**Original Article**
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# The Cytotoxicity of Tellurium Nanoparticles on Different Cell Lines and Their in vivo Anticancer Effects in an Animal Model

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## Abstract

**Background:** Tellurium- containing compounds are suggested as the treatment agents for different diseases. This study aimed to synthesize tellurium nanoparticles (TeNPs) and study their in vitro and in vivo effects on tumour cells.

**Method:** In this experimental study, the synthesis of TeNPs in an aqueous solution was achieved with lactose as a reducing agent. The cells ($2\times10^4$) were seeded, in triplicate, in 96-well plates and exposed to different concentrations of TeNPs for 48 hours. The determination of cell viability was done by MTT assay. In vivo studies were performed using breast cancer-bearing mice treated with TeNPs at different doses via intraperitoneal (IP) and intravenous (IV) injections.

**Results:** After 48 hours of treatment with TeNPs at different concentrations, cancer cell line viability was significantly decreased compared with control at almost all concentrations. Moreover, the $IC_{50}$ of TeNPs in the non-cancerous cell line CHO (50.53 µg/mL) was far above that of EJ138 (29.60 µg/mL) and 4T1 (7.41 µg/mL) cell lines, revealing their lower toxicity in normal cells in comparison with cancer cells. The in vivo study's findings also showed that both delivery methods significantly inhibited tumor development, and that breast cancer-bearing mice lived longer than control mice, particularly when the largest dosage (400 µg, injected three times a week) was used.

**Conclusion:** These results demonstrate TeNPs as promising therapeutic agents for cancer treatment. However, further investigation is still needed to determine the in vitro and in vivo anticancer mechanisms of TeNPs.

***Keywords:*** Anticancer, Cytotoxicity, Cell line, Experimental mammary neoplasm, Metal nanoparticles

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## Introduction

Tellurium (Te) is a toxic, non-essential trace element which exists in its elemental (Te0), inorganic-telluride (Te2-), tellurite (TeO32-), tellurate (TeO42-), and organic forms in the environment.[1] Tellurium is the fourth most abundant trace element in quantities of about 0.7 mg in the average human body (after Fe, Zn, and Rb).[2] Toxicity of tellurium compounds depends on the chemical form and the amount of the elements utilized.[3]

Since Alexander Fleming first reported the oxyanion tellurite's antibacterial capabilities in the 1930s, it has been used in the treatment of microbiological illnesses.[4] Immune-modulating medications containing tellurium were first suggested as AIDS and cancer treatments in 1988.[5, 6] Ammonium trichloro (dioxoethylene-*o,o'*) tellurate (AS-101) inhibits the production of IL-10, IFN-γ, IL-2R, IL-5, while protecting bone-marrow stem cells during chemotherapy.[7] Other effects include induction of hair growth, enhancement of neuronal survival, and protection and restoration of dopaminergic neurons.[8]

Animal studies showed that exposure to tellurium derivatives causes a broad diversity of toxic effects, including reversible limb paralysis and neurotoxic symptoms such as significant impairment of learning and spatial memory.[9] However, these drugs are not selective for cancer cells, as normal cells are affected, leading to dose-limiting toxicities.[10] So far, nanotechnology has offered appealing solutions for treating many cancer kinds, such as tailored medication delivery techniques that might potentially eradicate tumors with with little harm to healthy tissues.[11] Thus, it is conceivable to consider the synthesis of tellurium nanoparticles (TeNPs) able to offer a more acceptable level of toxicity and enhanced antitumor activity. Currently, significant efforts were focused on preparing the elemental tellurium nanomaterials.[12] Using $TeO_3^{2-}$ or $TeO_4^{2-}$ as tellurium supply, various reducing agents were employed to prepare TeNPs with different size ranges by a hydrothermal/solvothermal or surfactant-assisted hydrothermal/solvothermal reduction process.[13] TeNPs were synthesized via a synthetic chemical pathway with lactose as a reducing agent. Subsequently, their effect on cancerous cells was measured using an MTT

