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In Vitro Determination of the Cytotoxicity of Cerium Oxide Nanoparticles Against HBL-100 and Rat's Embryonic Fibroblast Cell Lines

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Abstract

This work was conceived as a contribution to the study of the cytotoxicity of different concentrations of cerium oxide nanoparticles (CeO_2NPs) (10, 30, 60, 90, and 120 µg/ml) against two cell lines involving human breast epithelial HBL-100 and Rat's Embryonic Fibroblast (REF) *in Vitro*, by using 3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide (MTT) assay technique. The nanoceria made it much less likely for HBL-100 cells to survive at all concentrations than the control. The only concentration that did not significantly reduce cell viability compared to the control was 60 µg/mL. This concentration had an IC50 value of 81.00 µg/mL for HBL-100.Meanwhile, the cell viability of REF was reduced with a high significant difference by all nanoceria concentrations compared with control, and the IC_{50} value of the nanoceria was 1.56 µg/mL. So, we may conclude that nanoceria with the >25nm particle size has high cytotoxicity for REF cell line at low and high concentrations compared with the HBL-100 cell viability that decreased exponentially with the concentration.

Keywords: cytotoxicity, HBL-100, nanoceria, REF.

Introduction

The nanomaterials (materials that have at least one nanoscale dimension between 1-100 nm in size) have numerous disadvantages, such as environmental impacts and health risks, especially if inhaled or in contact with the skin due to their tiny size, so they can penetrate the biological membrane, accumulate in the various tissues and cause several harmful effects on humans (1). The nanomaterials have unpredictable behavior due to their unique properties at the nanoscale, making it difficult to assess their long-term stability

and interactions with other materials (2). So, researchers are trying to develop new nanomaterials with better properties and safer to use in nanotherapeutics.

Cerium is one of the most prevalent trace elements in the Earth's crust, which occurs naturally in the soil as hydroxyl bastnasite, rhabdophane, zircon, and bastnasite or other cerium compounds from various sources, including sewages, landfills, electronic device waste, and ceramic manufacturing waste (3). Due to the environmental and biological activities of microorganisms or plants that secrete various secondary metabolites, these cerium compounds may be reduced naturally to cerium oxide nanoparticles (4). The nanoceria is used in gas sensors, polishing agents, UV absorbers, fertilizers, and medicinal agents. Since 2004, it has been added to tobacco used in the cigarette industry. It is one of the products of burning diesel fuel, so smoking activities and diesel engine exhaust continuously release the element into the atmosphere (5). Thus, humans are exposed to the nanoceria by inhaling and skin contact (6).

Cerium has attracted the attention of researchers due to its unique electronic distribution, which gives it two valences—a triple valence (III) and a quadruple valence (IV) Its nanoparticles have a lot of cerium ions in them. Adding or subtracting electrons in the same nanoparticle allows these ions to have valence states (7). This phenomenon affects the nanoceria behaviour in redox reactions in the cells exposed to nanoceria. It may exhibit pro-oxidant or antioxidant behaviour (5,8).

So, nanoceria has been used in beneficial applications in various fields during the past three decades, especially in biomedical applications in drug delivery, cancer therapy, and tissue engineering. In order to keep them safe, it is important to understand their effects on cells, tissues and organs (9). Based on the ratio between the Ce^{+3}/Ce^{+4}, the nanoceria can mimic the actions of CAT and SOD because they can scavenge reactive oxygen species (ROS), reduce oxidative stress, and protect cells from the harmful effects of free radicals, so a study of cytotoxicity helps clarify the balance between therapeutic and adverse effects (10,11). Due to the increased use of nanoceria in consumer products, concerns have been raised about the potential release of nanoceria to the environment and subsequent exposure of human cells to these particles. Knowledge of their cytotoxicity can help inform their safety for humans and ecosystems (5). Nanoparticles, such as nanoceria, interact with biological systems differently than bulk materials and have mechanisms of action different from those of large materials. It can penetrate biological barriers. It may activate immune responses or damage cell membranes, DNA, or other cell structures. These interactions require scrutiny to mitigate any negative consequences (12).

