Research Article

Title: The cytotoxic effects of titanium dioxide nanoparticles on MCF-7 cancer cell line

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Abstract

Cancer is a widespread disease worldwide, affecting many people with various types. Today, titanium dioxide nanoparticles have substantial therapeutic applications. We conducted a study to see how harmful titanium dioxide is to breast cancer cells.

MCF-7 cancer cells and HFF cell lines were cultured. We tested how cells survived when exposed to different amounts of titanium dioxide nanoparticles. The concentrations examined have been 25, 50, 100, and 200µg/ml. We measured the survival rate at 48, 72 hours and determined the IC50. We determined that the rate toxicity occurred while MCF-7 and HFF cells had been exposed to 200µg/ml of titanium dioxide. Apoptosis in MCF-7 and HFF cells emerges as shown with the aid of way of Annexin V-PI staining and go with the flow cytometry. Under a microscope, it was found that titanium dioxide nanoparticles can be harmful in specific amounts. At a dose of 200µg/ml, after 48 and 72 hours of treatment, MCF-7 and HFF cells were affected. The mitochondrial membrane broke when breast cells were exposed to titanium dioxide nanoparticles. The matrix leaked into the cytoplasm, and the rough endoplasmic reticulum swelled. These observations occurred after 72 hours of treatment with a concentration of 200 µg /ml. In keeping with the acquired effects, titanium dioxide nanoparticles may be

advocated as potential medicinal candidates for pharmaceutical purposes, even though further research is required.

Keywords

TiO2 Nanoparticles, Flow Cytometry, Micronucleus Assay, MTT Assay, TEM

Abbreviations

NP: Nanoparticle

TiO2: Titanium dioxide

UV: ultraviolet

ROS: Reactive oxygen species

FBS: Fetal bovine serum

TEM: Transmission electron microscope

DMEM: Dulbecco's Modified Eagle Medium

DMSO: Dimethyl Sulfoxide

Introduction

Nanotechnology is a broad field of applied physical sciences, chemical engineering, and biological engineering. Nanoparticles (NP) are tiny particles with dimensions less than 100 nm. Nanotechnology is used to supply cosmetics and drugs. NPs have completely lengthy records and were utilized by artisans within the 9th century to polish on the surface of pottery. Titanium dioxide (TiO2), known as titanium IV, was first commercially extracted from ore in 1923. Titania exists in three forms: rutile, anatase, and brookite. Due to its luster, TiO2 is used as a light-reflecting coating in papers and tablets as a white pigment, and also as an ultraviolet (UV) inhibitor in sunscreen. Oxidative stress caused by environmental pollution and harmful gases such as greenhouse gases play an essential role in aging. Also, the accumulation of reactive oxygen species (ROS) damages the nucleic acid of the cell and can lead to aging.

NPs build up rapidly in the environment, and the unique behavior of nanoparticles, especially their high surface-to-volume ratio, is the reason for their high reactivity and ability to pass through cell membranes. The toxicity of nanoparticles causes cell damage and inflammation due to the production of free radicals in cells [1]. The autosomal cell cycle has four phases. The first phase is called S phase, where DNA synthesis and replication occur. The second phase is called M phase, where cell separation happens. In addition to S and M phases, the cell cycle has three other phases: G1, G2, and G0. Cyclin kinases are responsible for controlling these phases. There are two types of tumors: benign and malignant. Malignant tumors are cancerous and grow fast. They can spread to other tissues and invade the body [2]. Cancer can enter the bloodstream or lymphatic system and spread to distinct elements of the frame. All forms of most cancers are as a consequence of troubles inside the cellular. Usually, cells divide to make new cells simplest at the same time as they are needed, preserving stability amongst cell increase and cellular loss of life. While the manage system that regulates cellular boom is disrupted, cells divide uncontrollably and form tumors. Mutations that increase cell branches

and prevent cell loss of existence can cause maximum cancers. In modern-day years, scientists have discovered mutated genes in human cancer cells. These genes are divided into three sections: proto-oncogenes, tumor suppressors, and DNA restore genes. Mutations in those genes can set off proto-oncogenes or inhibit tumor suppressor genes, leading to out-of-control cell growth and immortality. Mutations in DNA repair genes can also cause the accumulation of more significant mutations. Maximum cancers are currently the second primary motive of death worldwide. Breast cancer is the most unusual cancer for women. It causes more deaths than lung and stomach cancers. The survey display that, there were 40,430 deaths from breast most cancers (40,000 women, 430 men) in 2014 [3]. Cancer is the leading cause of loss of life in Iran, after coronary heart illness and accidents [4]. Reducing death rates from breast cancer is difficult in developing countries like Iran [5]. Treating breast cancer is difficult because chemotherapy has limited effectiveness and side effects. Therefore, today the focus is on controlled and targeted drug delivery systems. NPs can target and deliver anticancer drugs to maximize effectiveness and minimize side effects [6]. Therefore, there is an urgent need to find new substances for treatment. NPs are an alternative for treating diseases due to their biological effects and small and unique size. TiO2 are used in many industries, such as paper, plastic, cosmetics, and paint. They are also used as disinfectants and biological sensors, and to kill tumor cells [7]. The anticancer consequences of TiO2 have been investigated on several cancer, and the experiments showed that most cancers viability depends on the particle doses and counseled that TiO2 NPs can be used for cancer treatment. TiO2 NPs affect MCF-7 and HFF cell traces in distinctive concentrations. This cell line has been considerably used as a human breast most cancers version cell line inside the development of recent antitumor treatment. The purpose of this is to use laboratory research to assess the cytotoxic activity of TiO2 NPs.

