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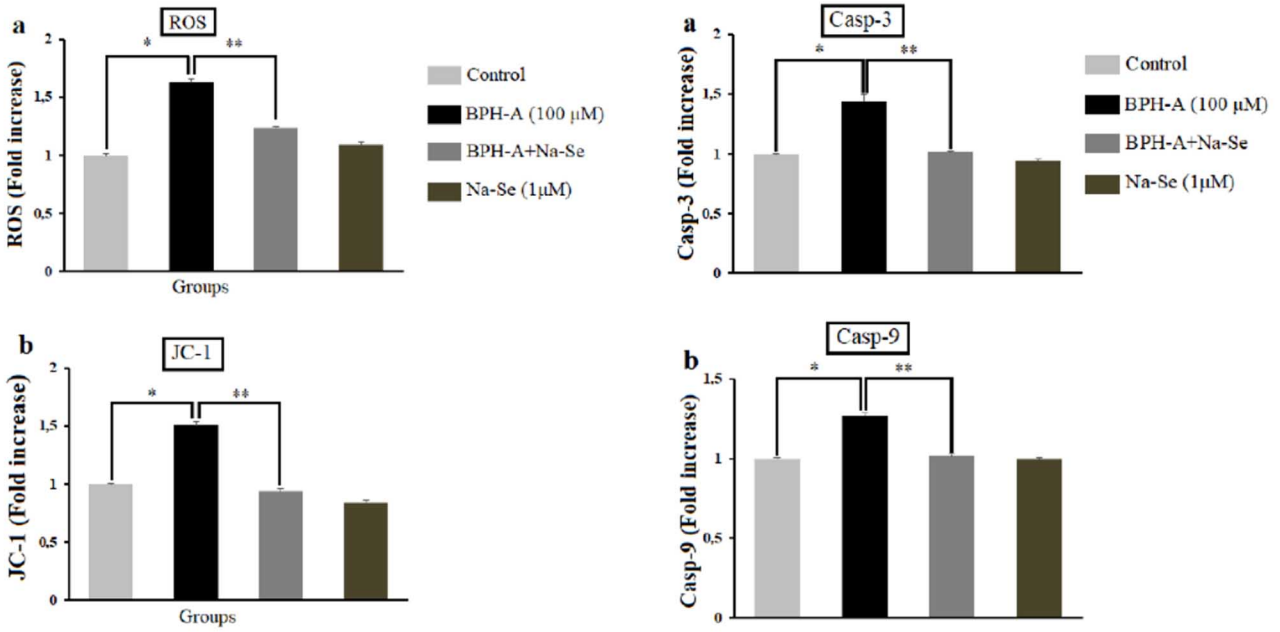

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AIM AND SCOPES
Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

Areas of particular interest are four topics. They are;

A- Ion Channels (Na^+- K^+ Channels, Cl^- channels, Ca^{2+} channels, ADP-Ribose and metabolism of NAD^+, Patch-Clamp applications)

B- Oxidative Stress (Antioxidant vitamins, antioxidant enzymes, metabolism of nitric oxide, oxidative stress, biophysics, biochemistry and physiology of free oxygen radicals)

C- Interaction Between Oxidative Stress and Ion Channels in Neuroscience
(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD^+ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

D- Gene and Oxidative Stress
(Gene abnormalities. Interaction between gene and free radicals. Gene anomalies and iron. Role of radiation and cancer on gene polymorphism)

READERSHIP

Biophysics	Biochemistry
Biology	Biomedical Engineering
Pharmacology	PhysiologyGenetics
Cardiology	Neurology
Oncology	Psychiatry
Neuroscience	Neuropharmacology

Keywords
Ion channels, cell biochemistry, biophysics, calcium signaling, cellular function, cellular physiology, metabolism, apoptosis, lipid peroxidation, nitric oxide, ageing, antioxidants, neuropathy, traumatic brain injury, pain, spinal cord injury, Alzheimer's Disease, Parkinson's Disease.

