

Protective Role of Curcumin on Apoptosis Levels in Sodium Azide-Induced Stress Model in SH-SY5Y Cells

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ABSTRACT

Oxidative stress, impairments of cellular ATP production and changes in membrane integrity of mitochondria are components of mitochondrial dysfunction and are cross borders of several neurodegenerative diseases. Sodium azide is a chemical agent targeting mitochondrial oxidative phosphorylation and widely used in experimental stress models and hypoxia in neuronal cells. Therefore, in this study it was aimed to investigate the possible role of curcumin on changes in molecular pathways in SH-SY5Y cells induced by SA by using different biochemical methods.

SA-gene interactions analyses were done with The Comparative Toxicogenomics Database. Pathway analysis was studied with Enrichr. Dose determination of SA was done with MTT cell viability assay and after that apoptosis, mitochondrial membrane depolarization and intracellular reactive oxygen species production assays were performed in study groups.

In this study, it has been shown that the SA model of mitochondrial stress can be decreased by curcumin treatment. Curcumin administration reverses cell death and decrease mitochondrial depolarization levels. However, it seems that curcumin may also be insufficient to decrease intracellular reactive oxygen species production. Thus, combined therapeutic approaches enhancing mitochondrial antioxidative capacity are thought to elucidate potential role of curcumin on SA-induced stress model in SH-SY5Y neuronal cells.

Keywords: Sodium azide, Curcumin, Mitochondria, SH-SY5Y cells

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INTRODUCTION

Except producing cellular energy molecule (ATP) via oxidative phosphorylation, mitochondria perform fundamental functions such as maintaining cellular redox balance, regulating intracellular calcium signaling, and controlling programmed cell death mechanisms. Neuronal cells, which have high energy requirements, are particularly affected by disruptions in mitochondrial function. Disruption of the electron transport chain can lead to decreased ATP production, increased intracellular reactive oxygen species (ROS) production, and impaired mitochondrial membrane integrity caused to mitochondrial dysfunction. If these changes become persistent, they can overwhelm the capacity of intracellular antioxidant defense systems, resulting in the activation of mitochondria-mediated apoptotic pathways. Therefore, mitochondrial dysfunction is considered a key pathophysiological mechanism in various neurodegenerative diseases, including Parkinson's and Alzheimer's diseases [1,2]. The SH-SY5Y neuronal cell line, derived from human neuroblastoma, is a widely used *in vitro* model for neurodegenerative diseases, neurotoxicity and neuroprotection studies due to its ability to acquire neuron-like characteristics, show sensitivity to chemicals that cause oxidative stress or mitochondrial impairment [3]. Sodium azide (NaN_3 , SA) inhibits mitochondrial cytochrome c oxidase, also known as complex IV, the terminal enzyme of the electron transport chain [4]. Suppression of complex IV activity limits the transfer of electrons to molecular oxygen (O_2), leading to decreased oxygen consumption, increases hypoxia and because of limited oxidative phosphorylation resulted in decrease of ATP production. The close relationship between mitochondrial dysfunction, oxidative stress, and cell death has increased research into the potential neuroprotective effects of naturally occurring compounds. Curcumin, a polyphenolic compound obtained from the rhizome of *Curcuma longa* L., stands out for its antioxidant, anti-inflammatory, and regulatory properties of cellular stress responses [5]. In addition to its direct free radical scavenging effect, curcumin is reported to support endogenous antioxidant defense mechanisms such as Nrf2/HO-1, regulate glutathione homeostasis, and limit mitochondrial membrane damage due to oxidative stress [6,7]. It is also stated that curcumin can exert regulatory effects on mitochondria-mediated apoptotic processes such as Bax/Bcl-2 balance, cytochrome c release, and caspase activation [6]. These properties make curcumin a potential protective compound that may be investigated against cellular damage caused by mitochondrial toxins in neuronal cells. Hence, in this study, the aim was to perform a

cellular stress model associated with mitochondrial dysfunction in SH-SY5Y cells by applying SA and to investigate the possible protective effects of curcumin administration against SA-induced cellular stress and apoptotic damage using different biochemical tests.

