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CRUCUMIN ROLE IN BREAST CANCER TREATMENT

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ABSTRACT

One of the most common forms of malignant tumors is breast cancer worldwide, has a high fatality rate. The development of novel chemicals and technological advancements that will allow the adoption of safer and more efficient therapeutic techniques has received a lot of attention in order to address this problem. In order to maximize tumor growth inhibition and reduce side effects, it has been suggested that combining nanoparticles with well-known anticancer agents including compounds derived from plants, like curcumin is an effective strategy. Curcumin exploits a complex network of molecular signals, including the proliferative, ER, and HER2 pathways, to exert its anticancer actions. According to experimental results, curcumin controls genes associated to cell phase, microRNA, and apoptosis in breast cancer cells.

KEYWORDS: Curcumin, Breast Cancer, Curcuma Longa, Chronic Inflammation, Drugs

INTRODUCTION

Belonging to the ginger family, the herbaceous plant Curcuma longa, is known by the common name "turmeric." (1) The plant also includes curcumin, an active hydrophobic polyphenol diferuloymethane, in addition to flavonoids, alkaloids, tannins, and phenolic acids, which is particularly noteworthy (3). Two scientists from the Harvard College Laboratory, Vogel and Pelletier, isolated it for the first time in 1815. Since then, curcumin has attracted more scientific interest, and its health benefits are becoming more and more obvious. Numerous chronic conditions, including neurological disorders, inflammatory diseases, metabolic syndrome, arthritis, liver disease, obesity, and, most significantly, different cancers, have been proven to respond favorably to curcumin treatment. Recent years have seen a decline in mortality attributable to earlier diagnosis and more options for treatment. However, the rise of cancers that are resistant to conventional therapies necessitates the search for novel, strong drugs (4). Numerous pieces of evidence point to the importance of inflammatory pathway disturbance in the emergence of cancer. (5).

In developed nations, cancer is one of the leading causes of death (6). Despite the fact that there is a lot of awareness about the disease and the availability of treatment alternatives with several targets, pancreatic cancer fatality rates remain high (7). Signaling pathways involved in angiogenesis, growth, metabolism, movement, and immunological control, and survival are among those that are disrupted in cancer cells (8). Curcumin, according to study, has a number of effects on cancer cells that prevent the spread of cancer. Both on its own and in combination with other antineoplastic medications, curcumin has demonstrated good outcomes in the treatment of a number of cancers. It influences a number of signaling pathways, which makes it possible to alter the course of the growth and development of some malignancies.

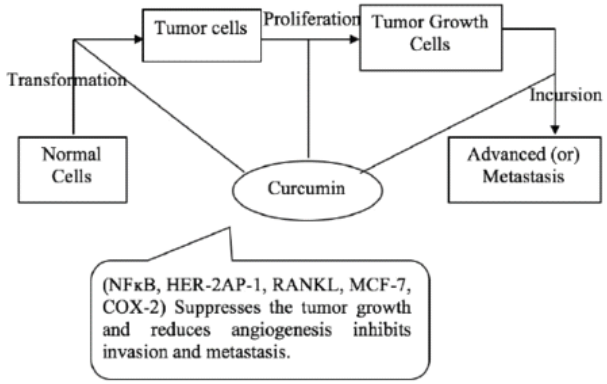

Fig. 1. Circumin Anti-Cancer Characteristics.

Figure 1, demonstrates curcumin's anti-cancer properties, which limit tumor cell proliferation and prevent cancer invasion and spread. Turmeric's curcumin and water extracts defend against DNA deterioration. The herb's anti-inflammatory and

antioxidant properties seem to prevent cancer that is brought on by the cell cycle. Turmeric's curcumin, which promotes cancer cell death, reduces inflammation, and slows tumor development, is essential in the treatment of a several cancers, including breast cancer.