RESEARCH ARTICLE

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Protective role of selenium against bisphenol-A induced oxidative stress, cytokine generation and apoptosis in SH-SY5Y neuronal cell line

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List of Abbreviations :

***BPH-A**, bisphenol A; **Ca^{2+},** calcium ion; **GSHPx,** glutathione peroxidase; **IL-1β,** interleukin 1-beta; **JC-1,** 5,6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolyl carbocyanine iodide; **MTT,** 3-[4,5-Dimethyl-2thiazolyl]-2,5-diphenyl_2-tetrazolium bromide; **Na-Se,** sodium selenite; **NOS**, nitric oxide synthase; **OS,** oxidative stress; **ROS,** reactive oxygen species; **Se,** selenium; **TNF-α,** tumour necrosis factor α*

Abstract

Despite the clear effects and harm of the Bisphenol-A (BPH-A) chemical, it is one of the highest produced chemicals worldwide. The main areas of use include building materials, from automotive to food materials. It is important to find therapeutic agents against the damage caused by the BPH-A. Bisphenol A exposure is the major cause of increased oxidative stress (OS) and mitochondrial dysfunction, especially in cells. Thus, our study aimed to research the protective effect of selenium in BPH-A-induced SH-SY5Y neuroblastoma cells. The SH-SY5Y cells were divided into 4 groups as 1- Control group: No drug was applied to these cells. 2- BPH-A group: Bisphenol A was incubated with 100 μM for 24 hours. 3- BPH-A+Na-Se group: This group was incubated with BPH-A for 24 hours. Na-Se (1 μM) was added in the last 2 hours of the 24 hours. 4- Na-Se group: Na-Se was incubated with 1 μM for 2 hours. In the cells, intracellular ROS and JC-1 levels were highest in the BPH-A group, although there was a significant reduction in the selenium-treated group (BPH-A+Na-Se). In addition to these, when the Caspase-3 and Caspase-9 enzyme activities were examined between the groups, it was seen

that Selenium reduces the increased caspase activity caused by BPH-A. Finally, when the apoptosis and MTT analysis results between the groups were examined, it was observed that apoptosis and MTT levels were highest in the BPH-A group, while it was significantly lower in the Na-Se group compared to the BPH-A group. In conclusion, this study revealed that Selenium, with its antioxidant properties, can be used as a neuroprotective agent by reducing BPH-A-induced oxidative stress.

Keywords: Bisphenol A, Selenium, SH-SY5Y cells, Apoptosis, Oxidative stress, Caspase activity.

Introduction

Bisphenol A (BPH-A) is an organic synthetic estrogen with the formula $(CH_3)_2C(C_6H_4OH)_2$ in phenol structure, which was first used to make commercial epoxy resins. Nowadays, BPH-A is used in many consumer products, including plastics, windows, food packaging, dental sealants, and thermal plugs due to its clear, tough, and flame resistance(Cig et al., 2020).

Many of us are unconsciously exposed to BPA chemical compound by skin-to-skin contact with food containers and inhaling household dust (Rochester, 2013). BHP-A exposure of packaged food consumers will increase, especially because of the use of BPH-A in the containers where packaged food is placed, and the food left in these containers for a long time (Makris et al., 2013). Despite these health hazards, it is possible to say that it is one of the most produced chemicals all the world over (Vandenberg et al., 2007). Moreover, studies based on how BPH-a affects the molecular mechanisms in cells have indicated that even very low concentrations of BPH-A can stimulate cells. (Murata et al., 2018). In the researches, it has been concluded that living beings cause damage to the endocrine gland functions after being exposed to BPH-A. In addition to this effect, they also concluded that BPH-A exposure can cause many health problems such as cardiovascular diseases, diabetes, thyroid dysfunction, obesity, and reproductive disorders (Ma et al., 2019; Peretz et al., 2014).