METHODS

Cell Culture and Study Groups

The SH-SY5Y cells were cultured with DMEM/F12 basal medium containing 10% FBS and 1% Penicillin-Streptomycin at 37 °C in a 5% CO_2 humidified incubator (Heal Force HF90, Smart Cell, Japan). 7-13 number of passages of the cells included for the experiments. In this study, there was not any differentiation protocol, only naïve SH-SY5Y neuronal cells were used for all experiments. To investigate the time- and dose-dependent effects of SA on SH-SY5Y cell viability, cells were seeded into 96-well plates (~10,000 cells/well) and incubated for 24h under culture conditions to allow them to adhere to the bottom of the wells. And study groups formed as given below following dose determination of SA with MTT test;

Group I was the Control group, and SH-SY5Y cells were incubated with growth medium at standard culture conditions (37 °C and 5% CO_2) for 24h.

Group II was the Curcumin group (Cur), and SH-SY5Y cells were incubated with 10 μM Curcumin for 24h [8].

Group III was the SA group, and SH-SY5Y cells were incubated with 5 mM SA for 24h [9,10].

Group IV was the Cur+SA group, and SHSY5Y cells were pre-incubated with 10 μM Curcumin for 24h, followed by another incubation with 5 mM SA for 24h.

Chemical-Gene Interactions

To get chemical-gene interactions of SA molecule, curcumin and their related genes, The Comparative Toxicogenomics Database (<https://ctdbase.org/>) was used [11]. After the CTD query, the top ten genes interacted with SA from previous published literature were given in a bar graph in Figure 1. For pathway analysis, the gene set enrichment analyses were done with The Enrichr web tool (<https://maayanlab.cloud/Enrichr/>) and with top ten or fifteen interacted genes of SA and curcumin, respectively and target pathways were shown in **Figure 1** [12].

Cell Viability Test

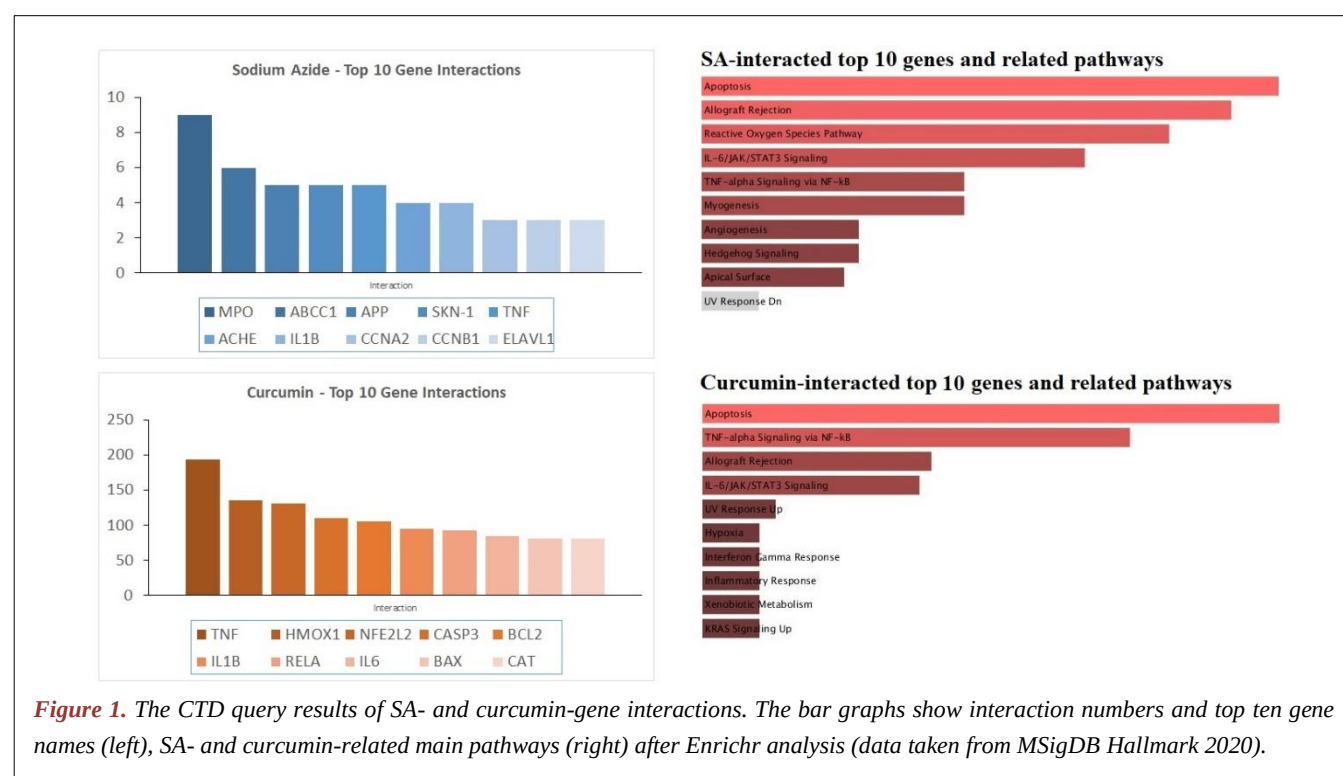
Control (SA-free medium) and 9 different doses of SA at mM concentrations (0.25, 0.5, 1, 2.5, 5, 10, 25, 50, 100) were added to the wells and incubated for 24h. After the period of

