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Research Article

Anticancer effects of sodium selenate in human neuroblastoma, breast cancer, and melanoma cells

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Abstract: Sodium selenate (Na_2SeO_4) is one of the oxidized inorganic forms of selenium. Effects on cytotoxicity, total antioxidant level, total oxidant level, oxidative stress, and genotoxicity status and its anticancer effect on SH-SY5Y human neuroblastoma, MCF-7 human breast cancer, and 451Lu human melanoma cells were investigated in this study. Sodium selenate exhibited a highly cytotoxic effect at all concentrations (0.078125 - 10 mg/mL) against SH-SY5Y, MCF-7, and 451Lu cancer cell lines. In addition, sodium selenate reduced the total antioxidant levels, increased the total oxidant levels (except for SH-SY5Y), and induced oxidative stress significantly in SH-SY5Y, MCF-7, and 451Lu cells. However, in agarose gel electrophoresis images, it was observed that sodium selenate did not have any genotoxic effect on SH-SY5Y, MCF-7, and 451Lu cancer cells. Sodium selenate can be used in cancer treatment because of its antioxidant, as well as pro-oxidant and anticancer properties, which depend on the concentrations used.

1. INTRODUCTION

Sodium selenate (Na_2SeO_4) is a microelement among the oxidized inorganic forms of selenium. The high bioavailability of sodium selenate not only allows it to play important roles in biological processes but also provides various health benefits. Sodium selenate serves as a selenium source in the human body and participates in the structure of enzymes such as glutathione peroxidases (GPx), thioredoxin reductases (TrxR), selenoprotein P and iodothyronine deiodinases (DIO), which play a critical role in the antioxidant defense system and provide protection against oxidative damage (Arnér, 2009; Brigelius-Flohé & Maiorino, 2013; Burk & Hill, 2015; Köhrle, 2000; Rayman, 2012).

Oxidative stress occurs as a result of the imbalance between free radicals and reactive oxygen species (ROS) that occur as a result of various biochemical events in the human body and cellular antioxidant defense systems. It is known that oxidative stress plays an important role in the pathogenesis of many diseases, including cancer (Birben *et al.*, 2012). However, recent studies have shown that oxidative stress may have anticancer effects under certain conditions (Gorrini *et al.*, 2013).

In addition to its antioxidant properties, sodium selenate increases oxidative stress depending on the dose and application method and can also show anticancer effects against various types of cancer through increased oxidative stress. It is stated in the literature that sodium selenate

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triggers apoptosis in cancer cells and stops the cell cycle and tumor growth (Cao *et al.*, 2019). In addition, it is stated in the literature that sodium selenate has antiproliferative effects against cancer cells at low concentrations, while it has toxic effects on cancer cells at high doses (Foster & Sumar, 1997). Sodium selenate has become a molecule that has attracted attention in recent years due to its properties (Rayman, 2012).

Cancer is the second most common cause of death worldwide. In 2022, there were almost 20 million new cases of cancer and 9.7 million deaths from cancer. Estimates suggest that approximately one in five men or women will develop cancer in their lifetime, while about one in nine men and one in 12 women will die from it. Brain, and central nervous system cancer was the 19th most frequently diagnosed cancer in 2022, responsible for almost 321476 new cases, with 1.6% of all cancers globally. Brain, and central nervous system cancer was also one of the leading causes of cancer death, with an estimated 248305 deaths (2.6%). Female breast cancer was the second most frequently diagnosed cancer in 2022, responsible for almost 2.3 million new cases, or one in eight cancers world-wide (11.6% of all cancers globally). Female breast cancer was also one of the leading causes of cancer death, with an estimated 665684 deaths (6.9%). Melanoma of skin cancer was the 17th most frequently diagnosed cancer in 2022, responsible for almost 331647 million new cases, with 1.7% of all cancers globally. Melanoma of skin cancer was also one of the leading causes of cancer death, with an estimated 58645 deaths (0.6%) (Bray *et al.*, 2024). The anticancer activity of sodium selenate has been studied in some cancer cells (Corcoran *et al.*, 2010; da Costa *et al.*, 2023; Tsukamoto *et al.*, 2013).

In this study, the effects of sodium selenate on the total antioxidant, oxidant, and oxidative stress status of SH-SY5Y human neuroblastoma, MCF-7 human breast cancer, and 451Lu human melanoma cells and its cytotoxic effect on these indicated cancer cell lines were investigated. No studies have yet been conducted on the anticancer effects of sodium selenate on the SH-SY5Y human neuroblastoma, MCF-7 human breast cancer, and 451Lu human melanoma cells. Our study aims to give an idea to the cancer research to be made with sodium selenate.

