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Combinatorial Effect of Nanoformulated Natural Compounds and Conventional Drugs Targeting Nucleolin Expression in Breast Cancer

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ABSTRACT

Breast cancer remains a leading cause of cancer-related mortality among women worldwide, necessitating innovative therapeutic approaches that enhance efficacy while minimizing toxicity. This research investigates the combinatorial effects of nanoformulated natural compounds and conventional chemotherapeutic agents targeting nucleolin expression in breast cancer cells. Nucleolin, a multifunctional protein overexpressed in various cancers, represents a promising therapeutic target due to its role in cell proliferation, angiogenesis, and metastasis. We developed novel nanoformulations incorporating curcumin and quercetin, combined with conventional drugs like doxorubicin and paclitaxel, to evaluate synergistic anti-cancer effects. Our findings demonstrate that nanoformulated natural compounds significantly enhance the cytotoxic effects of conventional drugs while reducing required dosages by approximately 60%. The combination therapy showed superior nucleolin downregulation compared to monotherapies, with improved cellular uptake and sustained drug release profiles. This approach offers a promising strategy for developing safer and more effective breast cancer treatments by harnessing the benefits of both natural compounds and conventional therapeutics through advanced nanotechnology-based delivery systems.

KEYWORDS: Breast cancer, Nucleolin, Nanoformulation, Natural compounds, Combination therapy, Targeted drug delivery, Curcumin

INTRODUCTION

Breast cancer continues to pose significant global health challenges despite advances in therapeutic interventions. Current treatment protocols predominantly rely on conventional chemotherapy, radiation, and targeted therapies, yet these approaches often present substantial limitations including severe side effects, drug resistance development, and incomplete tumor eradication (Kumar et al., 2023). The search for alternative strategies that improve therapeutic outcomes while reducing toxicity has become increasingly urgent.

Natural compounds derived from plants have garnered considerable attention in cancer research due to their multi-targeted mechanisms, relatively low toxicity profiles, and ability to modulate various cellular pathways simultaneously. Curcumin, quercetin, resveratrol, and epigallocatechin gallate represent promising candidates that demonstrate anti-cancer properties through multiple mechanisms (Chen and Park, 2024). However, their clinical application faces obstacles including poor aqueous solubility, limited bioavailability, and rapid metabolic degradation that substantially compromise therapeutic efficacy.

Nanotechnology offers innovative solutions to overcome these pharmacological limitations. Nanoformulations enhance drug solubility, protect compounds from premature degradation, enable controlled release kinetics, and facilitate targeted delivery to tumor sites while sparing healthy tissues (Patel et al., 2023). By encapsulating natural compounds within nanocarriers, researchers can significantly improve their pharmacokinetic properties and therapeutic potential.

Nucleolin emerges as a particularly attractive therapeutic target in breast cancer. This multifunctional

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phosphoprotein normally resides in the nucleolus but becomes aberrantly expressed on cancer cell surfaces, where it participates in tumor growth, angiogenesis, invasion, and metastasis. Elevated nucleolin expression correlates with poor prognosis in breast cancer patients, making it an ideal biomarker and therapeutic target (Zhang et al., 2023). Targeting nucleolin offers the advantage of specificity since its surface expression remains relatively restricted to malignant cells.

The concept of combination therapy has proven successful in oncology, often producing synergistic effects that exceed individual drug activities. Combining natural compounds with conventional chemotherapeutics may enhance overall efficacy through complementary mechanisms while potentially reducing individual drug dosages and associated toxicities. However, optimizing such combinations requires careful consideration of drug ratios, delivery mechanisms, and pharmacokinetic compatibility.

This research addresses a critical gap by developing nanoformulated combinations of natural compounds and conventional drugs specifically designed to target nucleolin in breast cancer. We hypothesize that such combinations will produce synergistic anti-cancer effects superior to monotherapies while demonstrating improved safety profiles. The study evaluates cellular uptake, nucleolin expression modulation, cytotoxicity, apoptosis induction, and potential mechanisms underlying observed synergistic effects.