It may encounter many studies stating that BPA exposure causes a rise in oxidative stress (OS) and mitochondrial dysfunction, especially in cells (Huang et al., 2020; Murata et al., 2018). Therefore, it would be interesting to explore the relationship between BPH-A and OS in detail. OS is an imbalance between free radicals and reactive metabolic products called oxidants or reactive oxygen species (ROS) and molecules called antioxidants. This oxidant/antioxidant imbalance causes a harmful effect on the living organism (Reuter et al., 2010). For these reasons, ROS, which is a metabolic product in the cell, plays a considerable role in the continuation of the vital activities of the cells. The ROS level is maintained and kept in balance by many mechanisms within the cell (Gassman, 2017). However, exposure to BPH-A disrupts this balance and damages the cell by increasing the amount of intracellular ROS. Thus, antioxidant substances can be used to restore the oxidant/antioxidant balance (Cig et al., 2020). In one study, it was stated that BPH-A induces OS, furthermore, this study showed results related to tau-related proteins in the plasma and brain of rats due to excessive ROS increase (Kobayashi et al., 2020). An epidemiological study was emphasized that long-term exposure to BPH-A may trigger reproductive, developmental, and metabolic diseases by causing OS (Rochester, 2013). The common opinion in these studies is that BPH-A administration causes a decrease in ROS clearance capacity in plasma, which shows that BPH-A reduces its antioxidative capacity.

Selenium (Se) is an essential trace element for mammals, discovered in 1817 (Mistry et al., 2012). Se exists in nature in two forms, inorganic and organic, inorganic forms are Na-selenite and selenate. In general, its organic forms are selenocysteine, selenomethionine and Se-methylselenocristeine. Se molecules treat as a cofactor of particular enzymes (Naziroglu et al., 2012; Pillai et al., 2014). In recent years, selenium has attracted great interest due to its antioxidant properties, strong bioactivities and its role in preventing various diseases. Although selenium is known for its toxic effects, studies have emphasized that selenium can clear intracellular ROS thanks to its antioxidant properties (Naziroglu et al., 2020).

In this study, we investigated the protective effect of Se on cellular damage which is leaded by BPH-A in SH-SY5Y cells. Our results showed that Se prevents cellular damage by balancing the intracellular ROS level with its antioxidant properties.

Material and Method

Reagents

Selenium (Sodium-selenite (Na-Se)), Bisphenol-A

(BPH-A), dimethyl sulfoxide (DMSO), L-glutamine, penicillin/streptomycin, Trypsin-EDTA and 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide dye was purchased from commercial firms.

Cell culture

The neuroblastoma cell line SH-SY5Y (ATCC®, Germany) was grown in equal amount DMEM and Ham's F-12 with 10% FBS and 1% penicillin/streptomycin were inset to medium mixture. The SH-SY5Y cells were incubated at 37℃, 5% CO_2 (NB203QS, Korea). SH-SY5Y cells were divided into 4 groups, 1- Control group: No drug was applied to these cells. 2- BPH-A group: Bisphenol A was incubated with 100 µM for 24 hours (Guzel et al., 2020). 3- BPH-A+Na-Se group: This group was incubated with BPH-A for 24 hours. Na-Se (1 µM) added in the last 2 hours of the 24 hours. 4- Na-Se group: Na-Se was incubated with 1 µM for 2 hours (Sakalli Cetin et al., 2017).

Assay of intracellular ROS and mitochondrial membrane potential in the SH-SY5Y cells

The SH-SY5Y cells were stained with DHR-123, a non-fluorescent probe for intracellular ROS assay. The cells were used JC-1, a cationic fluorescent dye for mitochondrial membrane potential assay. The all analyzes were performed using a microplate plate reader (Infinite pro200, Austria) (Cig et al., 2020). The mean values were presented as fold increase (experimental/control)

Assay of Casp-3 and Casp-9 enzyme activity in the SH-SY5Y cells

Casp-3 (AC-DEVD-AMC) and Casp-9 (AC-LEHD-AMC) enzyme activities were determined in the SH-SY5Y cells using a microplate plate reader (Infinite pro200, Austria) (Cig et al., 2020). The mean values were presented as fold increase (experiment/control)

