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TRANSDERMAL DELIVERY OF CURCUMIN IN BREAST CANCER: ADVANCES, CHALLENGES, AND FUTURE PERSPECTIVES

Pasupuleti Sreenivasa Rao*[1abc], Ramalinga Viswakumar[2], Byna Syam Sundar Rao[3], Priyanka Mangala[4], Narasaiah Kolliputi[5]

[1a]Professor, Department of Biochemistry
[1b]Senior Research Scientist, Central Research Laboratory (ARC), Narayana Medical College.
[1c]Research advisory professor, Narayana College of Pharmacy, Nellore-524003, Andhra Pradesh, India
[2]Professor, Department of Pathology, Narayana Medical College.
[3]Research Assistant, Central Research Laboratory (ARC), Narayana Medical College and Hospital.
[4]Professor, Head, Department of Biochemistry, Narayana Medical College.
[5]Associate Professor, Division Director of Research Education, Division of Allergy and Immunology, Department of Internal Medicine, Department of Molecular Medicine, College of Medicine, MDC 19, Room: 4134, University of South Florida 12901 Bruce B. Downs Blvd, Tampa, FL 33612.

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***Corresponding author:**

Pasupuleti Sreenivasa Rao

Professor, Department of Biochemistry, Senior Research Scientist, Central Research Laboratory (ARC), Narayana Medical College and Hospital, Nellore-524003, Andhra Pradesh, India.
sraopasupuleti@yahoo.com

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ABSTRACT

Traditional medicine continues to play a significant role in primary healthcare systems worldwide, particularly in low- and middle-income countries. In several phytotherapy-based medical practices, native medicinal plant/herbal extracts are widely used to treat various disorders and diseases. Their usage is rapidly developing due to its beneficial effects and assumed with less toxic side effects. *Curcuma longa* is one such important medicinal plant with high medicinal values. Its usage is common in ethno-traditional medicine and in all other medical practices. It is a rich source of various bioactive compounds. Curcumin is the primary ingredient and is widely used in multiple therapeutic applications that include cancer. Breast cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide. Many researchers are looking for appropriate anti-cancer agents for treating Breast cancer. Curcumin has gained considerable attention as a potential therapeutic agent in breast cancer. Transdermal drug delivery systems (TDDS) act through topical skin and deliver drugs into blood circulation through the skin. TDDS has many advantages when compared to conventional dosage forms that may increase patient compliance by lower dose frequency, with minimal side effects, and non-invasive delivery of drugs. Several drugs are employed through the transdermal route. However, the present review highlights the transdermal administration of Curcumin in breast cancer with major challenges, and future perspectives.

KEYWORDS: Curcumin, Secondary metabolites, breast cancer, nanoparticles, transdermal chemotherapeutic agents.

INTRODUCTION

The majority of the global population up to 80 percent in developed and as well as developing nations depend on traditional medicine for their primary health care. Currently, medicinal plant/herbal medicine for treating various disorders and diseases is rapidly emerging, since they offer less toxic side effects.[1] The Medicinal /herbal Plants may encompass active constituents, which have been shown to efficiently hinder the disease or disorder symptoms in a synergistic manner.[2] These active ingredients from these Medicinal /herbal plants may possess

polysaccharides, pigments, steroids, terpenoids, flavonoids, alkaloids, etc. Earlier studies have shown that Medicinal/herbal plant extracts and purified molecules efficiently managed to control several diseases and disorders.[1-9] Secondary metabolites derived from plants are also referred to as "phytochemicals" which have gained global attention among the scientific communities, because of their role in managing health and controlling diseases. *Curcuma longa* is an important plant belonging to the ginger family (Zingiberaceae), which has rhizomes. Curcuma longa has been used for centuries as a remedy in traditional Indian medicine to treat several varieties of illnesses, including inflammation, gastric, hepatic, and infectious diseases, as well as blood disorders. Curcumin is a major polyphenol found in *Curcuma longa*, which has a wide range of therapeutic effects such as antioxidant, anti-inflammatory, antimicrobial, antitumor, and hepato-protective action.[10]

