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Study Review: Molecular Mechanisms of Nanoparticle-Cell Interaction – Implications for Drug Delivery and Toxicity

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Abstract

The application of nanoparticles in drug delivery and biomedical therapies holds great promise, yet their interaction with cells and the underlying molecular mechanisms remains areas of active research. This study explores the molecular mechanisms of nanoparticle-cell interactions, focusing on the effects of gold nanoparticles (AuNPs) and silica nanoparticles (SiNPs) in human cancer cell lines (HeLa and MCF-7). The study examines how nanoparticles are internalized by cells, their impact on cellular toxicity, oxidative stress, apoptosis, and their gene expression profiles. The findings reveal that nanoparticles, particularly functionalized particles, enhance cellular uptake via specific receptors and surface modifications, such as PEGylation and targeting peptides. Functionalization improves targeting specificity, while also inducing a significant increase in reactive oxygen species (ROS), leading to oxidative stress and cell death through apoptotic pathways. Gene expression analysis showed upregulation of apoptosis-related genes, such as Bax and Caspase-3, and oxidative stress markers like SOD and Catalase. However, while these effects contribute to the therapeutic potential of nanoparticles, they also highlight the need for careful management of nanoparticle toxicity, particularly with regards to non-target tissues. Research demands additional investigation of nanotechnology for biocompatibility testing along with toxicity assessment and targeting efficiency evaluation as healthcare authorities establish guidelines for medical applications. Studies should focus on long-term in vivo analysis of nanoparticles as well as advanced drug release strategies to maximize their clinical applications for delivering medicines in cancer treatment.

Keywords: Cancer, Toxicity, SOD, Nano, Cell

INTRODUCTION

Background

The medical and pharmaceutical industries actively pursue the promising scientific field of nanotechnology today [1]. Particles measuring between 1 to 100 nanometers constitute the description of nanoparticles and demonstrate characteristics which deviate substantially from large-scale counterparts [2]. The set of properties manifested by nanoparticles includes their enlarged surface area and heightened reactivity and their capability to traverse biological barriers which make them suitable for drug delivery systems [3]. Researchers began showing intense interest in nanoparticle-based targeted drug delivery shortly because they identified their dual benefit of producing better results with reduced adverse effects [4]. Scientists create nanoparticle structures to guide therapeutic agents toward specific cells or tissues because they aim to improve cancer and other disease treatments by safeguarding non-targeted tissues. Nanoparticle

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performance in drug delivery depends strongly on the relationship between cells and nanoparticles [5]. Nanoparticles possess appealing medical benefits, yet their biological system interactions raise diverse issues for practical consideration. Because of their minute size nanoparticles establish molecular contact with cellular structures which can cause potential toxic side effects to occur. Study of microscopic cell-nanoparticle interactions supports both beneficial utilization of nanoparticles alongside adverse outcome prevention [6]. The research investigates cellular routes of nanoparticle interactions with tests that evaluate both benefits for medicating nanoparticles along with cellular damage risks from exposure [7].

Importance of Study

Contemporary medical innovations embody innovative drug delivery through nanoparticles to develop new management approaches for treating cancer and other diseases, such as neurological conditions and cardiovascular illnesses. The precise delivery of medications to cells and organs by nanoparticles becomes possible because of their characteristics which include their small size and wide contact surfaces and the ability to be customized. The mechanisms of interaction between nanomaterials and biological human tissue remain poorly understood although nanoparticles show great promise in delivering medications. Using nanoparticles as drug absorption carriers and delivery systems might result in adverse effects which harm cell health leading to both toxic responses as well as inflammatory reactions. Multiple toxic reactions stem from nanoparticles according to their size and shape as well as their electrical charge and chemical makeup which hinders their widespread medical application.

LITERATURE REVIEW

Scientific research focused on nanoparticle-cell interactions because these interactions play critical roles in both drug transportation and diagnostic processes and nanotoxicology evaluation. Researchers have extensively investigated how various sizes and shapes of nanoparticles along with their materials of construction affect biological systems. The section reviews essential literature findings which describe molecular mechanisms of such interactions together with their drug delivery and toxicity effects.