Assay of IL-1β and TNF-α level in the SH-SY5Y cells

The supernatants from the cell's lysates were gathered by the centrifugation. The levels of IL-1β (Cat#:201-LB-025) and TNF-α (Cat#:210-TA-100) were examined in the automatic microplate plate reader (Infinite pro200, Austria) using the commercial ELISA assay kit, taking into account the instructions of manufacturer. The average values were presented as fold increase (experimental/control)

Assay of apoptosis and cell viability in the SH-SY5Y cells

The SH-SY5Y cells were incubated with the grown medium. Cell viability was resoved by using MTT ((Sigma-Aldrich®, Turkey) assay. The apoptosis assay was applied by means of a commercial kit (Biocolor Ltd., Northern Ireland). The assays were performed as to the instructions of manufacturer as described in previous studies (Yildizhan et al., 2020). The all analyzes were performed using a microplate plate reader (Infinite pro200, Austria). The mean values were presented as fold increase (experiment/control)

Statistical analysis

Prism 7.0 (GraphPad, USA) was used to perform the data analysis. All data are shown as means ± SD. Student's t-test was implemented for two-group comparison, and one-way ANOVA was applied for multiple-group comparison.

Results

Na-Se treatment decreased BPH-A-caused ROS and JC-1 in the SH-SY5Y cells

There are studies emphasizing that BHP-a affects membrane depolarization and increases the level of intracellular ROS in cells (Cig et al., 2020). Intracellular ROS occurs as a product in the mitochondrial respiratory chain and becomes toxic metabolic if excessively increased inside the cell. In addition, ROS is also involved in many physiological events, including cell survival and cell death. The study results showed that BPH-A-treated group was significantly higher than the Control and BPH-A+Na-Se groups ($p<0.01$; Figure 1a). There was no statistically significant difference between the control group and the BPH-A+Na-Se group ($p>0.01$; Figure 1a). When the BPH-A administered group was compared with the control and BPH-A+Na-Se groups, it was observed that the JC-1 level increased significantly in BPH-A group ($p<0.01$; Figure 1b).

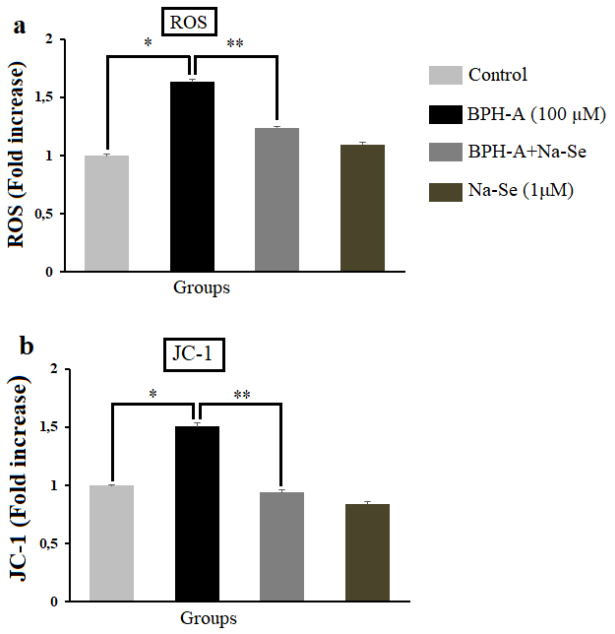

Figure 1. The modulator action of sodium selenite (Na-Se) on Bisphenol-A (BPH-A)-induced increase of ROS and JC-1 in the SH-SY5Y cells*. (Mean ± standard deviation and n=9) (*p<0.01 compared with Cont, **p<0.01 compared with BPH-A).*