2. MATERIAL and METHODS

2.1. Chemicals and Reagents

RPMI 1640 medium, Cell Viability Detection Kit-8 (CVDK-8), Phosphate Buffered Saline (PBS) (1x), pH:7.4, Genomic DNA Isolation Kit, ClearBand 6x DNA Loading Dye, ClearBand SAFE DNA Gel Stain Solution, 20,000x, TBE 10x, and 100bp DNA ladder were procured from EcoTech Biotechnology, Erzurum, Türkiye. Total antioxidant status (TAS) and total oxidant status (TOS) assay kits were purchased from Rel Assay Diagnostics, Mega Tıp, Gaziantep, Türkiye. Fetal bovine serum (FBS) and penicillin-streptomycin solution were procured from Gibco Life Technologies, Paisley, UK. Sodium selenate and all other chemicals were purchased from Merck (Darmstadt, Germany).

2.2. Cell Culture

Human neuroblastoma SH-SY5Y (ATCC: CRL-2266), human breast cancer MCF-7 (ATCC: HTB-22), and human melanoma 451Lu (RRID: CVCL_6357) cell lines were used in this study. The related cells were cultured in T25 flasks using RPMI 1640 medium supplemented with 10% fetal bovine serum and 0.5% penicillin-streptomycin antibiotic solution. The cells were grown in an incubator at 37 °C with 5% CO_2 and subcultured every two or three days.

2.3. Sodium Selenate Treatment

Experiments were started when the cells reached sufficient density (70-80%). The SH-SY5Y, MCF-7, and 451Lu cells were trypsinized, harvested, and then counted using a Thoma hemocytometer. 1×10^4 cells per well in a 100 µL medium were seeded in a 96-well plate for WST-8 cell viability, total antioxidant status (TAS), and total oxidant status (TOS) assays. For

DNA fragmentation assay, 1×10^6 cells per well in a 2 mL medium were seeded in a 6-well plate. After 24 hours, the media of SH-SY5Y, MCF-7, and 451Lu cells were removed, and for WST-8 cell viability assay; a new RPMI 1640 medium including 10% fetal bovine serum, 0.5% penicillin-streptomycin antibiotic solution, and varying concentrations of sodium selenate (from 0 to 10 mg/mL), for other assays; a new RPMI 1640 medium including 10% fetal bovine serum, 0.5% penicillin-streptomycin antibiotic solution, and 10 mg/mL sodium selenate added to cells. The cells were then subjected to an additional 24 hours of incubation in an incubator at 37 °C with 5% CO_2.

2.4. WST-8 Cell Viability Assay

Cell Viability Detection Kit-8 (WST-8 / CVDK-8) was used to determine the cytotoxic effect of sodium selenate on the SH-SY5Y, MCF-7, and 451Lu tumor cell lines. For this, at the end of the 24-hour incubation period, 5 µl of water-soluble WST-8 tetrazolium salt was added to each well of the cells in 96-well plates and incubated for 3 h. The absorbance was measured at 450 nm using a microplate reader (Rel Assay Diagnostics, BK-EL10C, Mega Tıp, Gaziantep, Türkiye). The cell death was determined using the following formula:

$$\text{Cell death (\%control)} = [1- ((OD_{sample}- OD_{blank}) / (OD_{control}- OD_{blank}))] \times 100$$

A nonlinear regression graph was plotted between % cell death and Log10 concentration and the calculation of IC_{50} value was determined using GraphPad Prism software 5.01 (GraphPad, San Diego, CA). Each assay was repeated in triplicate and the results were given as mean ± SD of independent experiments.

2.5. Total Antioxidant Status (TAS) Assay

The effect of sodium selenate on the total antioxidant levels of SH-SY5Y, MCF-7, and 451Lu tumor cells was assessed using the Total Antioxidant Status (TAS) Assay Kit, following the manufacturer's instructions with some modifications. Briefly, the cell culture media belonging to control and experimental groups of SH-SY5Y, MCF-7, and 451Lu cell lines in each well in the 96 well plates were collected in Eppendorf tubes according to their respective groups at the end of the 24-hour incubation period. 12 µL of each of the samples from Eppendorf tubes, standards, and dH_2O were added to the respective well of 96 well plates. 200 µL reagent 1 was then added, mixed well, incubated at room temperature for 30 seconds in the dark, and measured spectrophotometrically at 660 nm absorbance. The initial obtained values of absorption were recorded as A1. Subsequently, 30 µL of reagent 2 was added, thoroughly mixed, and then left to incubate at room temperature for 10 minutes in the dark. The final step involved measuring the spectrophotometric readings at 660 nm. The second obtained absorbance values were recorded as A2. The results were calculated according to the following formula, and expressed as µmol Trolox Equiv./L.

