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REVIEW ARTICLE

Chemopreventive approach of Indian spice "Curcumin" in the treatment of breast cancer

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ABSTRACT

One of the primary concerns for women in good health is breast cancer. The most typical hazardous growth is this one. It spreads easily, and the clinical conditions are terrible. Bosom illness is the second-most common type of malignant tumor that regularly causes women to pass away in the U.S. bosom malignant growth is the most well-known disease among women worldwide, with 2.1 million cases reported in 2018 and more than 620,000 fatalities per year. Natural components are viewed as promising alternatives for the development of novel anti-tumor drugs. Curcumin, also termed diferuloylmethane, is a yellow pigment made by the turmeric plant, *Curcuma longa Linn*. It is the curcuminoid and polyphenol present in the plant's root that is most abundant. The antioxidant and anti-inflammatory qualities of curcumin have been demonstrated, and it is frequently utilized in traditional medicine and cuisine. Due to its sophisticated pharmacological capabilities of chemoprevention and anticancer effects, curcumin, the main component of turmeric, has been linked to the treatment of breast cancer. The morbidity or mortality of the disease have not been significantly decreased by current breast cancer treatment options such as surgery, radiation, adjuvant chemotherapy, or hormone therapy. The expansion, estrogen receptor (trauma center), and human epidermal development factor receptor 2 (HER2) pathways are all involved in the activity of curcumin in illness. In breast cancer cells, curcumin is also known to regulate microRNA, cell stage-related characteristics, and apoptosis. This study reviews recent research on the atomic targets and anticancer effects of curcumin in breast cancer.

Keywords: curcumin; chemotherapy; breast cancer; HER2

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1. Introduction

The second most lethal disease in the world, cancer is one of the most serious health conditions. In the United States alone, there were more than 609,000 cancer-related deaths and 1.73 million new cases in 2018. Although there have been many improvements in cancer therapy methods, the mortality rate has remained mostly unaltered and has not decreased over the years[1]. The ongoing advancements have, to some extent, prevented deaths and saved lives[2]. Breast cancer is known as the most common form of cancer among women worldwide which is commonly diagnosed as a malignant tumor. 25% of female malignancies worldwide have a higher prevalence in developed countries. Breast cancer ranks as the second highest cause of mortality among women. Curcumin is a natural product that is widely used as a dietary spice turmeric but it is also a polyphenol derived from herbal remedy[3]. For the prevention and treatment of

cancer natural products are put to use like phytochemicals and their synthetic conjugates. Researchers have claimed curcumin to be one of the important natural remedies for cancer[4]. Turmeric's active component, curcumin (diferuloylmethane), is a perennial herb called *Curcuma longa*. This polyphenol has a yellow color, is a main portion chemically connected to it, and contains curcuminoids. This has been a long-time ingredient in the remedies of nations like China and India. It has been demonstrated to be advantageous in a variety of ways, including its anti-inflammatory and antioxidant properties[5].

Curcumin's anti-carcinogenic properties in animals have been attributed to phorbol esters' and other carcinogens' prevention of the development of tumors. According to the published studies, the use of curcumin during radiation therapy for patients with breast cancer improved treatment outcomes for these patients, including preventing skin symptoms, reducing pain and suffering, enhancing their quality of life during treatment, and reducing delays or unwanted stops throughout radiation therapy. Curcumin can control several molecular targets and signaling cascades[6–14]. This golden spice is a promising drug for the treatment and prevention of numerous human illnesses because of its low cost, pharmacological safety, effectiveness, and wide range of molecular targets. Recent reports have explained well the anti-tumor property of curcumin in cancers of different body parts like the colon, forestomach, breast etc.[15]

2. Breast cancer

In Western countries it has been seen that breast cancer rates increase with age, the rate of increase is found to be higher for women up to age 50 years and a slight decrease after the age of 50 years. Also, it is seen that breast cancer is more common in upper-class women than in the lower class, who are unmarried, and women living in urban areas[16]. According to studies, women of the age group 55–64 are the ones most affected by breast cancer, and under the age of 40 very few women accounting for only 5% have been reported. However, it is also seen that the rate of increasing also decreases with menopause[17]. Breast cancer in women is the most prevalent type of cancer out of all the different varieties. It is the second most common reason for mortality in females. Estrogen receptor (ER) positive antiestrogens can be used to treat a significant portion of breast tumors[8,18]. Carcinogenesis, which has six key qualities, can occur in each cell, tissue, and organ, bringing about degenerative changes that cause a huge extent of malignancies. Apoptosis aversion, a boundless limit with regards to division, expanded angiogenesis, protection against development signals, enactment of own development signs, and metastasis are the principal processes that permit it to advance[9]. Deaths from breast cancer are reported more frequently (occurrence rate is about 88% higher) in Melanesia, Western Africa, Micronesia/Polynesia, and the Caribbean when compared to developed nations (Australia/New Zealand, Western Europe, Northern America, and Northern Europe). Breast cancer is thought to be the leading cause of death for British women between the ages of 40 and 55. Compared to married women, unmarried women experience it more frequently[19]. Breast cancer is more likely to occur if there is a family history of it. This might be a result of family members sharing comparable genetic and environmental characteristics. Women who have a first-degree family who has breast cancer are at a two to three times greater risk, and at a two to three times lower risk if they have a second-degree relative who has breast cancer[10,20].

