

MOLECULAR MECHANISTIC AND BIOINFORMATICS PERSPECTIVES ON CURCUMIN FROM CURCUMA LONGA IN BREAST CANCER THERAPY

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Abstract

Breast cancer is one of the most important causes of cancer deaths around the world, and new strategies for treatment are urgently required that overcome tumor heterogeneity as well as treatment resistance. Curcumin, the main bioactive polyphenol compound of *Curcuma longa*, is becoming a promising anticancer agent because it exhibits pleiotropic molecular activities on several oncogenic pathways. This review aims to give a complete synthesis of curcumin therapeutic benefits in breast cancer in the light of molecular mechanisms, as well as bioinformatics and multi-omics approaches. Curcumin's anticancer properties include the modulation of cell proliferation, induction of apoptosis, modulation of autophagy, inhibition of migration and metastasis, and epigenetic actions, such as DNA methylation, histone modifications and non coding RNAs. Curcumin directly blocks the phosphorylation of STAT3, thus blocking its movement from cytoplasm to nucleus and blocking its DNA-binding activity, and consequently preventing tumor proliferation and survival. Alters important signaling pathways, such as PI3K/AKT/mTOR, MAPK/ERK, JAK/STAT, NF- κ B and Wnt/ β -catenin pathways. Bioinformatics has revealed that curcumin targets the molecular targets, AKT, TNF and TP53 with high affinity, and network pharmacology has helped reveal curcumin's multi-target mechanisms and protein interaction networks. The formulation of curcumin by liposomes has been shown to be more effective in the MCF-7 breast cancer cells, with the IC₅₀ decreasing from $19.81 \pm 1.03 \mu\text{g/mL}$ to $9.16 \pm 0.67 \mu\text{g/mL}$. Although preclinical data are promising, the delivery of these drugs to the clinic has been limited by poor bioavailability, metabolism and absorption. In order to overcome these limitations,

nanotechnology based delivery systems and combination strategies have been promising. Overall, this review sheds light on the potential of curcumin as a promising precision oncology drug, combining computational and experimental strategies to advance the treatment of breast cancer.

1. Introduction

Despite the fact that breast cancer incidence rates are increasing across different populations worldwide, and mortality due to breast cancer is high, it remains a major health problem around the world. This disease is highly molecularly heterogeneous, separated into different intrinsic subtypes that have very different genetic profiles and patterns of clinical behaviour and response to therapy: luminal A, luminal B, HER2-enriched and triple-negative breast cancer[1]. This heterogeneity is a fundamental problem in the treatment strategies, because tumours of the same clinical stage can have widely variable sensitivity to commonly used treatments. Although the recognition of molecular subtypes has led to a major revolution in the management of breast cancer, allowing more accurate choices of therapy, problems remain in the area of drug resistance, metastatic progression and recurrence. Given the burden of breast cancer globally, continual innovation in the fields of therapeutic interventions is required, especially agents that are capable of selectively targeting the various molecular pathways involved in breast tumour initiation, progression as well as therapeutic resistance[2].

Breast cancer manifests on the molecular level as the activation of several oncogenic signalling pathways, which coordinate cell proliferation, survival, migration and therapeutic resistance. Frequent deregulation of several pathways such as PI3K/AKT/mTOR, MAPK/ERK, JAK/STAT and NF- κ B is observed in all breast cancer types, leading to the uncontrolled proliferation and apoptosis resistance of these tumours[3]. The HER2-enriched subtype is characterized by amplification and overexpression of the HER2/neu oncogene, triple-negative breast cancer is characterized by the absence of expression of estrogen receptor, progesterone receptor and HER2, which is limiting in regard to targeted therapies. Therapeutic resistance is a serious problem; tumors are able to develop adaptive mechanisms such as activation of alternative

signaling pathways, over-expression of drug efflux pumps, and epithelial-mesenchymal transition[4]. The tumor microenvironment is complicated by interactions with cancer associated fibroblasts, tumor-associated macrophages, and tumor infiltrating immune cells, which promote angiogenesis, invasion and immune evasion. These complexities underscore the need for multi-target therapeutic strategies that can target multiple oncogenic drivers[5].

Historically, natural products have been a valuable source for anticancer drugs; indeed, nearly half of the clinically approved anticancer drugs can be found in or based on natural products. Plant-derived compounds have provided examples of success in the fields of structure and biological activity, leading to therapeutic successes such as paclitaxel, vincristine and camptothecin. Polyphenolic compounds, in particular, have become the subject of significant research because they are of low toxicity, have pleiotropic biological activity and can modulate multiple pathways involved in cancer. The bioactive polyphenols known as curcuminoids derived from *Curcuma longa* have been well studied for their anticancer properties, showing activity against various types of cancer by inducing apoptosis in cells, inhibiting proliferation, suppressing angiogenesis and regulating inflammatory signaling in cells. The multiple-target nature of natural products may be of great significance in treating breast cancer, in which pathway redundancy and compensatory signaling play a role in therapeutic resistance[6].

Curcuma longa, a herbaceous plant of the Zingiberaceae family, has been used for centuries in traditional medicines like Ayurveda and traditional Chinese medicine as a wound-healing herb with anti-inflammatory and antioxidant properties. In the last decades, the therapeutic potential of curcumin, the major bioactive compound of turmeric, has been extensively studied and demonstrated to exert a remarkable ability to interact with a large number of molecular targets and signaling

pathways. The chemical structure of curcumin, which consists of a bis- α,β -unsaturated β -diketone linking two aromatic rings with o-methoxy phenolic groups, is the basis for the pleiotropic biological activities and interaction with various cellular proteins. The compound has been shown to have anticancer properties against a wide range of cancer types, and it has shown to be especially effective against breast cancer prevention and treatment[7].

This review examines the therapeutic potential of curcumin in breast cancer comprehensively and integrally covers the molecular mechanisms, regulation of signalling pathways, epigenetic modifications, interactions with the tumour microenvironment, and bioinformatics perspectives. An innovative aspect of this review is the incorporation of computational tools, such as network pharmacology, molecular docking, and multi-omics, to offer mechanistic insights that supplement the experimental results. This covers the regulation of oncogenic signalling pathways, epigenetic and non-coding RNA modulation, impact on the tumour microenvironment and therapeutic translation, with a focus on combination strategies and nanotechnology-based delivery systems. This review summarises and focuses on the various anticancer actions of curcumin, highlights the current knowledge gaps and translational challenges, and proposes future directions in curcumin precision oncology.