TAS (µmol Trolox Equiv./L) = ([ΔAbs H_2O- ΔAbs Sample] / [ΔAbs H_2O- ΔAbs Standard]) x1000

ΔAbs of standard or sample or H_2O = A2– A1

2.6. Total Oxidant Status (TOS) Assay

The effect of sodium selenate on the total oxidant levels of SH-SY5Y, MCF-7, and 451Lu tumor cells was assessed using the Total Oxidant Status (TOS) Assay Kit, following the manufacturer's instructions with some modifications. Briefly, the cell culture media belonging to control and experimental groups of SH-SY5Y, MCF-7, and 451Lu cell lines in each well in the 96 well plates were collected in Eppendorf tubes according to their respective groups at the end of the 24-hour incubation period. 30 µL of each of the samples from Eppendorf tubes, and standards were added to the respective well of 96 well plates. 200 µL reagent 1 was then added, mixed well, incubated at room temperature for 30 seconds in the dark, and measured spectrophotometrically at 530 nm absorbance. The first obtained absorbance values were recorded as A1. 10 µL reagent 2 was then added, mixed well, incubated at room temperature

for 10 minutes in the dark, and measured spectrophotometrically at 530 nm absorbance. The second obtained absorbance values were recorded as A2. The results were calculated according to the following formula, and expressed as μmol H_2O_2 Equiv./L.

$$\text{TOS (μmol } H_2O_2 \text{ Equiv./L)} = (\Delta\text{Abs Sample} / \Delta\text{Abs Standard}) \times 10$$

ΔAbs of standard or sample= A2– A1

2.7. Oxidative Stress Index (OSI)

The effect of sodium selenate on the oxidative stress levels of SH-SY5Y, MCF-7, and 451Lu tumor cells was determined using the following formula;

$$\text{OSI (arbitrary unit)} = \text{TOS (μmol } H_2O_2 \text{ Equiv./L)/TAS (μmol Trolox Equiv./L)} \times 100$$

2.8. DNA Isolation

The SH-SY5Y, MCF-7, and 451Lu cells treated with or without sodium selenate were trypsinized, harvested, and washed with PBS. Genomic DNAs of SH-SY5Y, MCF-7, and 451Lu cells were obtained using the Genomic DNA Isolation Kit, following the manufacturer's instructions.

2.9. Analysis of DNA Fragmentation Using Agarose Gel Electrophoresis

25 μL DNA was loaded with 5 μL ClearBand 6x DNA Loading Dye on a 1.5% agarose gel (containing 5μl of ClearBand SAFE DNA Gel Stain Solution, 20,000x) and run in TBE buffer (90 mM Tris-HCl, 90 mM boric acid, 2 mM EDTA, pH 8.0) for 50 minutes at 80 V. After agarose gel electrophoresis, the gel was photographed under UV illumination. 100bp DNA ladder was used as marker.

2.10. Statistical Analysis

All measurements were repeated three times, and GraphPad Prism 5.01 software was applied for statistical analysis. Comparable datasets were assessed, and the analyses were conducted by using two-tailed Student's *t*-test. The data are represented by the mean ± S.D. from 3 independent experiments and are statistically significant at $p < 0.05$.

3. RESULTS

Sodium selenate increases cell death in SH-SY5Y human neuroblastoma, MCF-7 human breast cancer, and 451Lu human melanoma cells. The cytotoxic effects of sodium selenate on SH-SY5Y, MCF-7, and 451Lu cells were examined with the WST-8 assay. SH-SY5Y, MCF-7, and 451Lu cells were treated with sodium selenate at concentrations ranging between 0 (untreated, control) and 10 mg/mL for 24 h. The results showed that sodium selenate significantly inhibited the viability of SH-SY5Y, MCF-7, and 451Lu cells at all concentrations ($^{****}p < 0.0001$ vs 0 mg/mL), and the cytotoxic effect increased as the concentration increased (Figure 1). The cell death rates caused by sodium selenate at concentrations ranging from 0 to 10 mg/mL applied to SH-SY5Y cells were determined to be approximately 0, 66.39, 85.86, 91.03, 92.16, 92.76, 93.54, 94.53, and 95.37%, respectively (Figure 1A). The cell death rates resulting from the application of sodium selenate at concentrations ranging from 0 to 10 mg/mL to MCF-7 cells were approximately 0, 26.31, 26.69, 40.52, 57.26, 87.88, 97.53, 96.86, and 98.04%, respectively (Figure 1B). The cell death rates resulting from the application of sodium selenate at concentrations ranging from 0 to 10 mg/mL to 451Lu cells were as follows: 0, 81.95, 82.01, 87.52, 93.15, 96.30, 97.37, 98.08, and 99.21, respectively (Figure 1C).