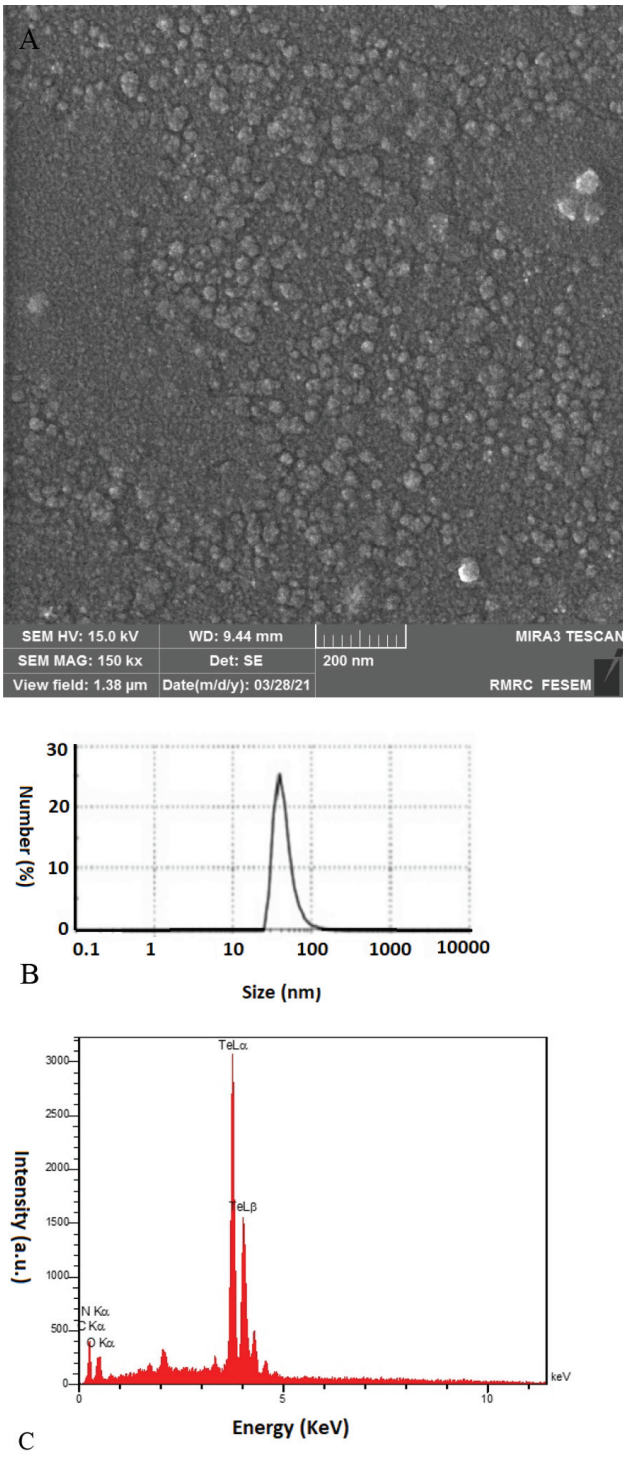


**Figure 1.** This figure shows the microscopic characterization of TeNPs. A) FESEM images of TeNPs. B) Size distribution of TeNPs analysed by DLS method. C) EDX spectrum of TeNPs

FESEM: Fied emission scanning electron micrograph; DLS: Dynamic light scattering; EDX: Energy-dispersive X-ray; TeNPs: Tellurium nanoparticles

assay. Meanwhile, in an in vivo study, the tumour volume and survival rate of breast cancer-bearing mice treated with TeNPs were investigated compared with the control group.

## Materials and Methods

### *Ethics statement*

This experimental study was conducted based on the basic and clinical pharmacology and toxicology policy for experimental and clinical studies.[14]

### *TeNPs synthesis*

Synthesis of TeNPs in an aqueous solution was performed with lactose (CAS. No. 63-42-3, Sigma Aldrich, Germany) as a reducing agent.[15] $K^{+}TeO_3^{2-}$ salts (CAS. No. 7790-58-1, Sigma Aldrich, Germany) were dissolved in distilled water until the final concentration of 10 mg/mL was achieved. 400 µL of 10 mg/mL $K^{+}TeO_3^{2-}$ solution was mixed with 0.1 g of lactose and diluted to 10 mL using distilled water. To complete the reaction, the stock was autoclaved at 120 ºC for 15 minutes, and the result was a solution containing 400 µg/mL TeNPs and 1 percent lactose. To create additional appropriate dosages, this stock solution was diluted.

### *TeNPs characterization*

A field emission scanning electron microscope (FESEM) equipped with energy-dispersive X-ray spectroscopy (EDS) was used for the characterization of the size and elemental composition of prepared TeNPs, respectively. For FESEM observation, NPs were mounted on specimen stubs and coated with gold. Samples were analyzed with MIRA 3 FESEM (MIRA 3, TESCAN, USA) operated at 15 kV, and EDS was recorded by focusing on a cluster of NPs. The size of NPs was determined using the dynamic light scattering (DLS) method (DLS Zetasizer, Malvern Panalytical, United Kingdom).

### *Experimental animals*

12 inbred female BALB/c mice, aged 5 to 7 weeks, weighing 25 to 30 g, were bought from the Iranian Pasture Institute (Tehran, Iran). The mice were kept in a 24-degree Celsius, 55 ±10% humidity environment with a 12-hour light/dark cycle. They were given unlimited access to water and regular mouse pellets. In vivo treatment panel