The cytotoxicity of nanoceria and their behavior as antioxidant or pro-oxidant agents depended on various factors, such as the aggregation and agglomeration states and the size and shape of the nanoparticles. Nanoceria with smaller sizes are more hazardous to the cells (13). The nanoceria with rod-shaped nanoparticles are the most hazardous compared to the octahedral and cubic-shaped ones (14). Additionally, the

process used to produce the nanoceria, the kind of materials used to coat the particles, the type of surface charge of nanoparticles, the type and physiological state of cells exposed to the action of the nanoceria, and the dosage, the amount of these nanoparticles, as well as the duration and frequency of exposure, and the pH value inside the cell effects on cytotoxicity of nanoceria, because it directly influences the transition of Ce^{+3} to Ce^{+4}, all of these factors may determine the cytotoxicity of nanoceria, so, examining their cytotoxicity guides safe dosage thresholds and appropriate therapeutic concentrations (15). Finally, in order to receive the regulatory approval that is necessary for both biomedical and industrial applications of nanoparticles, the individual nanoparticles must be shown to be non-toxic at the levels they will be exposed to during use (16). Due to the huge potential of nanoceria, it is very important to study how harmful these nanoparticles are to cells. This will ensure their safe use, with minimal side effects and maximum benefits. In order to find out how cytotoxic nanoceria is, we are using Rat's Embryonic Fibroblast (REF) cell lines and HBL-100 cell lines in this study.

Materials and Methods

Nanoceria >25 nm in size were acquired from the Sigma Aldrich/ USA. A 1000 µg/ml stock solution was prepared by dissolving 100 mg in 10 ml of dimethyl sulfoxide (Santa Cruz, USA). The solution was then placed in an ultrasonic water bath (Fuyang/ Chain) set at 40 °C for 10 minutes to scatter the nanoparticles. Different concentrations of 120, 90, 60, 30, and 10 µg/ml were made from stock solution using serum-free medium to be employed in ensuing cytotoxicity (17).

Preparation of Rat's Embryonic Fibroblasts (REF): At 18 days of pregnancy, the fetuses were retrieved from the pregnant rat moms. The fetus's skin, brain, and internal organs were removed, and the fetus was dissected in Petri dishes that contained serum-free Roswell Park Memorial Institute medium (RPMI) 1640 (Gibco/USA). The fetal tissues were then fragmented into little fragments. After transferring these components to 50 ml tubes, the 3% collagenase type I was added. The tubes were placed in the water bath at 37°C for an hour, with stirring performed every 10 minutes. The solution was filtered through three layers of medical gauze to separate and dispose of large fragments. After 5 minutes of centrifugation at 4000 rpm, the supernatant was entirely removed. The cell mass pellet was collected from the tubes' bases and resuspended with fresh RPMI medium supplemented with 10% fetal bovine serum (FBS, Gibco/ USA) and 100 mg/ml streptomycin/ampicillin in 25 ml cell culture flasks, which were placed in an incubator supplied with CO_2 at 37 °C. Using an inverted microscope, the cells were observed after 24 hours. After incubating for three days, the cells were used as a monolayer (18).

Cytotoxicity tests: The cytotoxicity effects of nanoceria were assessed at the Iraq Biotech Company-Basrah branch using the human breast epithelial cell line (HBL-100), which was obtained from this company's bank, and the REF, which was prepared as above.

Maintaining of cells: The HBL-100 and the REF cell lines were cultured in RPMI supplemented with 10% FBS and 100 mg/ml streptomycin/ampicillin. The culture was maintained at 37 °C and a CO_2 concentration of 5%. After trypsinization by passing through a trypsin-EDTA solution, the cells were subcultured in an RPMI medium containing 10% FBS in a fresh T-25 flask. Subsequently, the flask was incubated at 37°C and 5% carbon dioxide (CO_2) (19).