Globally, cancer is well associated with mortality and morbidity. It has been projected that nearly 1,958,310 new cancer cases will occur and 609,820 cancer deaths in the United States in 2023. It has been postulated that about 85-95% of cancer cases are due to exposure of carcinogenic chemicals radiation and pollution.[11] Among all breast cancer is the most common cancer found in women in both developing and under developed countries. Globally, for every one in four cancers is breast cancer, diagnosed in women.[11-13] Breast cancer is the most frequently diagnosed cancer in women and ranks second among causes of cancer-related death in women. It was estimated that nearly 297280 new cases would occur along with 43170 death cases, alone in the USA in 2023, while in India it was projected to 2.4 lakhs by the end of the year 2025. The ability to identify and diagnose breast cancer has improved markedly. Treatment decisions, which were based in the past predominantly on the anatomic extent of the disease, are shifting to the underlying biological mechanisms. Gene array technology has led to the recognition that breast cancer is a heterogeneous disease composed of different biological subtypes, and genetic profiling enables response to chemotherapy to be predicted. BRCA1 (Breast Cancer gene 1) and BRCA2 (Breast Cancer gene 2) are genes that generate proteins that repair damaged DNA.[12-14] Everyone will possess two copies of each of these genes—one copy individually inherited from each parent. BRCA1 and BRCA2 are sometimes referred to as tumor suppressor genes since they could have some unknown changes, which may be deleterious or pathogenic, variants or mutations, which could lead to cancers. People who inherit harmful variants in one of these genes will have increased risks for various cancers, notably breast and ovarian cancer. People who inherit either of these variants of BRCA1 and BRCA2 will have a higher chance of developing cancer at younger ages. In woman general population, nearly 13% will develop breast cancer.[11-14] In women by contrast, 55%–72% will inherit the BRCA1 variant, and 45%–69% will inherit the BRCA2 variant and will be having higher chances of getting breast cancer in between the age of 70–80 years.[14]

Breast conservation became an established standard of care, and the oncoplastic approach enables wide excisions without compromising the breast's natural shape. Sentinel lymph node biopsy has replaced axillary dissection as the standard procedure to stage the axilla and spared many patients the excess morbidity of axillary dissection. Different treatment regimens will be followed for treating breast cancer including chemotherapy, targeted therapy, immunotherapy, and hormonal therapy.[15] Majorly targeted therapy to the estrogenic receptor plays a major role in systemic therapy; pathways responsible for endocrine resistance have been targeted as well. Biological therapy has been developed to target HER_2 receptors and a combination of antibody-drug conjugates linked cytotoxic therapy to HER_2 antibodies. Meaningful improvements in survival resulted from the new effective systemic agents and patients with metastasis are likely to have a longer survival.[16] However, in spite of advancements in treatment modalities, breast cancer patients still experience tumor recurrence and metastasis. Therefore, new-age therapeutics are needed. Recent advancements in modern molecular biological tools like DNA sequencing, genetic engineering, gene targeting, and transgenic methodologies have established a new path for better understanding progression of breast cancer, which could deliver newer choices for developing novel therapeutics.[16-19] currently, to combat diseases like breast cancer.[16-21] In current world, several efficient drug development technologies have been introduced, through programs like in silico drug designing and synthesis of novel molecules.[16,22-26] However, the problems continue the same. Hence, alternatives are required. The delivery of drugs through the transdermal route is gaining significance. However, the scope of transdermal delivery of various small chemotherapeutics is not fully understood. Transdermal delivery not only facilitates the delivery of new chemical entities, such as small molecules but also improves their efficacy. Administering the drugs through a transdermal route to treat various types of cancers like breast cancer and skin cancers, as the delivery of drugs could be targeted to their respective sites.[27-28] In addition, transdermal delivery systems could be used for the effective co-delivery of more than one chemotherapeutic drug or combination therapy.[29] This approach may yield fruitful results in overcoming drug resistance to certain anticancer