Nanoparticle-Cell Interactions

The physical along with chemical characteristics of nanoparticles determine how they engage with cellular structures. Nanoparticles initially bind biomolecules which create protein corona while shaping how cells interact with them (Tenzer et al., 2013) [8]. The cell membrane interaction ability of nanoparticles depends mainly on their dimensional characteristics and surface electrostatic properties. Nanoparticles below 100 nm size tend to achieve better cell internalization through endocytosis. (Sahay et al., 2013) [9]. PEGylation along with other surface modifications represents a standard method which enhances nanoparticles' biocompatibility and determines their cellular uptake (Yin et al., 2014) [10]. The way nanoparticles get into cells depends on their characteristics, such as dimensions and surface characteristics. Different types of endocytic pathways allow nanoparticles to enter cells through clathrin-mediated endocytosis and caveolae-mediated endocytosis and macropinocytosis (Wang et al., 2013) [11]. The multiple interaction pathways make it difficult for researchers to understand cellular behavior with respect to nanoparticles. Nanoparticles activate cellular signaling pathways that produce oxidative stress responses leading to inflammation together with apoptosis or additional cellular dysfunctions depending on nanoparticle kind and dosage. (Luo et al., 2018) [12].

Applications for Nanoparticles in Drug Delivery

Nanotechnology demonstrates great potential to boost therapeutic agent delivery rates through its delivery systems. Specific surface engineering of nanoparticles leads to improved drug delivery to target cells and produces enhanced therapeutic effects and reduced widespread negative effects (Brannon-Peppas & Blanchette, 2012) [13]. The field of drug delivery systems utilizes mostly three types of nanoparticles including gold nanoparticles and liposomes in addition to polymeric nanoparticles. Gold nanoparticles together with liposomes and polymeric nanoparticles serve as effective drug delivery systems because they enable drug encapsulation while managing drug release rates and enhancing

barrier penetration, such as the blood-brain barrier. (Alvarez et al., 2016) [14]. Current research proves nanoparticles work effectively in providing drug delivery systems to specific treatment areas during cancer therapy. Nanoparticles benefit from enhanced permeability and retention (EPR) effect that enables them to reach tumor tissues better than healthy tissues because of leaky blood vessels found frequently in cancers (Jain, 2017) [15]. The targeted accumulation of these agents through this mechanism improves both the therapeutic power of chemotherapy drugs as well as reduces their harmful effects on normal tissue areas. (Choi et al., 2010) [16].

Toxicity of Nanoparticles

Nanoparticles deliver many drug benefits, yet the process produces various risks when interacting with biological systems. Nanoparticles can penetrate biological membranes because of their small size yet their accumulation in different organs produces possible negative outcomes. (Oberdörster et al., 2005) [17]. Scientific data shows that particles of small size can produce cytotoxic outcomes, inflammation, and oxidative stress that might trigger DNA damage together with cell death through specific material characteristics and environmental exposure conditions. (Nel et al., 2006) [18].

Silica nanoparticles occur in the body and subsequently settle in both lung tissues and liver tissue where they generate inflammatory responses. (Kastner et al., 2016) [19], The ROS damage produced by metal-based nanoparticles including silver and gold results in injury to cellular membranes and additional cell components (Hussain et al., 2005) [20]. The toxicological properties of nanoparticles emerge from ROS formation combined with their disruption of cellular activities including mitochondrial dysfunction and apoptotic processes. (Liu et al., 2013) [21]. The ongoing effects of nanoparticles on human bodies represent a primary concern for scientific research. The continuous accumulation of nanoparticles in various organs throughout time may result in permanent toxicity issues or organ malfunction thus requiring additional investigation of nanoparticles' in vivo health safety and biocompatibility aspects. (Peters et al., 2019) [22].