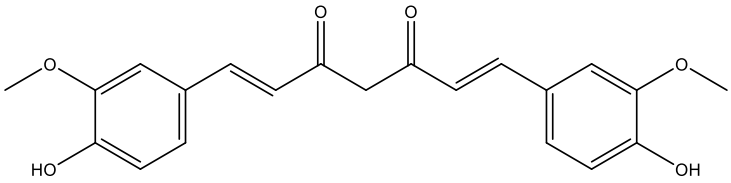
Development of breast cancer: How it occurs?

Breast cancer development is a sophisticated and complex process that is influenced by genetic and epigenetic changes as well as by the tumor microenvironment. The tumor microenvironment (TME) is a modified stroma that envelops cancer cells. It contains a variety of stromal cells, including fibroblasts, immunological cells, inflammatory cells, endothelial cells (ECs), pericytes, adipocytes, and cells originating from bone marrow[21–23]. Interactions between tumor and stromal cells via the secretion of proteins, cytokines, chemokines, and growth factors result in breast cancer development, progression, and metastasis creation. Angiogenesis, vasculogenic, chemotaxis, and coagulation must cooperate for a multi-step, intricate process known as metastatic development. Cancer cells develop a proangiogenic phenotype throughout this process,

which allows them to leave their original location, modify the extracellular matrix (ECM), intravagate into the blood, endure in circulation, and extravagate from blood arteries to colonize new organs. Regardless of the size of the initial tumor, it has been hypothesized recently that BC cells spread methodically during the early stages of the disease. Numerous cell types continuously release signaling molecules into the microenvironment as cancer develops, creating a complex web of communication that draws in new cell types to change the milieu around the tumor. Cancer is a disease in which cells mutate and divide uncontrollably, making genetically damaged cells more prone to uncontrolled division[24]. The hormones start functioning differently, the mammary gland starts to grow differently, and the risk of breast cancer is still present[25]. Contrarily, because they support mammary gland development, conditions like pregnancy, lactation, and polycystic ovarian syndrome (PCOS) may somewhat reduce the risk of cancer[26]. Different types of tumors can form in different places on the breast, but the majority of these tumors are caused by benign (non-cancerous) alterations in the breast. One non-cancerous condition that affects women's breasts is fibrocystic change. It manifests as lumpiness, areas of thickening, discomfort, or breast pain, as well as the creation of cysts (pockets of fluid accumulation), fibrosis (formation of scar-like connective tissue), and lumps[19]. Women are two to three times more likely to develop breast cancer if a first-degree relative has the disease than they are if a second-degree relative has the disease[16]. Compared to women who do not have any proliferative alterations in their breasts, women who have significant atypical epithelial hyperplasia in their breasts have a four to five times increased chance of having breast cancer[27].

3. Curcumin

Turmeric, a spice with a striking yellow color, contains curcumin, a hydrophobic polyphenol that is obtained from the roots of the *Curcuma longa* plant. 1,7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione is another name for it (**Figure 1**). Inflammatory mediators, growth factors, enzymes, carrier proteins, metal ions, tumour suppressors, transcription factors, oncoproteins, and cellular nucleic acids are just a few of the many compounds that curcumin may interact with to exhibits its health benefits[7].



Diferuloylmethane

Figure 1. Structure of curcumin.

It is known to exist in equilibrium with both its enol and tautomer and is a bis-a, b-unsaturated b-diketone. At pH 3–7, curcumin functions as a strong H-atom donor. It is well known that the cell membrane, as well as acidic and neutral water solutions, prefer the bis-keto form. It is also well recognized to possess anti-viral qualities against HIV. Curcumin has been used widely in Ayurveda, Siddha medicine, and traditional Chinese medicine for ages because it is recognized to have therapeutic qualities like antioxidant, analgesic, anti-inflammatory, antibacterial action, and anticarcinogenic activity (**Figure 2**). It is classified as generally safe (GRAS), according to the food and drug administration (FDA).

Clinical studies have demonstrated that people can safely eat up to 12 g of curcumin per day without experiencing any unfavorable side effects[28–41]. Just a few of the numerous substances that curcumin may interact with include inflammatory mediators, growth factors, enzymes, carrier proteins, metal ions, tumor suppressors, transcription factors, oncoproteins, and cellular nucleic acids. Curcumin is also known for its capacity to prevent certain viral infections[42].

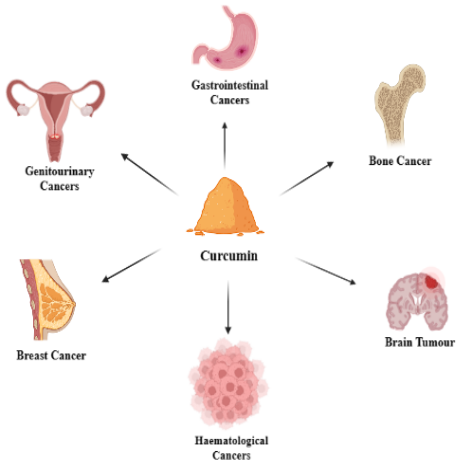


Figure 2. Action of curcumin in multiple organ system.