drugs. Moreover, the administration of various drugs and their dosage will be reduced in combination with synergistic effects or targeted delivery at the respective tumor sites to minimize the side effects. Through this approach, dose-related side effects would be reduced, thereby enhancing patient compliance.[29-30] In general, small molecules possessing a log P value ranging from two to four will be ideal for the transdermal formulation, whereas hydrophilic and large molecular weight therapeutic drugs could be delivered either by employing active enhancement methods like sonophoretic, iontophoresis, microneedles, and laser thermal ablation. Thus, by selecting appropriate excipients and permeation enhancement techniques, a broad range of chemotherapeutic formulations could be designed and delivered via the transdermal route.

Advances in Transdermal Curcumin Delivery: Challenges and Future Perspectives

Transdermal drug delivery systems (TDDS) act through topical skin and deliver drugs into blood circulation through the skin. TDDS has many advantages when compared to conventional dosage forms that may increase patient compliance, by lowering dose frequency, with minimal side effects, and non-invasive delivery of drugs. Several drugs are employed through the transdermal route. However, the present review highlights the transdermal administration of Curcumin in breast cancer.

Curcumin [1,7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptane-3, 5-Dione], a lipophilic polyphenolic molecule isolated from *Curcuma longa*, has gained attention due to its diverse pharmacological activities. Curcumin is a major ingredient and chief colorant of turmeric, which has been used for centuries in Asian countries as a spice, as a good anti-inflammatory agent. Curcumin has been proven for its wound healing, anti-microbial, anti-inflammatory and anti-cancer properties.[10,31] Moreover from our group, reported, the efficacy of Curcumin that attenuates replicative senescence in human dental follicle cells and also demonstrated their osteogenic potential.[32] Earlier studies revealed its chemotherapeutic effects against several tumor-bearing animal models, making it an ideal agent for transdermal delivery, particularly in the treatment of melanoma. However, the solubility and stability property of Curcumin was disadvantageous for its formulation preparation. Curcumin dissolved in methanol, ethanol, and propylene glycol, and slightly dissolved in water. It was not stable in a neutral medium, and generated ferulic acid. In addition, the aqueous solubility of Curcumin is as low as 0.004 mg /ml at pH 7.4.[33]

Many researchers were tried to address these problems. Few novel Curcumin formulations were investigated, including nanocrystals, followed by Solid lipid nanoparticles, transdermal films, microspheres, Nanospheres, Nanoemulsion, and phospholipid complexes, etc. Figure 2 explains the types of Curcumin nano-formulations whereas figure 3 demonstrates the transdermal delivery of Curcumin.[10,34]

Moreover integration of nanotechnology-based delivery systems like nanoemulsions and solid lipid nanoparticles (SLNs) has considerably improved the therapeutic potential of Curcumin, particularly for transdermal applications. Nanoemulsions are thermodynamically stable systems comprised of oil, water, and surfactants that enable better drug solubilization and permeation across the stratum corneum. Studies have confirmed that nanoemulsion-based transdermal delivery of Curcumin improves skin penetration and bioavailability, mainly in in vitro and ex vivo models, due to their minor droplet size and huge surface area.[33,38] These systems also advance drug dispersion and sustain release, allows them appropriate for localized and systemic delivery.
Similarly, Solid lipid nanoparticles (SLNs) are promising nanocarriers looks encouraging due to their capability to improve drug stability, protect Curcumin from degradation, and offer controlled release. SLNs are majorly comprised of biocompatible lipids that remain solid at physiological temperatures, thus improving drug encapsulation efficacy and stability during storage and administration.[36] Preclinical studies in animal models have shown that SLN-based Curcumin formulations displayed better pharmacokinetics with improved anticancer efficacy in comparison to conventional formulations.[34,36] Overall, these nano-formulations offer a strategic advantage in disabling the natural limitations of Curcumin that includes poor solubility, low bioavailability, and rapid metabolism, consequently supporting their potential use in transdermal chemotherapeutic applications.