MTT assay: The MTT assay was utilized according to (20) to study the cell growth inhibition rate. In brief, the cells were resuspended and seeded at the density of $1x10^4$ cells/well of 96-well microtiter plates for tissue culture containing 100 µl of RPMI media supplemented with 10% FBS. Plates were kept to form a monolayer of cells in a humidified incubator at 37 °C with 5% CO_2 for 24 h. then treated with 100 µl nanoceria at 120, 90, 60, 30 and 10 µg/ml concentrations. Where the control is made up of HBL-100 and REF cell lines and is not supplemented with nanoceria. For treated and untreated cell experiments, data were collected in triplicates. Plates were incubated for 72 h. in a humidified incubator at 37°C and 5% CO_2. Then, the medium was discarded, and 28 µl of MTT dye solution was added. The plates were incubated in a humidified incubator at 37 °C, with 5% CO_2 for 2 h. The cell culture plates were measured with a microplate reader at the wave length of 490 nm to determine the cell's growth rate. Ten readings were taken for each of the wells, and the mean absorbance value was used. Experiments were conducted thrice. The GraphPad Prism 8.1 program was used for determining the IC_{50} value (21).

Statistical Analysis: The percentage of cell viability of two cell lines was analyzed using One-Way ANOVA for different groups of nanoceria treatment, and a T-Test was applied to analyze IC_{50} value of different nanoceria between two cell line. All measurements were performed with GraphPad Prism (version 8.1) software (22).

Results

These were the statistical results of the cytotoxicity test for 120, 90, 60, 30, and 10 µg/mL of nanoceria against the HBL-100 and REF cell lines after 72 hours using the MTT assay method. The results showed that as the nanoceria concentration went up, the cell viability went down significantly ($P<0.0001$). Different concentrations had very different effects on the HBL-100 cell line. At 120 µg/mL, there was no change in the percentage of viable cells. There were 28.31%, 91.55%, 71.21%, and 67.52% changes between this and concentrations of 90, 60, 30, and 10 µg/mL (Figure 1 A). The correlation coefficient (r^2) was 0.94, which means there was a link between the amount of nanoceria and the percentage of living cells in this cell line. As for the REF cell line, the five different concentrations of nanoceria all affected its viability. The cell viability dropped significantly ($P<0.0001$) at 120 µg/mL, but not as much at 30 µg/mL ($P=0.0406$) or 10 µg/mL ($P=0.0206$). The percentage of living cells was 12.75 percent at 120 µg/mL, 18.01 percent at 90 µg/mL, 25.4% at 60 µg/mL, and 27.5 percent at 10 µg/mL (Figure 1 B). The correlation coefficient was 0.61, which means there

wasn't much of a link between the nanoceria concentration and the percentage of living cells in this cell line. Moreover, the IC_{50} value for the nanoceria inhibiting of the HBL-100 cell line was 81.00 µg/mL (Figure 2 A), which was significantly higher (P=0.0001) than the IC50 value of the REF cell line, which was 1.56 µg/mL (Figure 2 B, Figure 3).

Discussion

Only when specific receptors on the cell surface mediate phagocytosis or endocytosis can nanoceria infiltrate cells and cause harm. After successful entry, they redistribute within the cell and accumulate in various organelles, such as mitochondria, the endoplasmic reticulum, and ribosomes. They can also enter the cell nucleus, initiating their toxic effects (23). The nanoparticles can enter the cells through various mechanisms, and if their size is smaller than 40 nm, they can penetrate even the cell nucleus and exert more harmful effects (24). Several studies have suggested that the harmful effects of nanoceria are due to their role in stimulating and increasing the production of reactive oxygen species (ROS) inside cells, causing damage to various intracellular functions, DNA fragmentation, enzyme dysfunction, changes in the cytoskeleton, and activation of apoptosis pathways by caspase-3 and caspase-9, leading to cell death (25).