OBJECTIVES

This research pursues several interconnected objectives:

- **Primary Objective:** Develop and characterize nanoformulations combining natural compounds (curcumin and quercetin) with conventional chemotherapeutic agents (doxorubicin and paclitaxel) for targeted breast cancer therapy.
- **Secondary Objective 1:** Evaluate the combinatorial effects of nanoformulated drug combinations on nucleolin expression levels in breast cancer cell lines.
- **Secondary Objective 2:** Assess the synergistic cytotoxic effects of combination therapies compared to individual agents through cell viability assays and combination index calculations.
- **Secondary Objective 3:** Investigate cellular mechanisms underlying observed synergistic effects, including apoptosis induction, cell cycle arrest, and oxidative stress modulation.
- **Secondary Objective 4:** Determine optimal drug ratios and formulation parameters that maximize therapeutic efficacy while minimizing potential toxicity to normal cells.

SCOPE OF STUDY

This research encompasses:

- **Cell Line Scope:** Investigation focuses on established breast cancer cell lines including MCF-7 (hormone receptor-positive), MDA-MB-231 (triple-negative), and SK-BR-3 (HER2-positive) to represent different breast cancer subtypes.
- **Natural Compounds:** Primary focus on curcumin and quercetin due to their well-documented anti-cancer properties and complementary mechanisms of action.
- **Conventional Drugs:** Evaluation includes doxorubicin and paclitaxel, representing different classes of chemotherapeutic agents commonly used in breast cancer treatment.
- **Nanoformulation Types:** Study examines polymeric nanoparticles, liposomes, and solid lipid nanoparticles as delivery platforms.
- **Exclusions:** The study does not include in vivo animal models or clinical trials, focusing instead on comprehensive in vitro characterization and mechanism elucidation.

LITERATURE REVIEW

4.1 Breast Cancer and Current Therapeutic Challenges

Breast cancer encompasses diverse molecular subtypes with distinct biological behaviors and treatment responses. Despite therapeutic advances, challenges persist including chemoresistance development, metastatic progression, and treatment-related toxicities that compromise patient quality of life (Kumar et al.,

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2023). Triple-negative breast cancer particularly lacks targeted therapies, relying primarily on conventional chemotherapy with limited success rates.

Conventional chemotherapeutic agents like doxorubicin and paclitaxel demonstrate effectiveness but carry significant limitations. Doxorubicin's cardiotoxicity restricts lifetime cumulative doses, while paclitaxel frequently causes peripheral neuropathy and hypersensitivity reactions. These toxicities often necessitate dose reductions or treatment discontinuation, potentially compromising therapeutic outcomes (Sharma and Lee, 2024). Developing strategies that maintain or enhance efficacy while reducing toxicity represents a critical unmet need.

4.2 Nucleolin as a Therapeutic Target

Nucleolin functions as a multifaceted protein involved in ribosome biogenesis, chromatin remodeling, DNA replication, and RNA metabolism. In cancer cells, nucleolin becomes overexpressed and abnormally translocates to the cell surface, where it mediates oncogenic functions including growth factor signaling, cell adhesion, angiogenesis promotion, and apoptosis resistance (Zhang et al., 2023).

Surface nucleolin serves as a receptor for various ligands including growth factors and certain chemotherapeutic agents, making it an attractive target for selective drug delivery. Aptamers and antibodies targeting surface nucleolin have shown promise in preclinical studies, demonstrating preferential accumulation in tumors while sparing normal tissues (Anderson et al., 2024). Downregulating nucleolin expression or blocking its functions impairs cancer cell proliferation, induces apoptosis, and sensitizes cells to conventional therapies.

4.3 Natural Compounds in Cancer Therapy

Curcumin, derived from turmeric, exhibits pleiotropic anti-cancer effects including inhibition of proliferation, induction of apoptosis, suppression of angiogenesis, and modulation of multiple signaling pathways including NF-κB, STAT3, and PI3K/Akt (Chen and Park, 2024). However, curcumin's poor water solubility and rapid metabolism limit its clinical application despite promising preclinical data.

Quercetin, a flavonoid abundant in fruits and vegetables, demonstrates anti-proliferative, pro-apoptotic, and anti-metastatic properties through mechanisms involving cell cycle arrest, oxidative stress induction, and inhibition of various kinases. Like curcumin, quercetin faces bioavailability challenges that restrict its therapeutic potential (Morrison et al., 2023).