2. Curcumin: Chemical, Pharmacological, and Biological Characteristics

2.1 Botanical Origin and Phytochemical Composition of *Curcuma longa*

Curcuma longa is a member of the genus *Curcuma*, which has about 50 members found mainly in Southeast Asia, but smaller populations in the north of Australia, and in China. Turmeric is obtained from the rhizome of *C. longa* and contains a wide variety of bioactive phytochemicals, Australia and Asia but including curcuminoids, volatile oils and polysaccharides. The curcuminoids in turmeric make up about 2-9% of the total weight of the turmeric, and approximately 70-75% curcumin, 20% demethoxycurcumin and 5% bisdemethoxycurcumin are present in commercially available turmeric extracts.

Turmeric has been used in traditional cooking and medicine for thousands of years and is known to have medicinal properties in Ayurvedic medicine for inflammatory disorders, digestive disorders, and skin diseases[8], [9], [10].

2.2 Chemical Structure and Physicochemical Properties of Curcumin

Curcumin, 2,5-diferuloyl-1,4-dihydrazine, with a chemical formula of $C_{21}H_{20}O_6$ (molecular weight: 368.38 g/mol), has a unique bis- α,β -unsaturated β -diketone structure. This structure is constituted of two aromatic rings with o-methoxy phenolic groups linked by a seven-carbon linker that has the α,β -unsaturated β -diketone functionality. The phenolic hydroxyl groups and the β -diketone moiety are responsible for the hydrogen-donating property, metal-chelating property and free radical scavenging activity of curcumin. Curcumin is a keto-enol tautomer, the enol form being predominant in an organic solvent and the keto form in an aqueous solvent. Very poorly soluble in water but highly soluble in polar solvents such as DMSO and acetone, moderately soluble in ethanol and moderately soluble in methanol. These physicochemical properties have implications on its pharmacological behaviour and pose challenges to its potential therapeutic application[11].

2.3 Curcumin Metabolites and Biotransformation

Extensive biotransformation of curcumin is seen after administration, mainly involving the liver and intestinal mucosa. The compound is quickly metabolised by conjugation reactions, with the generation of two principal metabolites, curcumin glucuronide and curcumin sulphate. Enzymes like curcumin reductase convert curcumin into tetrahydrocurcumin, hexahydrocurcumin, and octahydrocurcumin, which might be biologically active and play a role in the overall pharmacological activity. Curcumin's methoxy groups can be demethylated, resulting in metabolites with different bioactivity. In rodents, the bioavailability of curcumin is found to be around 25%, most of the ingested curcumin being excreted either in the faecal matter or as metabolites. The fast metabolism and clearance

in the system play an important role in the low bioavailability of curcumin, as this poses a challenge in reaching therapeutic plasma levels[12].

2.4 Pharmacokinetics and Pharmacodynamics

Curcumin has a poor oral bioavailability and is extensively metabolized and eliminated. After oral administration, curcumin is metabolized in the intestine and liver, and is poorly detected systemically as an intact molecule. Peak plasma levels are reached in 1-2 hours after administration and levels drop quickly because of high metabolism and elimination. Curcumin has a relatively short half-life in the terminal phase (between 1 and a few hours and it depends on the formulation and administration route)[13]. Although curcumin has a relatively low systemic bioavailability, its therapeutic efficacy has been observed in a wide array of preclinical studies, implying that local actions in the gastrointestinal tract, local accumulation in target tissues or actions of metabolites may play a role in its pharmacological actions. Strategies to improve bioavailability include adjuvants like optimization with piperine (an inhibitor of glucuronidation), use of nanoparticle formulations, liposomal delivery systems and structural analogues with improved pharmacokinetic properties[14].

2.5 Bioavailability and Stability Limitations

However, the clinical application of curcumin is significantly limited by the poor bioavailability of curcumin due to its low aqueous solubility, high metabolic rate and poor absorption rate. The solubility of curcumin in aqueous media is about 11 ng/mL at pH 5.0 which is quite low and restricts its dissolution and consequent absorption in gastrointestinal tract. The compound is chemically unstable, undergoing autoxidation, photodegradation and hydrolytic cleavage, among other processes, at physiological conditions. Limitations in curcumin's stability in physiological environments include the fact that the β -diketone moiety is particularly sensitive to breakdown under alkaline conditions[15]. Tackling these limitations involves the creation of curcumin derivatives with improved aqueous solubility; delivery systems involving nanotechnology to shield curcumin from metabolism and to alter cellular uptake rates; and strategies that combine curcumin with other compounds to retard metabolic clearance. Despite these limitations, the vast amount of preclinical data demonstrating the biological activity of curcumin and its safety still gives impetus for research to develop strategies to overcome the bioavailability hurdle[14].



Figure 1.0. Curcumin bioavailability and stability limitations. Schematic overview of the major factors limiting curcumin bioavailability, including poor aqueous solubility, low absorption, rapid metabolism, chemical instability, and sensitivity to alkaline conditions.

3. Molecular Mechanisms of Curcumin in Breast Cancer

3.1 Regulation of Cell Proliferation and Cell-Cycle Progression

Curcumin has been shown to have strong antiproliferative activity in breast cancer cells by regulating cell cycle regulatory proteins and proliferation signalling pathways. The compound arrests the cell cycle at different stages with respect to the cell context and treatment conditions. In MCF-7 breast cancer cells, curcumin-loaded PLGA nanoparticles effectively arrested cellular growth in the G2/M phase with up to 50% reduced proliferation of the tumour cells. Curcumin is able to down-regulate the expression of cyclin D1 and cyclin E and up-regulate the expression of cyclin-dependent kinase inhibitors, p21 and p27, and thus inhibit the transition through the G1/S checkpoint. The compound also inhibits kinases that regulate the progression of the cell cycle, such as AKT, ERK and JNK. The cytostatic action of curcumin has been found in several breast cancer cell lines such as MCF-7, MDA-MB-231 and SK-BR-3, which exhibited a wide spectrum of antiproliferative effects. Curcumin "interferes" with the orderly passage through the cell cycle, thereby making a cell's environment less favourable for the growth of the tumours and more favourable for apoptosis to be induced[16].

3.2 Induction of Apoptosis and Mitochondrial Dysfunction

Apoptosis induction is a key mechanism of action of curcumin as an anticancer agent; curcumin can activate both intrinsic and extrinsic pathways of apoptosis. Curcumin causes mitochondrial dysfunction by disrupting the mitochondrial membrane potential, releasing cytochrome c and activating the caspase cascade. The compound induces the expression of pro-apoptotic proteins, like Bak and Bax, and represses the expression of anti-apoptotic proteins, such as Bcl-2 and Bcl-xL, thus favouring the execution of the apoptotic process. Liposomal curcumin formulations showed much higher apoptotic-inducing activity than free curcumin, as indicated by increased early and late apoptotic populations in the Annexin V/PI assay. Curcumin has been shown to synergise with standard chemotherapy agents,

resulting in the increase of apoptosis via different mechanisms. The mitochondrial pathway of apoptosis is of particular interest in the realm of breast cancer, where defects in apoptotic signalling are thought to cause the breast cancer cells to become resistant to treatment[17], [18].