Results

Cell Growth Inhibition Analysis of TiO2 NPs

TEM Technique

TEM image represents the morphology and organelles of MCF-7 and HFF cells via the usage of NPs handled. TEM analysis showing the structural adjustments and damages occur on remedy with TiO2.Intracellular uptake of TiO2 NPs established through a transmission electron microscope (TEM). MCF-7 and HFF cells have been incubated for 72h with 0 and 200µg/ml of TiO2 NPs.

Figure 2 (A and B) is related to fibroblast cells without treatment, where the organelles are seen healthy and intact. Moreover, the duration of 72 hours, the results show that the mitochondrial organelle is elongated and the rough endoplasmic reticulum is inflamed.

Figure 3 (A and B) is related to breast cancer cells without treatment. Compared to normal cells, these cells have many of mitochondrial organelles due to multiple and misplaced mitotic divisions. Figure 2 (C and D) are related to the treatment of breast cancer cells treated with a concentration of 200µg/ml for a period of 72 hours. Electron microscope images of the presence of TiO2 NPs inside the cell, as well as mitochondrial membrane rupture and leakage. It shows the swelling of the rough endoplasmic reticulum.

MTT Assay

In our study, we used TiO2 NPs to treat MCF-7 and HFF cell lines. The concentrations ranged from 25 to 200µg/ml. We used the MTT assay to measure cell growth inhibition. As the concentration of TiO2 NPs increased, we found that cell growth was increasingly inhibited. This was observed after 48 and 72 hours of exposure to the NPs. The cell viability decreased in a dose-dependent manner. Figure 4 show that the amount of inhibition of cells depends on the concentration. The graphs shows that the amount of inhibition of cells depends on the

concentration. At a concentration of 200µg/ml, cell death percentages were significantly lower after 48 and 72 hours of treatment ($p=0.01$, $p<0.05$). We calculated the IC50 values for TiO2 NPs. The values represent concentrations that cause 50% toxicity or death in MCF-7 cancer cells and normal HFF cells. These the IC50 were 420µg/ml and 1000µg/ml for MCF-7 and HFF, respectively.

Micronucleus Assay

The micronucleus technique is a very convenient and fast method in examining structural abnormalities of chromosomes, which is extensively used to research the cell morphology and study outcomes of NPs at the cell shape in vitro, have a look at changed into run beneath several groups. These groups included: absence of or presence of NPs. The results of light microscopy showed that TiO2 NPs can cause concentration-dependent toxicity at a dose of 200µg/ml in a treatment period of 48 and 72 hours in MCF-7 and HFF cell lines. As a result, at the concentration of 200µg/ml, the percentage of cell death in the treatment period of 48 hours and 72 hours ($p=0.01$) is significantly lower than other groups ($p<0.05$) (Figure 5).

Flow Cytometry Assay

To degree the amount of cell loss of life due to TiO2 NPs, MCF-7 and HFF cells had been handled with IC50 attention. The cells were then stained with FITC Annexin V and PI and analyzed the usage of flow cytometry. The flow cytometry consequences are proven in Figure 6. While exposed to 420µg/ml of TiO2 NPs, MCF-7 most cancers cells and HFF cells experienced a substantial decrease in viable cells. Moreover, the proportion of apoptotic cells extended. In the meantime, the percentage of necrotic cells could be tiny and negligible.

Discussion

NPs are necessity in physics and dentistry because they can contest bacteria, fungi, and viruses (8-10). However, researchers have limited the study of the antineoplastic capableness of TiO2 NPs. TiO2 NPs by myself did not harm glioma C6, RG2, mouse, or human glioma U373 cells. Copper–TiO2 NP was complicated turned into much less poisonous than copper on my own, indicating some protection from the hard with TiO2 NPs. However, the complicated became somewhat more venomous than cisplatin. The Copper-TiO2 complex can be a part of mitochondria and situation ATP composition. It may also lower the shaping of nitrogenic bases. Moreover, it may reach the cell nucleus and hook up with DNA base pairs. This occurs through interplay or groove binding. In the long run, it can motive apoptotic cellular death [11].

Reports indicate that TiO2 NPs, with added Au and Pt, effectively destroyed K562 tumor cells [12]. The way TiO2 NPs are taken up is not well understood. Some studies suggest that TiO2 NPs are taken up and stored in different cell parts, such as vacuoles, endosomes, and lysosomes. They may also be found in the cytoplasm because the lysosomal membrane breaks. Recently, it was found that TiO2 NPs can enter human cells through a specific receptor. Human bronchial epithelial BEAS 2B cells were treated with smaller than 25 nm uncoated anatase TiO2-NPs and 10-40 nm SiO2-lined rutile TiO2-NPs, individually.