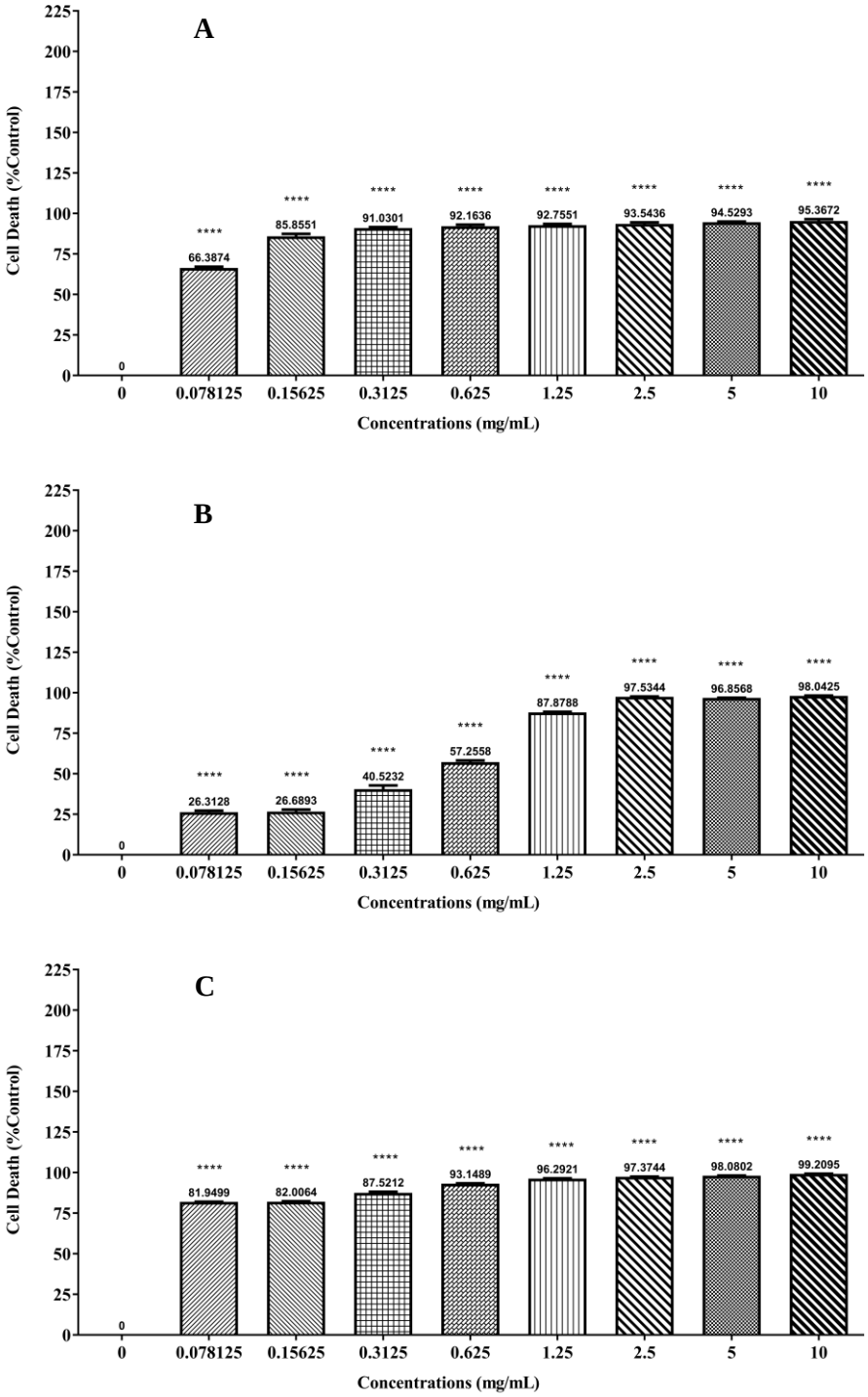

Figure 1. Cell death of SH-SY5Y human neuroblastoma **(A)**, MCF-7 human breast cancer **(B)**, and 451Lu human melanoma cells **(C)** (% of the control) after incubation with sodium selenate.