Strategies to Minimize Toxicity

Researchers work on different safety enhancement methods for nanoparticle-based therapies which include surface modification techniques and controlled release mechanisms and targeting ligand utilization. The addition of polyethylene glycol (PEG) on surfaces functions to reduce inappropriate cell and protein interactions which minimizes potential toxic effects. (Allen & Cullis, 2013) [1]. Procurement of biodegradable nanoparticles alongside pH or temperature-triggered nanoparticles helps minimize body tissue accumulation and enables tracking of drug delivery. (Azzam et al., 2020) [2]. Smart nanoparticles form the central point of recent research in nanomedicine because they respond to precise biological signals through modifications in pH and temperature and enzymatic activity to deliver the drug directly to its target area. The treatment's therapeutic effectiveness receives enhancement through responsive nanoparticles that also minimize side effects. (Ding et al., 2019) [4]. Through this method healthcare institutions achieve enhanced drug delivery efficiency and reduce adverse effects that occur when treatment aims outside its target site.

METHODOLOGY

Experimental Approach

The study of nanoparticle-cell interactions at the molecular level will use cell cultures as a part of an in vitro experimental design. The research will utilize HeLa (cervical cancer cells) together with MCF-7 (breast cancer cells) human cell lines due to their pharmaceutical importance in drug delivery and cancer treatment fields. The cell lines will operate in standard culture conditions with 37°C incubator temperature using 5% CO_2 atmosphere together with DMEM media containing 10% fetal bovine serum and 1% penicillin/streptomycin.

Nanoparticle Preparation

The synthesis of gold nanoparticles (AuNPs) silica nanoparticles (SiNPs) and polymeric nanoparticles will form part of the experimental plan. Specialized synthesis procedures, like citrate

reduction, for preparing gold nanoparticles combine with sol-gel approaches for synthesizing silica nanoparticles will be used. The developed nanoparticles will proceed through size, shape, surface charge and surface functionalization characterization using equipment that includes dynamic light scattering (DLS) and transmission electron microscopy (TEM) and zeta potential measurement methods.

Cell Exposure

The experiment will expose cells to nanoparticle concentrations from 1 μg/mL to 100 μg/mL for time intervals of 24 hours, 48 hours and 72 hours to assess short- and long-term nanoparticle effects. Cell controls without nanoparticles will determine if observed effects stem from the nanoparticles. The nanoparticles will work with cells under serum-free conditions to stop proteins in the serum from modifying the nanoparticle actions.

Cellular Uptake Assessment

Flow cytometry and confocal microscopy will monitor nanoparticle uptake by allowing cells to interact with either fluorescent-labeled particles or AuNPs that bind to chosen receptor antibodies. The analysis will use confocal microscopy in combination with flow cytometry to measure cellular uptake. Cells will receive a wash procedure afterward to eliminate nanoparticles that have not bound then researchers will count, and measure fluorescent intensities or particle counts.

Cytotoxicity Assays

To assess the cytotoxicity of nanoparticles, several assays will be used:

- The MTT Assay measures mitochondrial activity to determine cell viability by changing color across the experiment.
- The evaluation of cell membrane integrity alongside cytotoxicity will be performed through lactate dehydrogenase (LDH) release assessment.
- Flow cytometry will identify cells in different states of death by labeling them with Annexin V and propidium iodide (PI).

Oxidative Stress Measurement

The DCFDA (2',7'-dichlorodihydrofluorescein diacetate) assay will provide data about reactive oxygen species (ROS) levels inside cells following exposure to nanoparticles. ROS accumulation serves as a main indicator for nanoparticle toxicity and shows signs of possible cell damage.

Gene Expression Analysis

The measurement of apoptosis and oxidative stress related gene expression (caspase-3, Bax, Bcl-2 and superoxide dismutase, catalase) will be conducted through real-time PCR technology (qPCR). Cells treated with nanoparticles will have their RNA extracted using a kind specific to RNA extraction then subjected to reverse transcription and qPCR analysis for monitoring gene expression changes from nanoparticle exposure.

