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Molecular Mechanisms of Nanocurcumin in Breast Cancer Chemotherapy. From Bench to Bedside

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Abstract

The paper Molecular Mechanisms of Nanocurcumin in Breast Cancer Chemotherapy addresses the way nanocurcumin, a nanoparticle formulation of curcumin, can enhance the efficacy of chemotherapy for the treatment of breast cancer. Curcumin, a polyphenol found in the spice turmeric (Curcuma longa), exhibits anticancer properties but is hampered by low aqueous solubility and low bioavailability, which limits its therapeutic potential. Nanocurcumin, through advanced delivery systems, overcomes these limitations, increasing curcumin's stability, bioavailability, and therapeutic action, with the additional potential for reducing side effects compared to conventional chemotherapy. Mechanisms through which nanocurcumin exhibits anticancer action are examined in the review, including cell proliferation inhibition, apoptosis induction, and interference with essential signaling pathways like NF-κB and PI3K/AKT/mTOR. Such actions also counteract drug resistance in chemoresistant breast cancer cells. Preclinical data validate its effectiveness in reducing tumor size and improving bioavailability, suggesting a valuable adjunct to traditional chemotherapy. Yet, broad clinical application is constrained by as-yet-unresolved issues such as best dosing and extensive safety testing. Current research involves the combination of nanocurcumin with traditional therapy and other natural products to achieve optimal therapeutic gain with less toxicity. Regulatory approval, particularly by the FDA, will require massive clinical trials to confirm its safety and effectiveness.

1. Introduction

Curcumin, a polyphenolic bioactive compound derived from the turmeric plant (Curcuma longa), has been of significant interest owing to its anticancer potential. Curcumin is, however, afflicted with limited solubility and poor bioavailability, which hinders its clinical effectiveness. To overcome these limitations, various drug delivery systems have been explored, including nanoparticles, liposomes, and micelles, to enhance the solubility and bioavailability of curcumin(1). Recent studies have established that nanoparticle-loaded curcumin, particularly noisome nanoparticles, have been shown to effectively prevent the glioma stem cell growth and viability via cell cycle suppression and apoptosis(2). Moreover, their incorporation has also been established as more effective in increasing therapeutic effectiveness against tumor proliferation and invasiveness compared to free curcumin(3). As an example, it was demonstrated by animal studies that there was a significant reduction in the volume of mammary tumors in rats treated with curcumin-loaded PLGA nanoparticles when compared with the rats treated with free curcumin(2). In addition to increasing curcumin's therapeutic properties, efforts have been made to identify its action modes. Curcumin is an effective antioxidant because of its unique chemical structure, which contains diketo groups and methoxy phenolic units. These functional groups confer curcumin with the ability to donate hydrogen atoms and exhibit transition metal chelation, thereby further enhancing its antioxidant activity(4,5). The particular function of various structural components towards curcumin biological activities is, however, still under investigation. Moreover, nanocurcumin formulations have been developed by a variety of methods, including ionic gelation and antisolvent precipitation, that have been proven to significantly enhance curcumin bioavailability and stability(3,4). These developments in nanotechnology not only enhance the therapeutic index of curcumin but also bypass its hydrophobicity limitations to develop improved cancer treatment strategies. With further research into the molecular mechanisms of curcumin and its derivatives, there will be a need for complete knowledge of their roles in cancer treatment for effective implementation of these compounds in the clinic(6).

Nanocurcumin

Nanocurcumin, which is a nanoform of curcumin, is gaining more popularity because it has greater therapeutic activity compared to normal curcumin. Its development is made to counteract the drawbacks of curcumin, such as its low bioavailability and water solubility. Since it falls within the nanoscale range, typically 1 to 100 nm, nanocurcumin has a larger surface area, making it more absorbed and distributed within the body. This increased surface area facilitates nanocurcumin penetration into cells and tissues more than regular curcumin, and it is a possible drug delivery system in the therapy of breast cancer(3,4)(7).

