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Original Article

Effects of Gold Nanoparticles on Oxidative Stress Status in Bladder Cancer 5637 Cells

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Abstract

Introduction: Nanomedicine has recently been known as an emerging research area with promising applications in cancer diagnosis and treatment. Aside from this, gold nanoparticles (AuNPs), as one of the important components of nanomedicine, have attracted considerable attention due to their special physicochemical properties and lower toxicity than other nanoparticles. Despite the impressive advantages of AuNPs, it has not been yet determined whether oxidative stress contributes to the toxicity of AuNPs on bladder cancer.

Aim: The aim of this study was to address this issue by conducting experiments in order to investigate the effects of 20 nm AuNPs on human bladder cancer 5637 cells.

Materials and methods: The viability of 5637 cells was evaluated upon 24 hour exposure to different concentrations of AuNPs (0-50 μg/ml) by 3-(4, 5-dimethylthiazol, 2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay. In order to evaluate oxidative stress status, total antioxidant capacity (TAC), total oxidant status (TOS), malondialdehyde (MDA) and also activities of antioxidant enzymes including glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) were all determined by colorimetric assay kits.

Results: The results from our experiment showed that the cytotoxicity caused by AuNPs was dose-dependent and the IC50 value was found to be 43.14 μg/ml after 24-hour exposure. Furthermore, MDA and TOS levels were significantly increased in treated cells compared to untreated cells ($p<0.05$). In contrast, TAC level and the activities of SOD, GPx, CAT were significantly decreased in AuNPs-treated groups as compared with the untreated cells ($p<0.05$).

Conclusions: Overall, AuNPs decrease the cell viability and increase oxidative stress in bladder cancer 5637 cells.

Keywords

bladder cancer 5637 cells, cell viability, oxidative stress, gold nanoparticles

INTRODUCTION

Bladder cancer is one of the most commonly occurring human cancers linked with malignant tumors in the urinary tract. It affects both men and women. Despite the advances of surgery and chemotherapy, the specificity of these conventional therapies is decreased by dose-limiting toxicity. Furthermore, since using these therapy methods are limited due to their considerable side effects such as hemorrhagic cystitis, there are increasing attentions for alternative anticancer treatments. However, it has been a highly challenging task to find potential therapies for various types of cancer. Therefore, resorting to more effective yet less toxic therapies is inevitable for cancer treatment. It would probably seem that nanoparticles could revolutionize the treatment of cancer in the near future.[1] Nanoparticles are defined as particles between 1 and 100 nm in size with special yet different properties compared to their

bulky counterparts.[2] Metallic nanoparticles are certainly among the most important research topics in modern materials due to their chemical, physical, and biological properties and are now extensively utilized in biomedical sciences.[3] Although many noble metals have been used for therapeutic and diagnostic purposes, gold nanoparticles (AuNPs) are often preferred in medicine due to their easy synthesis, high stability, easy bio-bonding and biocompatibility. Despite several gold nanoparticles being in phase 2/3 clinical trials, the Food and Drug Administration (FDA) has not up to now certified any nanodrugs based on gold nanoparticles.[4] While AuNPs are usually considered non-toxic[5-7], research regarding the toxicity of these nanoparticles is still being reported[8,9]. This toxicity largely depends on surface chemistry, physical dimension, and shape of the AuNPs.[10] Similar to other nanoparticles, oxidative stress heavily contributes to the toxicity of gold nanoparticles.[4] Several studies have revealed the anticancer activity of gold nanoparticles where nanoparticles enter cells via permeability or endocytosis mediated by nonspecific receptor. Mechanistically, AuNP-treated cells produce lots of reactive oxygen species (ROS) causing membrane damage, increased mitochondrial activity and eventually cancer cell death.[11] Oxidative stress is often described as a cellular status caused by an increased amount of oxidants (free radicals or reactive species) over antioxidants. It is usually stated in this case that the free radicals destroy the antioxidants defense system. The body utilizes an enzymatic or non-enzymatic antioxidant defense system in order to mitigate the adverse effects of ROS. Superoxide dismutase (SOD) and glutathione peroxidase (GPx) are regarded as the most important antioxidant enzymes.[12] There has been recently an upsurge of research regarding anticancer properties of AuNPs in colon carcinoma HT-29 cell line[13], bladder cancer T24 cells[1], and HepG2 cells[14,15], to mention just a few. While some research works are performed to induce oxidative stress in AuNP-treated cell lines[16,17], to the best of our knowledge, the anticancer properties of these nanoparticles in bladder cancer 5637 cells, originating from a grade II bladder transitional cell carcinoma, has not yet been investigated.

