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Effect of curcumin acting as an antidote against breast carcinoma- A review

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Abstract

Breast cancer is a complex disease caused by irregular cell growth and proliferation. Women are more likely to suffer from it than men. Even with advances in technology and treatment strategies, therapeutic intervention is still warranted. Curcumin is an active bio-available compound found in turmeric, shows some anticancer properties. Cancer cell lines treated with curcumin showed increased levels of Bax, an apoptosis activator, and p53 DNA-binding activity. As apoptotic genes are expressed, TRAP3 and MCL-1 are upregulated, whereas TRAIL, AP13 are downregulated by breast cancer. miR-19a, miR-19b proteins are upregulated, and miR-19 is regulated by downstream expression. Curcumin exhibited its effect through different signaling pathways like nuclear factor kappa B(NF-kB) pathway, 3(STAT3) pathway, Mitogen activated protein kinase (MAPK) pathway, Wnt (Wingless-Int)/β-catenin signaling pathway etc. In this review, the role of curcumin as an antidote against breast cancer is explored with a focus on some specific genes and pathways involved in the progression of breast cancer.

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Introduction

Breast Cancer is easily treated carcinoma in woman. There is a chance of survival if it is found early. To start, a little lump that develops on the breast area, changes in breast size, and irregularities in the nipple are all signs of breast cancer. Mastectomy, chemotherapy, and radiation are still used to treat breast cancer.

Curcumin naturally derived from *Curcuma longa* (Turmeric) plants. It is a viable choice for cancer research since it possesses antioxidant, anti-inflammatory, and anticancer actions (Bordoloi *et al.*, 2018). In numerous preclinical and clinical studies, curcumin has shown promise as an adjuvant treatment option for multiple cancer types, including breast cancer. It demonstrates different signaling pathways, including the Wnt(Wingless-Int)/β-catenin signaling system, the nuclear factor (NF-kB) pathway, and the mitogen activated protein kinase (MAPK) pathway (Prasad *et al.*, 2009; Zhou *et al.*, 2011; Wang *et al.*, 2016). SNAIL, DNMT3b, TRAP, MCL-1, TRAIL, and API3 are examples of regulatory genes that curcumin can affect the expression of (Dong *et al.*, 2012; Vesuna *et al.*, 2012; Wang *et al.*, 2016). Understanding curcumin's effects as a treatment for breast cancer, especially when histone deacetylase (H-DAC) inhibition is present, holds potential for the creation of novel therapeutic modalities. In order to explore mechanisms and relevance of curcumin's role as an antidote in the treatment of breast cancer, this review study aims to provide a detail analysis of the current body of scientific literature.

Recent statistical analysis reveal that breast cancer has surpassed lung cancer as the most often diagnosed malignancy, with over 16 million people globally currently battling the disease (Roser *et al.*, 2015; Sung *et al.*, 2020.) According to scientist Lukasiewicz *et al.* (2020), breast cancer shows an immense impact on other prevalent form of cancer. Although routine clinical practice calls for screening and surveillance to aid in the early detection of breast cancer. In recent years, curcumin, a bioactive ingredient derived from the spice turmeric, has become a promising treatment for breast cancer. Curcumin is the most active bio-available products found in turmeric. Its pharmacological effects include anti-proliferative, apoptotic induction, anti-angiogenic, anti-inflammatory, and antioxidant capabilities. It also has various health benefits. It is a potential agent in breast cancer treatment and cost effective (Bordoloi *et al.*, 2018). P53 tumor suppressor genes which have the ability to regulate different metabolic activities like apoptosis induction, DNA repair and cell cycle arrange. More than half of human tumors no longer benefited from p53's protective effects, which led to apoptosis resistance and unabated growth (Kim S *et al.*, 2016). Mutant p53 is found in more than 50% of all human cancers, making it a suitable target (Parrales *et al.* 2015). Down-regulation of ERK (extracellular signal-regulated kinases)1/ERK2 mitogen-activated protein (MAP) kinases was observed in CUR-treated cells (Masuelli *et al.*, 2013), and enhanced G1 arrest was seen when mitomycin C (MMC) was added, p38-MAPK pathway inhibits abrupt proliferation of cancer cell and cycle progression both *in vitro* and *in vivo* (Zhou *et al.*, 2011). The AMPK, alpha-COX-2 pathway corelates anti-proliferative impacts of curcumin (Lee *et al.*, 2009). Breast cancer development has been linked to inappropriate activation of the Wnt (Wingless-Int) /β-catenin signaling pathway, as well as subsequent overexpression of β-catenin driven downstream targets c-MYC (Myelocytomatosis oncogene) and cyclin D1 (Benhaj *et al.*, 2006; Mohammadi -Yeganeh *et al.*, 2016). In breast cancer cell lines, curcumin showed to reduce the expression of numerous Wnt/β-catenin pathway elements, including cyclinD1 (Prasad *et al.*, 2009). ERK (Extracellular Signal-regulated Kinase) activates curcumin that have the ability to enhance caspase dependent apoptotic regulation in breast carcinoma. Through the Bcl-2 pathway, this co-treatment caused autophagic cell death (Wang *et al.*, 2016).