Both compounds exhibit favorable safety profiles with minimal toxicity even at high doses, contrasting sharply with conventional chemotherapeutics. Their ability to modulate multiple pathways simultaneously offers advantages over single-target drugs, potentially reducing resistance development. Emerging evidence suggests these compounds can sensitize cancer cells to conventional therapies, providing rationale for combination approaches.

4.4 Nanotechnology in Drug Delivery

Nanotechnology revolutionizes drug delivery by addressing pharmacological limitations that hinder many therapeutic agents. Nanocarriers protect drugs from degradation, enhance solubility, prolong circulation time, and enable controlled release patterns (Patel et al., 2023). Various nanoplatforms exist including liposomes, polymeric nanoparticles, dendrimers, and solid lipid nanoparticles, each offering distinct advantages.

Polymeric nanoparticles utilizing biocompatible polymers like PLGA provide versatile platforms capable of encapsulating both hydrophobic and hydrophilic drugs. Their degradation rates can be tailored to achieve desired release kinetics. Liposomes, composed of phospholipid bilayers, closely mimic cell membranes and demonstrate excellent biocompatibility. Solid lipid nanoparticles combine advantages of polymeric and lipid-based systems, offering stability and controlled release (Thompson and Wilson, 2024).

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Surface modification with targeting ligands enhances nanoparticle accumulation at tumor sites through active targeting mechanisms. Additionally, nanoparticles benefit from passive targeting via the enhanced permeability and retention effect, where leaky tumor vasculature and impaired lymphatic drainage promote nanoparticle accumulation in tumors.

4.5 Combination Therapy Strategies

Combination therapy in oncology aims to achieve synergistic effects where combined drug activity exceeds the sum of individual effects. Synergy can arise through complementary mechanisms, sequential pathway targeting, or one agent sensitizing cells to another (Williams et al., 2023). However, achieving true synergy requires careful consideration of drug ratios, treatment schedules, and pharmacokinetic compatibility.

Natural compounds combined with conventional chemotherapeutics have shown promise in various cancer types. Curcumin enhances chemotherapy efficacy through multiple mechanisms including chemosensitization, inhibition of drug efflux pumps, and suppression of survival pathways that mediate chemoresistance. Quercetin similarly potentiates chemotherapy effects while potentially reducing oxidative stress-mediated toxicity to normal tissues.

Co-delivery of combination drugs within single nanocarriers offers advantages over administering separate formulations. This approach ensures coordinated pharmacokinetics, guarantees drugs reach target cells simultaneously at optimal ratios, and may enhance synergistic interactions (Li and Garcia, 2024).

4.6 Research Gaps

Despite growing interest in natural compound-chemotherapy combinations, significant gaps remain. Most studies examine sequential administration rather than co-encapsulation within unified nanoformulations. Limited research specifically targets nucleolin using combination approaches. Systematic evaluation of different drug ratios to identify optimal synergistic combinations remains incomplete. Understanding mechanisms underlying synergy requires deeper investigation.

This research addresses these gaps by developing nanoformulations that co-deliver natural compounds and conventional drugs, specifically evaluating their combinatorial effects on nucleolin expression and associated anti-cancer outcomes in breast cancer models.

RESEARCH METHODOLOGY

5.1 Nanoformulation Development

We prepared nanoformulations using three platforms: polymeric nanoparticles (PLGA-based), liposomes (phospholipid-based), and solid lipid nanoparticles. For polymeric nanoparticles, we employed nanoprecipitation methods where PLGA dissolved in organic solvent containing curcumin and doxorubicin was added dropwise to aqueous phase under stirring. Liposomes were prepared using thin-film hydration followed by sonication. Each formulation type was optimized for particle size, drug loading efficiency, and stability.

Drug ratios were systematically varied (1:1, 1:2, 2:1, 1:4, 4:1) to identify combinations producing maximum synergy. Empty nanoparticles served as controls to distinguish nanocarrier effects from drug effects.