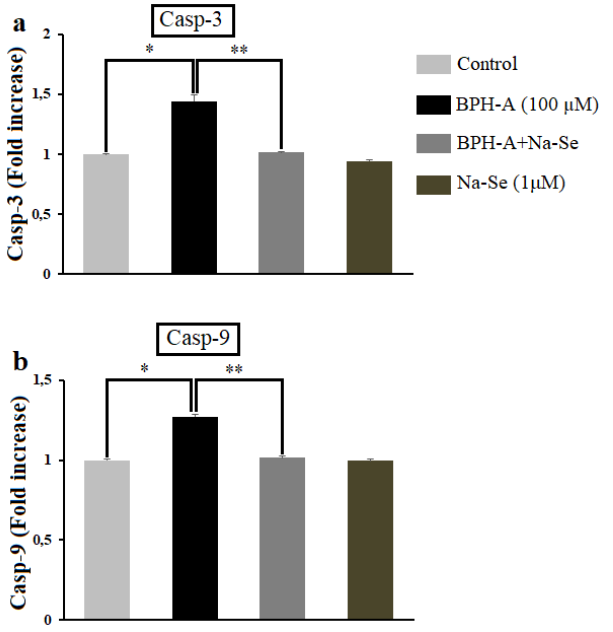

Figure 2. The protective effects of sodium selenite (Na-Se) on the Bisphenol-A (BPH-A)-induced increase of Casp-3 and Casp-9 level in the SH-SY5Y cells. *(Mean ± standard deviation and n=9) (*p<0.01 compared with Cont group, **p<0.01 compared with BPH-A group).*

Na-Se treatment decreased BPH-A-caused Casp-3 and Casp-9 enzyme activity in the SH-SY5Y cells

Casp-3 and Casp-9 are enzymes that have a crucial role in the apoptosis mechanism in mammalian cells. Casp-9 initiator and Casp-3 effector are described as caspase enzymes. It activates pro-Casp-3 with the proteolytic activity of Casp-9 enzyme. Pro-Casp-3 also activates Casp-3 (Cig et al., 2020). The study results demonstrated that when the BPH-A group was contrasted to the control and BPH-A+Na-Se groups, Casp-3 and Casp-9 enzyme activity significantly enhanced in BPH-A group ($p<0.01$; Figure 2).

Na-Se treatment decreased BPH-A-caused IL-1β and TNF-α level in the SH-SY5Y cells

IL-1β and TNF-α are the most substantial proinflammatory cytokines which have potent proinflammatory activities. They promote the secretion of many proinflammatory mediators. In addition, they have an important role in many physiological events in cells, especially apoptosis (Y. Wang et al., 2020). The study results showed that when the BPH-A-treated group was compared to the control and BPH-A+Na-Se groups, significantly increased IL-1β levels were observed between the groups ($p<0.01$; Figure 3a). When the BPH-A administered group was compared with the control and BPH-A+Na-Se groups, it was observed that the TNF-α level increased significantly in BPH-A group ($p<0.01$; Figure 3b).

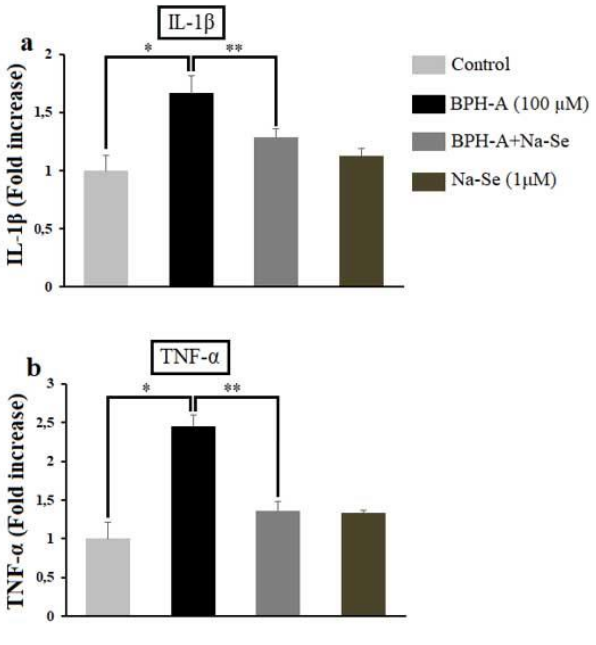

Figure 3. The modulator action of sodium selenite (Na-Se) on Bisphenol-A (BPH-A)-mediated increase of IL-1β and TNF-α level in the SH-SY5Y cells*. (Mean ± standard deviation and n=9) (*p<0.01 compared with Cont. **p<0.01 compared with BPH-A group).*