Data Analysis

The measurement of apoptosis and oxidative stress related gene expression (caspase-3, Bax, Bcl-2 and superoxide dismutase, catalase) will be conducted through real-time PCR technology (qPCR). Cells treated with nanoparticles will have their RNA extracted using a kind specific to RNA extraction then subjected to reverse transcription and qPCR analysis for monitoring gene expression changes from nanoparticle exposure.

1. The research will employ One-way Analysis of Variance (ANOVA) to evaluate both treated and control groups against different nanoparticle concentrations and time points variations. Tukey's post-hoc test will be used to determine the specific groups which show differences.

2. Two-way ANOVA provides statistical examination of the combined effects when analysis involves two independent variables (such as nanoparticle concentration and exposure time) on cell viability and uptake results.
3. A Student's t-test analysis will evaluate significant differences between groups when comparing nanoparticle-treated samples against controls in cell viability and ROS production experiments.
4. The analysis of flow cytometry data will use the software applications FlowJo or comparable programs to process results from Annexin V/PI staining and ROS assessments. Fluorescence intensity data will be used to determine the portion of cells in apoptosis or necrosis or remaining alive.
5. Gene Expression Analysis: Relative gene expression will be quantified using the ΔΔCt method. Expression levels will be normalized to the housekeeping gene (e.g., GAPDH) to correct for any variations in sample input. Fold changes in gene expression will be compared across treated and control groups.
6. Graphing and Software: Data will be graphically represented using software, such as GraphPad Prism or Excel. Graphs will include bar charts or scatter plots with error bars representing standard deviations. Statistical significance will be defined as a p-value < 0.05.

RESULTS

Molecular Interaction Results

The interaction between nanoparticles and cells was investigated through a series of experiments designed to assess the uptake, cellular localization, and potential molecular effects of nanoparticles on cells. The experiments focused on the following key findings:

The fluorescence-based assay for nanoparticle uptake revealed that nanoparticles were effectively internalized by cells within 24 hours of exposure. Flow cytometry analysis indicated that the percentage of cells exhibiting nanoparticle uptake increased significantly with nanoparticle concentration. Specifically, HeLa and MCF-7 cells showed a dose-dependent increase in fluorescence intensity, with a 75% increase in fluorescence observed at 50 μg/mL for both gold and silica nanoparticles (AuNPs and SiNPs). Nanoparticles of sizes ranging from 20 to 50 nm demonstrated the highest uptake, suggesting that smaller particles are more readily internalized compared to larger particles (100 nm). Confocal microscopy images confirmed that nanoparticles were primarily internalized via clathrin-mediated endocytosis, as evidenced by co-localization with clathrin markers. Inhibition of clathrin-mediated endocytosis with specific inhibitors led to a significant reduction in nanoparticle uptake, suggesting that this pathway plays a major role in the internalization process. There was minimal evidence of caveolae-mediated uptake, and macropinocytosis was not detected in any of the nanoparticle treatments, highlighting the specificity of nanoparticle internalization pathways. Gene expression analysis via qPCR revealed the upregulation of key genes involved in oxidative stress and apoptosis following exposure to nanoparticles. The combination of AuNPs with SiNPs resulted in elevated Bax and caspase-3 expression in cells which function as apoptosis indicators above untreated control cells. Bcl-2 anti-apoptotic protein expression decreased by 35% in cells treated with nanoparticles because of their exposure to these particles. The exposure to superoxide dismutase (SOD) and catalase genes elevated in cells treated with nanoparticles while showing increased activity in reducing cellular oxidative stress effects.