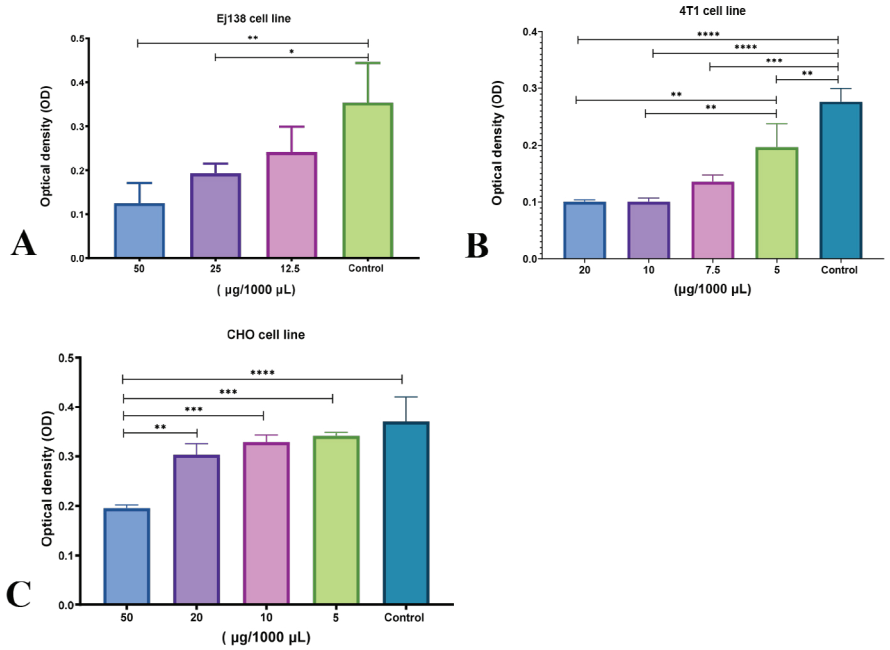


**Figure 2.** This figure shows the effect of different TeNP concentrations on cell proliferation. A) Ej138 cell line, B) 4T1 cell line, and C) CHO cell line.

TeNPs: Tellurium nanoparticles

lists the groups participating in the experimental studies.

### *Cell culture*

Rosewell Park Memorial Institute (RPMI) medium (Cat. No. 11-875-101), foetal bovine serum (FBS) (Cat. No. 11550356), penicillin and streptomycin (Cat. No. 11548876) were purchased from Gibco BRL (Life Technologies, Paisley, Scotland). Pasteur Institute of Iran's cell bank provided the human urinary bladder cancer EJ-138 cell line, mammary carcinoma 4T1 cell line, and Chinese hamster ovary (CHO) cell line. From Roche Diagnostics GmbH in Germany, 3-(4, 5-dimethyl-thiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) was purchased (Cat. No. 11465007001).The cells were cultured in RPMI medium with the addition of FBS (10%, v/v), streptomycin (100 µg/mL) and penicillin (100 U/mL). The cells ($2\times10^4$) were seeded, in triplicate, in 96-well plates and incubated at 37°C in 5% $CO_2$ atmosphere.

### *Treatment of normal and cancer cell lines with TeNPs*

Cultured cells were exposed to different concentrations of TeNPs for 48 hours. Cells were cultured in RPMI 1640 medium supplemented with 10% (v/v) FBS and 100µg-100 IU of antibiotics (Pen-Strep) and then incubated at 37ºC, 5% $CO_2$, and 95% humidity for 48 h. By assessing the degree of mitochondrial activity and reducing the tetrazolium salt 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) to formazan crystals, researchers were able to determine if cellular development occurred in the presence or absence of nanoparticles.[16] The rapidly growing cells were harvested and adjusted to $1\times10^6$ cells/mL and seeded into a 96-well plate with 100 µL in each well and incubated for 48 h. Thereafter, TeNPs were applied to the culture wells to reach the final concentrations of 12.5, 25 and 50 µg/mL for the EJ138 cell line; 5, 7.5, 10 and 20 µg/mL for the 4T1 cell line; and 5, 10, 20 and 50 µg/mL for the CHO cell line. After 48 h of incubation, 20 µL of MTT reagent was added to each well at a concentration of 5 mg/mL in PBS and incubated for a further duration of 4 h. Consequently, the medium was discarded and