BRCA1 is well known DNA repair protein that produced more quickly and is phosphorylated more frequently when curcumin is present. According to (Rowe *et al.*, 2009), BRCA1 cytoplasmic retention

hinders DNA repair and results in cell death. An important factor in concern with generation of tumor resistance and carcinogenesis is the silencing of genes by promoter hypermethylation. For instance, BRCA1 promoter CpG island hypermethylation has been discovered, for example normal BRCA1 tumor supressor gene generously suppressed in some non-familiar breast and ovarian cancer (Choudhury *et al.*, 2016) and is connected to enhanced cancer invasiveness and mortality (Xu *et al.*, 2008). Additionally, 20–60% of sporadic TNBCs and 11–31% of sporadic breast tumors have been found to have BRCA1 promoter methylation (Xu *et al.*, 2010; Sharma *et al.*, 2014). In a different instance, ER plays a crucial role in regulating transcription factors that control mammary gland development processes such cell division (Carroll, 2016). IGFs, or insulin-like growth factors, are effective mitogens for many different types of cancer cells. Breast cancer development has been connected to the IGF-1 system including IGFs (IGF-1 and IGF-2), the IGF-1 receptor (IGF-1R), and IGF binding proteins (Singer *et al.*, 1995). Activation of curcumin downregulates IGF 1 curcumin dampens IGF-1-stimulated breast cancer cell growth and reverses IGF-1-induced apoptosis resistance (Xia *et al.*, 2007). Curcumin decrease the microtubular instability of breast carcinoma inhibiting P53 depended apoptotic regulation activate mitotic checkpoints and delaying the passage of the mitotic cycle from metaphase to anaphase (Banerjee *et al.*, 2010).

Numerous impacts of curcumin on gene expression have been shown. It can activate tumor suppressor genes, which help regulate cell growth, and suppress oncogenes, which promote the progression of cancer. Inflammation, angiogenesis (the growth of new blood vessels), and metastasis (the spread of cancer cells) are other processes in which curcumin can affect gene expression. Following its translocation into a cancer cell's nucleus, curcumin activates p53 (Xu *et al.*, 2016). In BC cells, curcumin also promotes the expression of genes involved in apoptosis such as TRAP3 and MCL-1 while suppressing the expression of other genes such as TRAIL and AP13 (Wang *et al.*, 2016).

Curcumin enhance P53 regulation (Talib *et al.*, 2018). Curcumin increases the levels of the proapoptotic proteins Bax and p21 while decreases the levels of the antiapoptotic proteins B cell lymphoma-2 (Bcl-2) and p53 in another human BC cell line (MDA-MB-231) in a dose-dependent manner. The latter result is in opposition to multiple other research' findings that curcumin causes apoptosis via p53-dependent Bax in a human BC cell line (MCF-7) (Ramachandran *et al.*, 1999; Chiu *et al.*, 2009; Aggarwal *et al.*, 2003). Activity of curcumin against breast cancer is examined in this review.

Discussion

Curcumin inhibits tumor growth by three processes – 1) Cancer cell proliferation 2) Cancer cell senescence 3) Cancer cell apoptosis. These three processes can be happened by different signaling pathways and modulating agents.

Cancer cell proliferation

Cancer cell proliferation is the term used to describe the unchecked and rapid division of cancer cells within the body. Under normal circumstances, cell proliferation, a strictly regulated process, enables tissue development, repair, and regeneration. However, normal mechanisms that regulate cell growth and division are hampered in cancer, leading to abnormal cell proliferation. The oxygen content, availability of nutrients, and interactions with surrounding cells in the tumor microenvironment all have an impact on how quickly cancer cells divide. Tumors can continue to grow indefinitely due to signals that the tumor microenvironment can provide that promote cancer cell division and proliferation.

The cell cycle enhances cellular proliferative pathway through a variety of molecular interaction. It is easier for cancer to originate and spread when these regulatory systems are flawed. An essential goal of cancer treatment is to inhibit the cyclin-dependent kinases (CDKs) and cyclins that control cell cycle progression (Dickson *et al.*, 2009).