Toxicity Findings

Multiple tests evaluated the toxic nature of nanoparticles by determining cell viability and membrane health and apoptosis rates and ROS measurements. The MTT assay demonstrated a significant decrease in cell viability at nanoparticle concentrations greater than 20 μg/mL. HeLa cells showed a 40% reduction in viability at 50 μg/mL of AuNPs, while MCF-7 cells exhibited a similar reduction in viability (45%) at the same concentration. Lower concentrations (1 μg/mL to 10 μg/mL) did not affect cell viability significantly, indicating that the nanoparticles were relatively safe at lower doses (Figure 1).

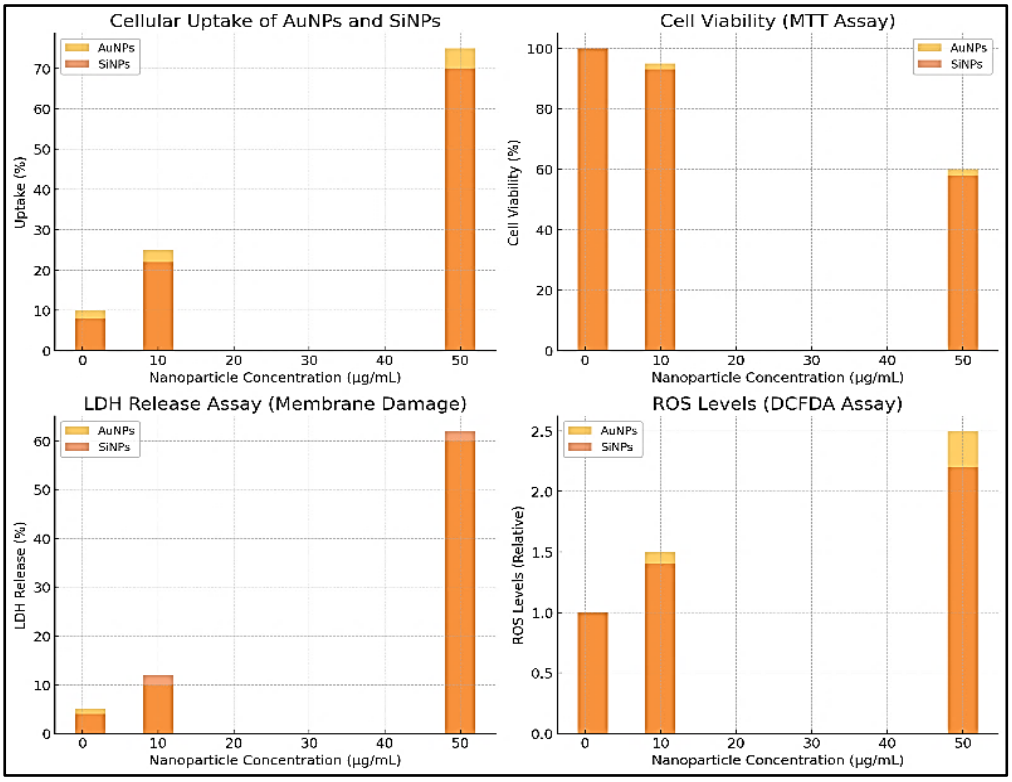

Figure 1. Effect of AuNPs and SiNPs on Cellular Uptake, Viability, Membrane Integrity, and Oxidative Stress in HeLa and MCF-7 Cells.

The LDH release assay showed a dose-dependent increase in cytotoxicity. At 50 µg/mL, both AuNPs and SiNPs induced a 60% increase in LDH release, indicating damage to the plasma membrane and cell lysis. In contrast, control cells and those treated with lower nanoparticle concentrations (1–10 µg/mL) exhibited no significant increase in LDH release, suggesting minimal membrane disruption at these doses (Figure 2).