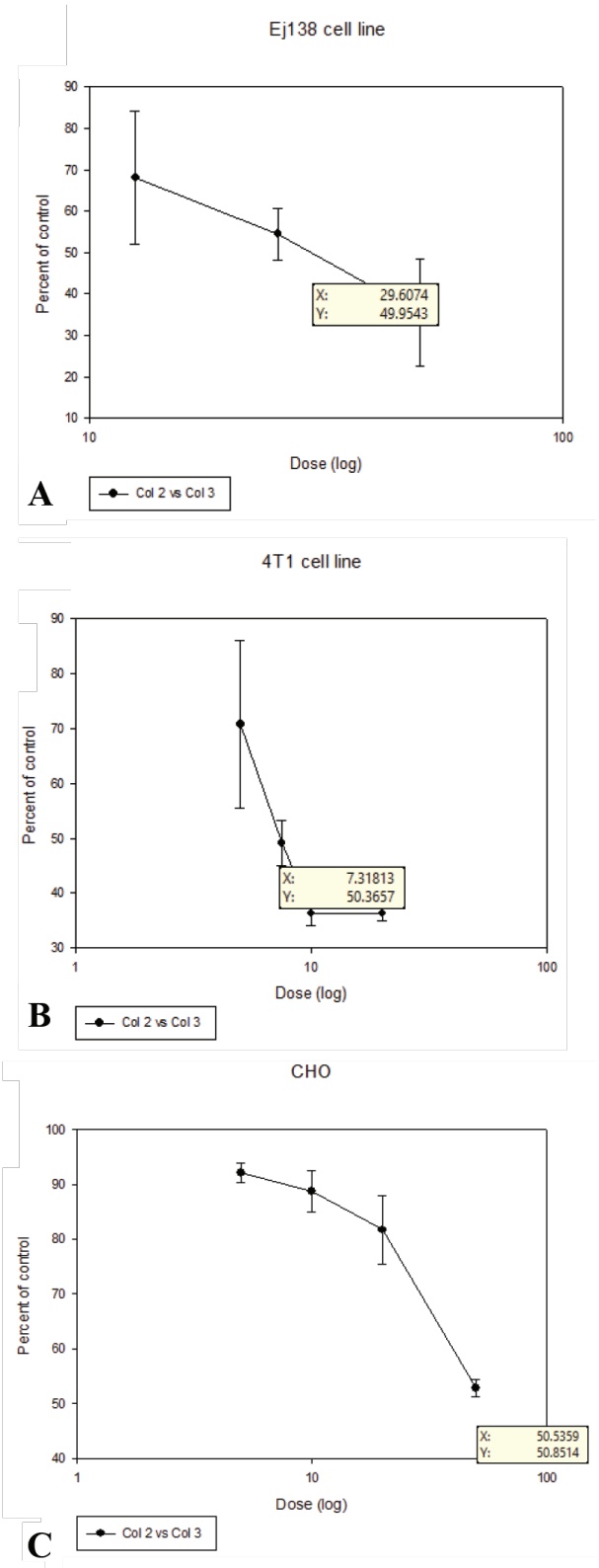


**Figure 3.** This figure shows the graph interpretation of $IC_{50}$ for TeNPs. A) Ej138 cell line, B) 4T1 cell line, and C) CHO cell line. (IC50: Half-maximal Inhibitory Concentration).
TeNPs: Tellurium nanoparticles

150 µL of DMSO (Cat. No. 67-68-5, Merck, Germany) was added to solubilize the formazan crystals. After 5 minutes of shaking to mix the formazan in the solvent, the optical densities were determined at 550 nm. MTT assay was performed in triplicates.

### *Determination of inhibitory concentration 50% ($IC_{50}$) values and cell viability*

Different TeNPs concentrations were applied to cancer and normal cell lines. To treat control cells, phosphate buffer solution (PBS) devoid of TeNPs was used. After MTT experiment, an ELISA plate reader was used to quantify the absorbance (A) of treated and untreated cells (Synergy HTX, BioTek, USA).The determination of $IC_{50}$ was carried out by plotting normalized average absorbance (A) values of MTT assay for different concentrations of each cell line against doses values in logarithmic scale, using SigmaPlot v.14.0. The dose regarding 50% reduction in absorbance with respect to control represents the $IC_{50}$ (50% inhibition of cell viability).

### *Tumour induction*

On the first day of the experiment, 300 µL of RPMI medium containing $1\times10^6$ cells of the 4T1 cell line (ATCC CRL-2539) were subcutaneously injected (SC) near the mice mammary glands. The mice were monitored until the tumour nodule appeared.

### *In vivo treatment panel*

12 mice were randomly divided into 4 groups (n = 3). Group I, which was considered as control group, received an intraperitoneal (IP) injection of normal saline 3 times per week. Groups II, III and IV were injected intraperitoneally with TeNPs (100, 200 and 400 µg/300 µL, respectively) 3 times per week for 4 weeks. In a second study, 15 mice were randomly divided into 3 groups. The control group (n=3) received an IP injection of normal saline 3 days per week and a same intravenous (IV) injection once a week. The mice in Group II (n = 6) received 400 µg/300 µL of TeNPs intraperitoneally 3 days per week and intravenously once a week for 4 weeks. Mice in Group III (n = 6) were injected IV with 400 µg/300 µL of TeNPs once a week. The volume of administration in all mice was 300 µL.

### *Measurement of tumour growth*

Tumour growth was checked every week using calliper measurements. The volume was calculated by following equation: $V\ (mm^3) = (W)^2\times(L)/2$, where W and L are width and length of the tumour, respectively.