Viral infections and chronic inflammatory diseases, which also contribute to the genetic instability thought to be a hallmark of cancer (10), are known to cause many types of cancer. Among the numerous pro-inflammatory substances are the NF-Kb (nuclear factor kappa-light-chain-enhancer of activated B cells), reactive oxygen species, cytokines, AKT, transcription factor, (COX-2) cyclooxygenase-2 and (AP-1), activator protein-1 are produced as a result of the inflammatory process and are connected to the onset and development of cancers (11). Some of curcumin's anticancer activities come from the way it affects the control of several immune modulators. ROS are secondary messengers in a number of cellular signaling pathways that are produced from oxygen. They promote cell survival, differentiation, and proliferation as well as inflammation, which aids in the development of various cancers (12). Some tumors may not spread or grow as a result of curcumin's direct binding to ROS scavengers (13). Interferons and cytokines are two examples of the proteins whose expression the NF-B factor regulates and controls. These proteins have a tight connection to the development of cancer and inflammation (14). Tumors are suppressed and apoptosis is induced in response to the blockage of the NF-B-dependent pathway by curcumin (15). Cytokines, important immune system regulators that enable cell communication across short distances, control leucocyte proliferation, survival, differentiation, and death. Interleukin (IL) 12 and 15, as well as IFN-a and IL-15 have lately been investigated in mouse cancer models. (16, 17). In order to stop the generation of pro-inflammatory cytokines, curcumin has been demonstrated to alter how nuclear proteins react interferons or interleukins (18). Curcumin inhibits the expression of the transcription factor (AP-1), which has been linked to both pro- and anti-apoptotic effects in certain cancer types. (19). When curcumin was present, it was discovered that microglial cells produced less COX-2, whereas melanomas cancer cells produced less COX-2 in a concentration-dependent way (20, 21).

Numerous immune system cell types, includes natural killer cells, B and T lymphocytes, and macrophages, have been demonstrated to be affected by curcumin (22). Immune cytokines' production and activity are controlled by curcumin. TNF-a is a versatile cytokine that supports immune system development and operation. The expression of this factor can be restricted by curcumin, which can also reduce the synthesis of TNF- induced by LPS (23). Curcumin also targets dendritic cells, which are well-known for their function in immunostimulation. Curcumin has been found to be particularly effective at capping myeloid DC maturation, mostly by suppressing CD80 and CD86 expression (24). Natural killer (NK) cell activity in rats was unaffected by early studies involved the injection of up to fourty mg per kg of curcumin around five weeks (25). In contrast other researchers investigated the characteristics of curcumin that modulate immunity in a different study and discovered that this medication may enhance NK cell cytotoxicity in vitro, and curcumin administration in conjunction with IFN therapy may enhance this effect even further. (26). A decrease in the activity of NLRP3 inflammasomes, according to recent studies, is what gives curcumin its anti-inflammatory effects (27). Multiprotein complexes called inflammasomes control the innate immune system. Inflammasomes' NLRP3 can start an immunological reaction by finding the metabolites of injured cells (28). Through regulating NF-B signaling, curcumin can stop the NLRP3 inflammasome being activated., which in turn stops the generation of IL-1 (29). For instance, It has been proven that curcumin has anticancer properties in malignant mesothelioma via controlling signaling pathways that influence inflammasomes like IL-1 and NF-B. Inflammatory- and cancer-fighting properties of curcumin have been discovered in other research as well, In a clinical experiment, TLRs, IL-6 ,IL-3, and STAT-1 production in human acute myelogenous leukemia cells (K562) was markedly reduced by curcumin therapyEighty patients with solid tumors were allocated at random in another double-blind, randomized, placebo-controlled research to receive either a matched placebo or 180 mg per day of curcuminoids for eight weeks. In compared to the placebo group, TNF-, monocyte chemotactic protein-1, and interleukins all displayed a significant drop (32). Twelve oral cancer patients participated in a randomized, phase 1 clinical experiment with double-blinding, curcumin, a component of the herbal drug APG-157, was given. This also included a number of different polyphenols. IL-1, IL-6, and IL-8 levels were observed to be lower in the patients' saliva 24 hours after treatment. (33).

ACTION OF CURCUMIN IN BREAST CANCER

The malignant tumor that affects adult females most frequently right now is breast cancer. Due to its great frequency, the leading factor in female fatalities is cancer. worldwide (34). Even if early detection is still