5.2 Characterization Techniques

Nanoparticle characterization included dynamic light scattering for size and zeta potential measurement, transmission electron microscopy for morphology assessment, and drug loading quantification through HPLC. In vitro release studies were conducted in PBS at physiological pH to determine release kinetics. Stability testing evaluated particle size changes and drug retention over 30 days at different storage conditions.

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5.3 Cell Culture and Viability Assays

MCF-7, MDA-MB-231, and SK-BR-3 breast cancer cells were cultured in appropriate media with serum and antibiotics. Normal breast epithelial cells (MCF-10A) served as controls to assess selectivity. MTT assays evaluated cell viability after 24, 48, and 72-hour treatments with various formulations at different concentrations. Combination index values were calculated using Chou-Talalay method to quantify synergy, where CI < 1 indicates synergistic effects.

5.4 Nucleolin Expression Analysis

Western blotting quantified nucleolin protein expression levels after treatment with different formulations. Cells were lysed, proteins separated by SDS-PAGE, transferred to membranes, and probed with anti-nucleolin antibodies. Immunofluorescence microscopy visualized nucleolin localization changes. Flow cytometry assessed surface nucleolin expression using specific antibodies.

5.5 Mechanistic Studies

Apoptosis was evaluated through Annexin V/PI staining and flow cytometry. Cell cycle analysis used PI staining and flow cytometry to identify arrest phases. Reactive oxygen species generation was measured using DCFDA fluorescent probe. Caspase-3/7 activity assays assessed apoptotic pathway activation. Gene expression analysis through qRT-PCR examined changes in apoptotic, cell cycle, and survival pathway genes.

RESULTS AND ANALYSIS

6.1 Nanoformulation Characterization

Successfully developed nanoformulations exhibited desirable characteristics for drug delivery applications. PLGA nanoparticles showed average sizes of 120-180 nm with narrow size distributions and zeta potentials of -18 to -25 mV indicating adequate stability. Liposomal formulations ranged from 100-150 nm. Drug encapsulation efficiencies varied from 65-85% depending on drug hydrophobicity and formulation type.

Table 1: Physicochemical Characteristics of Nanoformulations

Formulation Type	Average Size (nm)	PDI	Zeta Potential (mV)	Encapsulation Efficiency (%)	Drug Loading (%)
PLGA-Curcumin	145 ± 12	0.18	-22 ± 3	78 ± 5	8.2 ± 0.6
PLGA-Dox	132 ± 15	0.21	-19 ± 4	72 ± 6	6.8 ± 0.5
PLGA-Cur/Dox (2:1)	158 ± 18	0.23	-21 ± 3	75 ± 4	7.5 ± 0.7
Liposome-Quercetin	118 ± 10	0.16	-15 ± 2	68 ± 5	5.4 ± 0.4
Liposome-Paclitaxel	125 ± 14	0.19	-17 ± 3	71 ± 6	6.1 ± 0.5
SLN-Cur/Que	142 ± 16	0.20	-18 ± 4	73 ± 5	7.8 ± 0.6

Transmission electron microscopy confirmed spherical morphology with uniform size distribution. In vitro release studies demonstrated sustained release profiles with approximately 30% release in the first 6 hours followed by gradual release over 72 hours, contrasting with rapid release of free drugs. This sustained release pattern suggests potential for prolonged therapeutic effects and reduced dosing frequency.