AIM

The aim of this work was to address this issue by investigating the cytotoxicity and oxidative stress status in the presence of AuNPs.

MATERIALS AND METHODS

Chemicals

Spherical gold nanoparticle (20 nm, citrate-stabilized) dispersed in deionized water (99.95% purity) was purchased from Iranian Nanomaterials Pioneers Company, NANOSANY (Mashhad, Iran). Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) of AuNPs are shown in **Figs 1a** and **1b**, respectively.

Cell culture and treatment

Human bladder cancer 5637 cell line was obtained from Pasteur Institute, (Tehran, Iran) and cultured in RPMI-1640 (KRPM500) including 10% FBS (KFBS100), 1% penicillin streptomycin (BI-1203) at 5% CO_2 and 37°C. In order to subculture (passage) cells, 0.25% trypsin-EDTA solution (KRT100) was used. All experiments were done between passages 2 and 10. Different concentrations of AuNPs in serum-free RPMI-1640 were freshly prepared and were used to treat cells.

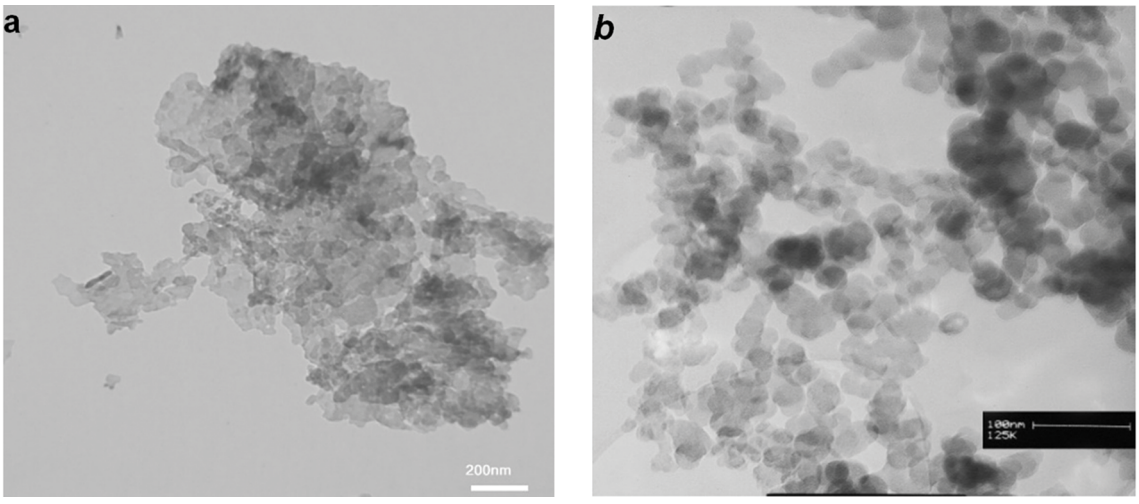

Figure 1. **a**) Transmission electron microscopy (TEM) and **b**) Scanning electron microscopy (SEM) of AuNPs from Iranian Nanomaterials Pioneers Company, NANOSANY.

MTT cytotoxicity assay

To evaluate AuNPs cytotoxic activity, the 3-(4, 5-dimethylthiazol, 2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) (Sigma Aldrich, St. Louis, MO, USA) assay was employed.