The cytotoxicity of nanoceria depends on the cell type, the shape and size of the nanoparticles, the cerium ion oxidation state, the exposure time and concentration, and the number of nanoparticles that successfully enter the cells (13). This variability helps explain the contradictory results in different studies on nanoceria toxicity (23). In this study, the difference in cell types affected the entry of nanoparticles into cells and their impact. This result agrees with the finding (26) that HEK293 cells took up nanoceria more than H9c2 cardiac myocytes. The difference in the toxicity of nanoceria between HeLa and HFL cells is attributed to the differential uptake of nanoparticles by different cell types (27). The study of (28) observed that ovarian cancer SKOV3 cells took up more nanoceria after 4 hours compared to colon cancer HT-29 cells. The same type of nanoparticles interacts differently depending on the cell type due to variations in endocytosis mechanisms, unique phenotypes, membrane fluidity, cell cycle, and receptors on the cell surface that influence nanoparticle uptake (23).

The variability in the cytotoxic effect of nanoceria on the HBL-100 and REF cell lines led to highly significant differences in IC_{50} values, consistent with the findings of (25), who studied nanoceria with 30-40 nm size and found that HEK293 cells had an IC_{50} of 92.03 µg/mL, significantly higher than the IC_{50} for HCT116 cells at 50.48 µg/mL. The significant difference in IC_{50} values between different cell lines observed by (19), is attributed to the cells' varying sensitivity to the toxicity of these nanoparticles. The nanoparticle shape influences the cytotoxicity of nanoceria ; the cubic-shaped nanoparticles, with a small specific surface area of 18.9 m^2/g, entered cells faster and affected mitochondrial membranes, increasing ROS production (29). The spherical-shaped nanoparticles used by (30) were taken up more quickly by human dental stem cells compared to

nanorods or nanowires, causing greater cellular effects. So, the current study found that nanoparticles were spherical or semi-spherical to cubic, with a small specific surface area, contributing to their cytotoxicity.

The high concentrations of nanoceria are directly related to the increased production of ROS in the cells (31). The percentage of cell viability decreased with increasing nanoceria concentration (25), and the highest concentration (over 60 µg/mL) caused significantly higher toxicity. The nanoceria's cellular uptake increased with higher doses and longer exposure times (32). The prolonged exposure to nanoceria significantly decreased cell viability in ARPE-19 cells, which is associated with increased ROS production (33). A study of (34) referred to HTR-8/SVneo cells obtained from the cytotrophoblast of the human placenta was not affected by nanoceria up to 100 µg/mL, while (35) observed that nanoceria significantly affected cartilage cell viability obtained from male rats at high concentrations (1280 µg/mL) after 48 hours of exposure. The nanoceria with 30-40 nm size used by (25) was toxic to certain cell lines, similar to the findings in the present study.

Conclusions

The nanoceria used in the current study has cytotoxicity with high concentrations and a long exposure period. This cytotoxicity varies depending on the type of cells exposed to nanoceria. Nanoceria does not affect the human breast epithelial cell line (HBL-100) in small amounts due to its very high IC50 value. At the same time, the stem cells derived from the rat's embryo (REF) were susceptible to all nanoceria concentrations.