In situ-forming, hydrogels (ISGs) are aqueous liquid solutions before usage, but gels under physiological conditions. Gelation occurs in situ with ionic cross-linking or after a shift in pH or temperature. ISGs are the most optimal transdermal formulations, because they possess several advantages, easy to mix, easy to apply, long adhesion time on the skin surface, and also have good permeation ability of therapeutic agents. Earlier studies also demonstrated that ISG-based Curcumin transdermal formulations were used in melanoma treatment.[10,34]

Poloxamers (Pluronic), are known as synthetic tri-block copolymers comprising central hydrophobic chains of poly (propylene oxide) connected between two hydrophilic chains of polyc(ethylene oxide). Their

chemical characteristics based on temperature-dependent self-assembly and thermo-reversible behavior along with biocompatibility and physiochemical properties make them ideal candidates for biomedical applications that include tissue engineering and drug delivery. Their microstructure, bioactivity, and mechanical properties tailored them to mimic the behavior pattern of several types of tissues. Additionally, their amphiphilic nature and the potential to self-assemble into the micelles allows them ideal drug carriers with the capability to improve the drug disposal to make cancer cells more vulnerable to drugs. Poloxamer block copolymers are the most significant chemo-selective hydrogel materials. This copolymer consists of ethylene oxide (EO) and Propylene Oxide (PO) blocks arranged in a triblock structure $(EO)_x$-$(PO)_y$-$(EO)_x$. Poloxamer (Pluronic®) is identified by the FDA as an "inactive ingredient" for various pharmaceutical applications that includes intravenous injections, inhalation, oral solutions/suspensions, ophthalmic or topical formulation.[10,44-45] The thermo-responsive solution-gelation transformation (reversible gelation) is basically driven by the physical interface among the segments of the triblock copolymers, specially between the hydrophilic polyethylene oxide (PEO) chains and the hydrophobic polypropylene oxide (PPO) block. The thermos-responsive solution-gelation transformation is attributed to the interaction between the segments of the temperature–sensitive copolymers.

Poloxamer 407 molecules in solutions aggregates into micelles with the increase in temperature, resulting from the dehydration of hydrophilic shells hydrated swollen polyethylene oxide (PEO) chains. The micelles would pack from a hydrogel network. At a temperature lower than the sol–gel, transition temperature ($T_{sol\text{-}gel}$) there was no intramolecular interaction between poloxamer molecules. As the temperature increased to $T_{sol\text{-}gel}$, hydrophilic PEO chain entanglement, and hydrophobic PPO dehydration led to the formation of micelles. At a temperature higher than $T_{sol\text{-}gel}$, the outer PEO chain of each micelle interacted due to hydrogen bonding, resulting in gel phenomena. The higher the concentration of the copolymer, the higher the amounts of micelles and the easier the formation of hydrogels. In general, poloxamer is the most common and appropriate excipient as the thermos-selective in situ gelling (ISG) matrix. Further, the solubility and stability of Curcumin was improved by preparing cyclodextrin complexes. High transdermal efficiency and good melanoma therapy were achieved with Curcumin-loaded ISGs. Furthermore, the physicochemical properties of the complexes, erosion of the ISGs matrix, drug release, cytotoxicity, and the inhibition mechanism on B16-F10 cells were also reported.[10,34-36]

