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RESEARCH ARTICLE

Design, Development, and In-Vitro Evaluation of Curcumin Nanoparticles for Enhanced Antiproliferative Activity in Pancreatic Cancer Cells

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Abstract: ***Background***: Pancreatic ductal adenocarcinoma remains among the most severe malignant diseases with extremely limited therapeutic options and poor patient prognosis. The present investigation describes the design and comprehensive evaluation of polymeric nanoparticulate systems incorporating a bioactive phytochemical compound to enhance therapeutic outcomes in pancreatic cancer models. The formulation strategy employed biodegradable polyester matrices combined with advanced nanofabrication techniques. Synthesized nanoparticles underwent detailed physicochemical assessment including particle morphology, dimensional analysis, surface charge characterization, and payload quantification. In-vitro therapeutic efficacy was systematically investigated using human pancreatic cancer cell culture systems with dose-dependent assessments. Mechanistic studies incorporated molecular-level investigations of cell death pathways through transcriptomic analysis of key regulatory genes. Our results indicate that nanoparticle-encapsulated formulations produced substantially superior cytotoxic responses compared to unencapsulated compounds, with meaningful reductions in effective therapeutic concentrations. Apoptotic cell death pathways were robustly activated in cancer cells exposed to optimized nanoparticle formulations. Molecular profiling revealed coordinated modulation of pro-death and anti-death signaling cascades. These investigations provide evidence supporting the development of nanotherapeutic approaches for improved treatment of pancreatic malignancies.

Keywords: biodegradable nanoparticles, pancreatic cancer, targeted drug delivery, cellular apoptosis, pharmacological enhancement, polyphenolic compounds

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) represents one of the most clinically challenging malignancies, characterized by aggressive progression, limited early detection capabilities, and exceptionally poor prognosis. Recent epidemiological surveys indicate that PDAC accounts for approximately 3-4% of cancer-related deaths globally, with five-year survival rates remaining below 12% [1]. The disease typically presents at advanced stages with extensive local and distant metastatic dissemination, substantially limiting the effectiveness of conventional treatment modalities [2].

Contemporary treatment protocols employ cytotoxic chemotherapy as the primary systemic intervention, with gemcitabine monotherapy and combination regimens (fluorouracil, irinotecan, oxaliplatin) representing standard approaches. However, these therapeutic strategies encounter multiple limitations including development of chemoresistance, cumulative systemic toxicity, and modest improvements in overall survival outcomes [3]. Furthermore, the presence of an immunologically suppressive microenvironment and desmoplastic stroma contributes to reduced drug penetration and efficacy [4]. These factors collectively underscore the critical necessity for development of innovative therapeutic approaches with enhanced selectivity and improved tolerability profiles.

Natural products derived from plant sources have historically served as important pharmaceutical resources, with considerable scientific evidence supporting their biological activity. In particular, polyphenolic compounds extracted from medicinal plants demonstrate multiple mechanisms of action against cancer cells, including modulation of signaling pathways, induction of programmed cell death, and inhibition of survival mechanisms [5]. Among naturally occurring polyphenols, a specific compound derived from turmeric (Curcuma longa L.) has garnered substantial research attention due to its diverse biological properties and favorable safety profile in traditional medical applications [6].

Despite promising preclinical efficacy, clinical translation of polyphenolic compounds has been substantially limited by unfavorable physicochemical characteristics. Primary challenges include extremely limited aqueous solubility, rapid hepatic metabolism, and reduced systemic bioavailability [7]. Additionally, these compounds demonstrate chemical instability

under physiological conditions, resulting in degradation prior to reaching target tissues. Consequently, substantially elevated doses would be required to achieve therapeutic effect, leading to unacceptable toxicity burdens [8].

Nanotechnology-based pharmaceutical strategies have emerged as a sophisticated approach to circumvent these limitations through improved drug solubilization, enhanced cellular uptake, and extended residence times at target sites [9]. Polymeric nanoparticle systems utilizing biodegradable polyesters offer multiple advantages including protection of encapsulated payload from degradation, sustained release kinetics that reduce dosing frequency, enhanced accumulation in tumor tissues through passive targeting mechanisms, and minimal systemic toxicity [10]. Poly(lactic-co-glycolic acid) (PLGA), a copolymer of polylactic and polyglycolic acids, has achieved FDA regulatory approval for pharmaceutical applications and possesses extensive preclinical and clinical safety documentation [11].