3.3 Modulation of Autophagy and Cellular Stress Responses

A cellular degradation process called autophagy can either promote cell survival or lead to cell death depending on the situation, and curcumin has the ability to modulate this process. The compound activates AMPK and inhibits mTOR, which induces autophagy in breast cancer cells, leading to a cellular stress response, which may underlie its anticancer activity. Whether curcumin induces autophagy or apoptosis seems to depend on the context: in some contexts, curcumin may cause autophagic cell death, but in other contexts, it might cause protective autophagy. Curcumin's modulation of cellular stress response is not limited to autophagy but also to endoplasmic reticulum stress, endoplasmic reticulum unfolded protein response activation and signalling of oxidative stress. The endoplasmic reticulum stress, produced by curcumin, is involved in the apoptotic process through activating the PERK/eIF2 α /ATF4 and IRE1/JNK pathways. The interactions between autophagy and apoptosis in curcumin-treated cells are intricate and likely depend on the specific breast cancer cell type, impacting the overall treatment efficacy[19].

3.4 Oxidative Stress and Redox Regulation

Curcumin has antioxidant and pro-oxidant properties; the redox-modulatory properties aid its anticancer activity in a cellular context and concentration dependent manner. Normally, curcumin protects cells by its antioxidant properties by scavenging free radicals, chelating metal ions and inducing antioxidant enzymes (via the NRF2 pathway). Cancer cells: Curcumin may be able to induce the production of reactive oxygen species, deplete the body of antioxidants (such as glutathione), and inhibit antioxidant enzyme systems. Such a pro-oxidant action is selectively targeted against cancer cells owing to

their high baseline degree of oxidative stress and low antioxidant capacity. The redox activity of curcumin is also involved in affecting redox-sensitive signaling pathways such as NF- κ B, AP-1 and NRF2[20]. Curcumin's dual redox-modulatory activity make it to be a potent protector of normal tissues and sensitizer of cancer cells for oxidative injury. It has been demonstrated that NRF2 depletion increases the therapeutic potential of curcumin presumably via an increase in ROS, indicating that the antioxidant protective versus oxidative stress is crucial for the anticancer effect of curcumin[21].

3.5 Inhibition of Migration, Invasion, and Metastasis

Curcumin has multiple interconnected mechanisms which inhibits breast cancer cell migration, invasion and metastasis. It is a compound that down-regulates Snail, Slug and Twist transcription factors and up-regulates

epithelial markers like E-cadherin, thus inhibiting epithelial-mesenchymal transition, a program which enables cancer cells to take migratory and invasive properties. Curcumin down-regulates the expression and activity of matrix metalloproteinase and thus prevents the degradation of the extracellular matrix and basement membrane[22]. The anti-metastatic and anti-invasive properties of curcumin in triple-negative breast cancer cells have been demonstrated to occur via the Hedgehog/Gli1 signalling pathway. The compound is also active against the Hedgehog (Hh)/Gli signaling pathway that is involved in the induction of epithelial-mesenchymal transition, cancer stem cell properties and metastatic spread. However, the inhibitory effect of curcumin on angiogenesis also prevents formation of metastatic lesions by cutting off the blood supply to growing tumour cells[19].

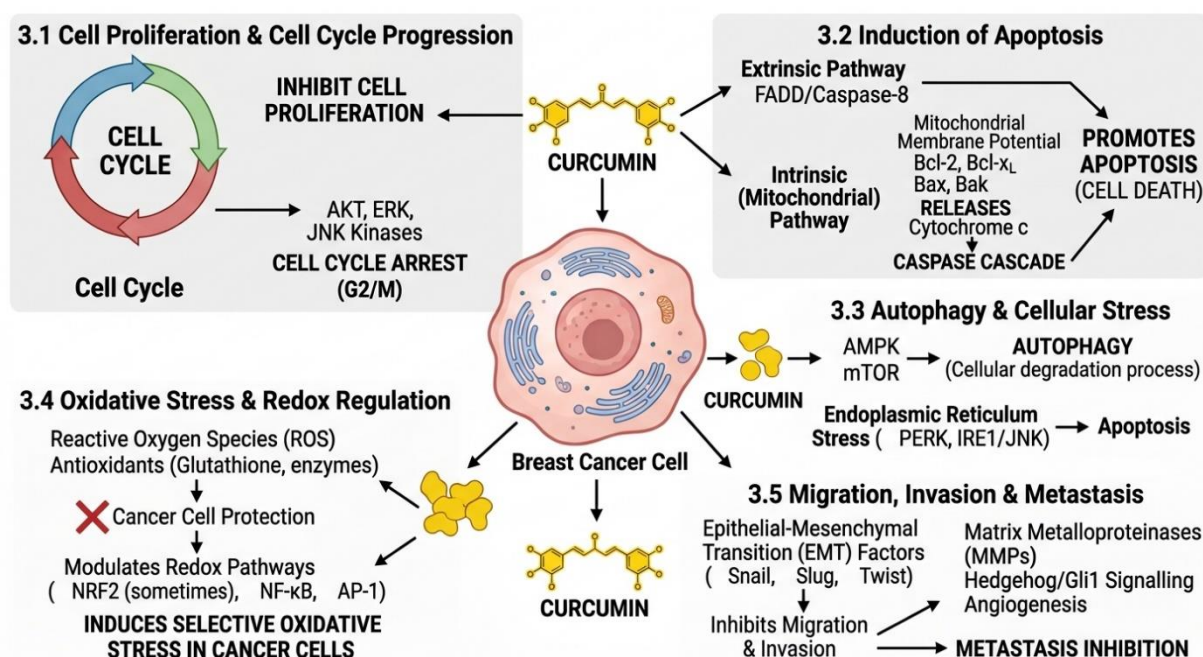


Figure 1.2 Multi-faceted anti-cancer mechanisms of curcumin. Curcumin inhibits cell proliferation, induces cell-cycle arrest (G2/M) in breast cancer cells, promotes apoptosis via intrinsic and extrinsic pathways, induces selective oxidative stress, induces endoplasmic reticulum stress, modulates autophagy, and inhibits EMT and metastasis.