Briefly, 5637 cells were grown in 96-well plates at a density of 2×10^4 cells per well. After 24 hours, the cells were treated with different concentrations of AuNPs (0, 1.5, 3.12, 6.25, 12.5, 25, 50 µg/ml). After 24 hours of incubation, MTT reagent (5 mg/ml in PBS) was added to each well and was then incubated for 4 hours. Next, the medium was depleted and 100 µl dimethyl sulfoxide (DMSO) (DNA biotech, Iran) was added to each well in order to dissolve the formazan crystals. Finally, the absorbance was evaluated at 570 nm using an ELISA plate reader (RT-2100C Microplate Reader, China). The experiments were run in triplicate. The 5637 cell viability was calculated using the following formula:

$$\frac{\text{OD of the AuNP treated cells} - \text{OD of the blanks}}{\text{OD of the untreated cells} - \text{OD of the blanks}} \times 100.$$

Lastly, IC50 was calculated from MTT results.

Morphological alterations assay

Cells were seeded in a 6-well plate at a density of 3×10^5 cells/well and treated with different concentrations of AuNPs (12.5, 25, and 50 µg/ml) determined by MTT assay. After 24 hours, the plate was observed under the inverted microscope (Nikon Eclipse TS 100) to evaluate morphological changes.

Cell lysate preparation

Cell lysates for evaluating TAC, TOS, MDA, GPx, catalase (CAT), SOD were prepared according to the Kiazist kit protocol (Hamedan, Iran). Overall, after 24 hours of treating with AuNPs (with concentrations of 12.5, 25, and 50 µg/ml), the 5637 cells were washed with cold PBS) pH 7.0) slowly and then dissociated with trypsin-EDTA, and collected by centrifugation at 1500 rpm for 5 min. Afterwards, the cells were resuspended in PBS or the buffer recommended by Kiazist company and lysed either by freeze-thaw or incubation at 4°C. Next, the cells were centrifuged at 12000×g for 15 min at 4°C. Finally, supernatants were separated and stored at −80°C. It is worth mentioning that protease inhibitor cocktail (PI; (KPIMM)) and butylated hydroxytoluene (BHT) solution were added in the lysis buffer for investigating antioxidant enzymes and MDA, respectively. Protein levels of each sample were estimated by the Bradford method[18] in which bovine serum albumin (BSA) was used as the standard. The amount of the protein obtained from the Bradford method was used to characterize the activity of each antioxidant enzyme and the levels of TAC, TOS and MDA.

Oxidative stress parameters assay

The levels of TAC (Kiazist, KTAC-96), TOS (Kiazist, KTOS-96), MDA (Kiazist, KMDA-96), were determined via the aforementioned kits according to the manufacturer's instructions. Briefly, TAC level was assessed based on CUPRAC assay in which the existing antioxidants make the cupric (Cu^{+2}) reduce to cuprous (Cu^{+1}) that produce color in the presence of chromogen. The TOS level was determined based on the oxidation of ferrous to ferric, which also produces color in presence of chromogen. In order to evaluate lipid peroxidation, MDA forms a complex with thiobarbituric acid (TBA), then absorbance was read at 532 nm. Oxidative stress index (OSI) was estimated according to the following formula:

$$\text{OSI (Arbitrary/ scale)} = \frac{\text{TOS}}{\text{TAC}}$$

The activity of antioxidant enzymes, [i.e., SOD (Kiazist, KSOD-96), GPx (Kiazist, KGPx-96), CAT (Kiazist, KCAT-96)], were determined using the aforementioned kits according to the manufacturer's instructions.

Statistical analysis

All experiments were performed in triplicate. Statistical analyses were conducted using SPSS 26 software (SPSS Inc., Chicago, IL) and GraphPad Prism 8 software (San Diego, CA, USA). First, the normal distribution and homogeneity of data variances were evaluated by Shapiro-Wilk normality test. Then, one-way ANOVA followed by post-hoc Tukey test were employed for multiple comparisons. Results were reported as mean ± SD, and the obtained p values less than 0.05 were considered statistically significant.