3.1. Pharmaceutical challenges of curcumin

Low natural mobility, poor absorption, rapid digestion, dormancy of metabolic products, as well as quick discharge and freedom from the body, are variables that contribute to a substance's decreased bioavailability in the body[26]. The bioavailability of a chemical inside the body can be influenced by a variety of factors, including low intrinsic activity, poor absorption, rapid metabolism and clearance, and inactivity of metabolic products. These components can make it more difficult for the agent to achieve its therapeutic goals. Curcumin has a high intrinsic activity and potential therapeutic efficacy for several illnesses, according to research. Curcumin's bioavailability is significantly hampered by poor absorption and quick metabolism, according to investigations on its distribution, metabolism, and excretion undertaken over the past three decades. Strong intrinsic activity and possible therapeutic usefulness for a number of illnesses make curcumin well known[43–47]. However, its poor bioavailability has been a major challenge in realizing its full therapeutic potential. Studies over the past three decades have shown that curcumin has limited absorption, rapid metabolism, and a short half-life, which severely restricts its bioavailability[7,9,13,14].

The limited absorption, tissue distribution, rapid metabolism, and short half-life of curcumin pose significant challenges in the development of curcumin-based therapeutics. Therefore, alternative strategies such as the use of novel delivery systems or the development of curcumin analogs with improved pharmacokinetic properties are necessary to improve the bioavailability and efficacy of curcumin as a therapeutic agent[48].

Oral curcumin is rapidly broken down in the liver and small intestine before being further broken down in the kidneys to become curcumin glucuronide, curcumin sulphate, and other methylated curcumins. The substances are then promptly eliminated by the body through the urine and feces. Curcumin's rapid metabolism and excretion significantly restrict its bioavailability. When curcumin is administered systemically, it quickly breaks down into metabolites including tetrahydrocurcumin, hexahydrocurcumin, and octahydrocurcumin, which are thought to have less biological activity than curcumin. The most common forms of curcumin found in blood are curcumin glucuronide, curcumin sulphate, and methylation curcumins[28,48–60]. These conjugates have a reduced biological activity and are swiftly eliminated through urine and feces. This causes a little concentration of free, bioactive curcumin to exist in the systemic circulation, which may be a factor in its low bioavailability and ineffectiveness[61].

3.2. Impact of curcumin on breast cancer

Molecular targets

The following methods explain how curcumin prevents the multiplication of breast cancer cells:

1) Curcumin can stop breast cancer cells from dividing and induce programmed cell death by activating the p53 gene, which controls cell cycle progression and cell death;
2) Changing the levels of various signaling proteins such as Ras, PI3K, Akt, mTOR, and Wnt/β-catenin;
3) Curcumin reduces the expression of certain transcription factors, which are proteins that control the transfer of genetic information from DNA to RNA;
4) Curcumin also inhibits the growth of tumors and angiogenesis, which is the formation of new blood vessels necessary for the growth and spread of tumors.

3.3. Effects of curcumin on CDK/cyclin complexes

In cancerous cells, loss of cyclin-dependent kinases (CDK) inhibitor expression is usually seen[62]. Overexpression of cyclin D1 because of dysregulated CDK action can prompt the improvement of forceful bosom disease because dysregulated CDK movement gives disease cells a development advantage[63]. Previous studies on mammary epithelial carcinoma cells have demonstrated that curcumin prevents cell division by impeding cyclin D1's ability to bind to CDK4, which eventually causes cyclin D1's activity to decline[64,65]. Curcumin slows down cell division in MCF-7 breast cancer cells by keeping them in the G1 phase. Curcumin induces proteasomal degradation of cyclin E and upregulates the CDK inhibitors p53, p21, and p27, resulting in cell cycle arrest. This effect can be partially reversed by specific proteasome inhibitors[66]. Cyclin E, a nuclear protein, interacts with CDK2, its catalytic partner, and the retinoblastoma (Rb) protein, and plays a vital role in the progression of the G1/S phase[67,68]. It looks probable that the downregulation of cyclin E by the proteasome and the overexpression of CDK inhibitors are what cause curcumin's anti-proliferative actions[67].

According to all reports, curcumin only inhibits cell growth in cells that have an overexpressed CDK 2 gene. In cells from bosom disease, curcumin suppresses the G2 phase of the cell cycle and initiates p53-subordinate apoptosis. Contrarily, curcumin disrupts CDK 4 and CDK 6's connection and prevents Rb from being phosphorylated in healthy human mammary cells, causing the cell cycle to stop at the G0 stage. Curcumin also slows the onset of the G2 arrest-associated p53-mediated apoptosis, which only impacts cells.

3.4. Effects of curcumin on the p53 pathway

One of the most crucial tumor suppressor proteins, p53 controls a variety of biological functions, such as cell division, DNA damage, and apoptosis[69]. Mutations in the p53 gene are present in numerous different types of human cancers. It regulates the transcription of the p53 gene, and when it is mutated, DNA checkpoints are lost, DNA repair processes are hindered, and uncontrolled cell growth occurs. As a result, cancer cells acquire immortality. Restoring p53 function is an interesting therapeutic strategy for the treatment of cancer[70]. Both p53-dependent and p53-independent methods can be used by curcumin to promote apoptosis in breast cancer cells. Curcumin causes cell cycle capture and starts p53-subordinate apoptosis in MCF-7 bosom disease cells[71]. The anti-proliferative characteristics of curcumin affect MCF-7 and TR9-7 cells that express p53, but not MDAH041 cells that do not need p53 or TR9-7 cells that express p53 at very low levels. Treatment with curcumin increases the expression of the pro-apoptotic protein Bax in MCF-7 cells. These data suggest that curcumin's anti-proliferative actions are the result of both p53-dependent and p53-independent mechanisms[15,71].