The IC50 values of sodium selenate in the SH-SY5Y, MCF-7, and 451Lu cells were found to be 0.0507 ± 0.004, 0.4554 ± 0.0152, and 0.0036 ± 0.0002 mg/mL, respectively. It was observed that sodium selenate significantly inhibited cell viability at all applied concentrations (0.078125-10 mg/mL), and also had a maximum cytotoxic effect at a concentration of 10 mg/mL on SH-SY5Y, MCF-7, and 451Lu cells. For this reason, the concentration value of 10 mg/mL, where sodium selenate showed maximum cytotoxic effect, was used in all remaining assays of the study.

Sodium selenate reduces total antioxidant levels in SH-SY5Y, MCF-7, and 451Lu cells. The effects of sodium selenate on total antioxidant levels of SH-SY5Y, MCF-7, and 451Lu cells were examined. The cells were treated with sodium selenate at concentrations of 0 mg/mL

(untreated, control) and 10 mg/mL for 24 hours. The total antioxidant levels in sodium selenate untreated (0 mg/mL) and treated (10 mg/mL) SH-SY5Y, MCF-7, and 451Lu cells were approximately 511.74 and 452.27 µmol Trolox Equiv./L, respectively, for SH-SY5Y; approximately 432.71 and 392.02 µmol Trolox Equiv./L, respectively, for MCF-7; approximately 437.40 and 351.33 µmol Trolox Equiv./L, respectively, for 451Lu (Figure 2). The results indicated that 10 mg/mL of sodium selenate, when compared with 0 mg/mL, significantly decreased the total antioxidant levels in SH-SY5Y, MCF-7, and 451Lu cells (*** p <0.001, $^{\#\#}$ p <0.01, and $^{++}$ p <0.01 vs 0 mg/mL) at the rates of 11.62, 9.40, and 19.67%, respectively.

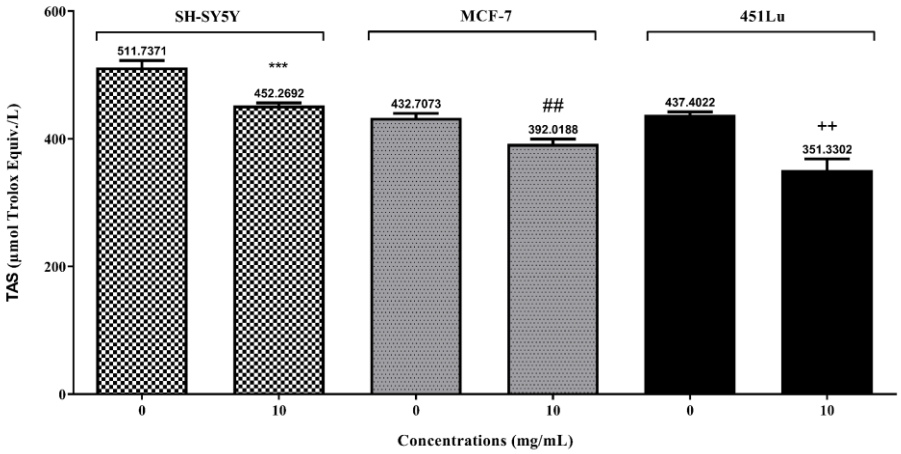

Figure 2. Total antioxidant status of SH-SY5Y human neuroblastoma, MCF-7 human breast cancer, and 451Lu human melanoma cells (% of the control) after incubation with sodium selenate.

Sodium selenate induces total oxidant levels in MCF-7, and 451Lu cells. The impact of sodium selenate on the total oxidant levels of SH-SY5Y, MCF-7, and 451Lu cells was investigated. The cells were treated with sodium selenate at concentrations of 0 mg/mL (untreated, control) and 10 mg/mL for 24 hours. The total oxidant levels in sodium selenate untreated (0 mg/mL) and treated (10 mg/mL) SH-SY5Y, MCF-7, and 451Lu cells were approximately 3.89 and 3.65 µmol H_2O_2 Equiv./L, respectively, for SH-SY5Y; approximately 2.54 and 3.63 µmol H_2O_2 Equiv./L, respectively, for MCF-7; approximately 2.54 and 4.00 µmol H_2O_2 Equiv./L, respectively, for 451Lu (Figure 3). The results indicated that 10 mg/mL of sodium selenate compared with 0 mg/mL statistically did not significantly change the total oxidant levels in the SH-SY5Y cell line, while increasing the total oxidant levels in MCF-7, and 451Lu cells (^{ns} p> 0.05, $^{\#\#\#}$ p <0,001, and $^{+++}$ p <0.001 vs 0 mg/mL) at the rates of 42.67, and 57.32%, respectively.