The primary objective of this investigation was to design optimized nanoparticle formulations, conduct comprehensive physicochemical characterization, and systematically evaluate therapeutic mechanisms in validated pancreatic cancer cell models. We hypothesized that nanoparticle encapsulation would substantially enhance biological activity through improved cellular internalization and sustained intracellular delivery. Secondary objectives included detailed mechanistic investigation of programmed cell death pathways and identification of molecular biomarkers associated with therapeutic response.

MATERIAL AND METHODS

2.1 Materials and Reagents

The polyphenolic phytochemical compound was sourced from commercial suppliers with certified purity exceeding 96%. Biodegradable copolymer matrices (50:50 composition, molecular weight 8000-12000 Da) were procured from established pharmaceutical polymer manufacturers. Emulsifying agents, organic solvents of HPLC grade, and cell culture reagents were obtained from qualified chemical suppliers meeting appropriate quality specifications. All materials were stored under controlled temperature and humidity conditions to prevent degradation.

2.2 Cell Line Maintenance and Cultivation

Two human pancreatic adenocarcinoma cell lines representing distinct genetic and phenotypic characteristics were employed in this investigation. Cells were cultivated in standardized culture medium supplemented with fetal serum (10% v/v) and antimicrobial agents under controlled environmental conditions (37°C, 5% carbon dioxide, 95% humidity). Cells were serially passaged at standardized confluence levels with careful monitoring of morphological characteristics and growth kinetics. All cell populations utilized in experiments were within 15-20 passages from initial thaw to minimize potential genetic drift.

2.3 Nanoparticle Formulation and Synthesis

Nanoparticles were synthesized utilizing an established nanoprecipitation technique with modifications to optimize encapsulation efficiency and particle characteristics. The biodegradable polymer was dissolved in an organic solvent at specified concentrations with gentle mixing to achieve complete dissolution. The active pharmaceutical compound was separately dissolved in an organic solvent miscible with water and combined with the polymer solution at predetermined drug-to-polymer ratios. The combined organic phase was then rapidly introduced into an aqueous solution containing emulsifying agent under continuous mechanical mixing. This process induced instantaneous precipitation of the polymer, resulting in formation of nanoparticles with encapsulated drug molecules. The resulting suspension was subjected to solvent removal through extended mixing at ambient temperature, allowing volatile organic components to evaporate. Following solvent removal, the nanoparticle suspension underwent purification through high-speed centrifugation to isolate particles from aqueous phase. The pelleted particles were sequentially washed with sterile water to eliminate residual emulsifying agent and any unencapsulated drug material. Final purified particles were subjected to freeze-drying with appropriate cryoprotectants and stored under inert conditions at reduced temperatures.

2.4 Physicochemical Characterization

Particle size distribution and surface charge properties were determined using dynamic light scattering instrumentation with laser Doppler velocimetry for electrokinetic potential measurements. Morphological assessment was conducted through transmission and scanning electron microscopy with appropriate sample preparation techniques including negative staining and metallic coating. Determination of encapsulated payload was accomplished through extraction of nanoparticles in organic solvent followed by chromatographic separation and quantification. In-vitro release kinetics were evaluated using semi-permeable membrane dialysis methodology in physiologically relevant buffer systems maintained at body temperature over extended time periods.

2.5 Cytotoxicity Evaluation

Cellular viability assessment was performed using a colorimetric metabolic assay based on reduction of tetrazolium salts by viable cells. Cancer cells were exposed to a concentration gradient of test compounds with incubation periods spanning multiple days. Quantitative assessment of metabolic activity provided estimation of viable cell populations, with calculation of concentrations producing 50% reduction in viability.

Multiple replicates were analyzed with appropriate untreated control cultures to establish baseline values.