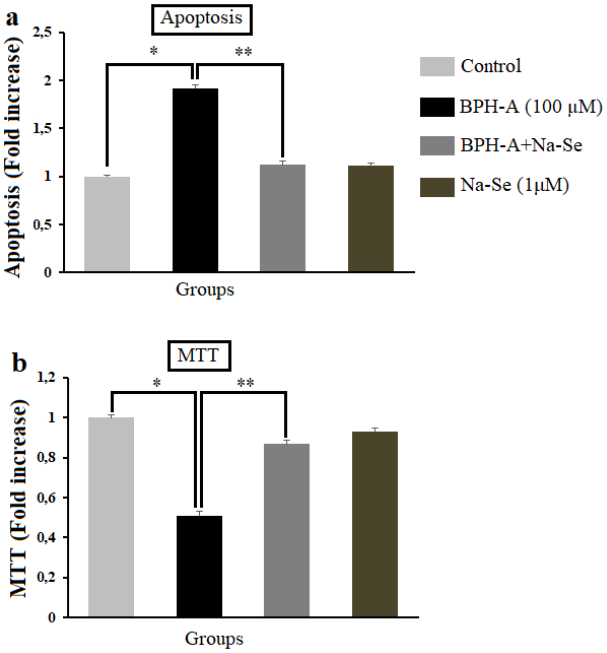

Figure 4. The modulator action of sodium selenite (Na-Se) on the Bisphenol-A (BPH-A)-induced changes of apoptosis and cell viability (MTT) in the SH-SY5Y cells*. (Mean ± standard deviation and n=9) (*p<0.01 compared with Cont group. **p<0.01 compared with BPH-A group).*

Na-Se treatment decreased BPH-A-caused apoptosis, but increased cell viability in the SH-SY5Y cells

Our study results demonstrated that the level of apoptosis was significantly increased when the BPH-A-treated group was compared with the control and BPH-A+Na-Se groups ($p<0.01$; Figure 4a). However, when the BPH-A treated group was compared with the control and BPH-A+Na-Se groups, it was observed that the MTT ratio decreased significantly in the BPH-A group ($p<0.01$; Figure 4b).

These results showed that against BPH-A exposure, which increased intracellular ROS, mitochondrial depolarization, caspase activity and proinflammatory cytokine in cells, a protective effect of Na-Se was observed.

Discussion

In the modern world, it has become impossible not to be exposed to BPH-A chemical. Because BPH-A is used everywhere in bill receipts, water bottles and canned food (Cig et al., 2020). Another important point here is that we can be exposed to BPH-A not only by mouth, but also by inhalation and skin contact (Macczak et al., 2017). Studies on BPH-A have shown that it has many harms, including possible carcinogenic effects (Cimmino et al., 2020; Rochester, 2013). The most important damage mechanism of BPH-A in cellular structures is oxidative stress as a consequence of increased intracellular ROS level (Guzel et al., 2020). ROS, a metabolic product, is formed in the process of cells' survival. The ROS level in the cell is constantly tried to be kept in balance by antioxidant mechanisms. As a result of the disruption of this balance, oxidative stress occurs in the cells (Macczak et al., 2017).

In current study, we investigated the protective impact of Se on cellular damage caused by BPH-A in SH-SY5Y cells. Our study results showed that the level of ROS in neuroblastoma cells ascended significantly after BHP-A exposure (Figure 1a). The level of JC-1 used in

one determination of mitochondria depolarization increased after BHP-A exposure (Figure 1b). Casp-3 and Casp-9 levels, which are among the most important parameters of intracellular apoptotic pathways, were highest in BPH-A group compared to other groups (Figure 2). The levels of proinflammatory IL-1β and TNF-α also increased statistically significantly after exposure to BPH-A (Figure 3). As a natural consequence of these results, the highest level of apoptosis in neuroblastoma cells was observed in the BPH-A group among the study groups (Figure 4a). With Se treatment significant decrease in ROS, JC-1, Casp-3 and Casp-9 activity, IL-1β and TNF-α levels were observed in the cells compared to the BPH-A group. An increase in cell viability was observed (Figure 1-4).