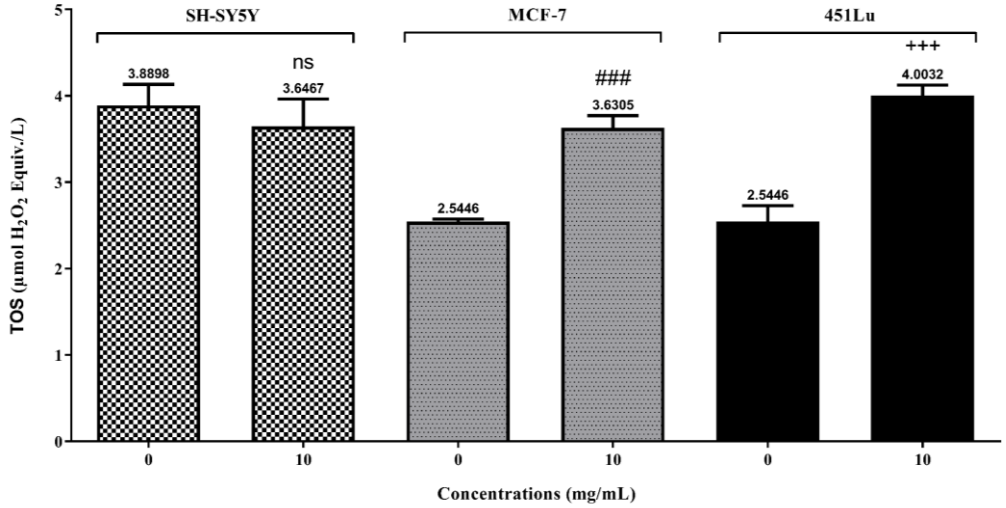

Figure 3. Total oxidant status of SH-SY5Y human neuroblastoma, MCF-7 human breast cancer, and 451Lu human melanoma cells (% of the control) after incubation with sodium selenate.

Sodium selenate induces oxidative stress in SH-SY5Y, MCF-7, and 451Lu cells. The effects of sodium selenate on oxidative stress of SH-SY5Y, MCF-7, and 451Lu cells were determined by the relative total oxidant levels to the total antioxidant levels of these cells, and the results were expressed as arbitrary units. Oxidative stress levels in the untreated control (0 mg/mL) groups of SH-SY5Y, MCF-7, and 451Lu cells were approximately 0.76, 0.59, and 0.58, respectively, while in the 10 mg/mL of sodium selenate-treated groups of these cells were in order of, approximately 0.81, 0.93, and 1.14 (Figure 4). The results indicated that 10 mg/mL of sodium selenate compared with 0 mg/mL statistically significantly increased the oxidative stress levels in the SH-SY5Y, MCF-7, and 451Lu cells (^{ns} p> 0.05, $^{###}$ p <0.001, and $^{+++}$ p <0.001 vs 0 mg/mL) at the rates of 6.65, 57.00, and 96.08 %, respectively.

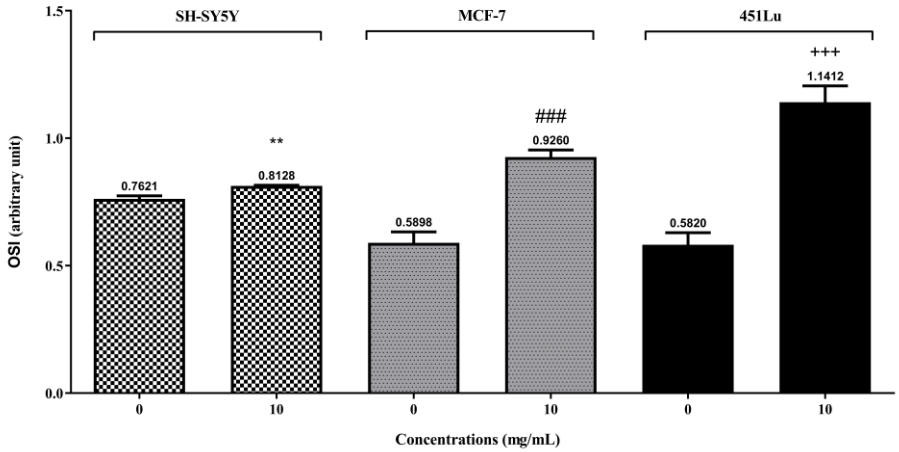

Figure 4. Oxidative stress index of SH-SY5Y human neuroblastoma, MCF-7 human breast cancer, and 451Lu human melanoma cells (% of the control) after incubation with sodium selenate.