Nanoparticle-Based Transdermal Delivery of Curcumin

Transdermal patches are defined as adhesive medicated patch that is placed on the above skin to deliver an exact dose of the drug through the bloodstream with a predetermined rate of release to reach the body. Transdermal delivery for poorly water-soluble Curcumin is believed to be a potential area of research as it delivers the drugs through the skin to the systemic circulation in a variety of clinical indications.[10,32-37] The transdermal delivery system is presently available for various disorders including skin cancer, Alzheimer's disease, Parkinson's disease, cardiovascular disease, depression, anxiety and attention deficit hyperactivity disorder (ADHD), female sexual dysfunction, and postmenopausal dysfunction.[10,32-37]

Transdermal delivery in the form of a patch is an exciting alternative for topical routes to give local or systemic effects. The low oral bioavailability of Curcumin trigged many researchers to study topical preparation. However, Curcumin exhibits low skin penetration resulting in poor efficacy. Nano-emulsion formulations possess improved transdermal and dermal delivery properties in vitro, such as ex vivo. Nano-emulsions have improved the transdermal permeation of many drugs over conventional topical formulations such as emulsions. Earlier studies described few potential strategies to deliver Curcumin via the transdermal route has been reported.[32-37] Similarly, Several formulations have been developed for the topical delivery of Curcumin, which have been reported.[10,32-37] Curcumin wound-healing properties in complementary medicine proven efficient against various skin diseases, including psoriasis, as evidenced from randomized clinical trials. Because of its hydrophobicity, low bioavailability, and chemical instability, a variety of advanced formulations to improve its therapeutic efficacy have been reported and recently reviewed.[32–38]

Curcumin is a good candidate for breast cancer therapy, however its delivery through the transdermal route face hurdles, due to its high melting point and less solubility further lowers its bioavailability. Moreover, the drug faces many hurdles during penetration through the stratum corneum, which have many phases, i.e. either it should absorb systemically or go through enzymatic metabolism or localization into the dermis or epidermis or deep penetration into adipose tissues. Hence, there are limitations Curcumin to being delivered through the skin into the systemic circulation. Therefore, the nanoparticle delivery

system can prove to be a significant carrier system to overcome the problems of Curcumin like low stability, poor bioavailability, very low solubility, and enzymatic breakdown while passing through the various skin layers. In contrast, nanoparticles have many advantages and can be used as an efficient system in transdermal and topical drug delivery for highly hydrophobic compounds. The comparison on delivery routes are documented in table1.

Barriers, Pharmacokinetics, and Clinical Feasibility of Transdermal Curcumin Delivery

Transdermal delivery of Curcumin offers a promising alternative to conventional administration routes; still, several critical tasks must be addressed. The primary barrier is the Stratum corneum, which considerably limits the permeation of hydrophobic and high-molecular-weight molecules like Curcumin. This barrier restricts passive diffusion, highlighting the importance of permeation development strategies that includes nanoparticles, microneedles, and chemical enhancers to develop transdermal flux.[27,37] From a clinical point of view, practicality, transdermal delivery offers distinct advantages, including avoidance of gastrointestinal degradation, reduced dosing frequency, and improved patient adherence, allowing them attractive for long-term cancer therapy.[15,37] Moreover pharmacokinetically, TDDS allows sustained and controlled drug release, sustaining steady plasma concentrations and decreasing peak-dose toxicity. In contrast, oral administration of Curcumin is linked with poor bioavailability due to quick metabolism and systemic elimination, while intravenous provision, although effective in attaining elevated levels of plasma, is restricted by invasiveness and potential toxicity.[33,40] Moreover, when compared to other conventional chemotherapeutic agents like tamoxifen and doxorubicin, Curcumin establishes lower toxicity but also displays reduced bioavailability, necessitating advanced delivery strategies. Thus, comparative analysis proposes that transdermal approach delivers a stable approach, combining moderate bioavailability with upgraded safety and patient compliance. Hence, in spite of prevailing permeability challenges, developments in nano-formulations and delivery technologies support the potential of TDDS as a feasible strategy for Curcumin-based breast cancer therapy.[34,36] In spite of positive preclinical findings, the clinical translation of transdermal Curcumin remains limited due to variability in skin permeability, lack of standardized formulations, and insufficient large-scale clinical trials.