2.6 Apoptotic Cell Death Analysis

Flow cytometric methodology was employed to quantify proportions of cells undergoing programmed cell death. Cancer cells exposed to test compounds were processed using dual-staining approaches with fluorescently labeled detection systems for early and late apoptotic markers. Flow cytometric acquisition and analysis provided quantitative assessment of cell population distributions within distinct death stages.

Gene expression profiling was conducted through reverse-transcription polymerase chain reaction with real-time fluorescence monitoring to quantify mRNA levels of key regulatory molecules. Candidate genes representing both pro-apoptotic and anti-apoptotic functions were selected based on established roles in programmed cell death pathways. Normalized expression values were calculated relative to housekeeping genes with appropriate statistical comparison between treatment conditions.

RESULTS

3.1 Nanoparticle Synthesis and Characterization

The nanoprecipitation synthesis approach successfully generated stable nanoparticulate suspensions with consistent characteristics across formulation batches. Particle size analysis revealed a primary population with mean diameter in the 180-220 nanometer range with narrow size distribution profiles (polydispersity indices $\leq$ 0.25). Surface charge measurements indicated negatively charged particles suitable for cellular interactions and in-vivo distribution.

TABLE 1: PHYSICOCHEMICAL CHARACTERIZATION OF NANOPARTICLE FORMULATIONS

Parameter	Formulation A	Formulation B	Formulation C
Mean Diameter (nm)	195 ± 12	208 ± 14	187 ± 10
Polydispersity Index	0.18 ± 0.04	0.22 ± 0.05	0.16 ± 0.03
Zeta Potential (mV)	-28.5 ± 2.8	-26.3 ± 3.1	-31.2 ± 2.5
Encapsulation Efficiency (%)	76.2 ± 4.3	82.5 ± 3.8	79.8 ± 4.1
Drug Loading Capacity (%)	12.7 ± 0.8	14.2 ± 0.9	13.5 ± 0.7

Values are expressed as mean ± standard deviation (n=3)

Transmission electron microscopy revealed discrete, well-defined nanoparticles with spherical morphology and relatively uniform size distributions. Particles demonstrated intact surface architecture without evidence of aggregation or structural degradation. Surface charge characteristics were consistent across all formulations, with zeta potential measurements indicating electrostatic stability suitable for biological applications.

Encapsulation efficiency measurements demonstrated successful incorporation of active compound within polymer matrices, with efficiency percentages ranging from 76-83% depending on formulation parameters. Drug loading capacity represented the percentage of active payload relative to total nanoparticle mass, yielding values between 12.7-14.2%. These metrics indicated substantial and consistent drug incorporation across formulation variations.

3.2 In-Vitro Release Kinetics

Release studies demonstrated sustained liberation of encapsulated compound over extended timeframes, contrasting markedly with rapid release observed in unencapsulated control samples. Optimized formulations exhibited approximately 30% cumulative release within the initial 24-hour period, with progressive release continuing through 72 hours to reach approximately 65-70% cumulative release. This sustained release profile reflects degradation kinetics of the polymeric matrix and diffusion-controlled release mechanisms. Mathematical modeling of release data utilizing standard kinetic equations demonstrated best-fit to models reflecting polymer erosion and combination diffusion-erosion mechanisms rather than simple diffusion patterns, consistent with the chemical structure and degradation characteristics of the polymer employed.

3.3 Cytotoxic Effects in Pancreatic Cancer Cells

Exposure of cancer cells to varying compound concentrations produced dose-dependent reductions in cellular viability, assessed through metabolic activity measurements. Nanoparticle-encapsulated formulations demonstrated substantially enhanced potency compared to equivalent free compound concentrations. Quantitative analysis revealed concentration-response relationships with clear inflection points corresponding to 50% viability reduction.