RESULTS

Cytotoxicity effects of AuNPs on 5637 cells

As shown in **Fig. 2**, low concentrations of AuNPs (1.56, 3.12 µg/ml) did not show any significant effects on cell viability compared with the untreated cells (cells with %100 viability which were also called control cells) (p>0.05). The first concentration leading to a significant change in cell viability was 6.25 µg/ml in which the cell viability was 82.72±9.3% compared to the untreated cells (p=0.01). At the 12.5 µg/ml concentration of AuNPs, the cell viability was reduced to 80.39±1.4% (p=0.006). Furthermore, AuNPs reduced cell viability at concentrations of 25 and 50 µg/ml to 68±3.57% and 42.57±1.4%, respectively. IC50 concentrations of AuNPs in 5637 cells were obtained 43.14 µg/ml after completion of 24 hours. Since there was not much meaningful difference between the concentrations of 12.5

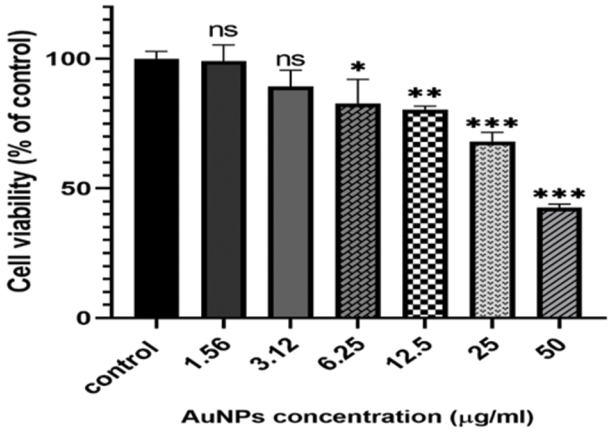

Figure 2. Inhibition of 5637 cell survival after 24-hour exposure to various concentrations of gold nanoparticles (AuNPs) (0, 1.56, 3.12, 6.25, 12.5, 25, and 50 μg/ml) according to the results of MTT assay. Asterisks indicate significant difference compared with the control cells (*p<0.05, **p<0.01, ***p<0.001). The results are shown as mean ± SD of three individual 96-well plates (n=3).

and 6.25 viabilities, (p>0.05), we selected the concentrations of 12.5, 25, and 50 μg/ml for further study.

AuNPs-induced morphological changes in 5637 cells

As shown in **Fig. 3**, AuNPs diminished the density of 5637 cells and led to a number of abnormalities including cell rugosity and rounded cell shapes in a dose-dependent manner. As shown in **Fig. 3b**, at a concentration of 12.5 μg/ml, there was no significant change in the morphology of the cells. At a concentration of 50 μg/ml **(Fig. 3d)**, morphological changes were more clearly seen.

Oxidative stress parameters

Changes in MDA, TOS and TAC levels according to different concentrations of AuNPs in 5637 cells are shown in **Fig. 4**. Treatments with doses of 25 and 50 μg/ml significantly increased MDA and TOS levels in 5637 cells compared with the control (p<0.001). Moreover, MDA and TOS levels were significantly increased with 12.5 μg/ml of AuNPs compared with the control (p<0.01). Our results showed that treatment with AuNPs significantly reduced the activity of GPx, SOD, CAT and TAC level in the 5637 cells. It was found that the TAC levels were decreased compared with the control cells (p<0.001) after 24 hours of AuNPs treatment with concentrations of 12.5, 25 and 50 μg/ml **(Fig. 4c)**. Similar to MDA and TOS levels, OSI showed a significant increase at doses of 25 and 50 μg/ml compared with the control cells (p<0.001).

As shown in **Fig. 5a**, GPx activity was significantly decreased in cells treated with the concentration of 50 μg/ml AuNPs relative to control cells (p<0.01), but there was no significant difference between the concentrations of 12.5 and 25 μg/ml compared with the control (p>0.05).

CAT activity was significantly decreased in 12.5, 25, and 50 μg/ml concentrations compared with the control cells (p<0.001) **(Fig. 5b).** The SOD activity (expressed as inhibition rate %) is shown in **Fig. 5c**. It was observed that treatment with concentrations of 12.5, 25, and 50 μg/ml could reduce SOD activity in a concentration-dependent manner.