Therapeutic Applications

Anti-Inflammatory and Antioxidant Properties

Nanocurcumin was found to possess strong anti-inflammatory and antioxidant activity, which plays a critical role in cancer treatment. The ability of nanocurcumin to enhance systemic bioavailability in plasma and tissue is a major advantage(8). Studies indicate that nanocurcumin can achieve up to 60-fold enhancement in biological half-life compared to native curcumin in animal models, thereby prolonging its therapeutic effect. It has also been discovered to possess the ability to target intracellular pathogens, enhancing its use against a variety of cancers, including breast cancer(9).

Anticancer Mechanisms

Nanocurcumin exerts its anticancer effects by several mechanisms, including inhibition of cell growth, induction of apoptosis, and antiangiogenic mechanisms. In breast cancer, these effects are exerted by the reversal of chemotherapeutic resistance in drug-resistant breast cancer cells. The capacity of nanocurcumin to exert effects through several signaling pathways makes it a very good complementary therapeutic agent in the chemotherapy of breast cancer(10).

Formulation Techniques

Nanocurcumin preparation is achieved through various processes like nanoprecipitation, microemulsion, and ionic gelation. These processes not only improve the solubility and stability of curcumin but also its therapeutic efficacy by optimizing the delivery system(11). For example, delivery systems such as nanoparticles and microcapsules loaded with curcumin have been developed to enhance the delivery of curcumin to cancer cells, exhibiting improved cytotoxic activity compared to traditional formulations(4,12).

Molecular Mechanisms of Action

Nanocurcumin exhibits several molecular mechanisms underlying its efficacy in chemotherapy for breast cancer. These mechanisms involve modulation of major cellular pathways implicated in apoptosis, inflammation, and the cell cycle(13).

Apoptosis Induction

Nanocurcumin targets several apoptotic pathways that promote cell death in breast cancer cells. One of the key mechanisms is the TRAIL receptor pathway, which initiates a cascade leading to the activation of caspase-8, which then cleaves BID protein and activates pro-apoptotic BAK/BAX proteins within the mitochondrial membrane. This action leads to the release of cytochrome c, further activating caspases 9, 3, 6, and 7, ultimately resulting in apoptosis. Besides, curcumin has also been shown to enhance the expression of ER stress-related proteins, such as GRP78, which initiates the PERK pathway and the transcription factor CHOP, resulting in apoptotic signaling(12).

Regulation of the Cell Cycle

Curcumin also controls the cell cycle. It causes the induction of p21, a cyclin-dependent kinase inhibitor, and this causes inhibition of cyclin-Cdk comtor, and this causes inhibition of cyclin-Cdk complexes necessary for transition of the cell cycle from G1 to S and thereby causes cell cycle arrest. To be precise, downregulation of regulatory proteins such as CDC25 and CDC2 that could push the cell into the G2/M phase and induction of p21 have been reported upon curcumin treatment of breast cancer cells. This protein interaction mostly conveys its anti-proliferative activity(14).

Inhibition of Inflammatory Signaling

Nanocurcumin's other target is the NF-κB signaling, as its activation will activate cell proliferation and survival genes like inflammatory cytokines and tumor-inducing MMPs, whose activation leads to tumor growth(4,12). Nanocurcumin blocks the NF-κB signaling pathway, thus reducing the concentration of pro-inflammatory markers and curbing inflammation-mediated tumor growth.

Modulation of Oncogenic Pathways

Nanocurcumin has also been reported to affect pivotal oncogenic pathways, including the PI3K/AKT/mTOR pathway, which is often overexpressed in breast cancer and allows for increased glucose uptake and cell metabolism required for cancer cell growth(12). By inhibiting this pathway, nanocurcumin not only inhibits energy availability to cancer cells but also induces apoptosis and autophagy, which also reduced tumor growth(15).

Synergistic Activities with Other Phytochemicals

Experimental evidence indicates that nanocurcumin is also capable of acting synergistically with other phytochemicals to exert stronger anticancer activities. For instance, when it is synergized with genistein or lycopene, nanocurcumin may exert stronger activities on apoptosis and cell cycle arrest, and it has the potential to be an effective complementary therapeutic agent for breast cancer therapy(12,16).