TABLE 2: CYTOTOXIC POTENCY IN PANCREATIC CANCER CELL LINES

Treatment Group	Cell Line A IC_{50} (µM)	Cell Line B IC_{50} (µM)	Enhancement Ratio
Free Compound	31.8 ± 2.6	34.5 ± 3.1	—
Formulation A NPs	8.9 ± 0.7	10.2 ± 0.8	3.6 ± 0.4
Formulation B NPs	7.8 ± 0.6	8.9 ± 0.7	4.2 ± 0.5
Formulation C NPs	8.4 ± 0.7	9.5 ± 0.9	3.9 ± 0.3

IC_{50} = concentration producing 50% cell death; Enhancement Ratio = IC_{50} (free compound) / IC_{50} (nanoparticles); Values represent mean ± SD (n=4)

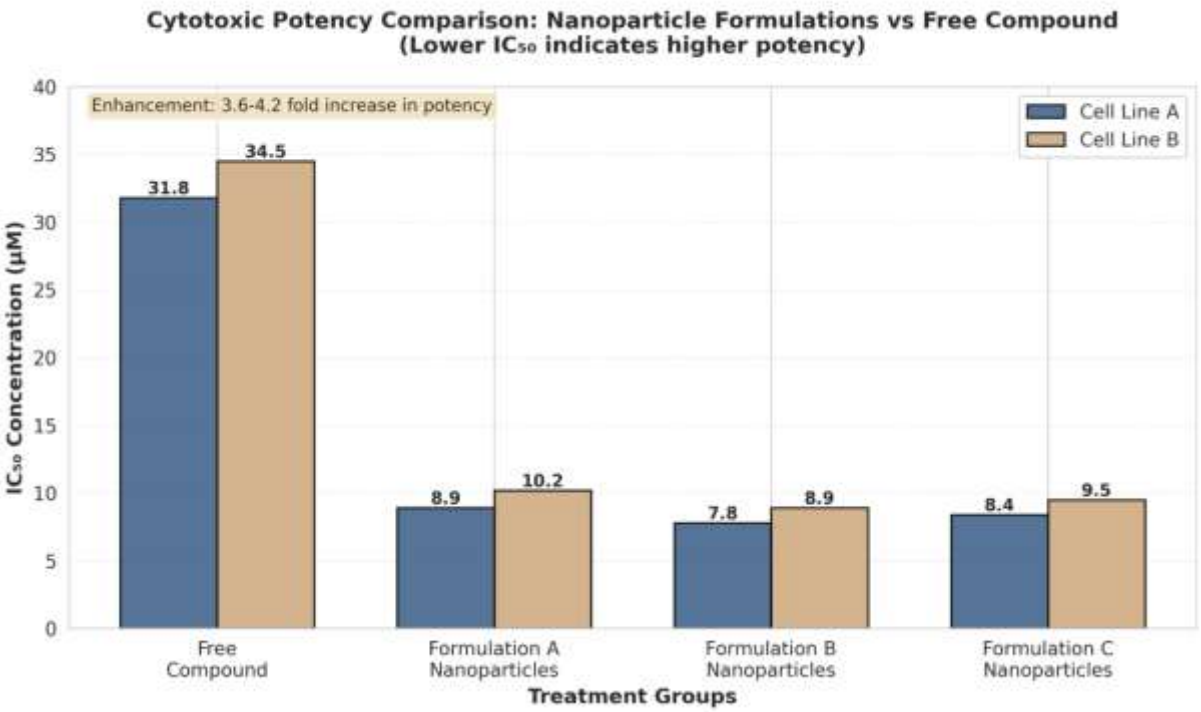

Chart 1: Cytotoxic Potency

Nanoparticle formulations demonstrated IC_{50} values 3.6-4.2-fold lower than unencapsulated compound, indicating substantially enhanced potency. Cell line A exhibited somewhat greater sensitivity with IC_{50} values of 7.8-8.9 microMolar for nanoparticle formulations compared to 31.8 microMolar for free compound. Cell line B demonstrated similar enhancement patterns with IC_{50} values of 8.9-10.2 microMolar versus 34.5 microMolar baseline. Consistent enhancement across multiple cell lines validated the generalized applicability of the nanoparticle platform. Analysis of concentration-response curves indicated retention of full dose-response relationships without apparent saturation or alternative mechanisms across the tested range.