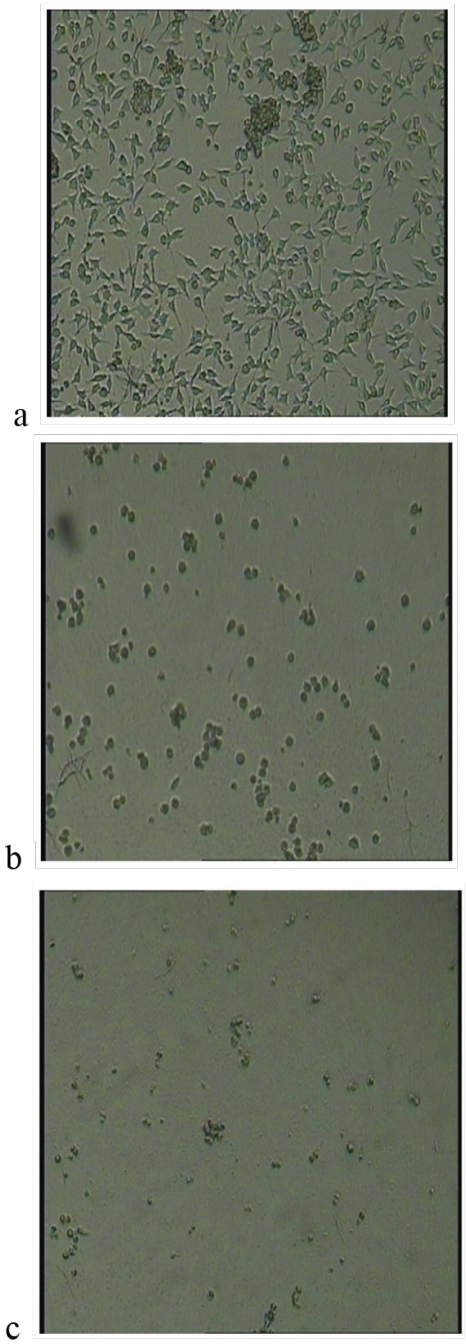


**Figure 4.** This figure shows the 4T1 cancer cells microscope imaging. (A) untreated, B) treated with 5 µg/100ml TeNPs and C) treated with 10 µg/100ml TeNPs.
TeNPs: Tellurium nanoparticles

### *Survival rate*

After the tumor cells were injected, the mice's survival rate was assessed. Every day, the mice's appearance and physiological circumstances were checked. Statistical analysis

Values were expressed as mean ± SD of three repeats in each group. Data were analysed using one-way ANOVA analysis with a P-value of less than 0.05 considered as statistically significant.

## Results

### *TeNPs characterization*

Te NPs were synthesized using lactose as reducing agent and their shape and size were confirmed by FESEM and DLS Malvern-Zetasizer, as shown in Figures 1A and 1B. TeNPs are shown in Figure 1A's FESEM image, which shows their spherical form and size of less than 100 nm. Dynamic light scattering (DLS) analysis was used to determine the average particle diameter.DLS pattern represented that the particles size range is below 100 nm, with an average size of about 45 nm (Figure 1B). The elemental composition of nanostructures with EDX microanalysis (Figure 1C) confirmed the presence of Te atoms and oxygen groups, which could be related to the hydroxyl groups.

### *Effect of TeNPs on EJ 138, 4T1 and CHO cells viability*

The effect of different concentrations of TeNPs on EJ 138, 4T1 and CHO cells viability was determined using the MTT assay (Figure 2). For the EJ 138 cell line, after 48 h of treatment at concentrations of 50 and 25 µg/mL, an approximate reduction of 64.5% and 45.5% in cell viability was observed, respectively; which confer a statistical significance compared to the control group ($P < 0.05$). All doses (5, 7.5, 10, and 20 g/mL) administered to the 4T1 cell line resulted in substantial decreases in cell viability, with *P*-values all below 0.05. For the noncancerous CHO cell line, only the 50 g/mL dosage demonstrated statistical significance above the control group. $IC_{50}$ for all cell lines was inferred from the aforementioned plots, as depicted in Figure 3. $IC_{50}$ values for 4T1, EJ 138 and CHO cell lines were determined as 7.41, 29.60 and 50.53 µg/mL, respectively. Microscopic image of 4T1 cell line treated with TeNPs is shown in Figure 4.

Effect of TeNPs administration on tumour growth and survival of mice in different groups

Breast cancer bearing mice were injected IP for 4 weeks with TeNPs at doses ranging from 100 to 400 µg, 3 days per week. The average tumour volume decreased in mice that received

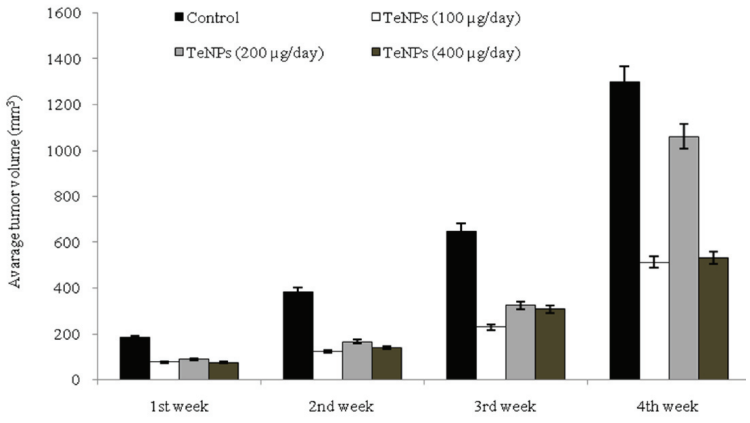


**Figure 5.** This figure shows the average tumour volume of the breast cancer bearing mice. Mice were treated with different doses of TeNPs IP injection 3 days/week for four weeks. The significant decrease in tumour volume were observed form the second week of study in all treatment concentrations in comparison to control (Significance considered as $P \leq 0.05$).
TeNPs: Tellurium nanoparticles; IP: Intraperitoneal