3.5. Curcumin's targets in Ras signaling

Ras is a small transmembrane protein that promotes guanosine triphosphate hydrolysis to help in signal transmission within cells. It is a member of the big GTPase family of enzymes. The three Ras proteins that are present in mammalian cells—K-, H-, and N-Ras—each play a particular function[72]. It makes sense to stop oncogenic Ras signaling while treating cancer. In-depth research has been done on curcumin's impact on oncogenic Ras signaling pathways. Curcumin causes the formation of reactive oxygen species in H-Ras-

transformed MCF-10A human breast epithelial cells. This upregulates the activities of Bax and caspase-3 while downregulating MMP-2 and Bcl-2[73]. Through a presumably somewhat equivalent mechanism, curcumin prevents Ras-transfected Witch 1 human adenocarcinoma cells from entering the G2/M phase of the cell cycle. This is achieved by upregulating Bax and extracellular signal-regulated kinase 1/2 expression while downregulating Bcl-xL expression. According to these results, curcumin may be a successful treatment for tumors that overexpress the Ras gene[74].

3.6. Curcumin's PI3K/Akt/mTOR signaling targets

The PI3K family of lipid kinases phosphorylates inositol phospholipids in the plasma membrane to produce the secondary messenger phosphatidylinositol-3,4,5-trisphosphate[75]. To cause Akt's translocation into the cytoplasm, PI3K and Akt interact to carry out cell cycle progression, and cell survival[75]. Many malignant malignancies commonly exhibit constitutive expression of PI3K and Akt, as well as the Glycogen synthase kinase 3 (GSK3) and phosphatase and tensin homolog are silenced. As a result, targeting PI3K/Akt-mediated signaling is attractive for the treatment of cancer[76,77]. Disease cells enact endurance pathways, like PI3K, Akt, and mTOR, notwithstanding against apoptotic pathways including Bcl-2, to support their development and expansion. Very metastatic breast cancer is likely to be difficult to treat without targeting the survival and apoptotic pathways. In breast cancer cells, curcumin modestly induces apoptosis; however, it more potently induces apoptosis when combined with the PI3K-specific inhibitor LY294002[78,79].

3.7. Focuses of curcumin in Wnt/β catenin flagging

Many human cancers have been linked to improper control and hyperactivation of Wnt/-catenin signaling. Constitutive stimulation of cell proliferation is caused by overexpression of catenin[80]. In order to treat cancer, it is appealing to target the Wnt/-catenin signaling pathway[81,82]. Curcumin inhibits Wnt/-catenin signaling to stop the cell cycle in G2/M cells in MCF-7 and MDA-MB-231 cells. In these cells, curcumin increases GSK3 expression while decreasing nuclear -catenin expression. As a consequence, cyclin D1, a downstream target of nuclear-catenin, is inhibited[83]. This shows that curcumin inhibits Wnt/-catenin signaling to provide its anti-cancer actions, at least in MCF-7 and MDA-MB-231 cells[83].

3.8. Targets of curcumin among nuclear factor-κB (NF-κB) Tran-scription factors

A family of transcription factors known as NF-B is implicated in inflammation and the immunological response. Triple-negative breast cancer (TNBC) is thought to be regulated by the NF-B pathway, with activation of NF-B signaling being closely linked to the pathogenesis of certain TNBCs, according to gene expression profiling studies. Inhibitors of NF-B (I-B) are a series of inhibitory proteins that bind to cytoplasmic NF-B, preventing the translocation of NF-B from the cytoplasm to the nucleus and inactivating NF-B and its downstream targets (**Figure 3**). Through transcriptional processes, NF-B initiates a few fundamental controllers of disease intrusion and improvement, including cytokines, chemokines, cell grip particles, and inducible favorable to fiery compounds[84].

Epithelial-mesenchymal transition (EMT) and breast cancer invasiveness have both been linked to NF-B[85]. As per various prior investigations, curcumin may stifle fiery cytokines such chemokine (C-X-C theme) ligand CXCL1 and CXCL2 by lessening NF-B union and thus other downstream flagging pathways[85]; NF-B-intervened bosom malignant growth obtrusiveness and EMT have all been connected to changes in the outflow of MMP-9, urokinase plasminogen activator (uPA), uPA receptor, intercellular attachment atom 1, and chemokine receptor. According to this strategy, curcumin probably suppresses NF-B signaling pathways, which in turn possibly prevents breast cancer from developing and migrating. The downregulation of target qualities, like Bcl-2, ornithine decarboxylase (ODC), and c-myc, which are ensnared in cell endurance and demise, can result from curcumin's concealment of NF-B enactment.