Sodium selenate did not have a genotoxic effect on genomic DNAs obtained from SH-SY5Y, MCF-7, and 451Lu cells. The genotoxic effect of sodium selenate on the SH-SY5Y, MCF-7, and 451Lu cells was evaluated by subjecting genomic DNAs to agarose gel electrophoresis (Figure 5).

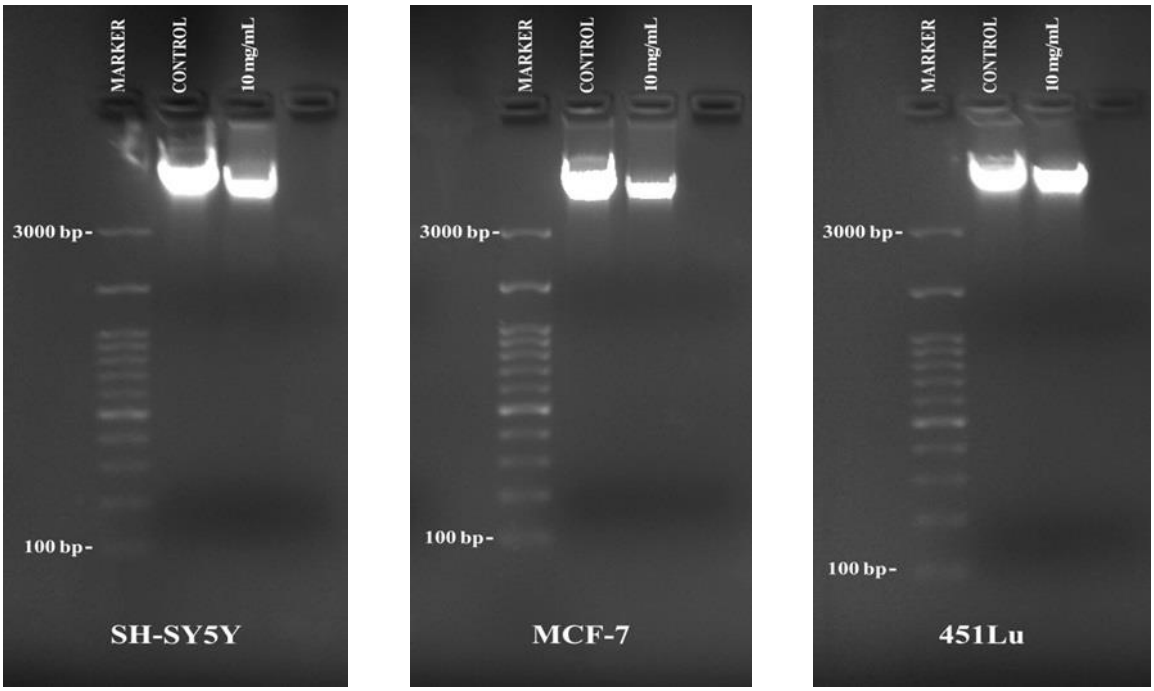

Figure 5. Agarose gel electrophoresis of genomic DNA from untreated (control) and 10 mg/mL sodium selenate treated SH-SY5Y human neuroblastoma, MCF-7 human breast cancer, and 451Lu human melanoma cells.

No degradation, such as DNA laddering or smearing, was observed in the integrity of DNA extracted from SH-SY5Y, MCF-7, and 451Lu cells treated with 10 mg/mL sodium selenate. In the control and sodium selenate treated samples, no migration of genomic DNAs was observed. After being subjected to electrophoresis, the DNA was almost still found to be localized at the starting point. This indicated well-preserved genomic integrity of the DNA isolated from SH-SY5Y, MCF-7, and 451Lu cells that were not treated with sodium selenate.