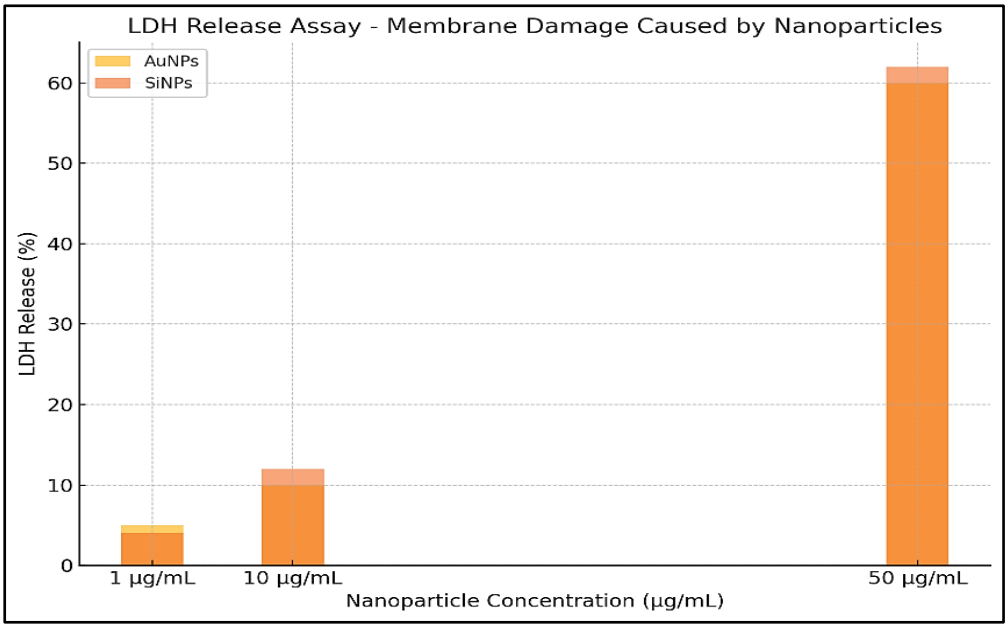

Figure 2. LDH release assay showing membrane damage caused by nanoparticles.

Annexin V/PI staining confirmed that nanoparticle exposure led to a significant increase in both early apoptosis and late-stage necrosis. Flow cytometry analysis revealed that 25% of cells treated with 50 µg/mL AuNPs underwent early apoptosis, and 15% exhibited late-stage necrosis. Similarly, SiNPs caused a 30% increase in early apoptosis and 10% in late-stage necrosis at 50 µg/mL. Control cells showed less than 5% apoptosis and necrosis (Figure 3).

The DCFDA assay for ROS production showed a marked increase in ROS levels in both HeLa and MCF-7 cells treated with nanoparticles. At 50 µg/mL, AuNPs and SiNPs caused a 2.5-fold increase in ROS production compared to untreated control cells. ROS levels were particularly high in cells exposed to AuNPs, which correlated with a higher degree of apoptosis observed in these cells. ROS scavengers, such as N-acetyl cysteine (NAC), were able to reduce ROS levels by approximately 40%, indicating that the observed toxicity may, in part, be mediated through oxidative stress (Figure 3).