The stimulation of signaling pathways involved in cell proliferation has an impact on the maturation of cancer cells as well.

By reducing the levels of nuclear factor kappa β (NF-kβ), cyclin D, and matrix metalloproteinase-1 (MMP-1), curcumin inhibits cell proliferation in breast cancer (Liu *et al.*, 2009). In numerous breast cancer cell lines, including antiestrogen resistant ones, curcumin has been demonstrated to produce cell cycle arrest in both the G2/S and G2/M phases (Mehta *et al.*, 1997; Jiang *et al.*, 2013). ERK (Extracellular signal-regulated kinase)1/ERK2, mitogen-activated protein (MAP) kinase activity was down-regulated in cells treated with CUR (Masuelli *et al.*, 2013), and mitomycin C (MMC) increased G1 arrest, which inhibited cancer cell proliferation and cycle progression both in vitro and in vivo via the p38-MAPK pathway (Zhou *et al.*, 2011). The AMPK (AMP-activated protein kinase) alpha-COX-2 pathway may play a role in the antiproliferative effects of curcumin (Lee *et al.*, 2009).

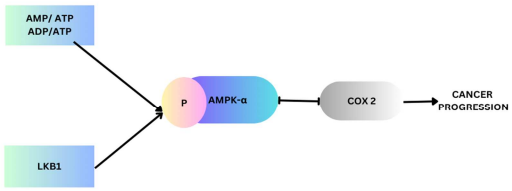

Fig. 1. AMPK pathway for cancer generation

According to research (Benhaj *et al.*, 2006; Mohammadi-Yeganeh *et al.*, 2016), inappropriate activation of the Wnt (Wingless-Int)/β-catenin signaling pathway, as well as contiuous overexpression of -catenin driven downstream targets c-MYC (Myelocytomatosis oncogene) and cyclin D1, is related to breast cancer development. Breast cancer has been associated with aberrant activation of the Wnt/β-catenin signaling system, which curcumin can target. In breast cancer cell lines, curcumin has been demonstrated to reduce the expression of numerous of Wnt/-catenin pathway elements, including cyclinD1 (Prasad *et al.*, 2009). Additionally, curcumin blocks the growth of breast cancer cells that are estrogen receptor (ER) positive using an ER-related route, possibly blocking the effects of 17- estradiol at the receptor level (Shao *et al.*, 2002).

Cancer cell senescence

Senescence in cancer cells is a permanent growth arrest that can be brought on by a number of cellular stressors or therapeutic actions. Senescence in cancer cells is characterized by a variety of traits. Senescent cancer cells have changed gene expression patterns, such as the overexpression of cell cycle inhibitors and tumor suppressor genes. This senescence can be prevented by the hTERT gene and p16 protein (Patel Priyanka *et al.*, 2016; Abou-Bakr Amany *et al.*, 2013).

The 40 kb DNA region containing the human telomerase reverse transcriptase gene (hTERT) comprises 16 exons and 15 introns (Cong *et al.*, 2002). A 130kD functional TERT protein is created by this gene from a 1132 amino acid polypeptide (Ly H., 2011). The four primary functional domains of hTERT are the N-terminal regulatory domain, the RNA binding domain, the reverse transcriptase domain, and the C-terminal dimerization domain (Kelleher *et al.*, 2002). Two G4 structures stacked end to end and connected by a hairpin loop that serves as a silencing element make up the hTERT core promoter region (Kang *et al.*, 2016; Song *et al.*, 2019). The hTERT G4-forming region is changed in several malignancies, resulting in a lack of G4 development and subsequent hTERT activation. Even in the presence of these mutations, Kang *et al.* and Song *et al.* showed that small molecule ligands that refold the hTERT promoter G4 result in transcriptional inhibition of hTERT and cancer cell death (Kang *et al.*, 2016; Song *et al.*, 2019).

The tumor suppressor protein p16, also known as cyclin-dependent kinase inhibitor 2A (CDKN2A), is crucial for controlling the cell cycle. It is encoded by the CDKN2A gene, which is found on chromosome 9p21. P16 functions as a negative regulator of the cell cycle by inhibiting the activity of cyclin-dependent kinases (CDKs) (Foulkes *et al.*, 1997). Breast cancers

with a poor prognosis have been associated with overexpression of the p16 protein (Hui *et al.*, 2000; Milde-Langosch *et al.*, 2001). One study (Palacios *et al.*, 2005) found that BLBC associated with BRCA1 gene inactivation expresses less p16 than BRCA2 gene-related carcinomas, which are more frequently ER positive. Additionally, BLBC and BRCA1-associated tumors were shown to have lower p16 levels than typical breast cancers in an analysis (Turner *et al.*, 2006).