incubation, 20 µl of MTT dye (5 mg/ml) was added to each well and incubated for 3-4 hours in incubator. Then, the wells were carefully aspirated, 150 µl of DMSO was added and the plate were gently shaken on an orbital shaker (Biosan, Latvia) at the dark for 5 minutes. Finally, absorbance data were taken at 490 nm and 650 nm wavelengths using a multi-plate reader (Tecan Infinite 200 Pro, Austria). Results were expressed as one-way analysis of variance with experimental/control coefficients. Results expressed as the fold of experimental to control [13].

chloride, 90 mg D-glucose added and pH adjusted to 7.35). Then, cells were incubated with 2 µM DHR-123 dye in a shaker bath at 37 °C for 30 minutes. After incubation, fluorescence intensity of Rh-123 was measured on a microplate reader (Tecan Infinite 200 Pro, Austria). Excitation was set at 488 nm and emission at 543 nm and data expressed as the fold of experimental to control [15].

Mitochondrial Depolarization Assay

To detect mitochondrial membrane depolarization JC-1 was used to exhibit potential-dependent accumulation in



Apoptosis Assay

Apoptotic cell death was assessed using the Cell-APOPercentage™ Apoptosis Assay kit (Biocolor Ltd., United Kingdom) according to the manufacturer's instructions. The dye penetrates the apoptotic cell via disrupting membrane asymmetry. The signal of dye in the apoptotic cells that turned red after the staining process was measured using a microplate reader (Infinite M200 Pro, Tecan, Austria). Results expressed as the fold of experimental to control [14].

ROS Production Assay Results

To detect intracellular ROS production, DHR-123 dye was used. Briefly, after detaching each study group of cells with 0.25% trypsin-EDTA, cell suspension centrifuged 125 g for 5 min and supernatant was discarded, the cell pellet was suspended in calcium buffer (50 ml HEPES, 50 µl calcium

mitochondria. After detaching each study group of cells with 0.25% trypsin-EDTA, cell suspension centrifuged 125 g for 5 min and supernatant was discarded, the cell pellet was suspended in calcium buffer. Then, cells were incubated with 1 µM JC-1 dye in a shaker bath at 37 °C for 30 minutes. After incubation, green JC-1 signal was measured at an excitation wavelength of 485 nm and an emission wavelength of 535 nm on a microplate reader (Tecan Infinite 200 Pro, Austria), and the red signal was measured at an excitation wavelength of 540 nm and an emission wavelength of 590 nm. Obtained fluorescent values proportioned red to green (590/535), and data expressed as the fold of experimental to control [16].

Statistical Analyses

After calculation of the data obtained from cell samples of study groups, OD values were used for the statistical analysis.