4. Curcumin-Mediated Regulation of Oncogenic Signaling Pathways

4.1 PI3K/AKT/mTOR Signaling

One of the key aspects of curcumin's anticancer effects in breast cancer is the suppression of the PI3K/AKT/mTOR signaling pathway. Curcumin targeting the PI3K/Akt pathway has therapeutic effects in a variety of cancers, such as glioblastoma, prostate cancer and breast cancer. Curcumin blocks the phosphorylation of AKT, which in turn blocks its kinase activity and subsequent signaling through mTOR and other effectors. The compound, which was found to reduce the level of PI3K expression, also inhibits the activity of the PI3K enzyme and the formation of phosphatidylinositol (3,4,5)-trisphosphate, which is crucial for the activation of AKT[23]. Curcumin suppresses the phosphorylation of downstream target proteins of AKT, such as the FOXO transcription factors, GSK-3 β and the mTOR substrates p70S6K and 4E-BP1. Curcumin has been combined with AKT inhibitors and other pathway targeting agents, which has proven to be more effective on cancer, acting in complementary ways. Molecular docking studies confirmed that AKT is a high affinity target for curcumin and the binding profile of curcumin with the receptor was favourable for the structural binding basis of pathway inhibition[24].

4.2 MAPK/ERK/JNK Signaling

Curcumin regulates the MAPK pathways, such as ERK and JNK pathways that regulate cell proliferation, differentiation and stress responses. The compound down-regulates the activities and phosphorylation of ERK which decreases signaling for proliferation that supports the growth of breast cancer cells. The interaction of curcumin with the ERK signaling pathway also synergizes its inhibitory activity at the PI3K/AKT pathway, giving a more detailed inhibition of proliferative signaling. Curcumin, in contrast, activates the JNK signaling which involves the phosphorylation of c-Jun and the activation of mitochondrial apoptotic pathway involved in stress-induced apoptosis. Curcumin's ability to differentially modulate ERK and JNK pathways leads to a pro-apoptotic signaling environment with inhibition of survival signal(s) and activation of death signal(s).

ERK and JNK signals are balanced between each other, and the extent of JNK activation and ERK inhibition is linked to sensitivity towards curcumin[25].

4.3 JAK/STAT Signaling

Curcumin's anti-breast cancer effects have been associated with its ability to impair various signaling pathways, including JAK/STAT, which is a well-studied mechanism. Curcumin directly suppresses the phosphorylation of STAT3, on which prevents its nuclear translocation and prevents its DNA-binding skill, thereby suppressing the transcription of the STAT3 target genes involved in cell proliferation, cell survival, angiogenesis and metastasis. Curcumin can inhibit the activation of STAT3 by IL-6, thereby suppressing pro-tumorigenic responses of the pathway including increased cell proliferation and metastasis[22]. Curcumin disrupts the IL-6/JAK/STAT3 signaling pathway, disrupting adaptive mechanisms of resistance and enhancing the action of current endocrine, chemotherapeutic, targeted and immunotherapeutic agents. Those genes that are found to be down regulated by curcumin are important STAT3 target genes involved in the pathways of tumour progression such as BCL-2, c-MYC, Cyclin D1, and VEGF. Some curcumin analogues have exhibited greater potency in blocking STAT3 activation, leading to decreased cell growth and higher rates of apoptotic cell death, including hydrazinocurcumin, FLLL11, FLLL12 and GO-Y030[26].

4.4 NF- κ B and Inflammatory Signaling

Curcumin is a strong inhibitor of NF- κ B signalling, which regulates inflammatory processes, cell survival and proliferation. The compound blocks the activity of the I κ B kinases, inhibiting the phosphorylation and degradation of I κ B which normally results in activation of NF- κ B. Curcumin inhibits nuclear translocation and binding of NF- κ B to DNA, thus repressing the activity of NF- κ B target genes such as pro-inflammatory, cell survival and pro-angiogenic genes. The anti-inflammatory effect of curcumin is not limited to NF- κ B, but is also known to suppress the production of COX-2, iNOS and pro-inflammatory cytokines[27]. Curcumin's anti-inflammatory properties could be especially

effective in the setting of breast cancer, which possesses an inflammatory microenvironment—hallmarked by high-level chronic inflammation and infiltration of immune cells. JAK/STAT and NF-κB pathways are linked pathways, and curcumin targets both pathways to render a complete anti-inflammatory and anti-tumorigenic signaling environment[28].

4.5 Wnt/β-catenin, Notch, and Hedgehog Pathways

Curcumin regulates developmental pathways that are often dysregulated in breast cancer including Wnt/β-catenin, Notch and Hedgehog and are involved in the maintenance of cancer stem cell and therapeutic resistance in breast cancer. Curcumin inhibits Wnt/β-catenin signaling by downregulating β-catenin

expression and its nuclear translocation, which leads to a decrease in the transcription of Wnt target genes for proliferation and survival. The compound downregulates the Notch receptors and ligands, thereby inhibiting the Notch signaling that promotes tumor progression and stem cell maintenance. Curcumin blocks Hedgehog/Gli1 pathway signaling in triple-negative breast cancer cells and leads to decreased epithelial-mesenchymal transition, cancer stem cell properties, and metastatic spread. Curcumin's ability to simultaneously inhibit several developmental signaling pathways is likely to provide an effective blockade of the stemness and plasticity that underlie tumor heterogeneity and the development of resistance[29].