DISCUSSION

It is well known that AuNPs originating from different sources such as biological[19] and chemical[20] can inhibit the growth of cancer cells. For example, Wu et al.[1] showed that AuNPs have considerable inhibitory effects on bladder cancer T24 cells and as many other anti-cancer drugs, can increase oxidative stress and apoptosis. In addition, it was demonstrated that citrate- capped AuNPs could reduce the viability of human hepatocellular carcinoma and peripheral blood mononuclear cells (PBMC). It was also shown that PBMC were less sensitive to DNA damage than cancer cells.[21] In contrast, Liu et al.[20] observed that citrate-stabilized AuNPs 20 nm and 40 nm in size had no inhibitory effects on lung cancer cell lines while the 5-nm and 10-nm AuNPs showed high cytotoxicity. Surprisingly, they observed that AuNPs had positive effects on the growth of A549 cells sizes 20 nm or 40 nm. Unlike Liu et al.[20], our work demonstrated that 20 nm citrate-stabilized AuNPs decrease cell viability in bladder cancer 5637 cells in a dose-dependent manner. According to the previous studies exploiting AuNPs[17], there is indeed a substantial controversy about the cytotoxicity of AuNPs. While there are some research works indicating the non-toxic effects of AuNPs[6,22], our results (along with some papers[1,23,24]) demonstrated that AuNPs have inhibitory effects on cancer cells. Specifically, this major change in cytotoxicity level might stem from the variations of a few parameters including the cell lines used in toxicity assays, concentrations, surface charge, coatings, incubation time and synthesis method. It is worth mentioning that the observed differences between our results and the aforementioned studies might be derived from the different nature of AuNPs and the studied cell lines. Aside from inhibitory effects, in the current study and some others[11], it was observed that morphological changes after treatment with AuNPs would depend remarkably on the concentration adopted from the MTT assay.

According to the obtained results from oxidative stress parameters, the levels of TAC, TOS, and MDA were fully consistent with the ones obtained from MTT assay. In order to explain in more details, unsaturated fatty acids and lipids are oxidated in the presence of ROS which can cause lipid peroxidation (LPO). Furthermore, MDA, resulting from the breakdown of polyunsaturated fatty acids (PUFAs) in lipid membranes, is a strong indicator of LPO.[25] Hence, since AuNPs increase ROS production, there might be a direct relation between ROS production and MDA level as shown by Li et al.[26] who demonstrated that both oxidative stress and LPO increased in MRC-5 (human