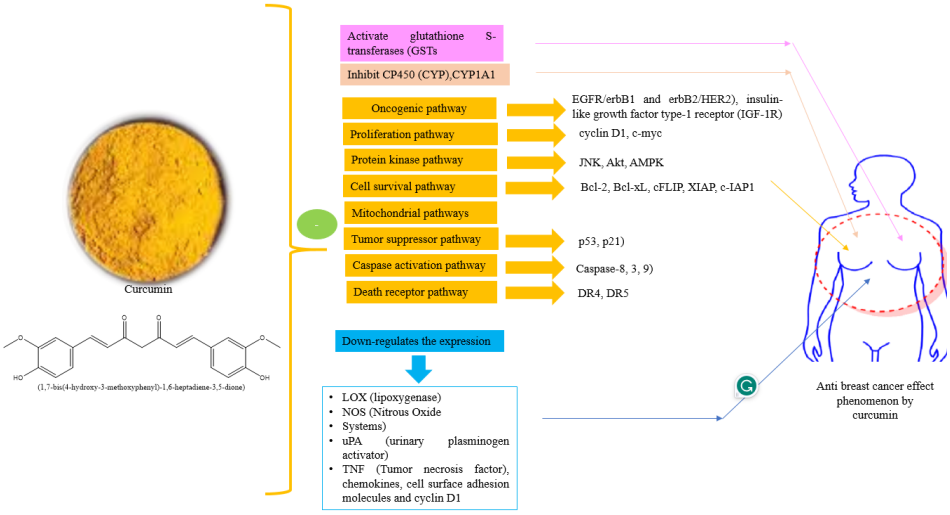


Figure 3. Mechanism of treatment of breast cancer by curcumin.

3.9. Curcumin's angiogenesis-related targets

Angiogenesis refers to the natural process by which pre-existing blood vessels are utilized to generate new blood vessels. Angiogenesis in tumors is essential for the development of cancer. By tumor angiogenesis, cancer cells obtain nourishment for their uncontrolled proliferation. Curcumin may suppress pro-angiogenic substances that tumor cells naturally produce, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor, to regulate tumor angiogenesis[38,86]. The growth of breast cancer tumors transplanted into hairless mice is hindered due to curcumin's ability to impede angiogenesis. Along with a reduced density of micro vessels, this outcome is related to the diminished expression of various VEGF isomers such as VEGF-A, VEGF-C, and VEGF receptor 2[40]. These findings support earlier research showing that VEGF function inhibition slows the development of breast tumors[40,87]. Osteopontin (OPN; also known as secreted phosphoprotein 1) was used to promote angiogenesis in nude mice after implanting them with MDA-MB-231 tumours. Curcumin obstructed the limiting of the NF-B/cyclic AMP-subordinate record factor ATF-4 and prevented OPN from expanding the degrees of VEGF[88]. This shows that curcumin controls OPN-induced tumour angiogenesis in breast cancer by acting as a powerful anti-angiogenic agent (**Figure 3**)[89].

3.10. Curcumin as chemoprotective agent

In breast cancer studies, it has been hypothesized that the mechanism of curcumin's inhibitory effect on the NF-B pathway functions by suppressing NF-κB expression and its translocation to the nucleus, inhibiting IKK activity, and IκB degradation, which reduces the expression of its target molecules, such as cyclin D1, IAP, surviving, EMT markers, etc.[90,91]. When curcumin targets different regulatory proteins, such as kinases, transcription factors, receptors, enzymes, growth factors, cell cycle, and apoptosis-related molecules, as well as miroRNAs, it has an anti-breast cancer effect. It has also been demonstrated to affect several important signaling pathways, including those for JAK/STAT, NF-κB, Wnt/-catenin, PI3K/Akt/mTOR, MAPK, apoptosis, and cell cycle pathways, that are implicated in the development and progression of breast cancer[92–94].

Curcumin interferes with the PI3K/Akt/mTOR pathway through its regulatory role on key molecule players of AKT, PTEN, HER2, and mTOR which may facilitate the inhibition of cellular growth, invasion, and metastasis in breast cancer[95,96]. This molecule is a potential breast cancer treatment agent due to its activity on a different pathway. Curcumin interacts with various signaling pathways to exert anticancer effect in hormone-independent breast cancer. The PI3K/Akt/mTOR pathway, JAK/STAT pathway, MAPK pathway, NF-B pathway, p53 pathway, Wnt/catenin pathway, as well as apoptotic and proliferative pathways, are the major intracellular signaling networks[97,98]. Tetrahydro curcumin, a curcumin metabolite, exhibited anticancer

properties by causing mitochondrial apoptosis and cell cycle arrest in human breast cancer cells by activating p38-MAPK.