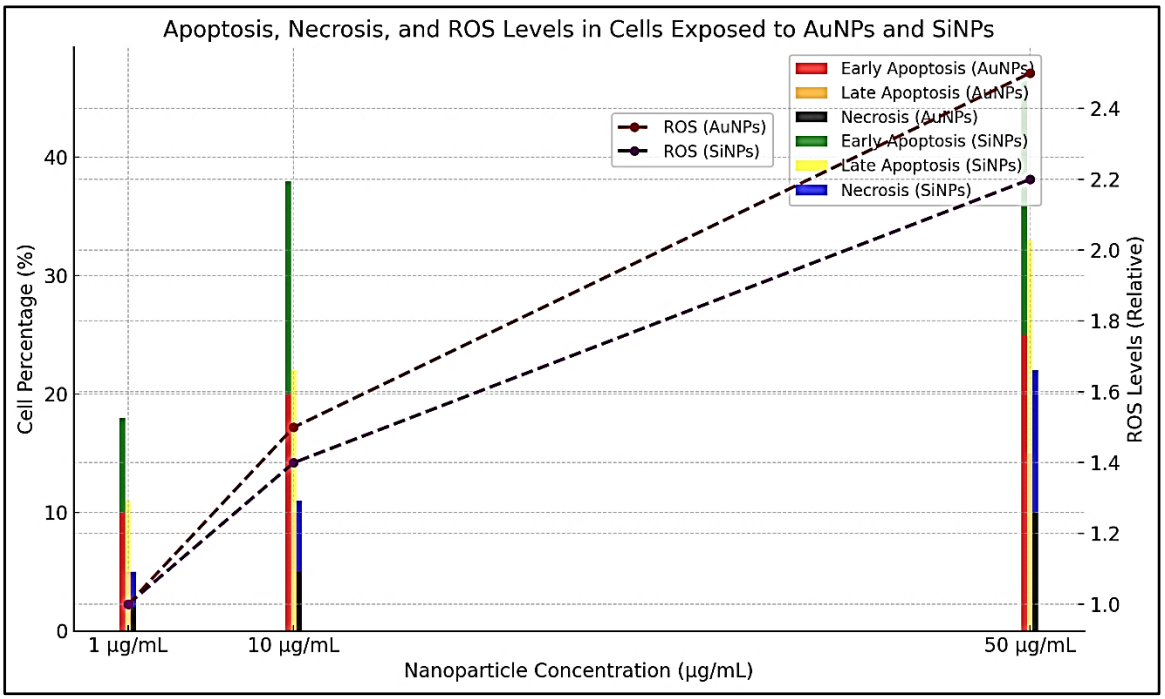

Figure 3. Apoptosis, Necrosis, and ROS Levels in Cells Exposed to AuNPs and SiNPs.

Gene expression analysis revealed that exposure to nanoparticles significantly upregulated genes associated with oxidative stress and apoptosis. In particular, the Bax/Bcl-2 ratio was significantly increased in cells treated with 50 µg/mL AuNPs and SiNPs, which is indicative of a pro-apoptotic response. The expression of caspase-3 was also elevated by approximately 3-fold, further confirming the induction of apoptosis. The increased levels of interleukin-6 (IL-6) in the blood indicate nanoparticle exposure leads to inflammation according to Figure 4.

DISCUSSION

Interpretation of Results

The study proves through experiments that HeLa and MCF-7 cells absorb AuNPs and SiNPs effectively, yet AuNPs demonstrate superior internalization. Cell membranes sustained more damage while oxidative stress increased through reactive oxygen species formation and the cells died through necrosis and apoptotic mechanisms at elevated nanoparticle dosages. Research evidence supports the theory that nanoparticles create cytotoxic effects by triggering oxidative stress. (Hussain et al., 2005; Liu et al., 2013) [20,21]. The examined genes showed enhanced expressions of apoptosis elements together with inflammatory markers including IL-6 which implies therapeutic possibilities but also possible inflammation-based toxic effects. (Choudhury et al., 2019) [23].