Mode of action and mechanism

As mentioned above Breast cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide. Most researcher's worldwide best looking for appropriate anti-cancer agents for treating Breast cancer. Many studies revealed in-depth analysis and characteristics of pure Curcumin.[10,39] Many researchers clearly reported the role and efficacy of Curcumin in several breast cancer cell lines in vitro apart from other cancer cell lines too.[40] Some pre-clinical and clinical investigations on Curcumin administration through the oral route have demonstrated the poor bio-distribution of Curcumin[39] However. Hosseini et al proved that Nano-formulated Curcumin (SinaCurcumin®) has shown higher bioavailability for oral consumption.[40] Earlier pharmacokinetic investigations in humans revealed that even after high oral dosage administration (Cmax) of 10 g and 12 g of Curcumin, only 2.30 and 1.73 µg/mL of Curcumin were found in the blood. It means that Curcumin undergoes various physiological changes as it enters into the liver and gut.[40-42] The mechanism and mode of action of Curcumin in breast cancer is quite complex. It executes various pathways which have been documented in figure-1. Curcumin affects, targeting protein kinase C (PKC), thioredoxin reductase, tubulin, 5-lipoxygenase, COX-2, cytokines, transcription factors, enzymes, growth factors, and their receptors, and genes that are actively involved in cellular proliferation and apoptosis.[40,42] Few researchers documented that Curcumin regulates pro-apoptotic proteins that include p53 and Bax. Some studies have shown that Curcumin induces apoptosis through activating p53 and downregulating PI3K, p-Akt, and p-mTOR substrates, in which PI3k/Akt/mTOR plays a crucial role in cancer cell survival pathways.[42]

In other words, Curcumin activates p53, which in turn repairs DNA that inhibits the protein kinase B (Akt), which causes enhanced expression of Bax genes, which induces apoptosis[40] In addition, NF-κB is a pro-inflammatory transcription factor that regulates the expression of IL-1, IL-2, and interferon-γ, which is involved in many cell-signaling pathways, and even in cancer progression and inflammation. Curcumin also downregulates the activator protein-1, which is linked with anti-apoptotic, mitogenic, and pro-angiogenic genes. Curcumin arrests NF-κB activity by suppressing NF-κB kinase activation and preventing the p65 subunit of NF-κB[40] Curcumin regulates various pathways hyperactivated in cancer stem cells, which include the Sonic Hedgehog, Wnt/β-catenin, Notch-1, AR, and RTK pathways[40-42] Matrix metalloproteinases (MMPs) belong to the family of zinc-dependent endopeptidases, which degrade proteins of the extracellular matrix. Studies reveal that MMP2 and MMP9 play a role in tumor angiogenesis when the extracellular matrix is degraded. Few studies reveal that Curcumin downplays the expression of the MMPs.[43-44] It has been shown that regardless of suppression of MMP

expression, in human breast cancer epithelial cells, Curcumin hampers the TPA-induced activation of ERK and NF-κB transcriptional activation. In another study, Curcumin downplays MMP9 expression by impairing NF-κB and AP-1 binding to the DNA promoter domain in brain tumors.[43] Curcumin also exerts its anticancer effects by derailing cyclin D1, which acts as a transcriptional co-regulator that modulates cell cycle progression. Few studies revealed that enhanced expression of cyclin D1 is linked with cancer development and progression. Curcumin actively inhibits cyclin D1 through NF-κB suppression.[45] The anti-proliferation effects of Curcumin have been reported in several studies as it regulates several factors like STAT-3, Forkhead Box O3 (FOXO3a), EGFR, and Eukaryotic initiation Factor (eIFs), and transforming growth Factor-Beta (TGF-ß).[45]