Regardless of the truth that the uncoated TiO2-NPs increased the micronucleus, the SiO2-protected NPs did no longer [13]. Guichard et al. [14] determined that none of the TiO2-NPs or TiO2 bulk behavior momentous starting of micronuclei shape after 24 hours exposure of these particles to SHE cells. Prasad et al. [15] decided that TiO2-NPs introduced on micronuclei pleasant in a common that facilitated the nethermost quantity of agglomeration, the pinnacle quantity of NP. The genotoxic capability of 20 nm TiO2-NPs became charged in SHE cells. The cells were treated with 1.0 mg/ml TiO2-NPs of the for 12 hours, 24 hours, 48 hours, 66 hours, and 72 hours. The micronucleus frequencies have been extended via the remedy in an age-setting method [15]. HepG2 cells had been treated with low dose of 30 nm TiO2-NPs and

a vital increase inside the micronucleus commonness has come to be placed in the treated cells[16].

Human epidermal cells (A431) were managed with 50 nm anatase TiO2-NPs a dose of 80 mg/ml. The treatment caused tremendous chromosome change a dose of 80 mg/mL [17]. Human lung cancer cells, A549, have been treated with 10 mg/mL and 50 mg/mL of TiO2-NPs for 24 hours micronucleus assay was executed to decide the genotoxicity of the debris and there was a high-quality response within the micronucleus induction for each of the treatment concentrations [18, 19]. The toxicity of NPs on cancer cells was evaluated compared to normal cells. Investigations showed that the rate of inhibition of cells depends on the concentration. However, with rising up in concentration, the rate of toxicity has been increased, and on the other hand, the rate of cell survival has been diminished. In any case, more thinks about are required to explain the comes about of TiO2 NPs, and to clarify the components of the TiO2 NPs toxicity on cells, with the reason of creating modern methodologies for the cure of cancer and another sickness.

Conclusion

In keeping with the received effects, TiO2 NPs may be endorsed as ability medicinal applicants for pharmaceutical features, despite the truth that further studies are required on this subject. According to these studies clinical studies on the animal and human model are necessary to confirm the effect of NPs as well as the effect of this nanoparticle on the normal cell line.

Materials And Methods

We obtained chemicals and reagents from different companies. RPMI1640 was from Biosera. Fetal bovine serum (FBS) was also from Biosera. TiO2 NPs (nano powder) were from Sigma-Aldrich/Germany. We used MTT, plastic dishes, 6-well and 96-well plates, doxorubicin, and DMSO from BETACELL.

Assay For TiO2 Np Topography and NPs Characterization

We purchased TiO2 NPs from Sigma-Aldrich company, United Kingdom. The TiO2 NPs used in this study were titanium (IV) oxide, and anatase, with a purity of 99.7%. We weighed the TiO2 nanoparticles and placed them in natural water. In order to reduce the length of nanoparticle aggregates, NPs have been sonicated three instances for 30 minutes. We analyzed the TiO2 NPs with the usage of a Particle length analyzer (D mean number 35.51n.m) (NanoQ Report). The topographical surface was then discovered with a transmission electron microscope (TEM). (LEO 912 AB) (Figure 1).

Cell Culture

MCF-7 and HFF cells (Ferdowsi University) have been cultured at 37˚C in RPMI 1640 and Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% heat-inactivated FBS, 500µg/ml, penicillin-streptomycin and 200µg/ml amphotericin B below a humidified atmosphere with 5% CO2. Cells were then harvested by treatment with 0.25% trypsin-EDTA.

Assay for Cytotoxic Activity

MTT test is used to check the share of living cells. In this way, a cell flask with 60% confluence turned into trypsinized, and after cell counting, it was transferred to a 6-well plate, so that about 150 $\times 10^3$ cells were placed in 200µl of way-of-life medium for every concentration of TiO2 NPs, and were incubated at 37°C for 48 and 72 hours. The check for determination of cellular survival was performed through adding 100µl MTT (5 mg/ml in PBS containing 10% fetal bovine serum (FBS) to each well, and the cells were incubated for every other 4 hours. To dissolve the resultant formazan, 100µl dimethyl sulfoxide was delivered, and the absorbance values were measured through a spectrophotometer a wavelength of 540 nm. Moreover, cell

lethality was calculated by the following formula. Considering the life of three repetitions for every experiment, via acquiring the average survival and standard deviation, SPSS software and Kruskal Wallis statistical take a look at have been used for statistical analysis of the information with an importance stage of $p<0.05$.

Percentage Survival =OD test/OD count ×100

Analysis of Apoptosis by Flow Cytometry

To measure cell death, we used a flow cytometry test called annexin V-FITC apoptosis detection kit. The test was done following the instructions provided by the manufacturer. We treated MCF-7 and HFF cells (5×10^5) with a solution of TiO2 nanoparticles at different concentrations: 25, 50, 100, and 200 (µg/ml). After 48 and 72 hours, we gently removed the cells from the dishes, washed them once with a medium containing serum, and put them in a 500µl buffer. Then, we added 5µl of annexin V-FITC and 5µl of propidium iodide. The cells were incubated at room temperature for 15 minutes in the dark. Finally, cells were analyzed using a flow cytometer called BD Falcon from the USA.