Cancer cell apoptosis

Apoptosis, a dysregulated form of programmed cell death, occurs in cancer cells. The body's natural defense mechanism called apoptosis eliminates damaged or unwanted cells, including cancer cells. The apoptotic process goes through several stages.

According to (Elmore, 2007), curcumin inhibits both intrinsic and extrinsic apoptotic processes. Both p53-dependent and p53-independent mechanisms can result in curcumin-mediated apoptosis in breast cancer. Numerous signaling pathways are performed in the dose- and time-dependent induction of apoptosis by curcumin in breast cancer cells (Masuelli *et al.*, 2013; Ramachandran *et al.*, 2005; Lv *et al.*, 2014). It triggered apoptosis through a p53-dependent pathway, with Bax serving as a downstream effector (Choudhuri *et al.*, 2002; Moghtaderi *et al.*, 2017). By raising ROS, altering the mitochondrial membrane, and decreasing glutathione, curcumin-alone or in combination with arabinogalactan-increased apoptosis (Moghtaderi *et al.*, 2017). By inhibiting Bcl-2 (B-cell lymphoma 2) and activating caspase-3, it increase the viability of a murine mammary gland adenocarcinoma cell line, but it also increases the production of mitochondrial Ca2+ and reactive oxygen species (ROS), which together cause transition of mitochondrial permeability and apoptosis (Ibrahim *et al.*, 2011).The only cells that produced significant amounts of ROS were breast cancer cells, which damaged antiapoptotic proteins such phosphorylated p53 and phosphorylated Bad and caused triggered apoptosis (Patel *et al.*, 2015).

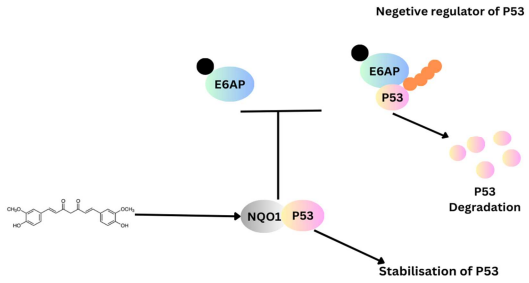

Fig. 2. P53 Dependent tumor supresive activity

Cells with weak homologous recombination repair mechanisms, such as BRCA1 and BRCA2, show higher levels of genomic instability, cell cycle arrest, and apoptosis after the stabilization of G4 structures (Zimmer *et al.*, 2016). In this scenario, stabilization of G4s hinders replication folding and causes single-stranded DNA gaps or breaks. Cell death results from the failure to repair this damage using the BRCA and non-homologous end joining pathways. This technique allows chemical CX-5461 to selectively kill cancer cells that lack the BRCA gene. (Kretzmann Jessica *et al.*, 2021). With and without chemotherapeutic drugs, BRCA1 significantly reduces cell viability (Choudhury *et al.*, 2016).

IGFs, or insulin-like growth factors, are effective mitogens for a variety of cancer cells. Breast cancer development has been linked to the IGF-1 system. This system includes IGFs (IGF-1 and IGF-2), the IGF-1 receptor (IGF-1R), and IGF binding proteins (Singer *et al.*, 1995). According to (Xia *et al.*, 2007) curcumin inhibits the IGF-1 axis, dampens IGF-1-stimulated breast cancer cell proliferation, and reverses IGF-1-induced apoptosis resistance at the transcriptional level.

Curcumin increases p53-dependent mortality by decreasing the microtubule instability of breast cancer cells, activating the mitotic checkpoint, and delaying the passage of the mitotic cycle from metaphase to anaphase (Banerjee *et al.*, 2010).

Both tumor initiation and tumor spread are mediated by CSCs. A crucial cell surface indicator for bCSCs is CD44.

It belongs to the STAT3-NFB signaling pathway's downstream genes. According to Chung *et al.* (2015) and Charpentier *et al.* (2014), a cellular component with high CD44 activity and increased levels of micro tentacles (McTNs) mediates the spread of cancer. (Chung *et al.*, 2015; Charpentier *et al.*, 2014). Cell reattachment during the metastatic cascade is facilitated by McTNs. Inhibiting STAT3 phosphorylation and impairing the connection between STAT3 and NFB in the nucleus are the effects of curcumin, either alone or in combination with epigallocatechin gallate (Chung *et al.*, 2015). As a result, CD44 expression is downregulated and the number of bCSCs decreases. The NF-kB, PI3K/Akt/mTOR, MAPK, JAK2/STAT3, and Wnt/-β catenin signaling pathways are most affected by curcumin's regulation of breast carcinogenesis, which has an anticancer effect.