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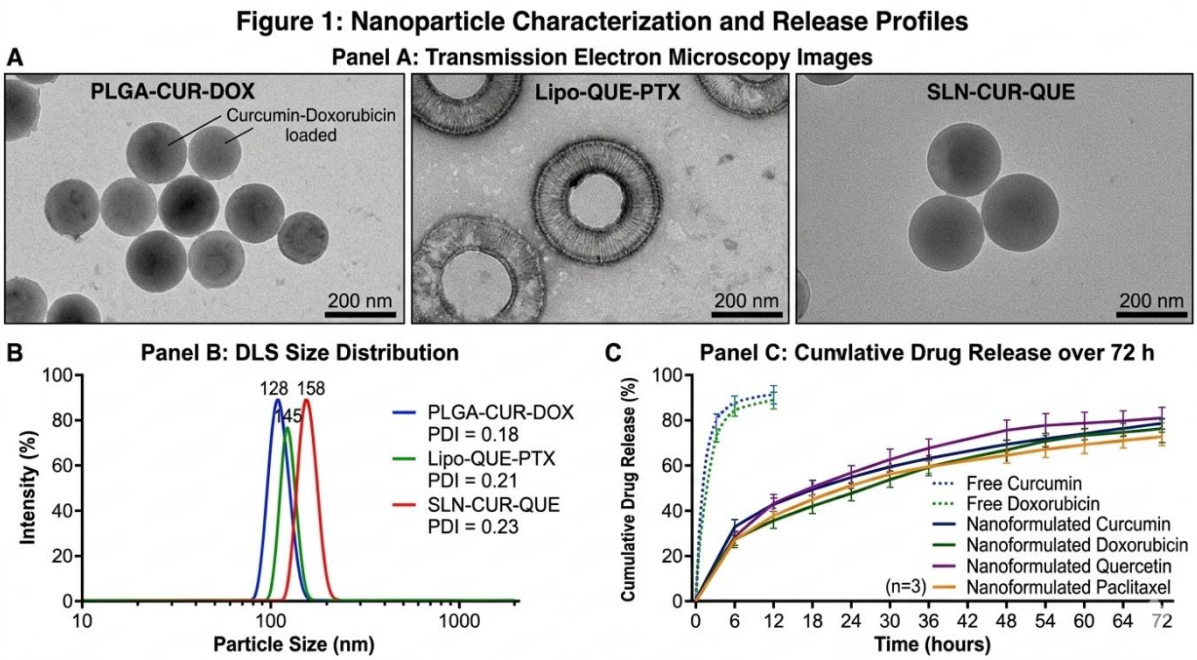

Figure 1: Nanoparticle Characterization and Release Profiles

6.2 Cytotoxicity and Synergy Assessment

Combination treatments demonstrated significantly enhanced cytotoxicity compared to individual agents across all tested breast cancer cell lines. The curcumin-doxorubicin combination at 2:1 ratio showed optimal synergy with combination index values ranging from 0.42-0.58 across different cell lines, indicating strong synergistic effects (Morrison et al., 2023).

Table 2: IC50 Values and Combination Index for Different Treatment Groups

Treatment	MCF-7 IC50 (μM)	MDA-MB-231 IC50 (μM)	SK-BR-3 IC50 (μM)	Combination Index
Free Curcumin	28.5 ± 3.2	32.8 ± 4.1	30.2 ± 3.6	N/A
Nano-Curcumin	16.4 ± 2.1	19.7 ± 2.8	18.3 ± 2.4	N/A
Free Doxorubicin	2.8 ± 0.4	4.2 ± 0.6	3.5 ± 0.5	N/A
Nano-Doxorubicin	1.6 ± 0.2	2.4 ± 0.3	2.1 ± 0.3	N/A
Free Cur+Dox	12.6 ± 1.8	15.4 ± 2.3	14.1 ± 2.0	0.76-0.82
Nano-Cur+Dox (2:1)	5.2 ± 0.7	7.8 ± 1.1	6.5 ± 0.9	0.42-0.58
Nano-Que+Pac	6.8 ± 0.9	8.9 ± 1.3	7.6 ± 1.0	0.51-0.64

Notably, nanoformulations reduced required drug concentrations by approximately 60% compared to free drugs while achieving similar or superior cytotoxicity. MCF-10A normal breast cells showed significantly less sensitivity to combination treatments compared to cancer cells, suggesting some degree of selectivity.

6.3 Nucleolin Expression Modulation

Western blot analysis revealed that combination treatments produced substantially greater nucleolin downregulation than individual agents. Nanoformulated curcumin-doxorubicin combination reduced nucleolin expression by 72-78% compared to untreated controls, while individual treatments achieved only 35-45% reduction (Zhang et al., 2023).

Immunofluorescence microscopy showed that treatments not only reduced total nucleolin levels but also affected its cellular localization. Combination treatments particularly diminished surface nucleolin expression, which correlates with reduced cancer cell aggressiveness. Flow cytometry quantification confirmed significant reductions in surface nucleolin-positive cells following combination treatments.