Intracellular Uptake of TiO2 NPs

We exposed cells to different amounts of TiO2 NPs for 48 and 72 hours. Then, we washed the cells three instances with PBS and stuck them for 1 hour with 2% glutaraldehyde in 0.1 M cacodylate buffer (pH 7.4) at 4˚C. We used a rubber scraper to collect the cells, dried them, and embedded them in Araldite M. Samples were stained with uranyl acetate and lead citrate. Finally, thin sections were observed under a LEO 912 AB TEM at a magnification of ×4,000.

Slide Preparation for Micronucleus Assay

We created two slides for every sample. The quantity of fixative varies depending on the pellet. We produced a total of four slides for each sample. On each slide, we introduced two drops of cell suspension, each 20µl. Then, we allowed the slides to dry in the air. We stained the slides with 10% Giemsa stain in phosphate buffer for 10 minutes. After that, we allowed the slides to dry in the air for a single day. Subsequently, the slides are covered with a cover slip.

Statistical Analysis

Distribution of MTT and Micronucleus value among control and four groups receiving different doses of TiO2 were compared using non-parametric Kruskal Wallis test. Pairwise comparison was performed using Mann-Whitney U test with Bonferroni adjustment applied.

Comparison of MTT and Micronucleus value between MCF7 and HFF cell lines and also between 2 assessing time (48 and 72h) performed using the Mann-Whitney U test. The data were analyzed using IBM SPSS Statistics 26 software (IBM SPSS Statistics, Chicago, USA).

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Author's Contributions: Investigation, writing the original draft and formal analysis: RJ. Conceptualization, supervision, software, draft-review, and editing: RJ, AR, HM, MA. All authors have been involved in writing the article, and accept responsibility for its content.

Conflict of Interest: The authors declare that there is no conflict of interest.

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Figures

Figure 1. Detection of aggregation of TiO2 nanoparticles (NPs) by transmission electron microscopy (TEM).

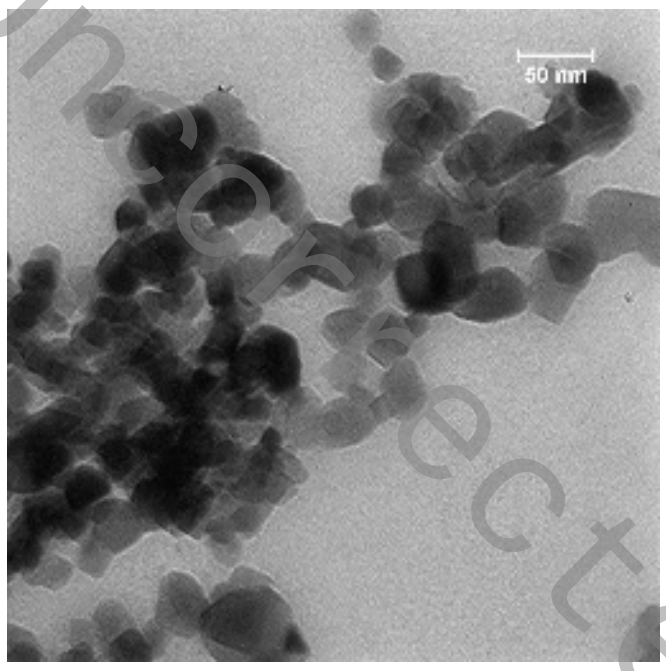


Figure 2. Effect of 200 µg/ml concentrations of TiO2 NPs on HFF cell line.

A, B: Control group-HFF cell, ×4000; C, D: Dose 200 µg/ml-HFF cell, ×4000. Lys, lysosome; MT, mitochondria; ERr, rough endoplasmic reticulum; H-N, heterochromatin nucleus; N, nucleus; TiO2, TiO2 nanoparticle; dMT, damage mitochondria; N, nucleus.