4. Combination therapy and synergistic effect

When coupled with doxorubicin, paclitaxel, 5-fluorouracil, and cisplatin, curcumin is effective in the treatment of breast cancer. Since they fall under the categories of antitumor antibiotic, antimitotic, antimetabolic, and alkylating agent, respectively, these drugs are the most often used chemotherapies for clinical management and treatment of breast cancer patients. The MCF-7 MDA-MB-231 cell line exhibits increased sensitivity to doxorubicin when coupled with curcumin[96,99]. The combination of curcumin and doxorubicin increased the susceptibility of breast cancer cells to the drug, decreased the activity of breast cancer B4, increased intracellular levels of doxorubicin, and reversed chemoresistance in doxorubicin-resistant MCF-7 and MDA-MB-231 cell lines[100]. Curcumin and doxorubicin combination also Enhanced the sensitivity of BC cells to doxorubicin and Inhibited ABCB4 activity in doxorubicin-resistant MCF-7 and doxorubicin resistant MDA-MB-231 cell line[76]. In breast cancer cells, curcumin and paclitaxel promote caspase 3 activation, PARP breakage, and membrane integrity loss[101]. He synergistic effects of curcumin and 5-FU were independent of receptor state. Along with enhancing apoptosis, this combination also causes DNA fragmentation, increased caspase-3, -8, and 9 cleavage, and enhanced PARP cleavage. This combination also inhibits the Akt/PI3K and MAPK pathways, which are stimulated by 5FU, and it facilitates the induction of apoptosis[101,102]. Curcumin is also valuable to develop as an adjuvant for combination chemotherapy with existing medications to treat breast cancer since it may enhance the clinical use of chemotherapy agents in breast cancer therapy[103].

4.1. Nano formulation of curcumin

Poly-glycerol-malic acid- dodecanedioic acid (PGMD)/curcumin nanoparticles were successfully created utilizing both PGMD 7:3 and PGMD 6:4 polymer versions. By using the MTT assay, both curcumin 7:3 nanoparticle and curcumin 6:4 nanoparticle demonstrated potential anticancer activity against the breast cancer cell lines MCF-7 and MDA-MB 231. There was no discernible difference between the anticancer effects of both the nanoparticle formulations on breast cancer cell lines, despite the fact that the polymer PGMD 6:4 is more hydrophilic than PGMD 7:3[104]. Three distinct nonionic surfactants (span 20, 60, and 80) were employed to manufacture diverse curcumin-loaded noisome (Nio-Cur) in order to improve the cancer therapeutic effects of curcumin. Then, to prevent breast cancer, synthetic Nio-Cur was embellished with folic acid (FA) and polyethylene glycol (PEG). The outcomes demonstrated that the greatest preponderant endocytosis was present in the PEG-FA-modified noisome. PEG-FA@Nio-Cur is a potential method for the delivery of Cur in the treatment of breast cancer, according to in vitro research. Breast cancer cells took up the produced nano formulations and displayed characteristics of prolonged drug release[105].

Breast cancer was treated in vivo using immobilized curcumin as a photosensitizer agent on Fe_3O_4/SiO_2 nanocarriers. According to the in vivo findings, the implanted tumors in the control group grew gradually over the course of the entire treatment time. The average tumor volume reached 600 mm^3 at the conclusion of the treatment, which is a growth of 530% over its starting volume. This suggests that if no treatment was used, the breast tumor could grow significantly larger than its original size. A neoplastic disease with a high mortality rate in women. Due to their minimum invasiveness, photodynamic therapy (PDT) and photothermal therapy (PTT) have recently garnered a lot of attention. The PTT method relies on the production of hyperthermia, while the PDT method uses laser irradiation to activate a chemical called a photosensitizer. With the help of a combination of photodynamic and photothermal techniques, a dual-functioned nanocomposite (NC) was created in the current study to treat a breast cancer model in Balb/c mice[106]. The surface of curcumin nanocrystals (Cur-NC) was modified with hyaluronic acid (HA) to produce surface-reformed hydrophilic HA@Cur-NCs with protracted biodistribution. Additionally, in MDA-MB-231 cells that overexpress CD44,

HA@Cur-NC exhibits improved intracellular uptake, but reduced uptake when pre-treated with HA. The flow cytometry-verified apoptotic results imply that HA@Cur-NC could exhibit strong anticancer efficacy against MDA-MB-231 cells[107,108].

In order to create an electro spun nanofiber-mediated drug release system (CUR@MSNs/PLGA NFs), the natural antitumor compound curcumin (CUR) was incorporated into the mesoporous silica nanoparticles (MSNs). The CUR-loaded MSNs (CUR@MSNs) were then embedded into poly (lactic-co-glycolic acid) (PLGA) via a blending electrospinning process. This composition successfully treated breast cancer[109]. Radio sensitizing effect of curcumin-loaded lipid nanoparticles in also showed beneficial effect in breast cancer cells[110]. On the other hand, in breast cancer curcumin derivative WZ35 inhibits tumor cell growth via ROS-YAP-JNK signaling pathway[111].