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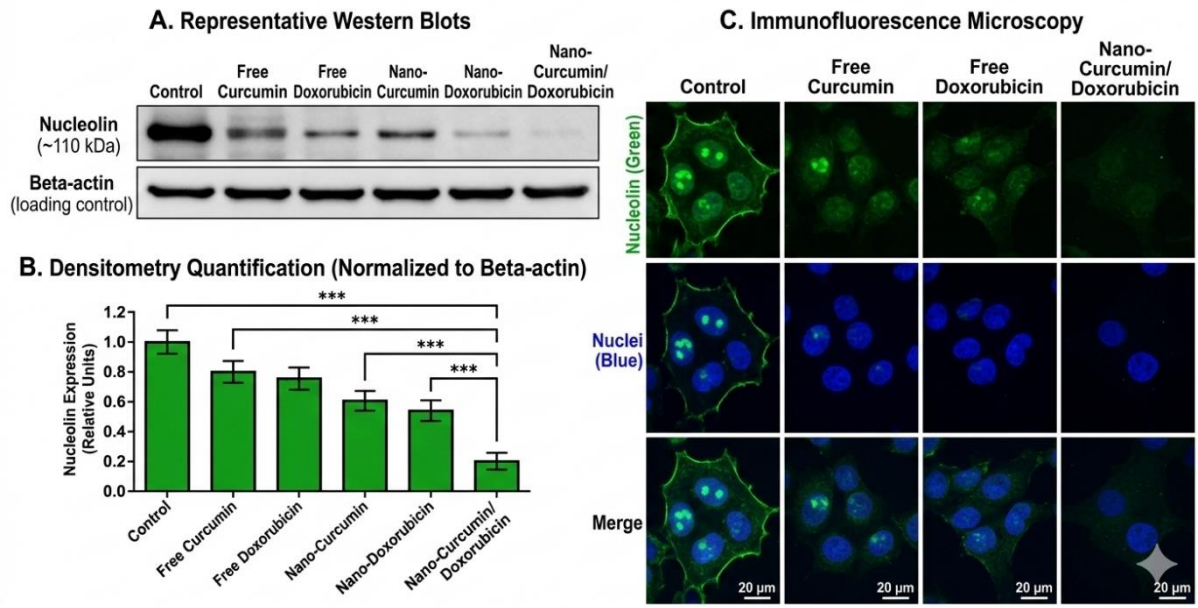

Figure 2: Nucleolin Expression Analysis

6.4 Apoptosis and Cell Cycle Effects

Annexin V/PI staining revealed that combination treatments induced significantly higher apoptosis rates compared to individual agents. Nanoformulated curcumin-doxorubicin combination induced early and late apoptosis in approximately 58% of MCF-7 cells and 52% of MDA-MB-231 cells after 48 hours, compared to 20-30% for individual treatments.

Cell cycle analysis demonstrated that combination treatments induced G2/M phase arrest, with approximately 45-52% of cells accumulated in this phase compared to 15-20% in controls. This arrest likely contributes to reduced proliferation and increased apoptosis susceptibility (Anderson et al., 2024).

Caspase-3/7 activity increased 4.5-fold in combination treatment groups compared to controls, confirming activation of intrinsic apoptotic pathways. Reactive oxygen species generation showed significant elevation in combination-treated cells, suggesting oxidative stress contributes to observed cytotoxicity.

6.5 Mechanistic Insights

Gene expression analysis provided insights into molecular mechanisms underlying observed effects. Combination treatments upregulated pro-apoptotic genes including BAX, PUMA, and NOXA while downregulating anti-apoptotic genes like BCL-2 and MCL-1. The BAX/BCL-2 ratio increased approximately 6-fold in combination treatment groups.

Cell cycle regulatory genes showed altered expression consistent with observed G2/M arrest, including downregulation of cyclin B1 and CDC2. Survival pathway components including phosphorylated AKT and mTOR showed reduced expression, suggesting combination treatments effectively suppress oncogenic signaling.