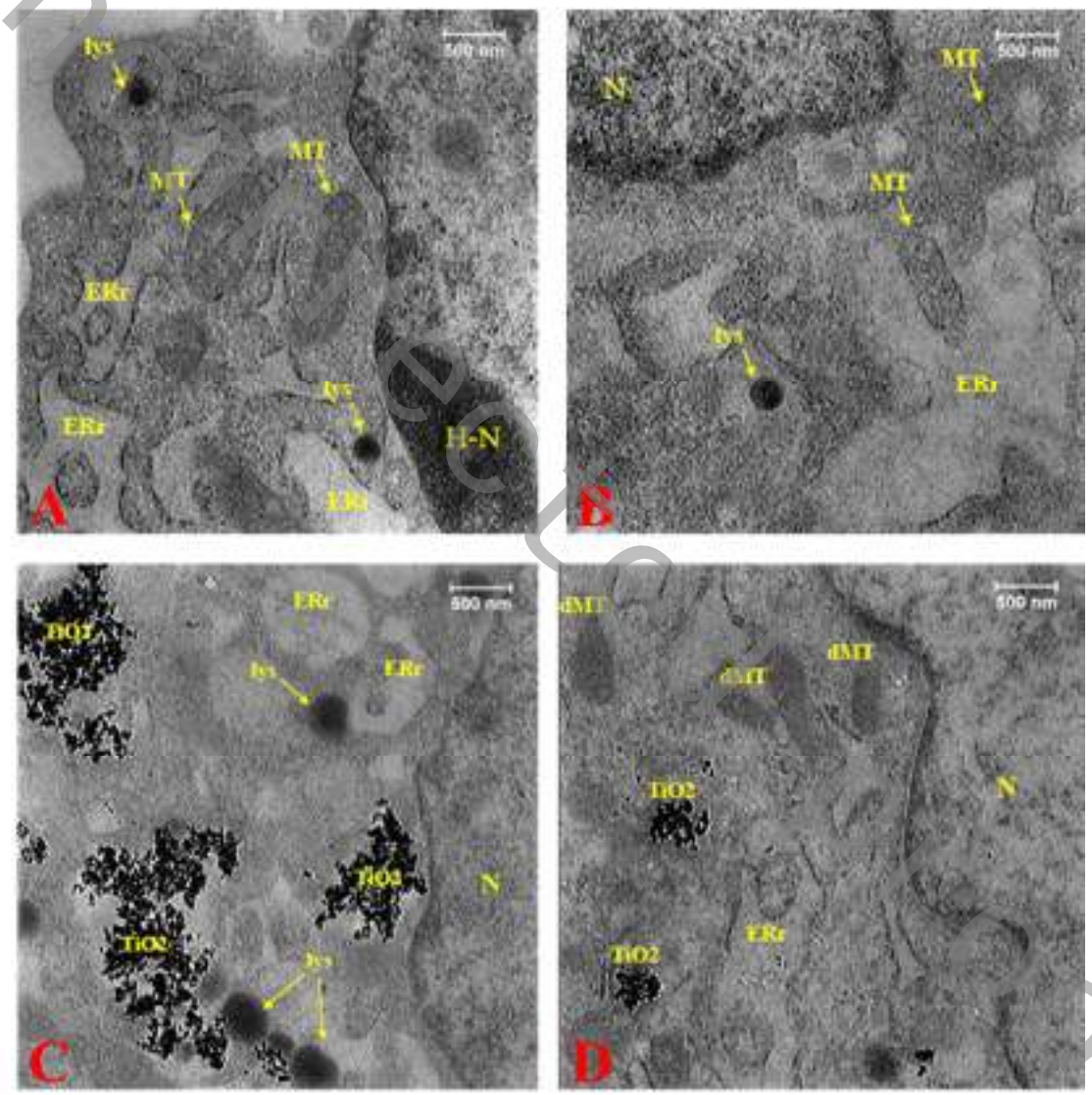


Figure 3. Effect of 200 µg/ml concentrations of TiO2 NPs on MCF-7 cell line.

A, B: Control group-MCF-7 ×4000; C, D: Dose 200 µg/ml-MCF-7. Lys, lysosome; MT, mitochondria; MV microvilli; V, vacuole cytoplasm; N, nucleus; ERs, smooth endoplasmic reticulum; dMT, damage mitochondria; ERr, rough endoplasmic reticulum; TiO2, TiO2 nanoparticle.