For instance, Curcumin suppresses the STAT3 phosphorylation in SCLCNCI-H446 and NCI-1688 cancer cells in vitro and also decreases cyclin B1, which promotes cell cycle progression from G_2 to M phases and finally inhibits cell proliferation. Several researchers demonstrated that Curcumin enhances the expression of FOXO3a in A549 and H460 human lung cancer cells in vitro thereby elevating ROS production. This increased expression of FOXO3a targets a few genes like p27, Bim, and p2.[43-45] Several studies revealed the significant role of the JAK2/STAT3 signaling pathway, which has a critical role in various stages of cancer development. Therefore, arresting the JAK/STAT3 signaling pathway by Curcumin resulted in suppression of JAK2 activity with less number of tumor spheres.[43-45]

In one study, it has been reported that Curcumin treatment in human A549 lung adenocarcinoma cells, resulted in induction of apoptosis. Moreover, elevated levels of superoxide dismutase and also decrease in the levels of malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) were observed suggesting reduction in oxidative stress, with decreased lipid peroxidation. Apart from that, an increasing tendency in phosphorylation of JNK and p38 is noticed, while a decreasing tendency in ERK phosphorylation was observed. In A549 cells treatment with Curcumin-induced apoptosis through the activation of p38, JNK, ERK, and MAPK pathways.[46]

miRNAs (microRNAs) are small, non-coding RNAs that play a major role in cancer by mediating gene expression, either directly acts on oncogenes or tumor suppressors to govern cell proliferation, apoptosis, metastasis, and angiogenesis. Dysregulation of miRNAs neither through overexpression (oncomiRs like miR-21) nor downregulation (tumor suppressors like let-7) that triggers tumor initiation, progression, and chemotherapy resistance. Recent studies demonstrate that Curcumin's antitumor activities are mediated by miRNAs. For example, miRNA-194-5p is down regulated in gastric cancer; while its over-expression suppresses tumor growth.[47] In that study they demonstrated that Curcumin suppresses the progression of gastric cancer by mediating with circ-0056618. Interestingly its over-expression promoted cell proliferation, migration, and invasion, which in turn induces apoptosis and cell cycle arrest. In other words, Curcumin treatment affected the growth of gastric cells by downregulating and upregulating miR-194-5p.[48]

Summary concludes that Curcumin exhibits its anticancer effects through various interconnected multiple signaling pathways rather (Figure-1) than acting on a single molecular target. Earlier studies proved that genetic variations in several key genes are responsible for risk to cancer that includes majorly breast cancer and colorectal cancer.[49] In breast cancer, its action is largely regulated with utmost coordination for survival, proliferation, inflammation, and apoptosis-associated pathways. The major core to this activity is the down regulation of pro-survival signaling cascades like NF-κB, PI3K/Akt/mTOR, and JAK/STAT pathways, which are often dysregulated in cancer progression.[40–42] Instead of operating independently, these pathways display significant cross-talk, and Curcumin looks to serve as a multi-target regulator that interrupts this signalling pathways. For instance, NF-κB inhibition not only decreases inflammatory cytokine generation but also targets downstream targets that are responsible for cell proliferation and angiogenesis. Similarly, down regulation of the PI3K/Akt/mTOR axis causes decrease in cell survival rate and further enhances sensitivity to apoptotic stimuli, while modulation of STAT3 signaling further restricts tumor growth and metastatic potential.[40–43]

Prominently, Curcumin modifies the cellular balance toward apoptosis by up regulating tumor suppressor proteins like p53 and other pro-apoptotic mediators such as Bax, whereas concurrently down regulating anti-apoptotic and proliferative signals. This synchronised regulation causes cell cycle arrest and stimulation of programmed cell death. As well, Curcumin also influences extracellular matrix remodeling by decreasing the expression of matrix metalloproteinases (MMPs), thus inhibiting tumor invasion and metastasis.[43–44] In spite of these positive molecular effects, it is mandatory that most evidences are obtained from in vitro and preclinical studies, however translating these mechanisms into clinical practice remains challenging. The pleiotropic nature of Curcumin, sometimes beneficial, also presents the tasks in identifying accurate therapeutic