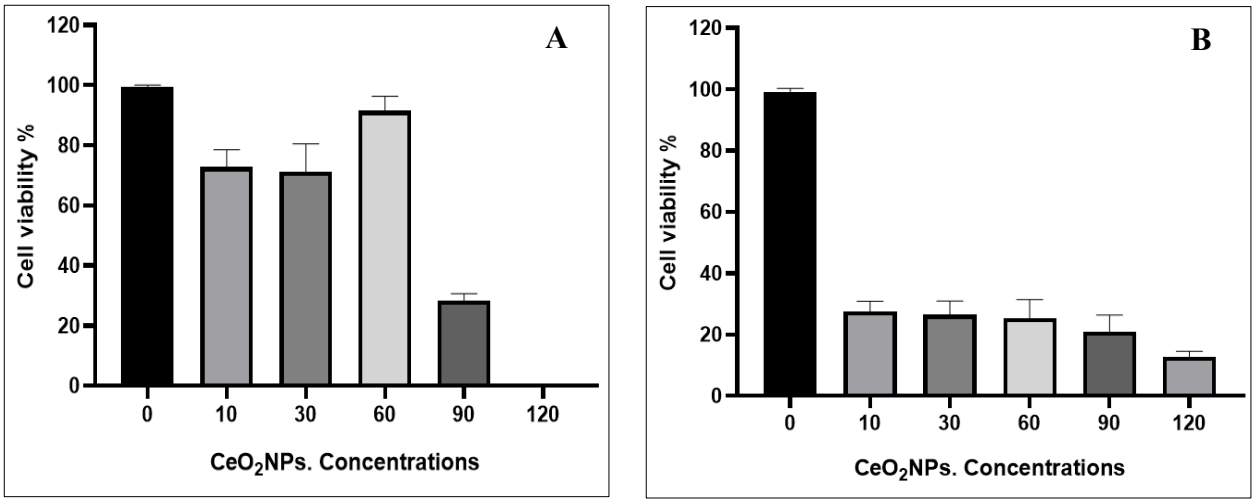

Figure 1: The percentage of the cell viability rate of the: A: HBL-100, B: REF cell lines, that were treated with different concentrations of nanoceria for 72 h. by using the MTT assay.

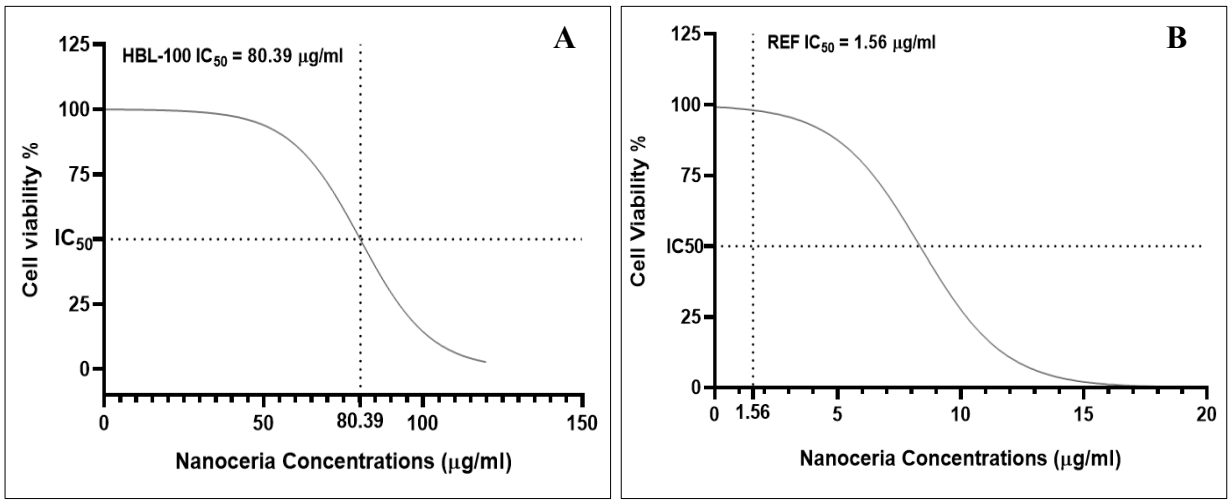

Figure 2: The IC_{50} value of the A: HBL-100, B: REF cell lines, were treated with different concentrations of nanoceria for 72 hours by using the MTT assay technique which calculated by GraphPad prism 8.1