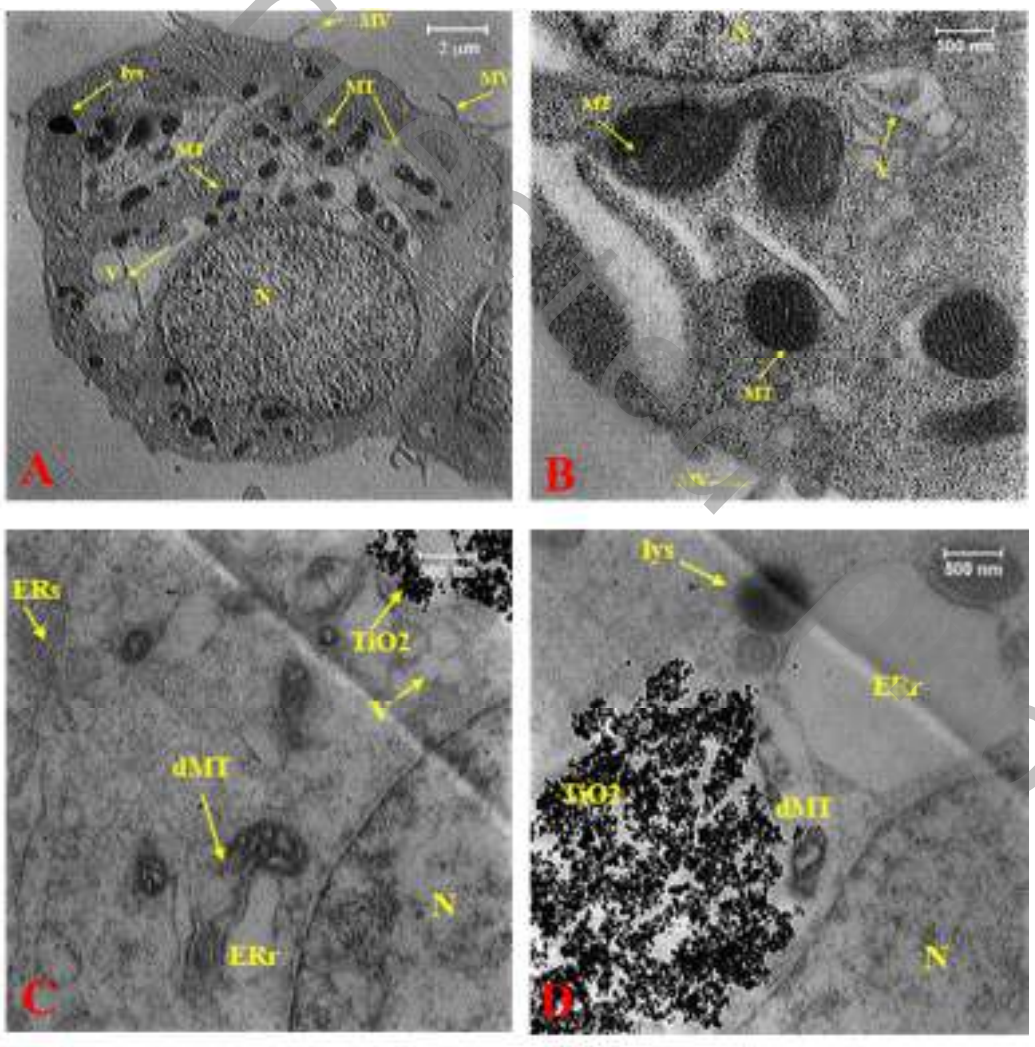


Figure 4. Effect of different concentrations of TiO2 NPs (µg/ml) on HFF and MCF-7 cells line.

A: 48h, HFF cell line; B: 72h, HFF cell line; C: 48h, MCF-7 cell line; D: 72h, MCF-7 cell line.

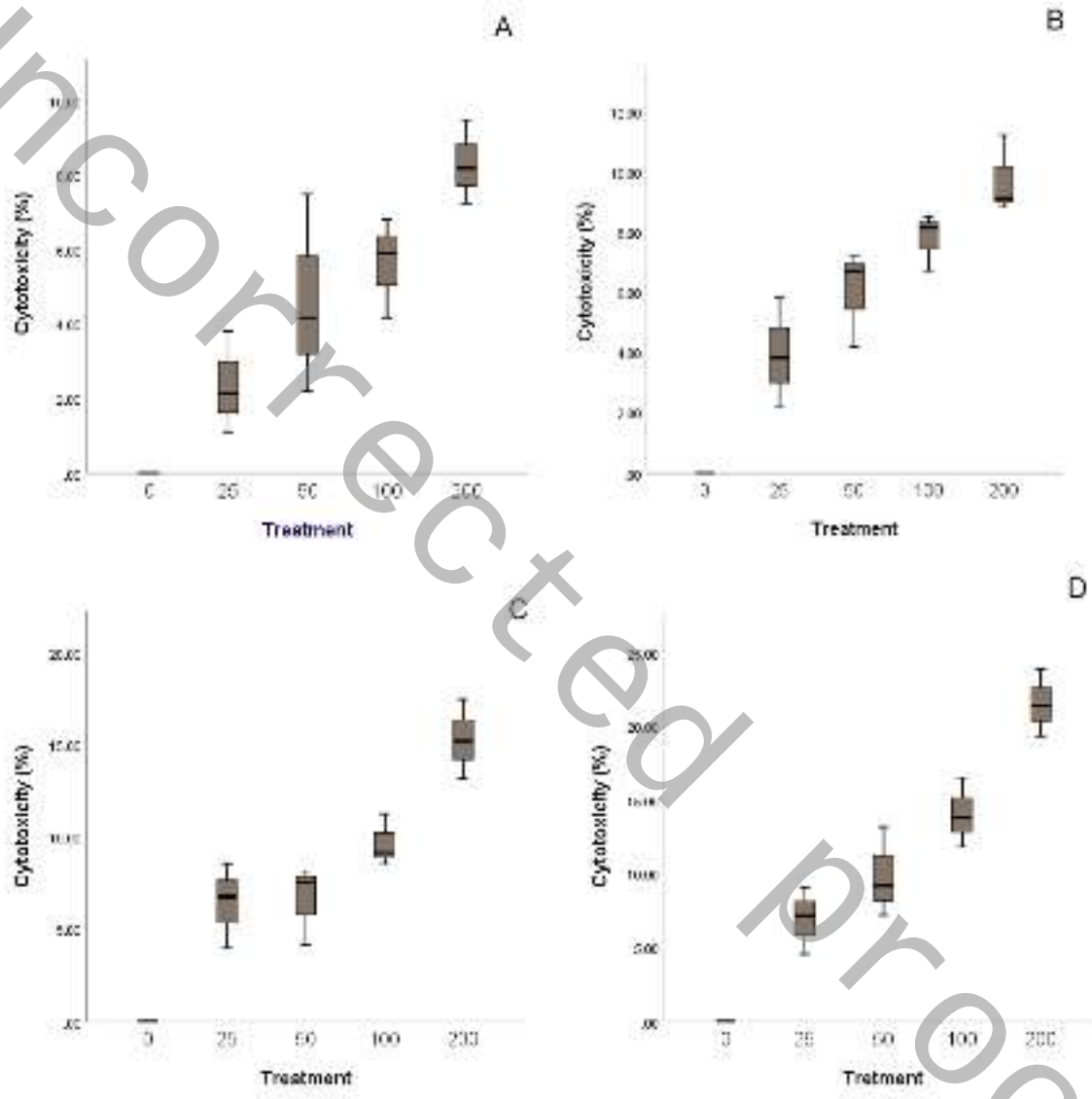


Figure 5. Effects of different concentrations of TiO2 NPs (µg/ml) on HFF and MCF-7 cells line.