4.2. Therapeutic approaches for the treatment of breast cancer

Breast cancer can be localized in certain women and not spread further. Typically, screening mammography detects these early breast cancers, which are largely curable with local or regional therapy alone[34]. Most women with initial breast cancer have subclinical metastases after receiving seemingly curative surgery (with or without radiation), and a significant proportion of patients later acquire distant metastases[112]. Breast cancer is typically identified by screening or with a symptom (such as pain or a palpable tumor) that demands a diagnostic examination. Smaller, less likely to metastasize, more amenable to breast preservation and restricted axillary surgery, and less likely to require chemotherapy tumors are discovered when healthy women are tested. This condition leads to decreased treatment-related morbidity and enhanced survival[27]. Radiotherapy is an essential part of breast-conserving treatment. In a recent randomized experiment, chemotherapy was given first when radiation and chemotherapy were both given postoperatively, boosting the chance of survival[112]. Surgery is still the mainstay of regional and local breast cancer treatment. In the early half of the 20th century, radical mastectomy originally described by William Stewart Halsted in 1894 was frequently used to treat breast cancer in women. Fischer et al. and Veronesi et al., who developed breast conservation surgery (BCS), reported that survival after lumpectomy and radiation therapy was comparable to that after mastectomy in the treatment of early breast cancer. Diagnoses of nonpalpable malignancies as a result of improved breast cancer screening called for the development of a localization strategy for surgical therapy[27]. A lumpectomy, re-excision, partial mastectomy, quadrantectomy, segmental excision, and extensive excision are all types of breast-conserving surgery. A different incision is used to extract the axillary lymph nodes for examination. A modified-radical mastectomy is the most usual method of removing breast tissue. This technique entails making an elliptical incision around the nipple and biopsy scar, removing that region, and then tunnelling under the skin to remove the breast tissue and several lymph nodes[113].

5. Advanced technology for breast cancer

5.1. Improvement in the collection of samples

Analyses based on liquid biopsies that concentrate on circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), tumor-educated platelets, and extracellular vesicles (EVs) in bodily fluids such as blood, urine, and saliva have been proposed to overcome the difficulties of techniques that have traditionally been used for identifying and validating clinical biomarkers[114–118].

5.2. Treatment through vaccine and immunotherapy: Clinical trials

Humans have long been protected by vaccines from both contagious and non-contagious diseases. As a result, the term “vaccine” is typically associated with the battle against infectious diseases. Immune responses are triggered by vaccinations, which causes them to work. This is accomplished by injecting attenuated/detoxified germs, viruses, or extracted poisons into a healthy person[119,120]. Immune surveillance is

the mechanism through which the immune system keeps living things in a condition of homeostasis. There has been a lot of research on how tumor cells evade the immune system[121]. These investigations led to the discovery that cancer immunoediting is the tumor cells' method of immune evasion. Antitumor immune reactions mediated by TME-antigens may be the reason[122,123]. Numerous substances, such as antibodies, peptides, proteins, nucleic acids, and immune-competent cells including dendritic cells and T-cells, have been created as tools for cancer immunotherapy[123,124].

NCT00854789 (E75 and GM-CSF), NCT00892567 (Her-2/neu; CEA and CTA), NCT02019524 (E39 and J65 peptides), NCT04270149 (ESR1 peptide vaccine) are in Phase of clinical trial. NCT00343109 (HER-2/neu), NCT00524277 (HER2-derived peptide GP2; GM-CSF), NCT01570036 (HER2-derived peptide E75; GM-CSF; Trastuzumab), NCT02061332 (HER; DC vaccine), NCT00399529 (HER2; GM-CSF; Cyclophosphamide; Trastuzumab) are now in phase II of clinical trial while NCT01479244 (HER2-derived peptide E75; GM-CSF) are in phase III of clinical trial[2,125]. Cancer immunotherapies, employed either alone or in combination, are now regarded as the fourth therapy approach. Coley's toxin was first used in the therapy by William B. Coley in 1891 to treat sarcoma patients[124–126].

Curcumin has currently been tested in a number of clinical trials in breast cancer patients, mostly following oral delivery regimens (e.g., NCT03980509, NCT01042938, NCT03847623, NCT03865992, NCT01740323, NCT01975363, NCT02556632, NCT01246973, NCT03482401). The only clinical trial that has been registered thus far (NCT03072992) uses the intravenous injection of a curcumin water-soluble formulation (CUC-1®) in combination with paclitaxel in breast cancer patients[97,127,128].

5.3. Adverse effects of curcumin

The Joint Joined Countries and World Wellbeing Association Master Advisory group on Food Added substances (JECFA) and the European Food handling Authority (EFSA) have laid out that the Satisfactory every day Admission (ADI) range for curcumin is between 0 to 3 mg for each Kg/BW. Numerous research on healthy people have supported the efficacy and safety of curcumin. The effectiveness and safety of curcumin have been verified by numerous research on healthy individuals[129–135]. Despite the drug's well-known safety, certain unfavorable side effects have been documented. In a dose-response experiment, seven participants who received doses ranging from 500 to 12,000 mg over 72 h reported symptoms like diarrhea, headaches, rashes, and yellow feces. In a different study, people who took curcumin daily for one to four months experienced adverse effects including nausea, diarrhea, and increased levels of the blood enzymes lactate dehydrogenase and alkaline phosphatase[1,59].

The blood thinned by curcumin may harm blood flow and raise the risk of an ischemic stroke[136]. It might also prevent chemotherapeutics from causing the formation of ROS and block the c-Jun NH2-terminal kinase pathway. Curcumin, like many other antioxidants, may even have pro-oxidant effects[137]. Human breast cancer xenografts in mice are strongly inhibited by curcumin from regressing after exposure to cyclophosphamide[138,139]. Curcumin may reduce by around 70% the ability of camptothecin, mechlorethamine, and doxorubicin to induce apoptosis in cultures of MCF-7, MDA-MB-231, and BT-474 human breast cancer cells[127]. HIF-prolyl hydroxylase activity may be inhibited by curcumin by acting as an iron chelator[138]. Therefore, it is vitally necessary to conduct more research to determine whether curcumin intake should be restricted for chemotherapy-treated breast cancer patients.