the greatest way to improve outcomes and survival, the usage of different drugs is still a beneficial breast cancer treatment. Antiestrogens are typically utilized as the main treatment since oestrogen receptor (ER) positive breast cancer makes up more than 70% of cases. However, mounting data indicates that the most effective method for managing breast cancer is the combination of a number of medications. A transcription factor called NF-B that encourages inflammation is necessary for breast cancer cells to proliferate. It regulates over 500 distinct genes, leading to the production of inflammatory and cellular signaling pathway-related proteins. Drugs that interact with NF-B can be used to treat cancer by suppressing it. By lowering the genes that cause NF-B, curcumin has been shown to have an impact on breast cancer cell invasive and proliferation (35, 36). The (HER2) human epidermal growth receptor 2, an EGFR family tyrosine kinase (TK) receptor, is another target that inhibits the proliferation of breast cancer cells. It is believed that HER2 could be an appropriate target for cancer treatment because of the role that HER2 overexpression plays in the formation of different cancer types (37). To suppress breast cancer cell lines, curcumin by itself or in conjunction with its analogues can inhibit HER2-TK. (38). The specificity of the inhibitory effect against HER2 was enhanced by the immuno-liposome encapsulation (39). The protein kinase B gene known as Akt is altered (mutated and amplified) during carcinogenesis (40). The regulated process of cancer cell growth and proliferation was disrupted by mTor (kinase) and Akt. (41). Curcumin blocked the ubiquitin-proteasome system, downregulated the Akt protein, and activated autophagy in dose- and time-dependently eradicate breast cancer cells (42). According to a recent study (43), curcumin may also inhibit the PI3K/Akt signaling mechanism that causes breast cancer cells to die and undergo autophagy. In the case of MCF-7 cells exposed to curcumin and a PI3K inhibitor, curcumin's capacity to cause apoptosis also shown a synergistic impact (44). Cancer cell growth, adherence, migration, and transformation have all been associated with the EGFR family of receptor tyrosine kinases is another route that can be disrupted by curcumin (45, 46). As a result, controlling EGFR is an effective cancer treatment plan. By inhibiting EGFR signaling and lowering EGFR and Akt levels, Breast cancer cells' ability to grow and divide was restricted by curcumin. (47, 48). Through altering the transcription factor Nrf2, Curcumin exerts its chemo-preventive and antiproliferative properties through the control of many genes that produce proteins involved in the removal or repair of some of their damaged products as well as detoxification of ROS and electrophiles (49,50). Oestrogen is required for curcumin's antiproliferative actions on ER-positive MCF-7 breast cancer cells. It really suppresses the growth of ER in subsequent genes like pS2 and TGF-beta in ER-positive MCF-7 cells, and this impact is likewise oestrogen-dependent. Contrarily, curcumin stopped the oestrogen-free invasion of ER-negative MDA-MB-231 breast tumor cells in vitro. These fascinating behaviors seemed to be regulated by the molecules matrix metalloproteinase-2 (MMP-2) and tissue inhibitor of metalloproteinase-1 (TIMP-1), which have been linked to controlling cancer cell invasion (51). Curcumin may be able to regulate the non-coding sequences of miRNAs, which are 18 to 22 nucleotides long and linked to a number of illnesses, including cancer (52). The expression of particular miRNAs, including tumor-suppressive miRNAs Curcumin controlled In breast cancer cells, there are miRNAs that are both oncogenic (miR-19a and -19b) and non-oncogenic (miR-15a, -16, 34a, 146b-5p, and -181b). It was shown that apoptosis was encouraged while tumorigenesis and metastasis were inhibited. In several cancer types, including breast cancer, widespread treatment resistance has been observed. Curcumin has demonstrated promising benefits in reducing this phenomenon. For instance, cisplatin resistance is a result of the overexpression of Breast cancer cell lines that express the enzyme (FEN1) flap endonuclease 1. By lowering FEN1 expression in vitro, curcumin was reported to improve the susceptibility of breast carcinoma cells to the chemotherapy drug cisplatin (53). Paclitaxel, a crucial chemotherapeutic agent used to treat breast cancer, has demonstrated acquired P-glycoprotein overexpression and the presence of the multidrug resistance mutation 1 (MDR-1) gene result in resistance in breast cancer cell lines. By reducing the MDR-1 gene expression in the MCF-7 breast cancer cells, curcumin has demonstrated advantages in reducing this drug resistance. (54).

By focusing on numerous cell signaling pathways and transcription factors, Curcumin slows the development of breast cancer cells stimulates apoptosis, and causes senescence. MAPKs, or mitogen-activated protein kinases, are also known as nuclear factor kappa B. Wingless-Int/beta-catenin is referred to by the acronyms Wnt, IGF1, mTOR, ROS, and dsDNA. ROS is an acronym for reactive oxygen species. hTERT stands for human telomerase reverse transcriptase. STAT3 is an acronym for signal transducer and transcription activator 3. Nuclear factor (erythroid-derived 2)-like 2 is referred to as Nrf2. (figure:2)