A: 48h, HFF cell line; B: 72h, HFF cell line; C: 48h, MCF-7 cell line; D: 72h, MCF-7 cell line.

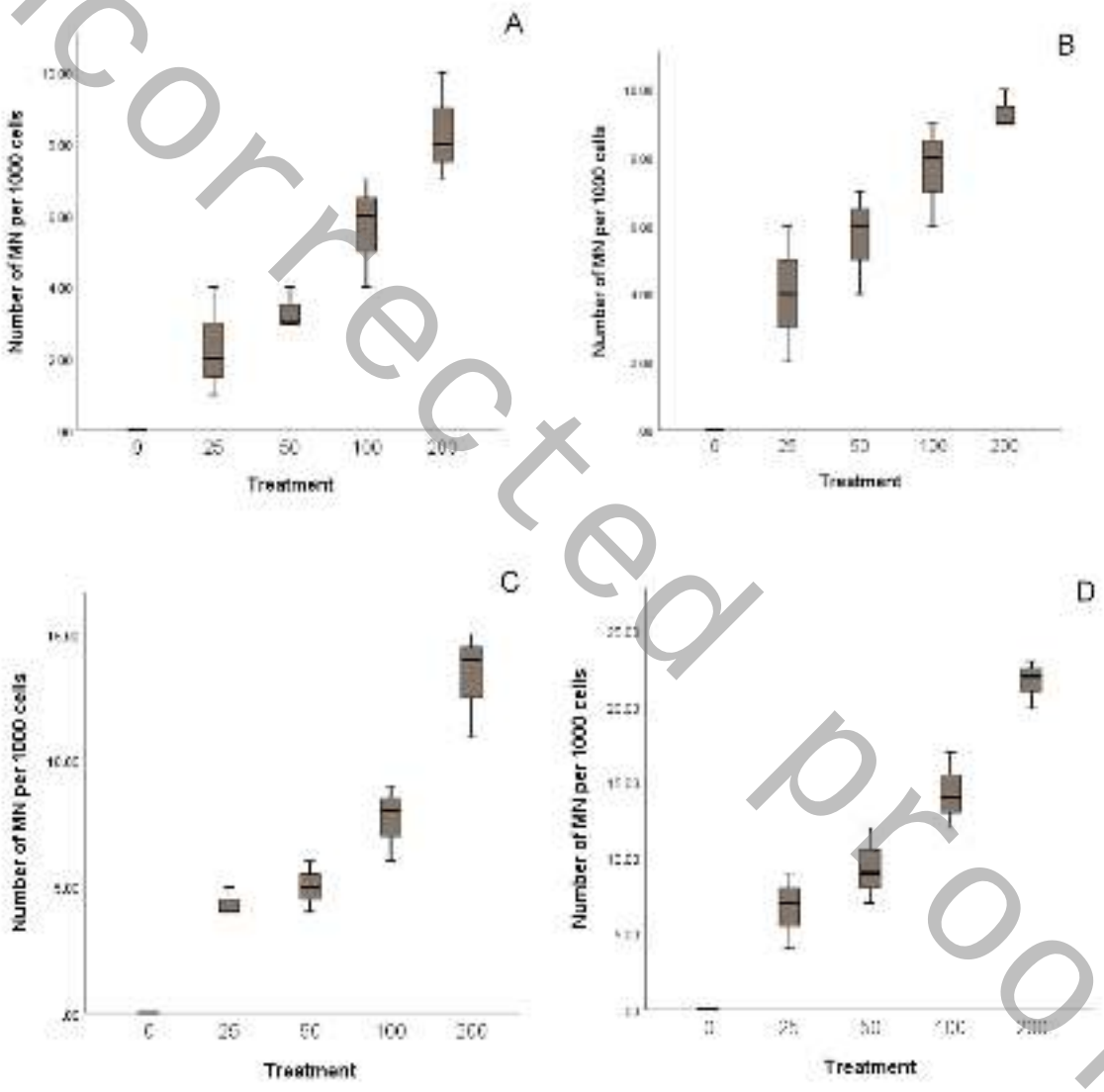
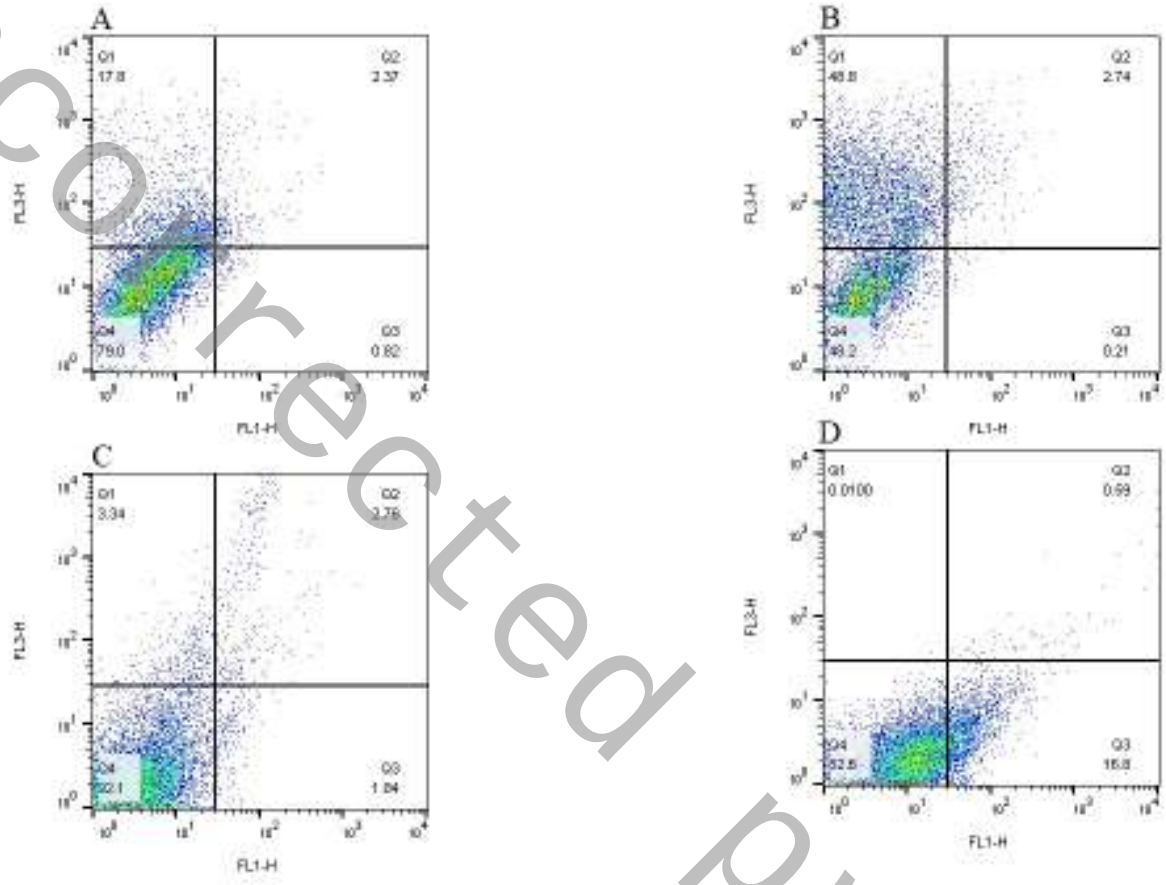