TeNPs for 4 weeks compared to the control mice (Figure 5). Moreover, the average tumour volume in mice that received TeNPs at the dose of 400 µg/300 µL via 2 routes (IP and IV) decreased significantly ($P < 0.05$) compared with control mice (Figure 6).

According to the findings, IP treatment of TeNPs may prolong mice's lives, particularly when 400 µg of TeNPs are given 3 times per week. Two mice that got the dosage of 400 µg IP 3 times a week lived up to 100 days, despite the fact that all animals in the control group perished before day 30. (Figure 7). Furthermore, three mice that received the 400 µg/week IV dosage lived for more than 100 days (Figure 8).

## Discussion

In our study, the result of the cytotoxic effect of TeNPs after 48 h of treatment at concentrations of 25 and 50 µg/mL showed a significant decrease in viability in the EJ138 cancer cell line. This significant reduction in viability was observed with all experimental concentrations of TeNPs (5, 7.5, 10, and 20 µg/mL) in the 4T1 cell line, indicating a remarkable anticancer potential for TeNPs. Furthermore, microscopic images of cancer cells treated with TeNPs aligned with MTT assay results that showed a decrease in cancer cells' densities. When tested in the normal cell line CHO, TeNPs proved no significant cytotoxicity in up to 50 µg/mL doses, with an $IC_{50}$ of almost 50.5 µg/mL. Moreover, the $IC_{50}$ values for the EJ138 and 4T1 cell lines proved 29.6 and 7.4 µg/mL, respectively. Given that the $IC_{50}$ values for the cancer cell lines are much lower than those for the healthy cell line CHO, these findings suggest a sufficient margin of safety for therapy with TeNPs. TeNPs may be regarded as powerful anticancer drugs since they have little impact on healthy cells. It's noteworthy that the 4T1 cell line's $IC_{50}$ value was much lower than that of the EJ138 cell line. Future research is required to determine if the observed difference may be attributable to the tumor's invasiveness or to other cell and tissue circumstances. The susceptibility of some cancer cells to oxidative signals is a therapeutic target for new anticancer agents.[17] Tellurium can induce oxidative stress by modulating levels of reactive oxygen species (ROS), such as the superoxide anion, hydrogen peroxide, and hydroxyl radicals. Tumor cells are more sensitive to oxidative stress since they have higher levels of ROS than normal cells in terms of the dysregulation of redox balance in response to increased intracellular production of ROS, lower antioxidant proteins, and oxidative DNA damage. Notably, Sandoval et al. have shown that the generation of ROS, particularly superoxide

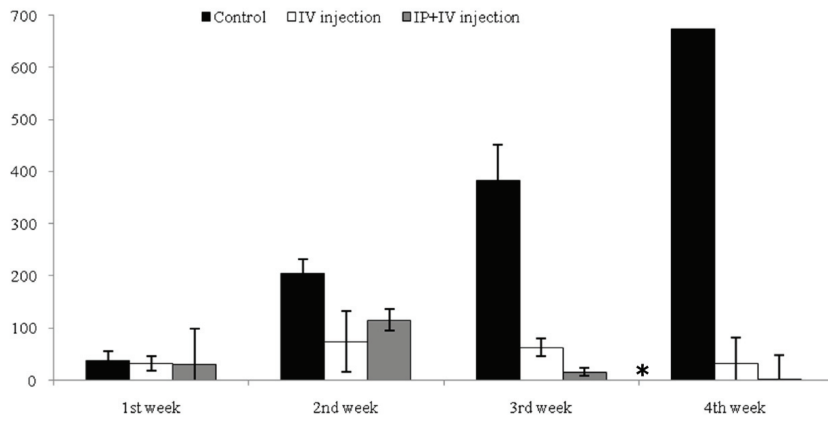


**Figure 6.** This figure shows the average tumour volume of the breast cancer bearing mice. Mice were treated with TeNPs (400 µg) IV injection once a week, or IP injection (3 days/week) + IV injection (once a week) for four weeks.
TeNPs: Tellurium nanoparticles; IV: Intravenous; IP: Intraperitoneal

anion, moderately mediates the toxicity of inorganic tellurium.[18] Inorganic tellurium-exposed bacteria show lower thiol levels, increased protein carbonylation and lipid peroxidation, inactivation of oxidative stress-sensitive [Fe-S] enzymes, and increased expression of superoxide-response genes.[19]