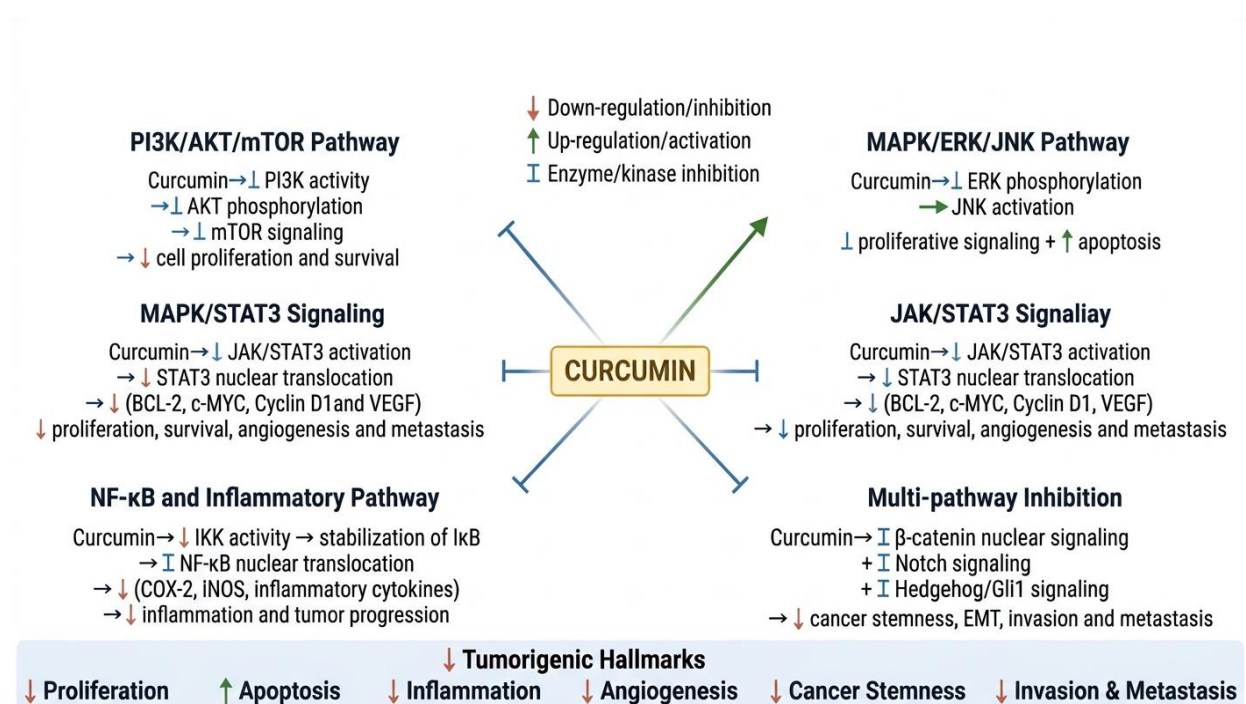


Figure 1.3: Curcumin-Mediated Regulation of Tumorigenic Hallmarks and Associated Signaling Pathways in Breast Cancer

5. Epigenetic and Non-Coding RNA Regulation by Curcumin

5.1 DNA Methylation and DNA Methyltransferases

Curcumin regulates the epigenome by interfering with DNA methylation patterns and DNA methyltransferase (MTase) activity. The compound is an inhibitor of the DNA

methyltransferase 1, 3a, and 3b, resulting in global hypomethylation, and reactivation of silenced genes, such as tumor-suppressor genes. This hypomethylation by curcumin has been reported in many types of cancer, such as in the regulation of genes like RASSF1A, p16 and E-cadherin[30]. The effects of the compound on DNA methylation is dependent on the context,

and might differ among breast cancer subtypes. Curcumin can reverse the abnormal DNA methylation pattern and thus restore the expression of the genes related to cell-cycle control, apoptosis and differentiation. Epigenetic actions of curcumin may be responsible for long-term anticancer actions and sensitizing cells to traditional therapies[30].

5.2 Histone Modifications and Chromatin Remodeling

Curcumin regulates the acetylation and deacetylation of histones by regulating histone acetyltransferases (HATs) and histone deacetylases (HDACs) as well as their activity, which affects chromatin structure and gene expression. The compound reduces the activity of histone deacetylases resulting in hyperacetylation of histones and activation of the expression of genes that control differentiation and apoptosis[31]. Curcumin also affects the epigenetic landscape at specific gene loci, by regulating the pattern of histone methylation, which is done by methylation and demethylation of histones, with enzymes called histone methyltransferases (HMT) and histone demethylases (HDE), respectively. Curcumin's effect on the combined action of histone acetylation and methylation produces a chromatin state that is conducive to the expression of genes that are tumor suppressive and to the suppression of tumor-genic genes. Curcumin is known to inhibit histone deacetylase, a property also seen with the already approved epigenetic therapies, which could indicate a possible use for combination therapy[32].

5.3 MicroRNA-Mediated Regulation

Curcumin changes the expression profile of microRNAs in breast cancer, thus post-transcriptionally regulating the genes associated with cell proliferation, apoptosis, metastasis and drug resistance. There are emerging evidences that curcumin has an impact on microRNAs and long non-coding RNAs in different types of cancers. Curcumin regulates the expression of tumor suppressor miRNAs such as miR-15a, miR-16, miR-34a, and miR-200 family whereas it suppresses the expression of oncogenic miRNAs like miR-21, miR-155 and miR-

221/222. Curcumin's effect on miRNA pathways, such as PI3K/AKT, MAPK and STAT3, helps underlie its anticancer effect. The effects of curcumin on miRNAs seem to be cell-type specific and could differ between different breast cancer types. Curcumin mediated modulation of miRNA expression can be a mechanism that affects gene expression in general by targeting multiple mRNA transcripts[33].

5.4 Long Non-Coding RNAs and Circular RNAs

Curcumin regulates the expression of long non-coding RNAs, as well as circular RNAs – new regulators of gene expression – whose expression is linked to breast cancer pathogenesis and therapeutic resistance. Curcumin is involved in the regulation of long non-coding RNAs (lncRNAs) which are involved in the breast cancer progression including HOTAIR, MALAT1 and NEAT1. Curcumin also exerts an inhibitory effect on oncogenic long non-coding RNAs and induces the expression of tumor suppressors, which can also play a role in its anticancer activity. One newer research field that may be relevant to the therapeutic use of the compound is its effects on circular RNAs, which act as miRNA sponges and gene expression regulators. The modulation of lncRNAs and circular RNAs by curcumin adds another layer of complexity to curcumin's epigenetic activity and could play a role in its pleiotropic biological activity[8], [34], [35].

5.5 Epigenetic Regulation of Tumor Progression and Resistance

In addition to direct regulation of protein-coding genes, the epigenetic impact of curcumin is thought to be the mechanism by which curcumin inhibits the progression of cancer and overcomes therapeutic resistance. Curcumin can alter DNA methylation, histone modifications and the expression of non-coding RNA molecules, leading to epigenetic reprogramming of the cancer cell towards a more differentiated and less aggressive phenotype. It is believed that curcumin can be used as part of combination therapies with conventional drugs because of its ability to re-epigenetically modify cells that were epigenetically changed by the drugs, thereby

reverting the drug resistant state. Epigenetic regulation by curcumin might impact cancer stem cells, which are especially vulnerable to epigenetic regulation for their stemness maintenance and therapeutic resistance. As curcumin can induce long-lasting epigenetic modulation, this effect might account for lasting responses and less relapse after application of curcumin[30], [36].

6. Curcumin and the Breast Cancer Tumor Microenvironment

6.1 Regulation of Cancer-Associated Fibroblasts

Curcumin affects the function of cancer associated fibroblasts (CAFs), which are one of the major stromal cell types in breast cancer and which have been found to positively influence the progression of breast cancer by extracellular matrix remodeling and paracrine signalling. CAFs secrete cytokines, chemokines and growth factors which promote cancer cell proliferation, invasion and angiogenesis. Curcumin blocks the activation and proliferation of cancer associated fibroblast and the production of pro-tumorigenic factors. The compound inhibits the expression of the cancer associated fibroblast activation markers, fibroblast activation protein (FAP) and α -smooth muscle actin (α SMA). Curcumin disrupts the supportive microenvironment that allows tumor growth and drug resistance by changing the stroma-tumor interaction. The modulation of activities of cancer-associated fibroblasts is associated with the inhibitory effects of curcumin on invasion and metastasis, involving the modulation of the extracellular matrix and stromal signaling[37], [38].