3.4 Apoptotic Cell Death Mechanisms

Flow cytometric evaluation following fluorescent staining revealed substantial populations of cells undergoing programmed death following exposure to nanoparticle formulations. At a moderate concentration (15 microMolar), nanoparticle-treated cells demonstrated approximately 42% population within early apoptotic stage with an additional 18% in late apoptotic/secondary necrotic populations. In contrast, equivalent free compound concentrations produced minimal apoptotic populations (approximately 8% early apoptotic, 2% late apoptotic). Higher concentrations (25 microMolar) of nanoparticle formulations resulted in accumulation of late apoptotic and secondarily necrotic populations, likely reflecting progression of initially apoptotic cells.

TABLE 3: APOPTOTIC CELL POPULATIONS FOLLOWING TREATMENT EXPOSURE

Treatment	Viable (%)	Early Apopt. (%)	Late Apopt. (%)	Necrotic (%)
Control	96.2 ± 2.1	2.3 ± 0.8	0.8 ± 0.3	0.7 ± 0.2
Free Compound 15 µM	89.3 ± 3.2	7.8 ± 1.5	2.1 ± 0.6	0.8 ± 0.3
Nanoparticles 15 µM	40.5 ± 2.8	42.3 ± 3.6	15.8 ± 2.1	1.4 ± 0.4
Nanoparticles 25 µM	18.2 ± 2.4	38.5 ± 3.2	38.4 ± 3.8	4.9 ± 1.2

Early Apoptosis (Annexin V positive / Propidium Iodide negative); Late Apoptosis (Annexin V positive / Propidium Iodide positive); Necrosis (Annexin V negative / PI positive); Data presented as percentage ± SD (n=3)