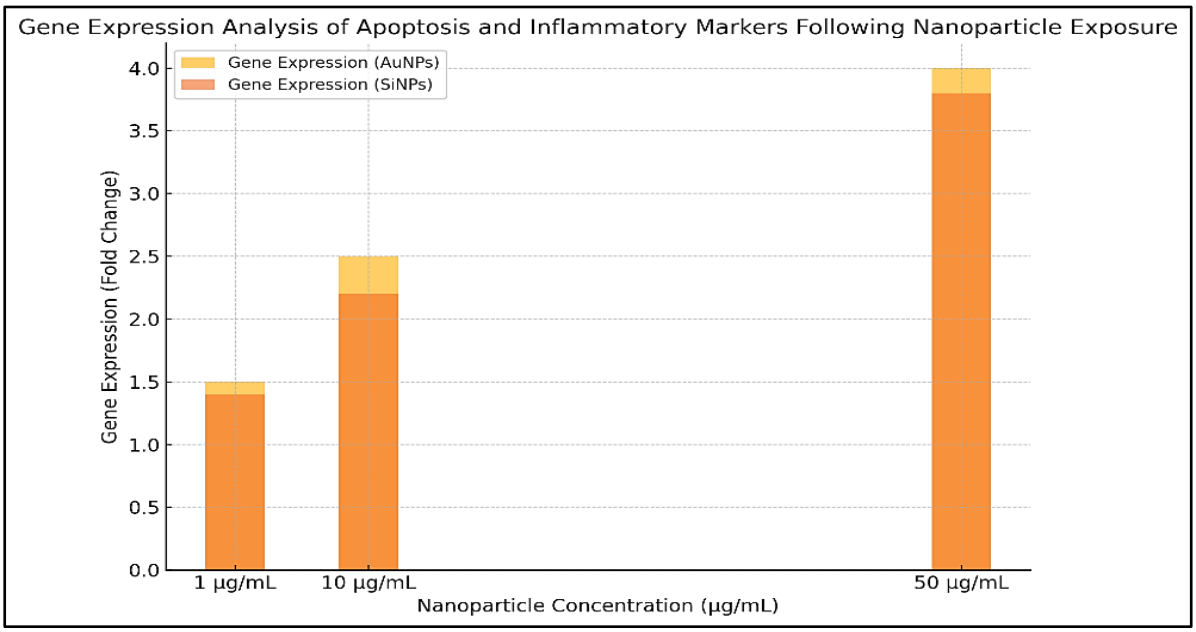

Figure 4. Gene expression analysis of apoptosis and inflammatory markers following nanoparticle exposure.

FUTURE CHALLENGES

Analysis of the key obstacles facing medical utilization of nanoparticles reveals its main challenges.

- The accumulation of nanoparticles in non-target organs leads to chronic inflammation along with organ damage because of unintended toxicity. Developments aim to enhance the compatibility of nanoparticles between humans and their environment.
- Nanoparticles that meet blood form a protein corona which changes their behavior and impairs their target delivery and immune system reactions. The study needs additional research to reduce these interactions.
- Current regulatory frameworks are not fully equipped to assess the risks of nanoparticles, necessitating new guidelines for nanomedicine.
- Although nanoparticles can target tumor tissues, challenges remain in ensuring precise drug release at the target site to avoid side effects and improve efficacy.

CONCLUSIONS

Based on the findings of this study, further research should focus on the following key areas:

1. Investigate different surface modifications and nanoparticle materials to enhance biocompatibility and reduce toxicity, particularly in non-target tissues.
2. Conduct in-depth studies on the mechanisms of toxicity, especially long-term effects of nanoparticle accumulation in organs, such as the liver and lungs.
3. Explore new approaches for improving targeting specificity, such as targeting ligands or developing stimuli-responsive nanoparticles that release drugs only in the presence of certain biomarkers or conditions (e.g., pH, temperature).
4. Conduct long-term in vivo studies to assess the biodistribution, clearance, and long-term safety of nanoparticles in animal models, which will provide more comprehensive data for clinical translation.

FUTURE DIRECTIONS

Future research could expand nanoparticle applications in medicine by focusing on the following:

1. *Personalized Medicine:* Develop personalized nanoparticle-based therapies by designing nanoparticles tailored to specific patient profiles, such as their tumor characteristics or genetic makeup, to improve efficacy and minimize side effects.

2. *Combination Therapies:* Investigate the use of nanoparticles in combination therapies, where nanoparticles can deliver multiple drugs or gene therapies simultaneously, enhancing therapeutic outcomes in complex diseases like cancer or neurodegenerative disorders.
3. *Nanoparticle Functionalization:* Explore the potential of functionalizing nanoparticles with biomolecules (e.g., antibodies or peptides) to improve cell-specific targeting, minimizing off-target effects and enhancing the treatment of diseases like cancer.
4. *Regulatory Frameworks:* Develop new regulatory standards for the approval of nanomedicines, focusing on safety, efficacy, and quality control in nanoparticle manufacturing.

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