Figure 6. Effect of TiO2 NPs 200 (µg/ml) on HFF and MCF-7 cells line.

A: control, HFF cell line; B: 72h, HFF cell line; C: control, MCF-7 cell line; D: 72h, MCF-7 cell line.



عنوان مقاله: اثرات سیتوتوکسیک نانوذرات دی اکسید تیتانیوم بر رده سلولی سرطانی MCF-7

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خلاصه فارسی: سرطان یکی از شایع ترین بیماری ها در سراسر جهان بوده و بسیاری از افراد از انواع مختلف سرطان رنج می برند. امروزه نانوذرات TiO2 کاربردهای درمانی گسترده ای دارند. مطالعه حاضر به منظور بررسی سمیت سلولی TiO2 بر رده سلولی سرطان پستان انجام شد. سلول های سرطانی MCF-7 و رده سلولی فیبروبلاست HFF کشت داده شدند و پس از تأثیر غلظت‌های 200، 100، 50، 25 میکروگرم بر میلی‌لیتر نانوذرات دی اکسید تیتانیوم، میزان بقای سلول‌ها با استفاده از روش MTT طی 48 ساعت و 72 ساعت اندازه‌گیری و IC50 تعیین شد. تیمار سلول‌های MCF-7 و HFF با غلظت‌های مختلف TiO2 نشان داد که نانوذرات دی اکسید تیتانیوم در غلظت‌های 200 میکروگرم بر میلی‌لیتر بیشترین سمیت سلولی را نشان می‌دهند. نتایج فلوسایتومتری نیز آپوپتوز را در سلول های MCF-7 و HFF تایید کرد. نتایج میکروسکوپ نوری نشان داد که نانوذرات دی اکسید تیتانیوم می توانند در دوز 200 میکروگرم بر میلی لیتر در یک دوره درمان 48 و 72 ساعت در رده های سلولی MCF-7 و HFF باعث ایجاد سمیت وابسته به غلظت شوند. نتایج تصویربرداری میکروسکوپ الکترونی از سلول‌های سالم و سرطانی پستان تیمار شده با غلظت 200 میکروگرم بر میلی‌لیتر نانوذرات دی اکسید تیتانیوم در مدت 72 ساعت نشان دهنده پارگی غشای میتوکندری و نشت ماتریکس به سیتوپلاسم و تورم شبکه آندوپلاسمی خشن است. با توجه به نتایج به‌دست‌آمده، نانوذرات TiO2 را می‌توان به عنوان کاندیدای دارویی آینده‌نگر برای اهداف دارویی توصیه کرد، اگرچه مطالعات بیشتری در این زمینه مورد نیاز است.

واژگان کلیدی: سرطان پستان، فلوسیتومتری، سنجش میکرونوکلئوس، سنجش MTT، TEM