6.2 Modulation of Tumor-Associated Macrophages

TAMs are responsible for both promoting and suppressing tumour growth, depending on their phenotype, and curcumin affects TAMs' polarization and activity. Curcumin blocks the conversion of macrophages to the pro-tumorigenic M2 phenotype and their secretion of suppressor and pro-angiogenic factors. The compound successfully suppressed the PI3K/AKT/STAT3 pathway in macrophages of Type 2 (M2), which greatly reduced their ability

to induce the chemoresistance of breast cancer cells. Curcumin induces macrophage polarization to the M1 type that favors antitumor immunity by producing pro-inflammatory cytokines. Curcumin can modulate macrophage function to remodel pro-tumorigenic tumor microenvironment to an antitumorigenic one[39].

6.3 Immune-Cell Regulation and Antitumor Immunity

Curcumin affects several components of the immune cell populations in the breast cancer environment impacting both innate and adaptive immunity. The compound regulates the maturation and functions of dendritic cells that affect antigen presentation and activation of T-cells. Curcumin is known to suppress the activity of regulatory T cells and myeloid-derived suppressor cells, types of immunosuppressive cells. Curcumin's ability to modulate immune checkpoint molecules, such as the expression of PD-L1, could improve the effectiveness of immunotherapeutic strategies. The compound stimulates the activity of cytotoxic T lymphocytes and natural killer cells, which are necessary for anti tumor immune responses. The immunomodulatory activity of curcumin on antitumor immunity is complex and depends on context to have immunostimulatory or immunosuppressive effects. Curcumin along with immunotherapeutic drugs could be a promising approach in boosting antitumor immunity[40], [41].

6.4 Angiogenesis and Tumor Vascularization

Curcumin has ant tumoural angiogenic activity which acts on endothelial cells and tumour cells by various mechanisms. The compound inhibits the expression and secretion of pro-angiogenic proteins, such as VEGF, bFGF, and angiopoietins, and inhibits the angiogenic signaling that promotes new blood vessel growth. Curcumin suppresses endothelial cell proliferation, migration and tube formation, thus interfering directly with the process of angiogenesis. Curcumin's inhibition of STAT3 also suppresses the expression of VEGF and other angiogenic factors, thereby inhibiting the process of angiogenesis. Curcumin has been shown to inhibit the development of

angiogenesis in a number of preclinical cancer models, including mouse models of human breast cancer, where curcumin inhibited tumor growth and cell proliferation while inhibiting angiogenesis. Curcumin exhibits anti-angiogenic effect which supports the anti-tumorigenic growth effect and might prevent metastatic dissemination[42], [43].

6.5 Hypoxia, Inflammation, EMT, and Metastatic Progression

Curcumin has a number of targets which involve many processes taking place during the metastatic process such as hypoxia adaptation, chronic inflammation, epithelial-mesenchymal transition, and dissemination. The compound blocks hypoxia-inducible factor signaling, which hampers the way cells adapt to low oxygen to survive, form blood vessels and spread. It is known that curcumin can inhibit the inflammatory cytokine-signaling that can induce EMT and invasion. The compound blocks EMT by regulating transcription factors and signalling pathways involved in the regulation of this phenotypic switch. Curcumin is a multifaceted blocker of metastatic progression through its ability to inhibit migration, invasion and angiogenesis. Curcumin has been shown to inhibit the metastatic progression in various experimental models and it has been shown to reduce incidence and extent of metastasis[40], [44].

7. Bioinformatics and Network Pharmacology Perspectives

7.1 Computational Prediction of Curcumin-Associated Targets

Through bioinformatics, the molecular targets associated with curcumin can be predicted systematically to gain a broad understanding of curcumin's polypharmacological profile. Computational prediction of curcumin targets has revealed hundreds of potential protein targets and curcumin can target multiple proteins due to its flexible chemical structure. Target prediction algorithms combine information about known interactions, structural similarity and chemical structure to determine the proteins that are likely to interact with curcumin. The GeneCards and Online Mendelian Inheritance in Man databases can be

used to find targets associated with breast cancer, for comparison with curcumin targets. The network pharmacology studies have been carried out on curcumin and its compounds, resulting in the identification of 132 drug-disease intersection genes and 138 enriched pathways. As per the computational prediction of curcumin targets it can serve as a framework to understand the multi-targeting capabilities of curcumin[45].

7.2 Gene Expression and Differential-Expression Analysis

The results showed that the gene expression profiles of breast cancer cells change significantly after curcumin treatment and that differential expression analysis identified the gene expression programs that responded to curcumin. Transcriptomic studies have provided genes which are found to be highly up- or down-regulated after treatment with curcumin, giving some clues of the molecular pathways involved. The results from integrated transcriptome and molecular docking approaches have shown that curcumin can inhibit the identified hub targets of curcumin in breast cancer cells. Curcumin causes changes in gene expression such as up regulation of pro-apoptotic genes and down regulation of proliferative and survival genes, in addition to modulation of genes that affect inflammation and metastasis. The study of differential gene expression results in a molecular fingerprinting that not only offers insight into curcumin's anticancer mechanism but it also serves to identify potential markers for treatment response[46].

7.3 Gene Ontology and Pathway Enrichment Analysis

The functional profiles of the genes related to curcumin are determined by gene ontology analysis that classifies the genes into three categories: biological process, cellular component, and molecular function. Curcuma-changed genes are associated with biological functions such as cell cycle, apoptosis, stress response and inflammatory signalling. Pathway enrichment analysis indicates the significantly altered signalling pathways, which are affected by curcumin and include PI3K/AKT, MAPK, JAK/STAT, NF- κ B and Wnt/ β -catenin signalling pathways. In total 67 cellular

components, 113 molecular functions and 2042 biological processes are associated with the genes affected by curcumin. The enrichment pathways found by pathway analysis include pathways which are directly involved in breast cancer pathogenesis. These curcumin-affected genes and pathways are functionally annotated, giving a systems-level understanding of its anticancer activity[47].