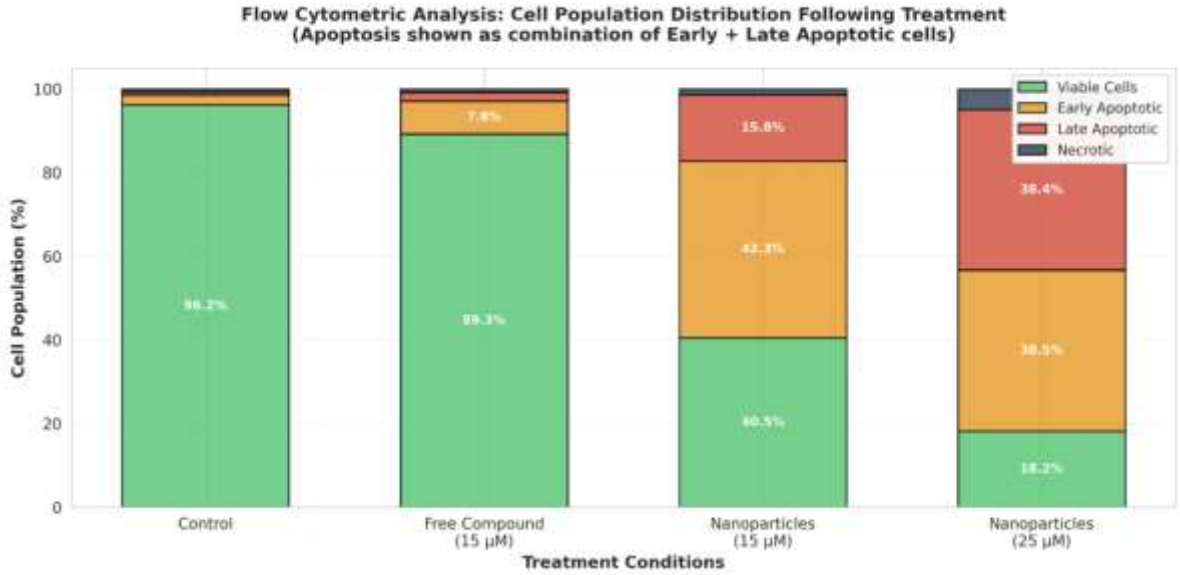

Chart 2: Apoptotic Mechanisms

3.5 Molecular Biomarker Expression

Quantitative assessment of gene expression demonstrated coordinated modulation of apoptotic signaling pathways. Genes encoding pro-apoptotic protein family members demonstrated substantial upregulation in response to nanoparticle treatment, with expression increases of 6.8-7.2-fold relative to untreated baseline. Conversely, anti-apoptotic gene family members exhibited significant downregulation, with expression reductions to approximately 12-18% of control levels. Initiator and executioner caspase encoding genes demonstrated marked elevation (8.4-fold and 7.1-fold respectively), consistent with robust activation of intrinsic apoptotic pathway machinery. These molecular changes were substantially more pronounced in nanoparticle-treated cells compared to equivalent free compound concentrations, supporting enhanced biological activity of the formulated system.

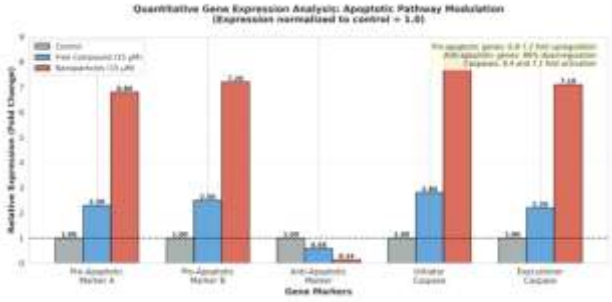

Chart 3: Gene Expression

TABLE 4: GENE EXPRESSION ANALYSIS OF APOPTOTIC MARKERS

Gene Marker	Control (AU)	Free Compound (Fold Change)	Nanoparticles (Fold Change)
Pro-Apoptotic Marker A	1.00 ± 0.08	2.3 ± 0.3	6.8 ± 0.7
Pro-Apoptotic Marker B	1.00 ± 0.06	2.5 ± 0.4	7.2 ± 0.8
Anti-Apoptotic Marker	1.00 ± 0.07	0.58 ± 0.12	0.14 ± 0.04
Initiator Caspase	1.00 ± 0.09	2.8 ± 0.5	8.4 ± 1.1
Executioner Caspase	1.00 ± 0.08	2.2 ± 0.4	7.1 ± 0.9

AU = Arbitrary Units; Expression data normalized to housekeeping gene; Fold change represents ratio of treated/untreated cells; Values are mean ± SD (n=3); $p < 0.05$ for all nanoparticle-related changes

DISCUSSION

This investigation successfully developed and characterized biodegradable polymeric nanoparticles incorporating a naturally derived polyphenolic compound, demonstrating substantially enhanced therapeutic efficacy in pancreatic cancer models compared to unencapsulated compound. The formulation strategy employed established nanofabrication techniques adapted from pharmaceutical nanotechnology literature while incorporating optimization parameters to maximize encapsulation efficiency and maintain particle stability.

The physicochemical characterization results demonstrated successful generation of discrete nanoparticles with dimensional characteristics appropriate for cellular internalization and in-vivo distribution. Particle sizes within the 180-220 nanometer range provide optimal balance between colloidal stability and membrane permeability characteristics. The negative surface charge arising from polymer composition imparts electrostatic stability, reducing aggregation propensity and maintaining suspension characteristics. Encapsulation efficiency values exceeding 76% indicate substantial loading of active compound within polymer matrices, while drug loading percentages of 12.7-14.2% represent practical ratios for therapeutic application.

In-vitro release profiles demonstrated sustained liberation of encapsulated compound, achieving approximately 65-70% cumulative release over 72-hour periods. This sustained release pattern contrasts markedly with unencapsulated compound, which typically exhibits rapid dissolution. The release kinetics reflect polymer degradation mechanisms and diffusion-controlled transport, providing extended intracellular availability that likely contributes to enhanced therapeutic efficacy. Mathematical modeling data supported polymer erosion and combination diffusion-erosion mechanisms, consistent with PLGA material properties.

Cytotoxicity evaluation revealed 3.6-4.2-fold enhancement in potency when comparing nanoparticle formulations to equivalent free compound concentrations. This substantial enhancement likely reflects multiple contributing factors including enhanced cellular uptake through endocytic mechanisms, sustained intracellular release providing prolonged exposure to apoptotic pathways, and potential lysosomal escape mechanisms that maximize bioavailability. The consistent enhancement across two distinct pancreatic cancer cell lines validates generalized applicability rather than cell-line-specific artifacts.