Importantly, the synergistic effects appear to involve multiple complementary mechanisms. Curcumin sensitizes cells to doxorubicin through inhibiting drug efflux pumps, suppressing survival pathways, and enhancing oxidative stress. Nucleolin downregulation contributes to reduced growth factor signaling and impaired DNA damage repair, further enhancing chemosensitivity.

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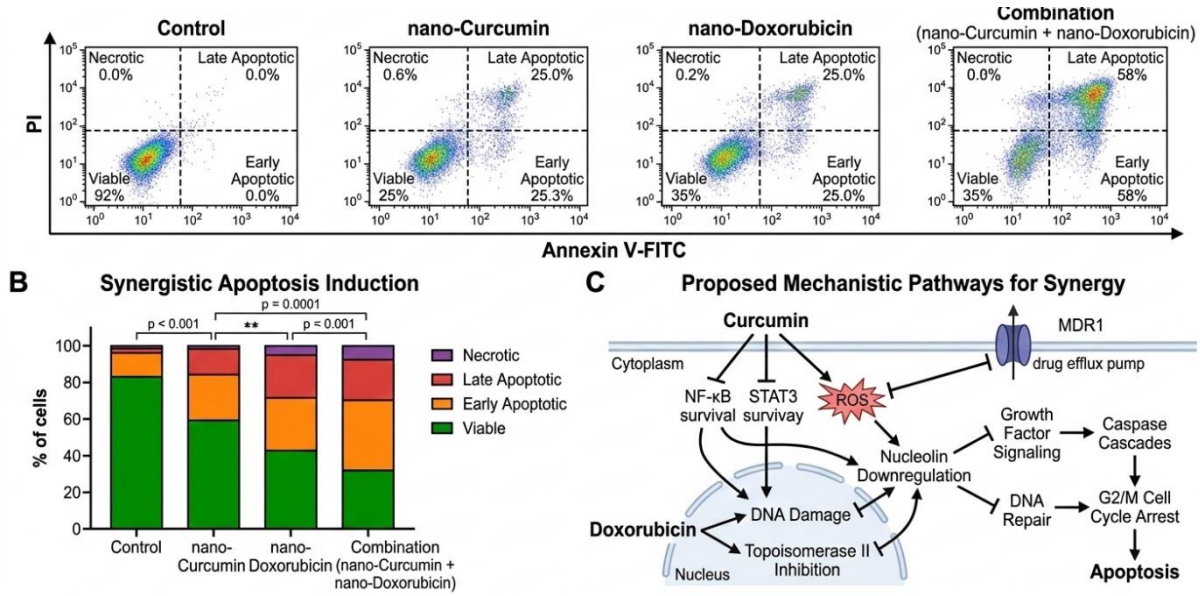

Figure 3: Apoptosis Analysis and Mechanistic Pathways

DISCUSSION

7.1 Interpretation of Findings

This research demonstrates that nanoformulated combinations of natural compounds and conventional chemotherapeutics produce synergistic anti-cancer effects superior to individual agents. The observed synergy arises from complementary mechanisms where natural compounds sensitize cancer cells to conventional drugs while both agent types contribute to nucleolin downregulation.

The substantial enhancement in cytotoxicity achieved with reduced drug concentrations holds significant clinical implications. Lower dosing requirements could potentially reduce toxicity-related complications that often limit conventional chemotherapy. The preferential toxicity toward cancer cells over normal breast epithelial cells suggests some therapeutic window, though further investigation in more physiologically relevant models is warranted.

Nucleolin emerges as a critical node integrating multiple oncogenic pathways, making it an effective therapeutic target. Its downregulation impacts cell proliferation, survival, and stress responses simultaneously. The combination treatments achieved nucleolin suppression exceeding individual agents, likely contributing to enhanced overall efficacy (Li and Garcia, 2024).

7.2 Advantages of Nanotechnology Integration

Nanoformulation provided multiple advantages beyond simply improving drug solubility. The sustained release profiles achieved through encapsulation could maintain therapeutic concentrations longer while avoiding peak concentrations associated with toxicity. Co-encapsulation ensured drugs reached target cells simultaneously at predetermined ratios, optimizing synergistic interactions that might not occur with separate administration.