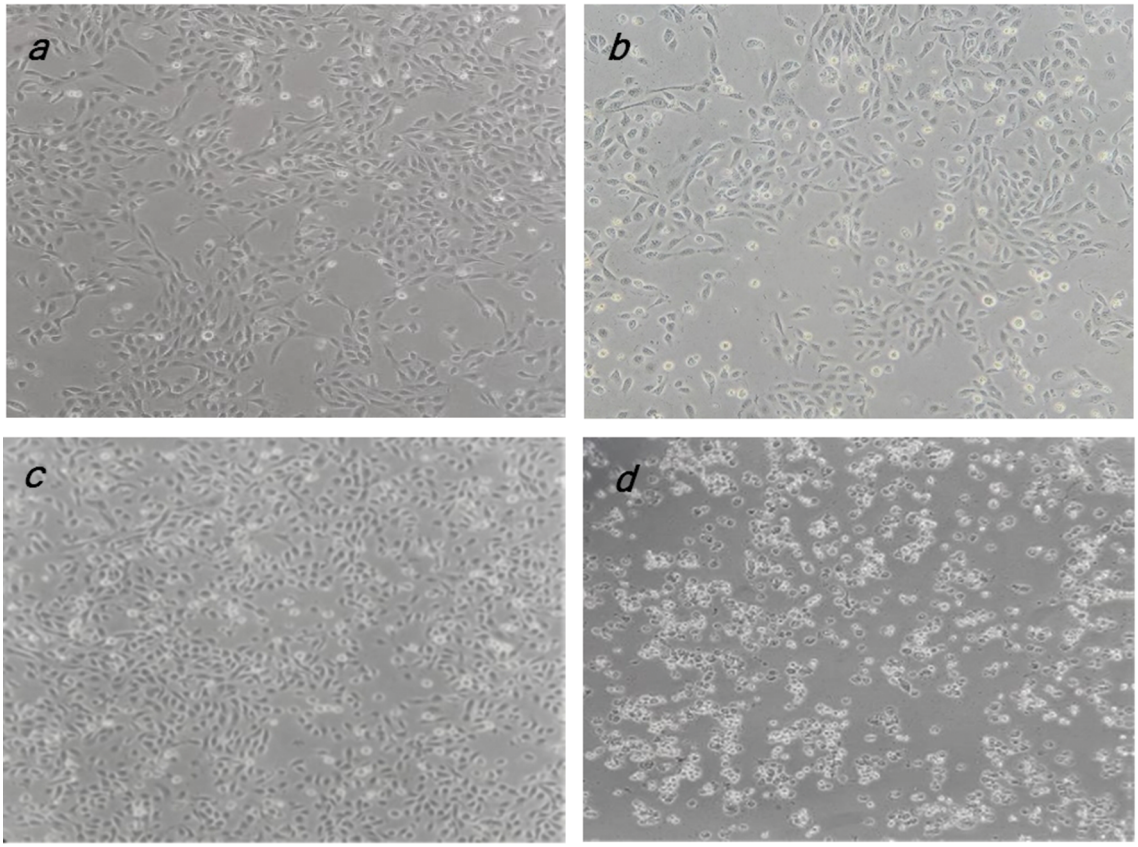

Figure 3. Morphological alterations in 5637 cells treated with 12.5 (**b**), 25 (**c**) and 50 μg/ml (**d**) AuNPs in comparison with untreated cells (**a**). It is noteworthy that the cell density was decreased while the number of rounded and wrinkled cells was increased in AuNPs-treated cells in a dose dependent manner. Objective magnification is 10×.