5.4. Patents for breast cancer treatment

Numerous patents have been applied for or issued in the domain of cancer diagnosis and therapy. Recent breast cancer patents are shown in **Table 1**. These discoveries provided a technique to improve a drug's ability to treat cancer in both people and animals.

Table 1. Patents for breast cancer treatment.

Patent number	Date of publication	Invention disclosed	Reference
US 2022/0195008 A1	23 June 2022	The antigenic specificity of the T-cell receptor (TCR) for the melanoma antigen family was revealed in this invention. It was discovered that the polypeptide in the TCR's functional region has amino acid sequences that are 16–21 amino acids long.	[140]
US 2022/0193199 A1		An immune cytokine that is a conjugation and an immunomodulatory antibody was described in this invention. It contained a polypeptide with the interleukin-15 (IL-15Ra) sushi domain. It was claimed that the immunomodulatory antibody or antigen-binding fragment could bind both PD-1 and PD-L1/L2.	[141]
US 2022/0193079 A1		The patent talked about a drug combination that included a CDK inhibitor and an antihormone that controls the P13K/Akt/m TOR pathway.	[142]
US 2022/0170012 A1	22 June 2022	In this invention, the formulations and procedures for creating RNA chimeric antigen receptors on transfected T cells were revealed. The eukaryotic messenger's 5′ end was added to the 5′ end of the RNA or its 7-methyl guanosine cap shortly after the transcription process began.	[143]
US 2022/0184111 A1	16 June 2022	This invention provided instructions for boosting chemotherapeutic drugs' cytotoxicity against cancer cells while decreasing it against non-cancer cells.	[144]
US 2022/0185892 A1		The anti-LAG-3 and anti-PD1 antibodies, which carry the CD-R1, CD-R2, and CD-R3 domains of the chain, are administered in an effective amount to cure solid tumors.	[145,146]
US 2022/0186323 A1		A nucleic acid sample could be the marker.	[147]
US 11,291,723B2	5 April 2022	This treatment selectively killed or prevented the growth of the target cell by using the Cas nuclease enzyme. It also involved cell populations, systems, arrays, cells, RNA, and other elements that affected the course of the therapy.	[148]
US 2022/0040278 A1	10 February 2022	This patent disclosed the presence of peptides on the tested tissue sample biopsies that helped to diagnose cancer. This patent also gave methods, such as antibody detection or spectrometry, for analyzing peptides.	[149]
US 11,220,715B2	11 January 2022	This innovation reported the expression of a group of genes as therapeutic prognostics for cancer patients' disease-free survival.	[150]
US 2022/0003792 A1	6 January 2022	The ways to identify a cancer kind in an animal's presence or absence were discussed in this innovation.	[151]

5.5. Improvement toward chemotherapeutic resistance: The golden spice curcumin

Chemotherapeutic resistance affects breast cancer patients frequently because the cancer cell has evolved to develop several defenses against the harmful effects of chemo-drugs. When anti-cancer medications are presented to cancer cells, numerous crucial multi-drug resistance (MDR) genes are upregulated, leading to acquired resistance to chemotherapeutic treatments. After curcumin treatment, the relative mRNA expression levels of the ABCC1, LRP1, and MDR1 genes were higher in scrambled control cells than in Silencing TM in MCF7 cells (TM-KD) cells. In conclusion, our findings showed that TM regulates curcumin sensitivity via interfering with ABCC1, LRP1, and MDR1 gene expression and suppresses the growth and metastasis of (estrogen receptors) ER + breast cancer[152,153]. A large part of breast cancers can be treated with antiestrogens which are classified as estrogen receptor (ER) positive[154]. Recent discoveries have demonstrated that using a single chemical to treat complicated cancer cellular networks is not very successful and can scarcely reduce cross-talk and negative feedback loops. As a result, drugs given in combinations target various pathology signaling pathways and have been regarded as an important trend in the design of drugs. The study has revealed a promising direction for eradicating endocrine-resistant breast cancer cells. However, given the implications of this research for both clinical practice and further investigation, there is a need for additional viable candidates for breast cancer treatments[155].

6. Future perspective and conclusion

Curcumin has exhibited critical anticancer advantages in the therapy of head and neck malignant growth, colorectal disease, bosom malignant growth, pancreatic disease, and prostate malignant growth both in vitro and in vivo. Numerous human clinical preliminary studies have also demonstrated its efficacy and safety in treating illness patients when taken either alone or in combination with other anticancer drugs. Curcumin is thought to inhibit or activate a number of cytokines, substances, and development factors, such as MAPK, EGF, NF-B, PKD1, COX-2, STAT3, TNF-, and I-K, as well as a number of cell pathways. However, curcumin's poor oral bioavailability, poor cell absorption, and poor synthetic stability have also limited the use of this compound as an anticancer agent. These limits have been circumvented in a number of ways, including the development of medicine delivery systems and structural changes. Future research should examine the effectiveness and bioavailability of various curcumin doses and/or forms. Furthermore, we need to confirm if curcumin and other chemotherapeutic medicines work in synergy. It is anticipated that results from current and upcoming clinical trials will aid in the practical application of curcumin in the treatment of various cancer types.

Conflict of interest

The authors declare no conflict of interest.

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