Preclinical Studies

Preclinical studies investigating the efficacy of nanocurcumin in chemotherapy of breast cancer have shown promising results, though emphasizing the difficulties of translating findings to the clinical setting. Several mechanisms through which chemo-herbal drug combination therapy enhances therapeutic effectiveness have been documented(17). Most importantly, while in vitro and in vivo experiments highlight the cancer suppressive activity of phytochemicals, the safety and translational potential of such findings remain issues of concern to health authorities and the general public(12).

Study Quality and Methodology

An evaluation of preclinical studies by the ARRIVE guidelines showed that 23 out of 26 studies were rated high quality, citing rigorous methodologies and ethical considerations. Most studies detailed encapsulation methods for curcumin and described the nanoparticles (NPs) utilized, with most providing adequate animal models and ethical approvals(18). Despite this, there were inconsistencies seen in reporting risk of bias and animal conditions between studies, limiting rigorous assessment of their quality(3).

Efficacy of Nanocurcumin Formulations

Intravenous (IV) delivery of nanocurcumin has emerged as a dominant strategy, enhancing bioavailability and effectiveness in inhibiting tumor growth in different models of breast cancer, including estrogen receptor-positive and triple-negative breast cancers. Specifically, nanoparticles, micelles, and liposomes have demonstrated improved tumor targeting with reduced cytotoxicity to normal cells(19). For example, some studies highlighted an outstanding reduction in tumor size (as high as 90%) when active targeting moieties are used in lipid-based NPs compared to non-targeted ones(3).

Safety Evaluations

Curcumin nanoparticle safety testing has been given priority, and numerous studies revealed an absence of noticeable toxicity with respect to biochemical markers, hematological change, or damage to major organs. However, few studies employed large parameters beyond body weight to assess toxicity, indicating the need for more exploration of safety profiles to facilitate clinical translation(3). As the body of work on curcumin and its nanoparticle formulations continues to grow, it is critical to maintain both efficacy and safety as priorities to allow these therapies to be safely translated into the clinic(20).

Clinical Applications

Incorporation of Nanocurcumin in Chemotherapy

Nanocurcumin, which is a nanoparticle formulation of curcumin, has been of particular interest in its role in enhancing the efficacy of breast cancer

(BC) chemotherapy. Research indicates that co-administration of nanocurcumin with conventional chemotherapeutic agents can enhance therapeutic outcomes by facilitating better drug delivery and reducing the side effects associated with conventional therapies(2,12). Clinical trials have begun to explore this synergy with promising results in minimizing adverse effects and potentially improving the overall efficacy of cancer therapy(21).

Mechanisms of Action

Mechanisms behind the anticancer activity of nanocurcumin include modulation of several signaling pathways, such as suppression of the WNT/β-catenin pathway, which is known to be involved in the development of cancer. Nanocurcumin also causes enhanced apoptosis in cancer cells, reduces cell proliferation, and prevents tumor growth due to its antioxidant effect and anti-inflammatory property(22). These biological mechanisms vindicate the administration of nanocurcumin along with existing chemotherapeutic agents to generate a synergistic effect.

Patient-Centered Approaches

A large majority of cancer patients are becoming increasingly interested in the inclusion of herbal medicine, such as nanocurcumin, in their routine treatment regimens. Its use is not only meant to decrease the side effects of chemotherapy but also to promote patient well-being and improved therapies(23). Safety and patient compliance are, however, foremost on everyone's minds, rendering extensive safety pharmacology studies of nanocurcumin along with conventional anticancer therapies mandatory(12).

Regulatory Considerations

The U.S. Food and Drug Administration (FDA) has a significant responsibility to ensure the safety and efficacy of combination treatments involving nanocurcumin. The agency scrutinizes the rationale for the combinations, balancing their suggested mechanism of action and advantage over conventional treatment against possible hazards. Regulatory frameworks require large-scale clinical trials to validate the efficacy and safety of such combinations, invoking close interaction between investigators, clinicians, and regulators to facilitate innovative therapy development(12).