The one-way analysis of variance (ANOVA) test used for the statistics analyses with Tukey's post-hoc test.

assayed with MTT test. SA gradually decreases cell viability in SH-SY5Y cells with a dose dependent manner in a 24h incubation period. At higher concentrations (10 mM, 25 mM and 50 mM), it appears that SA did not significantly change

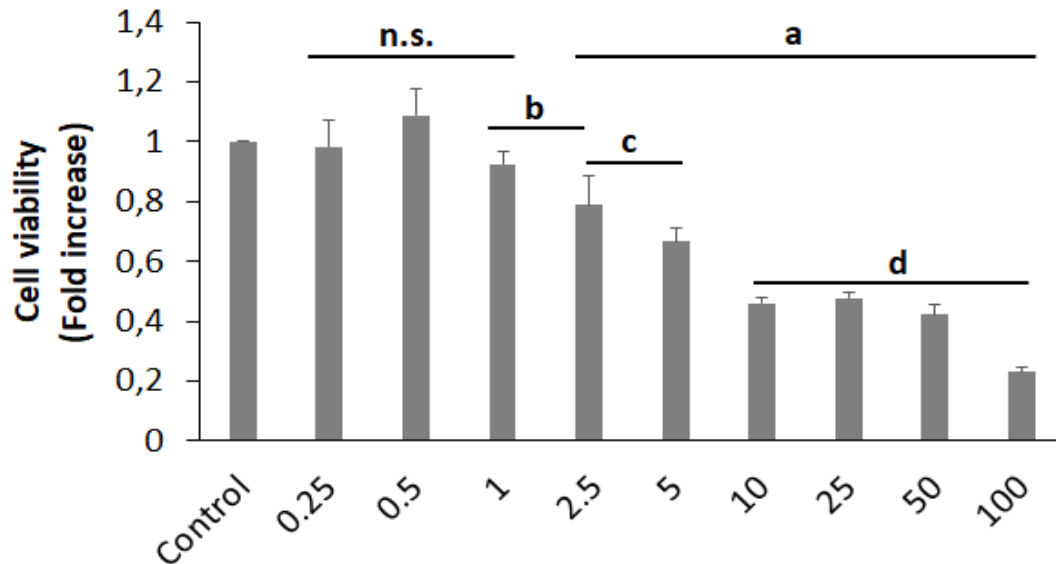


Figure 2. The dose determination results of SA. SA reduces cell viability in SH-SY5Y cells in a dose-dependent manner. (a; $p < 0.0001$ vs Control, b; $p < 0.005$ vs 1 mM, c; $p < 0.05$ vs 2.5 mM, d; $p < 0.0001$ vs 5 mM, mean $\pm$ SD; $n=6$).

RESULTS

Chemical-Gene Interactions

The top SA- and curcumin-interacted genes and their related pathways were given in Figure 1. SA-interacted top 10 genes are listed as MPO, ABCC1, APP, SKN-1, TNF, ACHE, IL1B, CCNA2, CCNB1 and ELAVL1 after CTD query. Because SA is a mitochondrial complex IV inhibitor, when these genes were taken into gene set enrichment analysis, the most common three pathways were found related to 'apoptosis, allograft rejection and reactive oxygen species pathway', respectively. Curcumin-interacted top 10 genes are listed as TNF, HMOX1, NFE2L2, CASP3, BCL2, IL1B, RELA, IL6, BAX and CAT after CTD query. When curcumin-interacted top 10 genes were analysed in Enrichr, the most common three pathways were also found related to 'apoptosis, TNF-alpha signaling and allograft rejection', respectively. Hence, in this study, it was aimed to investigate the possible role of curcumin pre-treatment on apoptosis levels on SA-induced cellular stress model in neuronal cells.

Dose Determination of SA

Effects of different SA concentrations on cell viability levels in SH-SY5Y cells were shown in **Figure 2**. The cells incubated with SA for 24h and then cell viability levels were

cell viability levels among the groups. Hence, 5 mM SA concentration was determined as effective dose to mimic moderate cellular stress in study groups for a 24h incubation.

Apoptosis Test Results

Effects of curcumin on apoptosis levels on SA-induced cellular stress model in SH-SY5Y cells were shown in **Figure 3**. The apoptosis levels were relatively higher in all study groups compared with control group ($p < 0.05$). However, apoptosis levels significantly decreased in Cur+SA group compared to SA group.