Dose-response study with IP injection of different doses of TeNPs (100, 200, and 400 µg) 3 days/week in mice bearing 4T1 breast tumor showed better outcomes through the highest dose administrated. At the end of the 4th week, the average tumor volume of mice receiving 400 µg of TeNPs 3 days/week was 530.843 $mm^3$ compared with 1300 $mm^3$ in the control group. In addition, the survival rate in this group was approximately 4-fold more than in the control groups. All mice in the control group died 25 days after tumor induction, while the test group mice survived for up to 100 days. Furthermore, during the course of the medication, the mice's body weights were examined, and no appreciable weight loss was seen. Mice were given the recommended dosage (400 µg) through IV injection once a week in one group and IP injection (3 days/week) +IV injection (once a week) in the other group to better understand the effectiveness of alternative administration methods. When the drug was administrated by both routes, a greater suppressive effect on tumor growth was observed; however, the survival of mice receiving TeNPs through IV injection as the single administration route was longer (3 mice survived for more than 164 days). The current study results are in line with the results obtained by Zhang et al. in 2010.[20] They found orally administered gold nanoparticles to cause considerable decreases in body weight, spleen index, and red blood cell counts. Of the three administration routes tested, the oral and IP routes had the highest toxicity, and the tail vein injection had the lowest toxicity. We suggest that targeted nanoparticles administered through tail vein injection may be an effective treatment after combining the findings of all investigations. Tellurium nanorods (TeNRs) were shown to be potent antioxidants for scavenging free radicals and novel anticancer agents in a research by Huang et al. in 2016. In addition, TeNRs effectively induced a decrease in the mitochondrial membrane potential in a dose-dependent manner, representing that mitochondrial dysfunction may play a significant role in TeNRs-induced

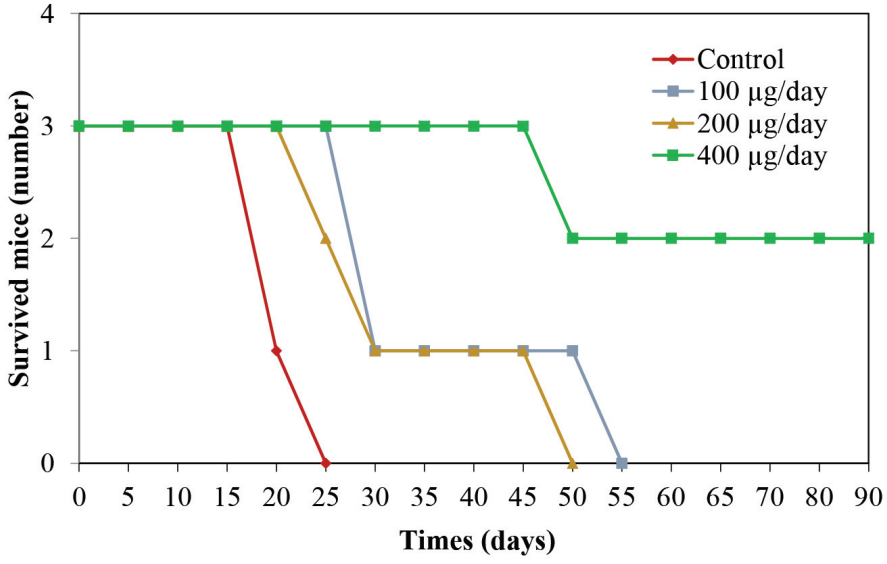


**Figure 7.** This figure shows the survival of the breast cancer-bearing mice. Mice received different doses of TeNPs via IP injection after tumour induction.
TeNPs: Tellurium nanoparticles; IP: Intraperitoneal

apoptosis.[21] As tellurium and selenium belong to the same chemical group of elements; tellurium is considered to have some chemical and biological characteristics similar to selenium. Some studies showed that colloidal elemental selenium nanoparticles reveal novel antioxidant activities both in vitro and in vivo.[13] In our previous study, supplementation with SeNPs induced an efficient immune response against cancer and accelerated the production of TH1 pathway cytokines in mice that received the different doses, with the best effect observed with the highest administered dose.[22]

In both inorganic and organic compounds, tellurium has specific biological actions, such as potent anti-oxidant, caspase, and cathepsin inhibitor activity.[23] Although elemental tellurium is regarded a non-essential and dangerous metalloid with little known biological and toxicological effects, there are claims that tellurium-containing compounds have anticancer properties. Ammoniumtrichloro[dioxoethyleneO, O']tellurate, known as AS101, a potent immunomodulator and non-toxic compound, has undergone clinical trials and exhibits anticancer activity. A phase I clinical trial outcome on patients suffering from advanced cancer treated with AS101 showed an increase in the production and secretion of a range of cytokines, indicating a dominance in T-helper 1 (TH1) responses, with a simultaneous decrease in T-helper 2 (TH2) responses.[24] Additionally, this agent maintains stem cell functionality and raises the survival rate of mice given different cytotoxic medicines.[24, 25] Another substance called SAS has shown enhanced inhibition of angiogenic-stimulated endothelial cell migration in multiple cancer types.[26] In other studies, tellurite was found to be cytotoxic to HeLa cells in a dose-dependent manner, and diaryl ditellurides showed a meaningful apoptosis induction of HL-60 cells at doses of 1 µmol/L. Although little is recognized about tellurium toxicity in humans, ingestion of $TeO_3^{2-}$ was verified to cause clinical symptoms, including metallic taste, nausea, and vomiting.[27] An study performed by Najimi et al. to assess the toxicities of biogenic tellurium nanorods (TeNRs) has shown the LD50 values of TeNRs and $K_2TeO_3$ 60 and 12.5 mg/kg, respectively. Moreover, no noticeable histopathological changes