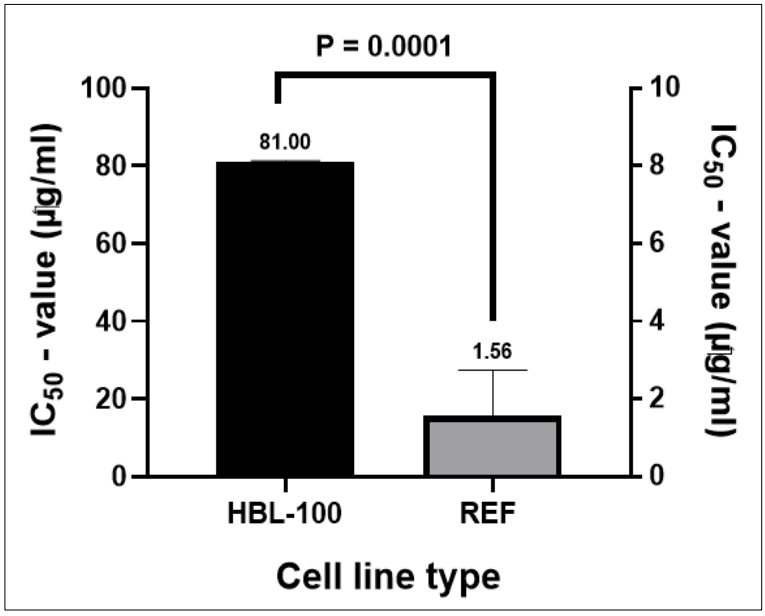

Figure 3: The result of T-test analysis between IC_{50} value of the HBL-100 and REF cell lines, were treated with different concentrations of nanoceria for 72 hours by using the MTT assay which calculated by GraphPad prism 8.1

Conflicts of interest

The authors declare that there is no conflict of interest.

Ethical Clearance

This work is approved by The Research Ethical Committee.

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تحديد السمية الخلوية لأوكسيد السيريوم النانوي تجاه خلايا الخط الخلوي HBL-100 وخط الخلايا الجذعية الجنينية لإجنّة الجرذان REF مختبرياً

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قسم علوم الحياة، كلية التربية للعلوم الصرفة، جامعة البصرة، البصرة، العراق

الخلاصة

أُجريت الدراسة الحالية لتحديد السميّة الخلوية لتراكيز مختلفة من لأوكسيد السيريوم النانوي CeO_2NPs هي 10، 30، 60، 90 و120 مايكرو غرام/مل تجاه أثنين من الخطوط الخلوية هي خط خلايا ثدي الأنسان الطبيعية HBL-100، وخط الخلايا الجذعية الجنينية لإجنّة الجرذان المختبرية REF بإتباع الطريقة اللونية MTT. بيّنت نتائج التحليل الإحصائي أن أوكسيد السيريوم النانوي قد خفّض حيوية خلايا الخط الخلوي HBL-100 بفروق معنوية في جميع التراكيز مقارنة بمعاملة السيطرة، ما عدا التركيز 60 مايكرو غرام/مل، فقد كانت حيوية خلايا هذا الخط الخلوي مقاربة لما موجود في السيطرة ومن دون فروق معنوية، وبلغ تركيز أوكسيد السيريوم النانوي المثبّط لنصف عدد خلايا الخط الخلوي HBL-100 81.00 مايكرو غرام/مل. وكانت حيوية خلايا الخط الخلوي REF قد انخفضت بفروق عالية المعنوية في جميع تراكيز أوكسيد السيريوم النانوي مقارنة بمعاملة السيطرة، وبلغ تركيز أوكسيد السيريوم النانوي المثبّط لنصف عدد خلايا الخط الخلوي REF 1.56 مايكرو غرام/مل. لذا نستنتج أن أوكسيد السيريوم النانوي ذو سميّة عالية تجاه خلايا الخط الخلوي REF في تراكيزه الواطئة مقارنة بخلايا الخط الخلوي HBL-100 التي انخفضت حيويتها عند التراكيز العالية منهُ.

الكلمات المفتاحية: السمّية الخلوية، الخط الخلوي HBL-100، أوكسيد السيريوم النانوي، الخط الخلوي REF.