ROS Production Assay Results

Effects of curcumin on intracellular ROS production levels on SA-induced cellular stress model in SH-SY5Y cells were shown in **Figure 4**. The intracellular ROS production levels were higher in all study groups compared with control group ($p < 0.05$). Furthermore, intracellular ROS production levels were higher in Cur+SA group compared to SA group. These results indicated that curcumin administration was not sufficient to reduce intracellular ROS production levels in SA-induced stress model.

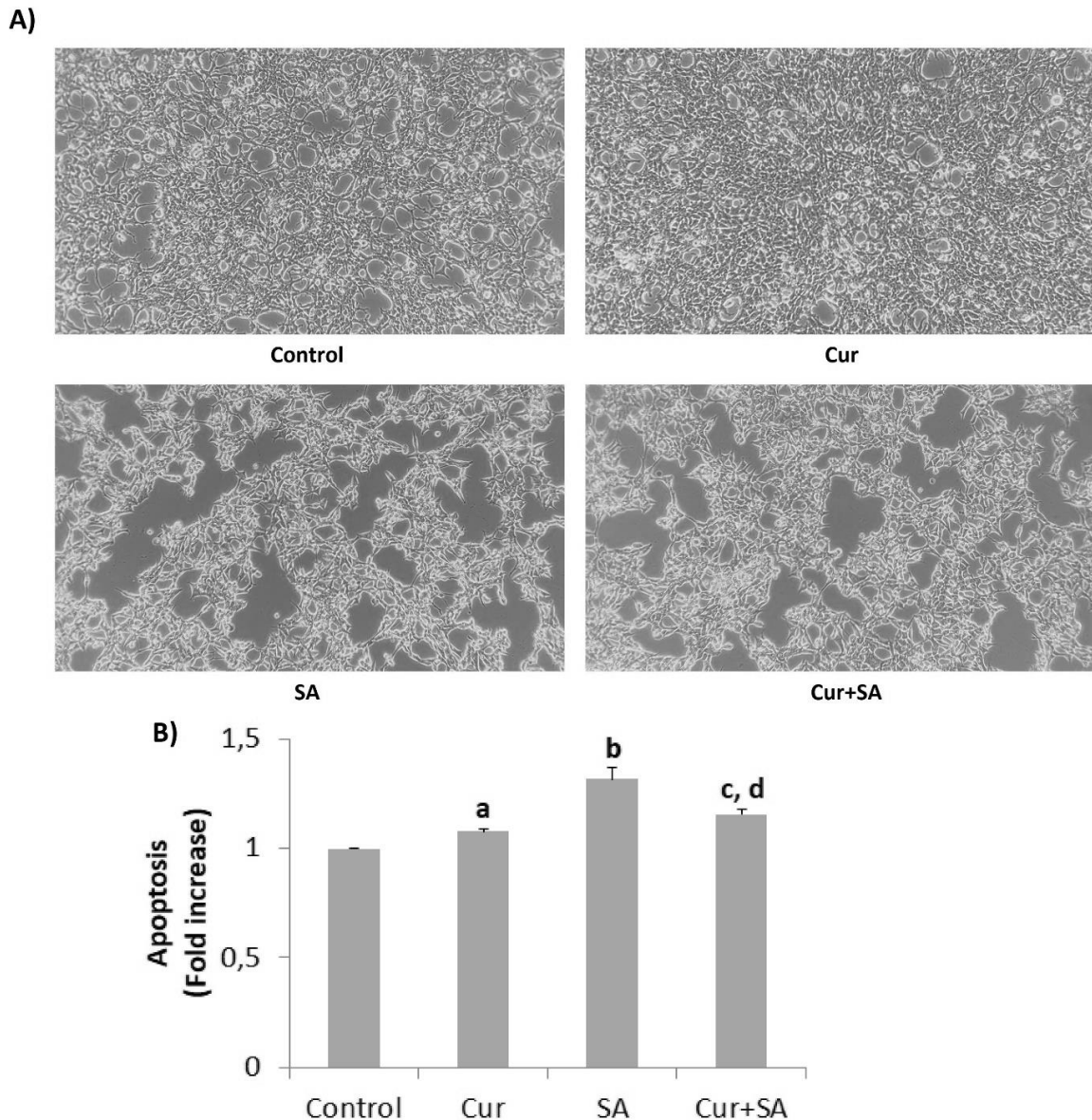


Figure 3. The apoptosis results of study groups. A) Bright-field micrographs of study groups. B) SA increases apoptosis levels in SH-SY5Y cells. (a; $p < 0.05$ vs Control, b; $p < 0.0001$ vs Control, c; $p < 0.005$ vs Control, d; $p < 0.001$ vs SA group, mean $\pm$ SD; $n=3$).