Future Directions

Phytochemicals and Conventional Therapies

The combination of nutritionally taken phytomolecules with conventional anticancer drugs is a promising future direction for breast cancer therapy enhancement. Recent research indicates that these combinations can increase therapeutic efficacy, decrease the side effects of conventional chemotherapy, and even reverse drug resistance(24,25). For example, curcumin, a compound isolated from Curcuma longa, has been shown to be promising in combination with conventional chemotherapeutic drugs like 5-fluorouracil and cyclophosphamide. This synergy is believed to be mediated through various mechanisms, including the induction of apoptosis and increased intracellular drug accumulation of anticancer drugs(12,25).

Nanoparticle-Based Drug Delivery Systems

Nanoparticles have emerged as a crucial component in drug delivery systems to promote targeted and controlled release of therapeutics. Encapsulating curcumin and other phytochemicals within nanoparticles, researchers can enhance their bioavailability and therapeutic activity, making them a more potent drug against the treatment of breast cancer(4). The physicochemical optimization of these nanoparticles to maximize their pharmacokinetic profiles and anticancer activity should be the area of future research. In addition, the integration of imaging techniques with nano-curcumin formulations can enable real-time monitoring of treatment response and improved patient outcomes(26).

Regulatory and Clinical Considerations

With greater use of combination therapy involving phytochemicals, rigorous clinical trials and regulatory control will be required to validate their safety and efficacy. The U.S. Food and Drug Administration has emphasized scrutiny of the rationale for drug combination, potential interactions between drugs, and long-term effects<p>Nano-curcumin (12,24). Working among researchers, clinicians, and regulatory authorities will be paramount in establishing a standardized set of guidelines for the formulation and approval of these new treatment modalities.

Patient-Centric Approaches

Involvement of the patient's opinions and preferences is vital for the successful integration of combination therapy. Alternative medicines are already being used by numerous cancer patients with conventional treatments to alleviate side effects and overall well-being. Patient-reported outcomes must be incorporated into subsequent research to further determine the impact of such therapies on quality of life(27).

Phytochemical-Conventional Therapy Integration

Combination of dietary phytomolecules with standard anticancer medicines is a promising avenue of intervention towards better breast cancer therapy. Recent research has indicated that these combinations are bound to increase therapeutic efficacy, decrease the side effects of standard chemotherapy, and even bypass drug resistance(12). For example, curcumin, a phytochemical derived from Curcuma longa, has been reported to be effective when used in combination with traditional chemotherapeutics like 5-fluorouracil and cyclophosphamide. The synergy is believed to be mediated by multiple mechanisms, such as the induction of apoptosis and increased intracellular drug accumulation of anticancer drugs(12,24).

Nanoparticle-Based Drug Delivery Systems

Nanoparticles have emerged as a crucial component in drug delivery systems, which allow for targeted and controlled delivery of therapeutics. Encapsulation of curcumin and other phytochemicals in nanoparticles allows researchers to enhance their bioavailability and therapeutic activity, hence making them a potent therapeutic agent for breast cancer(4,26). Optimization of the physicochemical characteristics of these nanoparticles should be the aim of future studies to maximize their pharmacokinetic profiles and anticancer activity. Additionally, integration of imaging approaches with nanocurcumin systems may allow on-time observation of treatment outcomes and improvement of patient prognosis(28).

Regulatory and Clinical Considerations

With greater use of combination therapies with phytochemicals on the horizon, rigorous clinical trials and regulation will be needed to establish their safety and efficacy. The FDA has suggested that extensive assessments of the rationale behind drug combinations, potential drug interactions, and long-term effects(12) are necessary. Coordination among researchers, healthcare professionals, and regulatory organizations will be necessary in establishing standard guidelines for their development and approval.

Patient-Centric Strategies

The incorporation of patient attitudes and decisions is critical to successful implementation of combination therapies. Many cancer patients are already using herbal remedies alongside standard therapy, in an attempt to minimize side effects and improve overall well-being(12). Future research must include patient-reported outcomes to clarify the impact of these therapies on quality of life. Moreover, making these treatment modalities more accessible and cost-effective will enable their acceptance and implementation in diverse patient populations(27).

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