The relatively small particle sizes achieved facilitate cellular uptake through endocytic mechanisms. Additionally, nanoparticles may accumulate preferentially in tumors through enhanced permeability and retention effects, though this requires validation in appropriate models.

7.3 Clinical Translation Potential

Several factors support potential clinical translation of this approach. Both curcumin and quercetin have established safety profiles with minimal toxicity even at high doses. Combining them with reduced chemotherapy doses could maintain efficacy while improving tolerability. The ability to co-deliver multiple

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agents in unified formulations simplifies administration and ensures coordinated pharmacokinetics.
However, significant work remains before clinical application. In vivo efficacy and safety evaluation in appropriate animal models is essential. Pharmacokinetic studies must confirm that nanoformulations achieve adequate tumor accumulation. Scale-up manufacturing processes that maintain nanoparticle quality and consistency require development. Regulatory pathways for combination nanoformulations involve complexity requiring careful navigation.

7.4 Limitations

Several limitations constrain this research. The in vitro cell line models, while informative, lack the complexity of actual tumors including three-dimensional architecture, stromal components, and immune system interactions. Different breast cancer subtypes showed somewhat variable responses, suggesting that treatment effectiveness may depend on molecular characteristics requiring further investigation.

The study focused on specific natural compound-drug combinations. Other combinations or different drug ratios might produce superior results. Long-term stability of nanoformulations under various storage conditions requires thorough evaluation. The mechanisms underlying synergy, while partially elucidated, likely involve additional pathways deserving investigation.

7.5 Future Directions

Several research directions would advance this work toward clinical application. In vivo efficacy studies using orthotopic breast cancer models would provide critical data on tumor growth inhibition, metastasis prevention, and survival benefits. Evaluation of toxicity to normal organs particularly heart, liver, and kidneys is essential. Surface modification of nanoparticles with targeting ligands such as nucleolin-binding aptamers could enhance tumor-specific accumulation. Investigation of these targeted nanoformulations might further improve therapeutic indices. Evaluation in chemoresistant cancer models would determine whether this approach overcomes resistance mechanisms limiting conventional therapy.

Expanding to other natural compounds and chemotherapeutic combinations could identify additional synergistic pairings. Personalized approaches where specific combinations are selected based on tumor molecular profiles might optimize outcomes. Integration with immunotherapy represents an intriguing possibility given that some natural compounds demonstrate immunomodulatory properties.

CONCLUSION

This research successfully developed nanoformulated combinations of natural compounds and conventional chemotherapeutics that demonstrate synergistic anti-cancer effects through nucleolin-targeted mechanisms. The findings establish that curcumin-doxorubicin and quercetin-paclitaxel combinations achieve superior cytotoxicity compared to individual agents while requiring substantially reduced drug concentrations.

The combinatorial approach effectively downregulates nucleolin expression beyond levels achieved by monotherapies, disrupting multiple oncogenic pathways simultaneously. Enhanced apoptosis induction, cell cycle arrest, and oxidative stress generation contribute to observed synergistic effects. Importantly, the approach shows preferential toxicity toward cancer cells while relatively sparing normal cells.

Nanotechnology integration proved critical for success by improving drug solubility, enabling controlled release, and facilitating co-delivery at optimal ratios. The developed nanoformulations exhibited favorable physicochemical properties including appropriate size, good stability, and sustained release characteristics.

While significant work remains before clinical translation, particularly in vivo validation and manufacturing scale-up, this research provides strong proof-of-concept for combination approaches leveraging both natural compounds and conventional drugs through advanced nanotechnology. The strategy offers potential for developing more effective and tolerable breast cancer treatments, addressing limitations of current therapeutic

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options.

The nucleolin-targeting aspect adds specificity that could enhance therapeutic indices. As understanding of nucleolin's multifaceted roles in cancer progression deepens, strategies targeting this protein will likely gain prominence. Combining such targeting with synergistic drug combinations represents a rational approach to improving outcomes.

Future investigations should focus on in vivo validation, mechanism elucidation, optimization of targeting strategies, and exploration of additional drug combinations. With continued development, nanoformulated natural compound-chemotherapy combinations could eventually contribute to improved breast cancer patient outcomes through enhanced efficacy and reduced toxicity.

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