Mitochondrial Depolarization Analyse Results

Effects of curcumin on mitochondrial membrane depolarization levels on SA-induced cellular stress model in SH-SY5Y cells were shown in **Figure 5**. The mitochondrial depolarization levels were higher in SA-induced groups compared with control group ($p < 0.05$). Moreover, mitochondrial depolarization levels were higher in SA compared to Cur+SA group. These results indicated that curcumin administration could be effective to reduce mitochondrial depolarization levels in SA-induced stress model.

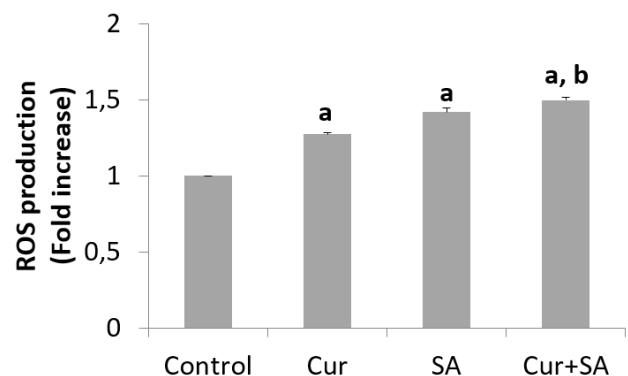


Figure 4. The ROS production assay results of study groups. SA increases ROS production levels in SH-SY5Y cells. (a; $p < 0.0001$ vs Control, b; $p < 0.005$ vs SA group, mean $\pm$ SD; $n=3$).

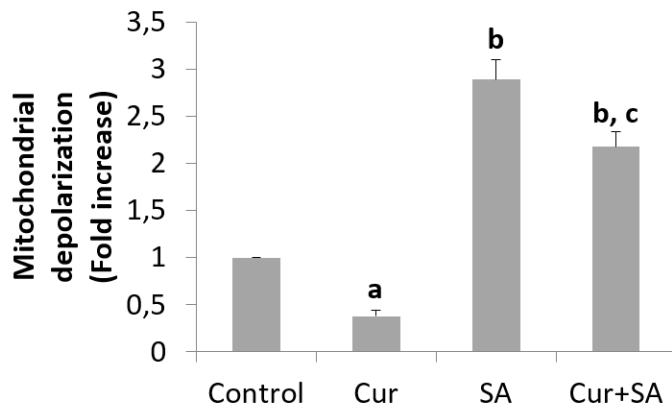


Figure 5. The mitochondrial depolarization assay results of study groups. SA increases mitochondrial depolarization in SH-SY5Y cells. (a; $p < 0.005$ vs Control, b; $p < 0.0001$ vs Control, c; $p < 0.005$ vs SA group, mean $\pm$ SD; $n = 3$).

DISCUSSION

Cellular models aim to study pathophysiological mechanisms and disease models *in vitro* conditions [17]. While mitochondria play a critical role in normal cells under physiological conditions, their dysfunction via toxins or mitochondria-targeting chemicals has been reported to be involved in the molecular mechanisms of various neurodegenerative diseases, too [18]. Oxidative phosphorylation is one of the most important cellular metabolic processes that provides the ATP needs of cells under normal physiological oxygen conditions. Neuronal cells are sensitive to hypoxia and oxidative phosphorylation-targeting toxins due to their higher oxygen consumption needs. Although SA administration is a chain-broken agent for oxidative phosphorylation in mitochondria, it is also accepted as a chemical model of experimental hypoxia, is frequently used in research [9,19,20].