4. DISCUSSION and CONCLUSION

The effects of selenium on human neuroblastoma, breast cancer, and melanoma cells have not been clearly elucidated. Given the anti-tumor effects of selenium, the study focused on the effects of sodium selenate, an inorganic selenium compound, on SH-SY5Y human neuroblastoma, MCF-7 human breast cancer, and 451Lu human melanoma cells. Recent studies have reported that selenium compounds exhibit dose-dependent cytotoxic (da Costa *et al.*, 2023; Yang *et al.*, 2018), antioxidant, or pro-oxidant effects (Misra *et al.*, 2015) in many cancer cells, triggering intracellular ROS and oxidative stress (Misra *et al.*, 2015; Zeng *et al.*, 2012), and demonstrating strong anticancer effects through both apoptotic (Rikiishi, 2007; Yang *et al.*, 2018) and non-apoptotic mechanisms (Sanmartín *et al.*, 2012). It was hypothesized that exposure to sodium selenate would lead to a cytotoxic effect, induce oxidative stress, and apoptosis or non-apoptotic events in SH-SY5Y, MCF-7, and 451Lu cells. Therefore, the study analyzed the effects of sodium selenate exposure on cell viability. The results showed that sodium selenate effectively reduced the viability of SH-SY5Y, MCF-7, and 451Lu cells. In the study carried out by da Costa *et al.* (2023), the authors, consistent with our findings, observed that sodium selenate reduced cell viability in breast cancer BT-549 and MDA-MB-231 cell lines. In addition, Tsukamoto *et al.* (2013) reported in their paper that sodium selenate induced cytotoxicity in the human colon adenocarcinoma DLD-1 cell line, and it showed an anti-cancer effect. Oxidative stress can be defined as a condition that occurs as a result of the disruption of the balance between intracellular oxidant and antioxidant molecules (Preiser, 2012). Selenium and its inorganic (e.g., sodium selenate) and organic compounds can act as a “double-edged sword”; depending on the dosage, they may exhibit antioxidant or pro-oxidant properties (Radomska *et al.*, 2021). According to the results of our study, sodium selenate was observed to have pro-oxidant properties on SH-SY5Y, MCF-7 and 451Lu cell lines when applied at a concentration of 10 mg/mL depending on the dose. This concentration significantly reduced intracellular total antioxidant activity in all cells, while it increased intracellular total oxidant levels in MCF-7 and 451Lu cells except for the SH-SY5Y cell line, and significantly increased oxidative stress in these cells. Selenium compounds might induce cell death through pathways other than apoptosis, involving both internal and external mechanisms (Radomska *et al.*, 2021). Non-apoptotic events, such as cell cycle arrest (Chen *et al.*, 2019; Sanmartín *et al.*, 2012; Sinha & El-Bayoumy, 2004), necrosis (Sinha & El-Bayoumy, 2004), autophagy (Sanmartín *et al.*, 2012), ferroptosis (Subburayan *et al.*, 2020), necroptosis (Misra *et al.*, 2015), entosis (Khalkar *et al.*, 2018), anoikis (Gandin *et al.*, 2018; Jiang *et al.*, 2001), NETosis (Zhang *et al.*, 2020), or mitotic catastrophe (Sanmartín *et al.*, 2012), may also occur. Among the types of cell death caused by selenium compounds, ferroptosis appears to be a particularly intriguing process (Mou *et al.*, 2019). In ferroptosis, oxidative stress increases significantly due to the increase in intracellular oxidant molecules and the decrease in antioxidant defenses. This process leads to the accumulation of lipid peroxides in the cell membrane. As a result, a non-apoptotic cell death occurs, and DNA fragmentation is not typically observed in this cell death. This cell death mechanism, unlike the classical apoptotic pathways, is associated with a particularly iron-dependent process and is a type of programmed cell death in which oxidative damage is intensified (Mou *et al.*, 2019; Ursini & Maiorino, 2020). Choi *et al.* (2015) showed that sodium selenate (Na2SeO4) induced cell growth inhibition via G2/M phase cell cycle arrest in MDR oral squamous carcinoma cells KBV20C. In our agarose gel electrophoresis results, none of the sodium selenate-treated SH-SY5Y, MCF-7, and 451Lu cells was not showed DNA band-type

phenotypes of apoptotic (DNA ladder) or necrotic (DNA smear). To sum up, used concentrations (10 mg/mL) of sodium selenate in this study caused a decrease in antioxidant activity, an increase in oxidative stress, high cytotoxic activity, and non-apoptotic and non-necrotic DNA band phenotypes on SH-SY5Y, MCF-7, and 451Lu cells. Therefore, all these findings suggest that sodium selenate exhibits anticancer activity in these cells through non-apoptotic ferroptosis cell death, depending on the dose. In conclusion, further molecular studies are needed to better elucidate the way in which sodium selenate exhibits anticancer activity on SH-SY5Y, MCF-7, and 451Lu cancer cells.

Conflicting Interests and Ethics

The author declares no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the author.

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