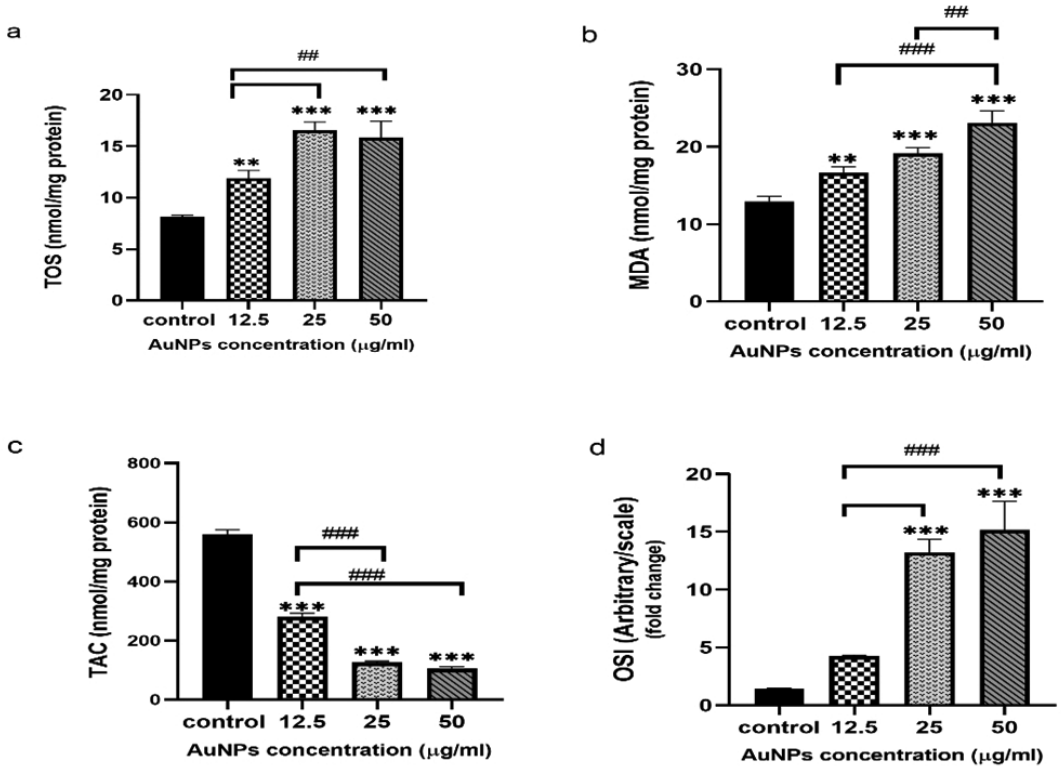

Figure 4. Effects of AuNPs on oxidative stress parameters in 5637 cells. **a**) total oxidant status (TOS), **b**) malondialdehyde (MDA), **c**) total antioxidant capacity (TAC), and **d**) oxidative stress index (OSI). Asterisks indicate significant differences relative to control (*p<0.05, **p<0.01, ***p<0.001). Number sign indicates significant differences between groups (#p<0.05, ##p<0.01, ###p<0.001).

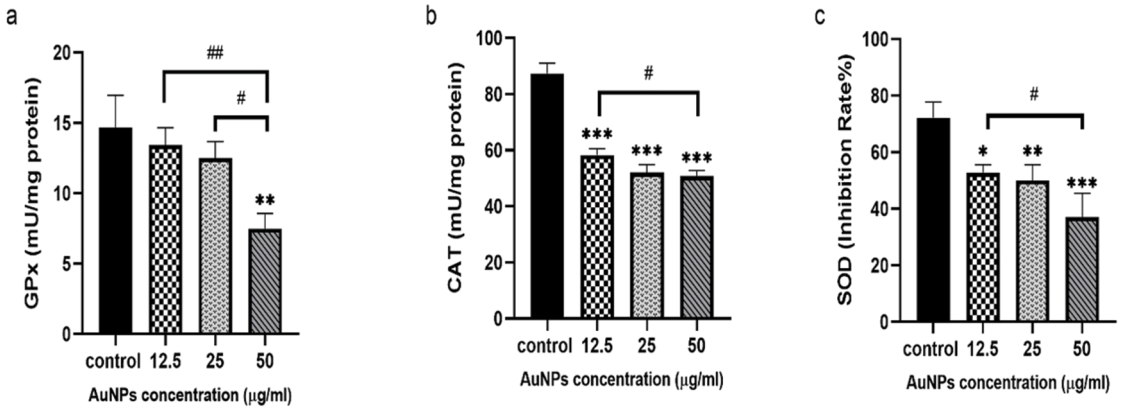

Figure 5. Effects of AuNPs on antioxidant enzymes activity in bladder cancer 5637 cells. **a**) glutathione peroxidase (GPx), **b**) catalase (CAT), **c**) superoxide dismutase (SOD). Asterisks indicate significant difference compared with control (*p<0.05, **p<0.01, ***p<0.001). Number sign indicates significant differences between groups (#p<0.05, ##p<0.01, ###p<0.001).

lung fibroblasts) cells treated with AuNPs. Also, Barreto et al.[27] showed that 7-nm AuNPs have higher effects on a liver organ culture of Sparus aurata compared to the 40-nm AuNPs. Besides, the 7-nm AuNPs increase LPO levels at 4 μg.L^{-1}.[27] In another similar study, Bin-Jumah et al.[28] measured the LPO and GSH (total glutathione) levels (as markers of oxidative stress) in liver cancer cells after exposure to AuNPs. LPO was increased and GSH quantity was decreased in treated cells when compared to the control cells in a dose-dependent manner. From the aforementioned results, it was concluded that decreasing TAC level while increasing MDA and TOS levels lead to increased oxidative stress.