As a strong antioxidant, curcumin is also widely used in experimental studies with SH-SY5Y cells provide direct evidence that curcumin may exhibit protective effects against various toxic stimuli including experimental oxidative stress [21]. In the former records, the approach of applying curcumin before the toxic agent is also based on previous neuroprotection studies carried out in SH-SY5Y cells. In a copper-induced neurotoxicity model, curcumin pre-treatment was reported to reduce intracellular ROS formation/production, limit the loss of mitochondrial membrane potential, and suppress mitochondrial-mediated apoptotic changes [22]. Similarly, curcumin applied before acrylamide exposure has been shown to mitigate cellular damage by reducing oxidative stress markers and the Bax/Bcl-2 ratio [23]. In a recent study, it was also reported that two different concentrations of curcumin (10 μ M and 15 μ M)

applied concomitantly with glutamate increased SH-SY5Y cell viability; in particular, 10 μ M curcumin significantly limited the decrease in total antioxidant capacity and DNA damage [24]. To our knowledge this study is the first to assess the role of curcumin on SA-induced stress parameters in SH-SY5Y neuronal cells. When examining SA-gene interactions, it is seen that it has been evaluated in previous literature studies with 10 different genes. Similarly, when the 15 genes with the most interactions for curcumin were evaluated, pathway analysis showed that both pathways formed by SA and curcumin may be related to apoptosis. It is suggested that while SA triggers apoptosis, curcumin has apoptosis-suppressing effects through the same pathway. To experimentally test this result, we performed cell viability, apoptosis, intracellular ROS production and mitochondrial membrane depolarization assays.

In our study, after dose determination of SA, we decided that to use 5 mM of SA to induce cellular stress conditions in SH-SY5Y neuronal cells and to investigate possible role of curcumin we used 10 μ M curcumin as antioxidant pre-treatment. Our findings on the concentration of SA on the cells were also parallel to former records [25,26]. However, the effects of curcumin may vary depending on the cell type, concentration, and concomitant toxic agent. For example, 10 μ M curcumin reduced cisplatin-induced damage in normal kidney cells while enhancing TRPM2 channel activation, mitochondrial ROS production, and apoptotic cell death in Hep2 laryngeal cancer cells [27]. This cell-type-specific bidirectional effect highlights the importance of including a control group in which curcumin alone was administered in the experimental design. The dose-dependent antioxidant effects of curcumin [28], particularly its increased effectiveness at low doses and the possibility of cancer cell death at high doses [29], have been studied in various cell types. In our study, using a previously used concentration of 10 μ M for SH-SY5Y cells, we found that curcumin itself increased ROS production in intracellular ROS production experiments. Therefore, the effective protective dose for these cells needs to be re-investigated at lower doses. Similarly, the statistically significant difference in ROS production in the Cur+SA group compared to the SA group may be due to the proximity of this dose of curcumin to a possible pro-oxidant effect.

In our study, we have also first observed that curcumin's potential pro-oxidant activity on SH-SY5Y cells with intracellular ROS production analysis results. With its well-known antioxidant properties, we have recorded that curcumin at 10 μ M concentration may also start ROS production in these cells, and it may be a limitation of this study.

Similarly, when looking at the findings obtained from our study, it is seen that curcumin pre-treatment reduces apoptosis on SA-induced stress model in SH-SY5Y neuronal cells as well as mitochondrial depolarization. However, it should also be noted that these depolarization levels are higher than the control level. Although there is a lot of study in the literature about the antioxidative role of curcumin and its powerful antioxidant effects on different cell lines including SH-SY5Y [30-32], in our results curcumin protection for intracellular ROS production was limited.

CONCLUSION

More experimental data related to mitochondrial physiology (i.e. oxygen consumption and ATP production) is needed to elucidate and understand the potential role of curcumin on cellular stress models in mitochondria-originated pathways. Moreover, mitochondria-targeting forms of curcumin or curcumin combinations with mitochondria-specific antioxidants could be an alternative future research [33,34].

Author Contributions

H.B. and A.Ö. designed the hypothesis and performed literature search. H.B. was responsible for the experimental analysis. A.Ö. was responsible for statistics and graphical design. H.B. contributed to writing the manuscript and A.Ö. edited and supervised the final form. All authors critically reviewed, revised, and approved the final version of the manuscript.

Disclosure

The authors have reported no conflicts of interest in preparing and publishing this article.

Data Availability

All data produced for this manuscript is available upon reasonable request.

Ethics Committee Approval

The study is not subject to ethics committee approval.

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Referee Evaluation Process

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