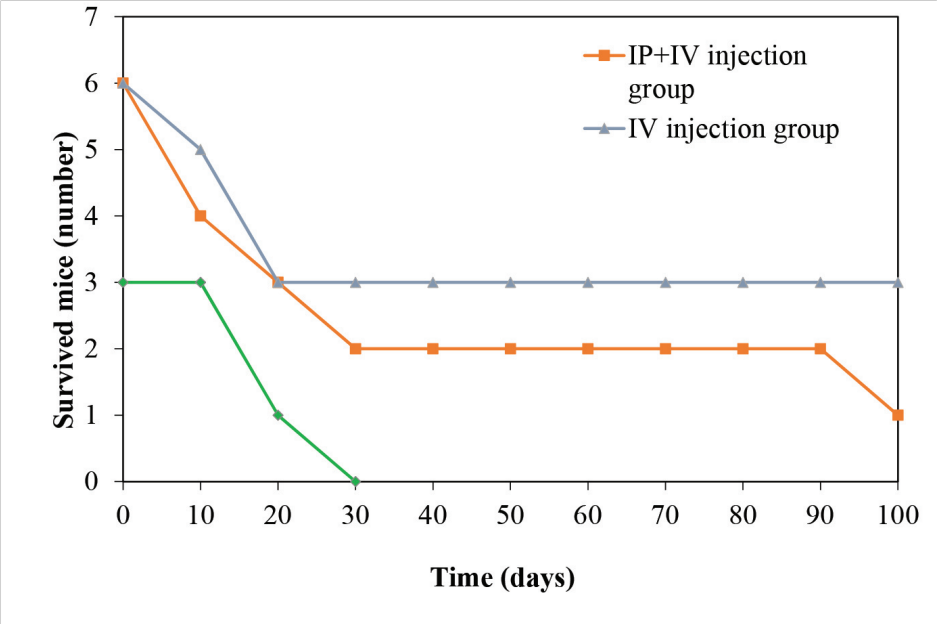


**Figure 8.** This figure shows the survival of the breast cancer-bearing mice. Mice received TeNPs (400 µg/300µl) via IV, or IV+ IP injections after tumour induction. The significant increase in the life span of the mice were observed in the IV (400 µg/300µl) of TeNPs in comparison with control.
TeNPs: Tellurium nanoparticles; IV: Intravenous; IP: Intraperitoneal

were seen in treatment with TeNRs, and biogenic TeNRs were less toxic than $K_2TeO_3$.[28] Moreover, TeNPs are perceived as valuable in the delivery of drugs and protection of biologically active enzymes or proteins. The cytotoxic potential of tellurium nanowires in BALB/3T3 fibroblast cells was recently studied by Seog Woo Rhee et al. Laser ablation, thermal breakdown, chemical reduction, and polyol synthesis are just a few of the 29 processes that have been created to far for the production of nanoparticles. We have utilized a chemical reduction method for the synthesis of nanoparticles. This technique is usually favored since it is easy, cost-effective, and efficient and can cause improved size and size dispersion control by optimizing the experimental factors such as the molar ratio of the fraction of reducing agent with the precursor salt.[29]

It should not be ignored that using additional animals in the in-vivo portion of this investigation may have some ethical implications in order to get better findings. Animal sample sizes that are larger might lead to more substantial changes in the outcomes. Although these results suggested the potential application of Te NPs as a suppressor of tumor growth in a cancer cell line with significantly less toxicity in the normal cell line; however, more data from in vitro and in vivo is required for more accurate results and conducting a clinical study in the future.

## Conclusion

To summarize, the use of non-toxic TeNPs, which exert multifunctional activities, demonstrates an excellent safety profile, suggesting their potential as a novel and promising agent for the treatment of different cancers. However, more studies that are both in vitro and in vivo will more thoroughly support this impact. It is important to remember that using more animals in the in vivo portion of this research may put certain ethical restrictions on our ability to get better results, and that this might have a substantial impact on the findings. Regarding to the results of IV injection of TeNPs on the life span of the treated mice, it can be concluded that this route has potential for reaching out to the better achievement in total. Although the possibility of blood clot in IV injection of NPs is still remain challenging, more advanced formulation of NPs like nanoliposomes may solve this problem and also can be considered as a new approach for further studies in this field.

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## Conflict of Interest

None declared.

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