019; 6(2): 124-130.