Today, it will be seen that studies on BPH-A damage gain popularity in the literature review. Thus, many institutions and organizations are now looking for ways to reduce the damage caused by BPH-A. In a recent study, it was stated that NO, Caspaze-8 and cytotoxicity increased in the neuroblastoma cell line after low-dose BPH-A exposure (Ayazgok et al., 2018). Guzel et al., conducted that there was an increase in intracellular Ca^{2+} ion, apoptosis, and mitochondrial oxidative stress in MCF-7 cells after exposure to BPH-A. In another study, it was stated that the use of Na-Se reduced cellular damage caused by BPH-A exposure (Guzel et al., 2020).

In an in vitro study in mouse kidney cortical collecting duct cells, it was noted that the increase in ROS, JC-1 and caspase activity after BPH-A exposure decreased after resveratrol treatment (Cig et al., 2020). In a study by Jang et al., it was determined that exposure to BPH-A and formulations increased cytotoxicity in human B cells. In experiments conducted by Jang et al., exposure to BPH-A and its formulations was determined to increase cytotoxicity in human B cells. Xiong et al. emphasized that low-Dose BPH-A activates NF-KB/IL-6 signalling pathways by increasing its malignancy in neuroblastoma cells. However, in vivo studies have shown that exposure to BPH-A causes damage in many tissues by the reason of oxidative stress (Xiong et al., 2017). However, in vivo studies have demonstrated that exposure to BPH-A causes damage in many tissues due to oxidative stress (Hassan et al., 2012; Ullah et al., 2019). The results of this study concluded that oxidative stress is the most substantial factor in the damage mechanism caused by BPH-A. Although our study results support the literature studies, the use of selenium has been very important in reducing the damage caused by BPH-A.

Se is an essential trace element necessary for human health. Se, in the form of selenoproteins, is essential for normal health and metabolism to perform various functions. On the other hand, Se shows a prominent antioxidant activity, especially in protection against GSHPx, ROS and NOS (Naziroglu et al., 2020). Khalaf et al. investigated that the protective effect of Se on reproductive toxicity created with BPH-A in male rats in their study. The results showed that Se had directly a positive effect on lipid peroxidation, DNA damage and apoptotic factors caused by BPH-A-induced OS (Khalaf et al., 2019). In another study, it was emphasized that selenium has a healing effect against the damage in the liver tissue caused by BPH-A-induced oxidative stress in rats (Amraoui et al., 2018). Although most studies of BPH-A related damage are reproductive, recent studies have also shown that BPH-A can trigger neurodegeneration. In a study conducted in human embryonic stem cells, it was found that BPH-A caused neurodegeneration by disrupting the intracellular Ca^{2+} balance, especially in neurons. The point emphasized in this study was that BPH-A, especially by activating the NMDA receptor, increased the amount of intracellular Ca^{2+}, and as a result, the intracellular ROS level increased, causing neurons to enter apoptosis (H. Wang et al., 2019). In a study investigating the effect of BPH-A on the hippocampus of the rat brain. It has been emphasized that chronic prenatal and postnatal exposure of BPH-A causes adverse effects on the progress of the hippocampus region of the rat brain. For this reason, it has been recommended to avoid BPH-A exposure in early neurodevelopmental stages and adults (Tiwari et al., 2015). When the literature studies are examined, it is generally accepted that the most significant factor in the damage caused by BPH-A exposure is the OS in the living thing (Kobayashi et al., 2020).

In conclusion, we investigated the protective role of selenium against BPH-A induced oxidative stress, cytokine production and apoptosis in SH-SY5Y neuroblastoma cells. As a result, we have seen that Se can be used as a neuroprotective agent by reducing BPH-A-induced oxidative stress with its antioxidant properties.

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