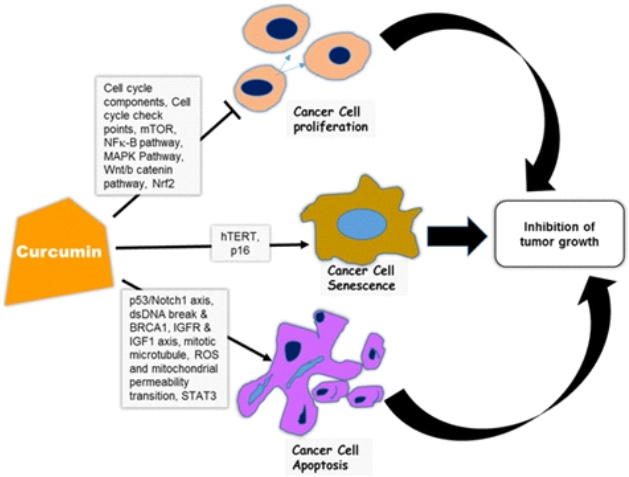

Fig: 2- Targets for Curcumin-mediated Growth-inhibition of Breast Tumors

DISCUSSION

Curcumin interacts with molecules in a range of breast cancer-related pathways via Hydrophobic, hydrogen bonds, non-covalent bonds, and covalent bonds ways as a result of its chemical makeup. (55,56). Curcumin reportedly prevents tumor invasion, cell division, and angiogenesis. Curcumin produces p53-dependent apoptosis and cell cycle arrest as an anti-proliferative drug. Akt, and other signaling proteins include phosphatidylinositol-3-kinase (PI3K) are expressed and Ras is also changed by it (57). Inhibiting EZH2, a protein subunit involved in histone modification and tumor development the potential for metastasis, and the management of therapy resistance, has also been suggested as a possible goal for curcumin. Studies on the disease show that curcumin inhibits the development of MDA-MB-435 human breast cancer cells by decreasing the expression of EZH2. (58, 59)

Many different apoptotic signaling pathways can be altered by curcumin. Depending on the cell type, level of differentiation or quantity of curcumin present, either the extrinsic (extracellular) or the intrinsic (mitochondrial) apoptotic mechanism is more frequent(receptor-mediated) . DNA breakage, telomerase suppression, among the apoptotic pathways that curcumin induces in certain Increased Bax/Bcl-2 ratio and redox signaling are indicators of breast cancer cells. Free curcumin can halt the cell cycle, which may be related to its antiproliferative properties. (60,61). The complex Investigations into the effects of curcumin are extensive to determine the molecular processes and cellular targets involved in the curcumin pathways. The versatile chemical curcumin has several therapeutic applications. Due to the fact that it can interact with a wide range of compounds, regulate a number of chemical processes, and influence the targets of those pathways, curcumin has a broad spectrum of effects (62). Curcumin has a number of enticing qualities that make it suitable for medicinal application, including low toxicity, which means that consumption up to a level of 10 g per day has no negative consequences (63). Large doses of curcumin can stop the growth of cancer cells without damaging healthy cells (64, 65). In order to address and research the therapeutic efficacy and its analogs of free curcumin in a variety of human ailments, including cancer, neurological disease, etc, more validation studies are required. There are several drawbacks to the therapeutic use of curcumin as well as to a comprehensive safety/toxicity profile and analysis based on data are included to demonstrate its efficacy. Additionally, curcumin's nanocarriers as well as an effective delivery technique for its targeted and therapeutic use are unknown. To find the best formulation and delivery method for each biological use, more study is needed. Additionally, clinical trials must be conducted to evaluate the improved therapeutic efficacy of structural analogs of curcumin, its nanoform, and delivery technologies. Curcumin, a naturally occurring polyphenol turmeric is derived from the rhizome and used as a natural pigment, food colorant, and food additive and has a variety of therapeutic effects. Curcumin may provide additional benefits with a relatively low dose a number of health benefits for those with any kind of medical condition. Recent research has focused on improving curcumin's therapeutic effectiveness and clinical uses to more successfully treat a variety of diseases and conditions. However, direct application of curcumin in therapeutic applications is difficult due to its poor solubility and low bioavailability.

CONCLUSIONS

Finding new cancer medicines is a challenging endeavor. Numerous natural substances have drawn the attention of researchers as potential chemotherapeutic therapies because of their potency and safety. Numerous studies have been conducted Curcuma longa's rhizomes contain curcumin, a hydrophobic polyphenol that is active. It has showed promise in the treatment of a number of ailments, including certain malignancies. According to the findings of this study, curcumin specifically targets a number of pathways of signaling involved in the development, expansion and development of malignancies. Curcumin's molecular targets include growth factors, transcription factors, and protein kinases, which has been found to greatly reduce the growth of a range of different cancers. It is need to do additional in vitro research and human clinical trials to ascertain this medication's precise method of action in every type of cancer while also assuring user safety.

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