Our results also showed that AuNPs can reduce antioxidant enzymes activity e.g. CAT, SOD, GPx. In consistency with our study, Costa et al.[29] found that concentrations above 4 μg.L^{-1} of AuNR reduced the activity of CAT in tadpoles after completion of 72 hours.[29] In connection with the importance of CAT activity in cancer, it was reported that inhibition of CAT activity can remarkably increase oxidative stress status and hydrogen peroxide resulting in cancer cells death.[30]

Our results emphasize that fact that the activity of SOD is decreased under treatment with AuNPs. Specifically, it is reported that SOD and GPx activities are usually decreased in cancers depending on excess production of ROS.[31] In this regard, Mateo et al.[17] showed that SOD activity and total GSH content are reduced in HepG2 cells. However, in HL-60 cells treated with AuNPs, there were no meaningful changes in the activity of SOD. On the contrary, ROS production was increased in both cell lines. Totally, their results show that oxidative stress contributes to AuNPs-induced cytotoxicity in HL-60 and HepG2 cells. Generally, different redox status from normal cells and increased levels of ROS in cancer cells provide bases for their growth and metastasis, though it might lead to oxidative stress and probably cell death. Also, cancer cells are more vulnerable to ROS production than normal cells. This difference creates a therapeutic window based on which anticancer agents are produced. Due to considerable increase of TAC in cancer cells and that ROS production is not per se sufficient for eradicating cancer cells, there is a strong need for agents to inhibit antioxidant defense system.[32] Our results showed that the AuNPs at doses above 3.12 μg/ml can reduce the 5637 bladder cancer cells survival meanwhile decreasing antioxidant defense which can both lead to cancer cells death. Therefore, the AuNPs have high capabilities to be used as anticancer agents in bladder cancer therapy. It seems that further studies are needed to investigate apoptosis pathways involved in AuNPs toxicity in bladder cancer cell line.

CONCLUSIONS

Gold nanoparticles are one of the important metallic nanoparticles used in nanomedicine technology. According to our results, AuNPs can effectively reduce bladder cancer 5637 cells viability in a dose-dependent manner. We also found that AuNPs have the ability to reduce the antioxidant capacity of cancer cells and increase oxidative parameters. It seems that oxidative stress contributes to the toxicity of AuNPs. However, further investigations considering different signaling pathways involved in cancer development or progression are needed to prove it.

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Conflicts of Interest

There is no conflict of interest in this paper.

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Folia Medica

Влияние наночастиц золота на статус окислительного стресса в клеточной линии 5637 рака мочевого пузыря

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Резюме

Введение: В последнее время наномедицина стала известна как развивающаяся область исследований с многообещающими применениями в диагностике и лечении рака. Кроме того, наночастицы золота (AuNPs) как один из важных компонентов наномедицины привлекают значительное внимание в связи с их особыми физико-химическими свойствами и меньшей токсичностью по сравнению с другими наночастицами. Несмотря на впечатляющие преимущества AuNPs, еще не установлено, способствует ли окислительный стресс токсичности AuNPs при раке мочевого пузыря.

Цель: Целью данного исследования было решение этой проблемы путём проведения экспериментов по изучению влияния 20 nm AuNPs на клеточную линию 5637 рака мочевого пузыря человека.

Материалы и методы: Жизнеспособность клеточной линии 5637 оценивали при 24-часовом воздействии различных концентраций AuNPs (0-50 μg/ml) бромидом 3-(4,5-диметилтиазол,2-ил)-2,5-дифенилтетразолия. Для оценки состояния окислительного стресса определяли общую антиоксидантную способность (ОАС), общий оксидантный статус (ООС), малоновый диальдегид (МДА), а также активность антиоксидантных ферментов, включая глутатионпероксидазу (ГП), каталазу (КАТ) и супероксиддисмутазу (СОД) наборами для колориметрического анализа.

Результаты: Результаты нашего эксперимента показали, что цитотоксичность, вызванная AuNPs, зависела от дозы, и было обнаружено, что значение IC50 составляет 43.14 μg/ml после 24-часового воздействия. Кроме того, уровни МДА и ООС были значительно повышены в обработанных клетках по сравнению с необработанными клетками (p<0.05). Напротив, уровень ТАС и активность СОД, ГП, КАТ были значительно снижены в группах, обработанных AuNPs, по сравнению с необработанными клетками (p<0.05).

Заключение: В целом, AuNPs снижают жизнеспособность клеток и усиливают окислительный стресс в клеточной линии 5637 рака мочевого пузыря.

Ключевые слова

5637 клеток рака мочевого пузыря, жизнеспособность клеток, окислительный стресс, наночастицы золота