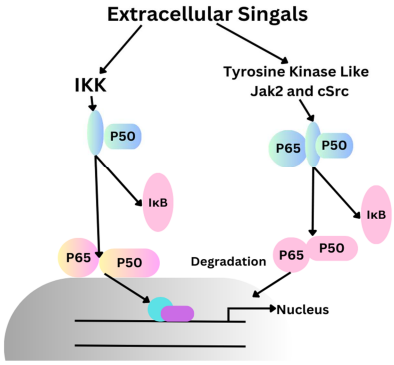

Fig. 3. Regulation Of NF- kB

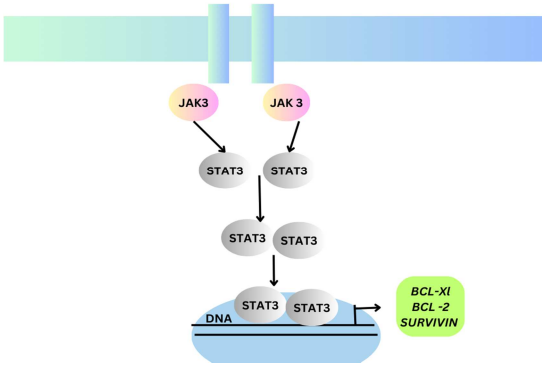

Fig. 4. JAK-STAT pathway Transcription factor regulators

Many breasts cancer forms, especially estrogen-negative and TNBC, have constitutive activation of the transcription factor STAT3 (Banerjee *et al.*, 2016).

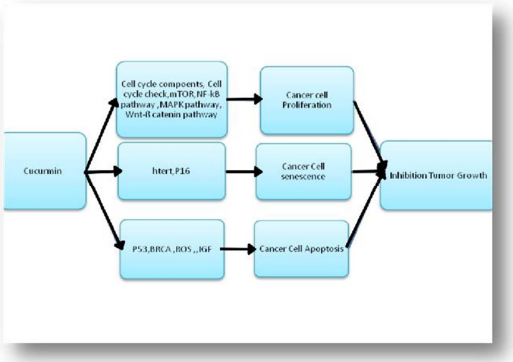

Fig. 5. Curcumin inhibits tumor growth

Conclusion

The comprehensive study highlights the enormous potential of curcumin as a breast carcinoma. Breast cancer's effect on the world's health persists, and finding effective treatment options is essential. Curcumin, a naturally occurring substance derived from turmeric, has a wide range of pharmacological actions and molecular mechanisms, making it a possible treatment for breast cancer.

Several cellular signaling mechanisms, such as the (NF-kB) pathway, Mitogen-Activated Protein Kinase (MAPK) pathway, Wnt (Wingless-Int)/β-catenin signaling pathway, etc. interact with curcumin to affect breast cancer (Zhou *et al.*, 2011; Prasad *et al.*, 2009; Wang *et al.*, 2016). Cell survival, proliferation, angiogenesis, and metastasis are all significant processes in the development of breast cancer, and pathways play crucial roles in each of these processes. By changing these pathways, curcumin exerts control over crucial cellular processes, slowing the growth and spread of tumors.

Curcumin also controls the expression and activity of genes linked to breast cancer, including SNAIL, DNMT3b, TRAP, MCL-1, TRAIL, and API3 (Dong *et al.*, 2012; Vesuna *et al.*, 2012; Wang *et al.*, 2016). These genes take involvement in critical cellular processes that support the development and spread of tumors.

By focusing on these regulatory genes, curcumin increases apoptosis, decreases DNA methylation, and inhibits the epithelial-mesenchymal transition.

Last but not least, curcumin has a wide range of impacts on breast cancer, including interactions with signaling pathways and regulatory genes, which point to its huge potential as a treatment for this fatal condition. To completely comprehend curcumin's therapeutic effects and clear the way for its inclusion in standard breast cancer treatment regimens, more research and clinical examines are needed. Due to its wide range of abilities and outstanding safety profile, curcumin exhibits tremendous potential as a useful addition to the arsenal against breast carcinoma, offering hope for better patient outcomes and a more promising future in breast cancer care.

Future scope

If the trial sessions of curcumin as an antidote will be increased in a broader spectrum in the near future, then there is a higher possibility, that curcumin can be used as an alternative treatment for breast cancer instead of chemotherapy which creates other health complications.

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