7.4 Protein-Protein Interaction and Hub-Gene Identification

Protein-protein interaction network analysis reveals the molecular interactions and hub genes involved in curcumin's anticancer effects. By constructing protein interaction networks for curcumin targets, affected proteins in the network can be shown to be interconnected, and highly connected hub proteins in the network can be identified. These hub genes are essential nodes in the mechanism of action of curcumin and may be the target for further studies. The protein interaction network of curcumin in breast cancer has been established, and studies have been based on the interaction between the target of curcumin and genes related to breast cancer through databases like String and Cytoscape. Key regulators of signal transduction, apoptosis and cell-cycle progression are among these hub genes identified in these networks[48].

7.5 Curcumin-Target-Pathway Network Construction

Network pharmacology methods can be used to integrate curcumin, targets, and affected pathways into comprehensive networks to fully demonstrate the multi-targeting mechanism of action of curcumin. The curcumin-target-pathway networks illustrate the relationship between the compound, the targets directly involved in the relationship and the pathways the targets regulate as well as the biological functions impacted. These networks illustrate that an anticancer effect of curcumin is not a result of a single interaction of the molecule with a pathway or a target but a combination of multiple interactions. Using curcumin-target-pathway networks, the same researchers have now been able to use the networks to analyse the mechanism of curcumin for breast cancer, uncovering an intricate network and potential

new therapeutic targets. By using network analysis, one can appreciate the interconnectedness of the effects of curcumin and obtain a framework for understanding the pleiotropic nature of the biological activities of curcumin[49].

8. Structural Bioinformatics, Molecular Docking, and Artificial Intelligence

8.1 Molecular Docking with Breast Cancer-Associated Targets

Using molecular docking studies, the binding interaction between curcumin and proteins involved in breast cancer pathogenesis has been predicted, offering a structural mechanism of action of curcumin in breast cancer. The docking analyses have revealed that AKT (PDB ID: 2UZR), TNF (PDB ID: 4RSU) and TP53 (PDB ID: 6VIP) are protein targets with favourable docking interactions with curcumin. Transcriptomic findings and molecular docking have revealed that curcumin can inhibit these high-scored targets at the protein level and that they can play the roles of self-feedback factors, based on the cascading repressive effects in the network. The inferred binding modes indicate the nature of the interaction between curcumin and its protein targets and offer implications into the structural determinants of the binding affinity and specificity. In vitro cell line studies give insight into the use of curcumin and resveratrol co-delivery on chemoprevention and therapy in breast cancer[50], [51].

8.2 Binding Interactions and Structural Determinants

The binding interactions of curcumin with its protein targets depend on the chemical structure of curcumin and the three-dimensional architecture of the protein targets. The two aromatic rings linked by the β -diketone moiety in the structure of curcumin can interact in several ways: hydrogen bonding, hydrophobic interactions, π - π stacking, and van der Waals forces. The o-methoxy phenolic groups of curcumin are capable of hydrogen bonding with amino acid residues and the aromatic rings can interact with aromatic residues in the pocket by π - π stacking interactions. The structure-based interaction studies have indicated that curcumin is a high-affinity binder to the targets involved in

breast cancer, which makes it a good inhibitor. These structural determinants of curcumin binding may be used as a basis to develop analogues with greater binding affinity and specificity[52].

8.3 Molecular Dynamics and Binding Stability

Molecular dynamics simulations help to determine the stability of protein-protein complexes and the temporal evolution of binding interactions, such as curcumin-protein. The simulations offer insight into the conformational changes upon binding of curcumin and into the stability of the interaction under physiological conditions. Dynamics studies have found high binding efficiencies for curcumin and resveratrol, and curcumin is found to be more stable than resveratrol. A molecular dynamics study of BRCA1/TP53 inhibition by curcumin analogues has shown that they possess strong antiproliferative activity and are potential inhibitors for tumours. Analysis of the binding stability by MD simulation aids in the selection of high-confidence targets of curcumin and the design of optimised curcumin analogues[53].

8.4 Machine Learning and AI-Assisted Target Prediction

AI and machine learning have been increasingly used to identify the potential targets of curcumin and enhance its therapeutic uses. Machine learning models combine chemical structure, known interactions and biological activity to highlight new curcumin targets and explore their functional relevance. These methods may reveal the patterns of curcumin-target interactions which are not obvious with the conventional computational methods. AI-assisted target prediction has been used for curcumin in breast cancer to identify possible targets and to predict its impact on cellular mechanisms. Combining AI and machine learning with molecular docking and network pharmacology is a thorough computational approach to comprehending the mechanism of action of curcumin[47].

8.5 Computational Validation and Limitations

Experimental validation is necessary to validate computational studies of curcumin in breast

cancer to ensure that the interactions predicted are relevant and have been experimentally determined to be biologically significant. Computational predictions may give potential targets and mechanisms, but in vitro and in vivo test must be done for the validation of the findings. Computational approaches have limitations such as the oversimplification of molecular interactions, not taking the cellular context into account and the possibility of false positives. These constraints notwithstanding, computational approaches offer an important blueprint to help direct experimental research and decipher the intricate mechanism of action of curcumin. Computational and experimental methods have proven to be the best approach to elucidate the therapeutic potential of curcumin in breast cancer[47].

9. Multi-Omics and Precision Therapeutic Perspectives

9.1 Transcriptomic Responses to Curcumin

The transcriptomic analysis describes the global changes of gene expression induced by curcumin, allowing to gain insights into the molecular programs that are affected after treatment. Curcumin has been found to upregulate genes associated with apoptosis and cell cycle arrest and to downregulate genes associated with cell proliferation and survival, and metastasis. Curcumin causes different transcriptomic responses in the various breast cancer subtype, reflecting the differences in the underlying molecular characteristics and pathway dependency. Hub targets of curcumin identified by integrated transcriptome and molecular docking approaches are confirmed to be inhibited at the protein level and exhibit self-feedback mechanism[47].

9.2 Proteomic and Phosphoproteomic Alterations

Curcumin-treated breast cancer cells show changes in the expression of proteins, post-translational modifications and activity of signaling pathways by Proteomic analysis. Curcumin affects the kinase signalling pathways by changing the phosphorylation patterns. Proteomic alterations have been shown to be associated with cellular changes such as

migration inhibition, cell-cycle arrest, and induction of apoptosis[54].

9.3 Metabolomic and Lipidomic Signatures

The metabolomic analysis allows one to obtain the changes of small molecules induced by curcumin, which reflects its activities on cellular metabolism. Curcumin makes changes in glucose metabolism, lipid metabolism and mitochondrial function. Metabolomic signatures can be used as a biomarker for curcumin response, and may give insights on the mechanism of curcumin's anticancer activity[55].