targets and improving dosing strategies. Therefore, further studies integrating molecular insights with clinical outcomes are essential to validate its role as a therapeutic agent in breast cancer.[40–45] Despite these promising molecular effects, it is important to recognize that most evidence is derived from in vitro and preclinical studies, and the clinical translation of these mechanisms remains limited. The pleiotropic action of Curcumin presents significant challenges in recognising precise therapeutic targets and also instituting optimum dosage strategies. Hence, studies needed in integrating molecular insights with clinical outcomes to authenticate its role as a therapeutic agent in breast cancer.[40–45]

Figure 1: Mechanisms of Curcumin in Breast Cancer

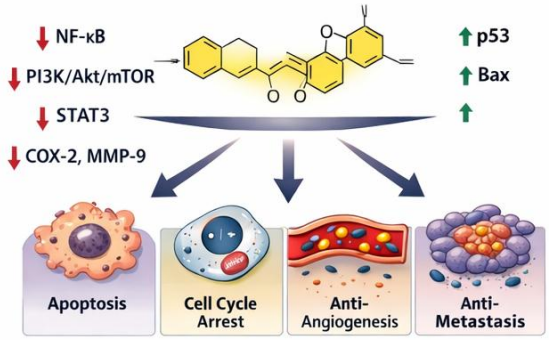

Figure 2: Transdermal Delivery of Curcumin

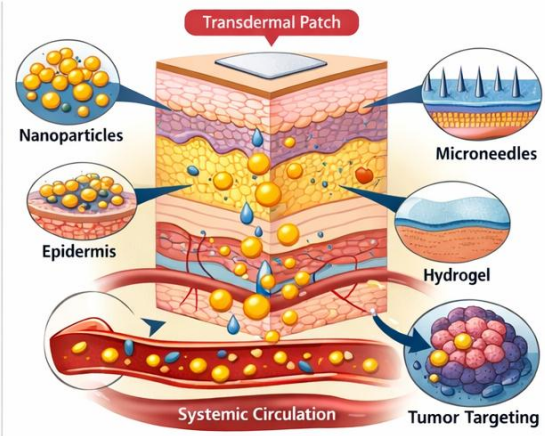

Figure 3: Curcumin Nanoformulations

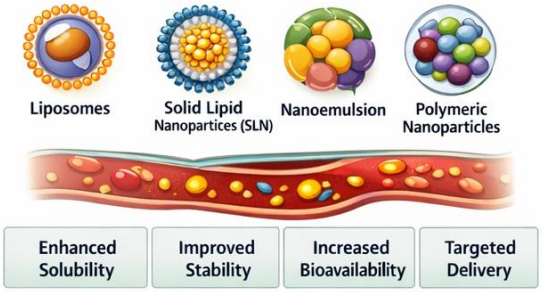

Figure 4: Comparison of Delivery Routes

Route	Bioavailability	Advantages	Limitations
	Low	Convenient	First-Pass Metabolism
	High	Rapid Action	Risk of Toxicity
	Moderate	Non-Invasive	Skin Barrier

CONCLUSIONS

Curcumin represents a powerful connection between natural product chemistry and molecular oncology, exercising multi-target effects that extend from biochemical to epigenetic regulation. It regulates DNA methylation, histone modification, also regulates mRNA stability, translation, and gene expression at a post-transcriptional level. Further arrests tumor initiation, progression, and metastasis. Curcumin's clinical application is poor due to less bioavailability. Modern Nano technologies and bioenhancers have considerably improved its solubility, stability, and therapeutic index, supporting its candidature as a valuable anti-cancer transdermal therapeutic agent for tumors like breast cancer. However, future research needed on nanoformulations, and clinical trials to validate transdermal nano particle efficacy and safety of Curcumin.

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