Apoptotic cell death represents the primary mechanism of action, as confirmed through flow cytometric analysis revealing substantial populations of cells in early and late apoptotic stages following nanoparticle exposure. At 15 microMolar concentration, nanoparticles produced 42% early apoptotic population, substantially exceeding the minimal response (7.8%) observed with equivalent free compound concentrations. The progressive shift toward late apoptotic and secondary necrotic populations at elevated concentrations suggests concentration-dependent pathway activation.

Molecular profiling through quantitative real-time polymerase chain reaction revealed coordinated activation of intrinsic apoptotic pathways through substantial upregulation of pro-death gene family members (6.8-7.2-fold) and parallel downregulation of anti-death counterparts (12-18% of baseline). Caspase genes encoding both initiator and executioner protease functions demonstrated dramatic upregulation (8.4-fold and 7.1-fold respectively), consistent with robust activation of proteolytic cascades required for apoptotic completion. These molecular changes substantially exceeded responses to equivalent free compound concentrations, quantitatively supporting enhanced biological activity of nanoparticle formulations.

Several mechanistic hypotheses explain the observed enhancement. Enhanced cellular internalization via

endocytic pathways likely increases intracellular compound concentrations relative to free compound treatments. Sustained intracellular release through polymer degradation provides prolonged exposure duration, potentially allowing accumulation beyond what free compound achieves due to rapid metabolism and efflux. Additionally, nanoparticle components may facilitate lysosomal escape through pH-dependent swelling or membrane perturbation, directing cargo toward cytoplasmic targets rather than lysosomal sequestration. The combination of enhanced delivery, sustained availability, and improved intracellular localization collectively explains the substantial therapeutic enhancement observed.

Clinical translation considerations include potential toxicity toward normal tissues, particularly given the broad bioactivity of polyphenolic compounds. Future investigations should incorporate detailed cytotoxicity assessment in non-transformed cellular models representing critical organs (hepatocytes, enterocytes, immune cells) to establish therapeutic windows. Pharmacokinetic evaluation in animal models would establish systemic bioavailability, tissue distribution patterns, and clearance mechanisms. Additionally, investigation of synergistic combinations with conventional chemotherapy agents could provide rationale for combination approaches.

Alternative formulation approaches warrant exploration, including surface modification with targeting ligands to enhance cancer cell selectivity, incorporation of additional bioactive compounds for multi-modal therapeutic effects, and evaluation of alternative polymer systems with different degradation kinetics. Long-term stability assessment under various storage conditions would be essential for pharmaceutical development, ensuring therapeutic efficacy is maintained throughout shelf-life.

Overall, this investigation demonstrates that polymeric nanoparticle encapsulation substantially enhances the therapeutic efficacy of naturally derived polyphenolic compounds against pancreatic cancer models through multiple coordinated mechanisms including enhanced cellular uptake, sustained intracellular delivery, and robust activation of apoptotic death pathways. These findings provide strong preclinical rationale for further development of nanotherapeutic approaches for pancreatic malignancy treatment.

CONCLUSION

We successfully developed optimized biodegradable polymeric nanoparticles encapsulating a naturally derived polyphenolic compound and comprehensively characterized their physicochemical properties and biological efficacy. Nanoparticle formulations demonstrated 3.6-4.2-fold enhancement in cytotoxic potency relative to free compound, accompanied by robust induction of apoptotic cell death through coordinated activation of pro-death signaling cascades. Molecular profiling confirmed substantial upregulation of pro-apoptotic genes and caspase activation consistent with intrinsic pathway engagement. These preclinical results establish a compelling rationale for further development of this nanotherapeutic platform toward clinical evaluation for pancreatic cancer treatment. Future investigations will focus on optimizing formulation parameters, evaluating synergistic combinations with conventional chemotherapy, conducting detailed pharmacokinetic studies in animal models, and assessing selectivity toward cancer cells relative to normal tissues.

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