9.4 Integration of Multi-Omics Datasets for Biomarker Discovery

Combining transcriptomic, proteomic and metabolomic data allows for a broader picture of curcumin's cellular effects and allows for identification of biomarkers of response. Comparing and combining the results of these three omics provides a link between the changes in gene expression, protein levels and the metabolic profile which cannot be seen in the single omics. Integrated analysis can find signaling pathways impacted by curcumin consistently at various molecular levels[49], [56].

9.5 Breast Cancer Subtype-Specific and Precision Therapeutic Strategies

The differential efficacy of curcumin in breast cancer variants is indicative of the different molecular characteristics and pathway dependence. Curcumin might be especially effective against triple-negative breast cancer, a type of breast cancer that has no specific treatment. Curcumin could be used in combination with endocrine therapy for luminal breast cancers. Curcumin along with HER2-targeted agents might be effective in the treatment of HER2-enriched breast cancer[57].

10. Therapeutic Translation: Drug Resistance, Combination Therapy, and Delivery Systems

10.1 Curcumin-Mediated Reversal of Therapeutic Resistance

Curcumin works on therapeutic resistance by multiple mechanisms that act on cellular processes involved in therapeutic resistance. The compound is a modulator of ATP binding cassette transporters, which decreases the efflux

of chemotherapy agents from cancer cells. Curcumin is able to block activation of the survival pathways, such as PI3K/AKT and STAT3, that have been turned on by the treatment. Curcumin may be effective in reversing resistance by modulation of tumor microenvironment and cancer stem cells. Curcumin improves tamoxifen activity, and overcomes endocrine resistance by inhibiting proliferation, inducing apoptosis and blocking of survival pathways [48].

10.2 Combination with Chemotherapy and Endocrine Therapy

Curcumin combination with chemotherapy shows better anticancer activity with complementary pathways. A study in patients with advanced breast cancer has demonstrated tolerability of the combination and indication of improved response rates for curcumin and docetaxel . Curcumin boosts the effect of tamoxifen and helps to overcome endocrine resistance. Curcumin in combination with paclitaxel can increase overall response rate and physical performance. Combination therapy with curcumin and paclitaxel led to better treatment results, decreased fatigue and good tolerability in clinical trials. Curcumin is a representative MTT agent with multi-targeting mechanism, which makes it a good candidate for conventional chemotherapeutic agents[58].

10.3 Combination with HER2-Targeted and Immunotherapeutic Approaches

Curcumin might also improve the efficacy when given in combination with HER2-targeted drugs by blocking the feedback loops and resistance mechanisms. Curcumin has been shown to inhibit the STAT3 pathway, and inhibition of this pathway may re-sensitise cells to trastuzumab, suggesting its role in trastuzumab resistance. The possible immunomodulatory activity of curcumin could be useful when combined with other immunotherapeutic drugs, such as immune checkpoint inhibitors. Curcumin has been shown to selectively target several signalling pathways, and these findings suggest that curcumin could be a promising candidate for repurposing[59].

10.4 Nanotechnology-Based Curcumin Delivery Systems

The use of advanced formulations such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles in curcumin technologies benefits its bioavailability, stability, and tissue distribution. It has been observed that the liposomal curcumin formulations have much higher efficacy in breast cancer cells, with their IC_{50} decreased from $19.81 \pm 1.03 \mu\text{g/mL}$ to $9.16 \pm 0.67 \mu\text{g/mL}$. Curcumin-loaded PLGA nanoparticles can effectively arrest the cell cycle at the G2/M phase and decrease the proliferation rate of tumour cells by up to 50%. Curcumin has been found to inhibit the growth of tumours and metastasis at the preclinical level in mice when given intravenously. Curcumin formulations have been tested in clinical trials such as NCT01403545 (liposomal curcumin) and NCT03072992 (intravenous curcumin in combination with chemotherapy), showing their safety and potential clinical benefits[60].

10.5 Preclinical Evidence, Clinical Studies, Safety, and Translational Barriers

Preclinical data show that curcumin has a number of anticancer properties such as antiproliferative, proapoptotic and inhibition of metastasis. Curcumin-based therapies, along with combination therapy with conventional chemotherapeutics, have been shown to be safe and tolerable in early-phase clinical trials. The biggest challenge in the path to clinical translation is lack of bioavailability because of low solubility, fast metabolism and unstable absorption. Advanced delivery systems and combination strategies are potential ways of solving this limitation. But the heterogenic nature of the tumour makes its use in therapy difficult, since all breast cancers do not use curcumin-sensitive pathways equally[61].

11. Conclusion and Future Perspectives

The anticancer activity of curcumin can be attributed to a concerted effect on several signaling pathways, epigenetic regulation, and the tumor microenvironment. It is directly against STAT3 phosphorylation in order to reduce pro-tumorigenic signaling, and modulates the PI3K/AKT/mTOR, MAPK/ERK, JAK/STAT, NF- κ B and Wnt/ β -

catenin pathways. Mechanistic details are added by epigenetic regulation by DNA methylation, histone modifications and non-coding RNA modulation. Curcumin's multi-targeting properties resonate with the complex nature of breast cancer pathogenesis and its subsequent benefits over single targeting drugs.

The use of bioinformatics and integration of multi-omics has progressed the understanding of curcumin's mechanism by understanding its molecular targets and the affected pathways. Using network pharmacology, the multifaceted effects of curcumin are revealed. Combining the use of computational predictions with experimental validation seems to be the best approach to comprehend the therapeutic potential of curcumin.

Curcumin is active in all breast cancer subtypes, showing a special promise in inhibiting Hedgehog/Gli1 pathway in triple negative breast cancer. Curcumin has been found to be effective when used in combination with endocrine therapy for estrogen receptor-positive breast cancer. Curcumin with HER2-targeted drugs could prove useful in the treatment of HER2-enriched tumors. Further investigation is needed with subtype specific mechanisms and biomarker-driven approaches.

Low solubility, high metabolism and unreliable absorption are major challenges in clinical translation and are cause for poor bioavailability. The role of metabolites in the general anticancer activity needs to be studied. The formulation and administration of curcumin should be standardized. Patient populations and combination strategies need to be identified. The chronic effects of curcumin treatment in normal tissues should be evaluated. Tumor heterogeneity complicates clinical application. The future work could be directed towards developing optimized formulations to improve the bioavailability such as nanoparticulated delivery system. Identification of biomarkers for patient selection and monitoring is needed. One new trend is integration with immunotherapy. Curcumin with novel targeted agents could be a solution for the issue of pathway cross-talk and resistance. There is an opportunity for precision implementation with AI-assisted target prediction and digital health monitoring. Due to its pleiotropic anticancer mechanisms and

favorable safety profile, there is promise that curcumin will prove to be helpful as therapy for breast cancer.

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