Original Article

# Evaluation of the Neuroprotective Effect of Chalcone on P53 and Caspase III Expression and D2-Like Dopaminergic Receptor Up-Regulation *in vitro* Parkinson's Model

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## Abstract

**Background:** Parkinson's disease (PD) is a progressive neurodegenerative disorder of the central nervous system (CNS). Several studies indicated abnormal cell death in neurodegenerative diseases. Chalcone is a compound of natural origin with various properties such as antioxidant, anti-inflammatory, and inhibition of apoptosis. We investigated the impact of chalcone in an in-vitro model of PD.

**Materials and Methods:** PC12 cells were divided into four groups. Negative control, 6-hydroxy dopamine (6-OHDA) group (treatment with 75µM 6-OHDA), sham (treated with dimethyl sulfoxide), and the experimental groups with different dosages of chalcone treatment. Cell viability and reactive oxygen species (ROS) were assessed by MTT and ROS kit, respectively. The expressions of D2-like receptors, P53, and caspase III were evaluated by Western blotting.

**Results:** We found that 6-OHDA induced cytotoxicity and ROS production. The viability results showed that all doses of chalcone significantly increased viability after 48 hours compared to the control group ($P<0.01$). The western blotting results showed that caspase III and P53 expression decreased significantly in the experimental groups compared to the 6-OHDA group. However, D2-like receptor expression did not significantly differ between the experimental and the 6-OHDA group.

**Conclusion:** Complementary therapies, such as the use of antioxidants and the chalcone family, along with standard treatments for neurodegenerative diseases such as Parkinson's, may reduce the symptoms of the disease.

**Keywords:** Chalcone, Receptors, Dopamine, Apoptosis, Parkinson's Disease

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# Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, occurring worldwide and in all ethnic groups (1). PD is the second most common neurodegenerative disease, with a prevalence of approximately 2% in people over 50 years (1, 2). Pathogenesis of PD includes mitochondrial dysfunction, oxidative stress, and activation of apoptotic pathways, ultimately leading to the destruction of dopaminergic neurons (3-5). Participating factors include aging, environmental, and genetic factors (3, 5, 6). Environmental factors cause reactive oxygen species (ROS) production by three mechanisms: mitochondrial metabolism induction, redox cycle alteration, and oxidative stress (7). Oxidative stress is one of the leading causes of substantia nigra (SN) degeneration (8). Numerous studies have shown the high vulnerability of SN dopaminergic neurons to ROS (8). Generally, the level of dopamine and the number of its receptors within the basal ganglia decreases with age. Acceleration in this rate seems to cause PD (9).

Many therapeutic procedures have been proposed to treat PD (10, 11). Medication can help improve the quality of life and increase the functional capacity of patients with PD (11). They can help improve gait problems, bradykinesia, and tremor through a temporary increase in dopamine activity in the brain (12, 13). Therapeutic plans may need to be changed over time in the patient with PD (14).

Chalcones are a new generation of antioxidants with certain anti-cancer effects (15, 16). They decrease cancer cell proliferation by suppressing gene transcription (17). Over 90 types of chalcone with different anti-cancer properties have been developed over the past decades (18). Apoptosis induction is one of the most important known anti-cancer mechanisms of the chalcones (17). Chalcone anti-tumor therapy has shown positive results in reducing tumor cell proliferation in the skin and breast cancer (19). The most important challenge for chalcones is attributed to their pharmacokinetic properties and metabolic instability, which may be addressed by changes in their structure (20). This study aimed to investigate the neuroprotective effects of chalcone on the PC12 in vitro model of PD.

# Methods

**Cell culture**: PC12 cells were obtained from the cell bank of the Pasteur Institute of Iran. Cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) with 25 mM glucose and 10% fetal bovine serum (FBS), 5% horse serum, and 1% penicillin/streptomycin. The cells were incubated at 5% CO2, 37 °C, and 95% humidity.

**The studied groups:** The following groups were evaluated: (1) the control group; no treatment was performed on the cells, (2) the positive control group; treated with 75 µM 6-OHDA, (3) the sham group; treated with Dimethylsulfoxide (DMSO), and (4) the experimental group; treated with different dosages of chalcone new derivatives after treatment with 6-OHDA. The treatment was performed for 24 and 48 hours.

**MTT assay**: After three cell passages, PC12 cells were cultured at the rate of 1000 cells per well in 96 wells. For each group, 8 wells were considered, and after 24 hours, different dosages were used to obtain the best dosage of 6-HODA. The cell viability was evaluated using MTT. To evaluate the protective effect of chalcone after three passages, the cells were cultured in 96 wells. After culturing and treating with 75 µM 6-OHDA/24 hours, the cells were exposed to 10-20-40-60 µg/ml of chalcone. Then 10-20 µl of MTT solution 0.5 mg/ml were added to the culture wells and incubated for 4 hours at 37 ºC. After discarding the cell medium, 100 µl of DMSO was added to the precipitate, and their optical absorption was checked at 570 nm in an ELISA reader.

**ROS assay**: This test uses a compound called dichloro fluorescence diacetate (DCFH-DA). Cellular ROS Detection Assay Kit (ab113851) quantitatively measures the level of ROS production in PC12 cells using flow cytometry. The cells were collected in tubes, stained with DCFDA for 30 min at 37 ºC (without washing), and analyzed with flow cytometry. Therefore, the amount of fluorescence production can be used as the amount of intracellular free radicals.

**Western blotting:** The sodium dodecyl-sulfate

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polyacrylamide gel electrophoresis (SDS-PAGE) method was used to purify proteins. The proteins were extracted using a buffer, and the samples were run on SDS-PAGE protein gel. After the samples were threshed, an electroplating step was performed, and the protein samples were transferred from the gel to the polyvinylidene fluoride (PVDF) membrane. Finally, the desired protein samples were detected on the PVDF membrane using the Enhanced chemiluminescence (ECL) kit. The ECL kit was used to detect the protein band. All steps were performed in the darkroom. First, primary antibodies of P53 and T2-like and caspase III were added. After this stage, the secondary antibody was conjugated with the primary antibody. The radiology film was processed in the dark and scanned, and the protein bandwidth was read by Lab Total software.

**Statistical analysis:** Results are expressed as mean±standard error. The difference between the mean data in the studied groups was estimated using a one-way ANOVA test followed by the Student Newman-Kelus test. P <0.05 was considered the minimum significant level.

**Ethical publication statement:** All protocols were confirmed by the Ethics Committee of Shahid Beheshti University of Medical Sciences IR.SBMU.RETECH.REC.1400.432).

# Results

**MTT assay:** To find the effective concentration of 6-OHDA on cell death and viability, an MTT assay was performed, and the results showed that 75 µM led to 50% cell death in PC12 cells, which was appropriate to induce Parkinson's cell model (Figure 1).

This assay also showed no cytotoxicity on PC12 cells without any treatment. To determine the effects of chalcone on PC12 cells under normal conditions, PC12 cells were treated with dosages of 10, 20, 40, and 60 µg/ml chalcone for 24 hours. Cell viability results showed that these concentrations had no cytotoxicity effects on PC12 cells (Figure 2).

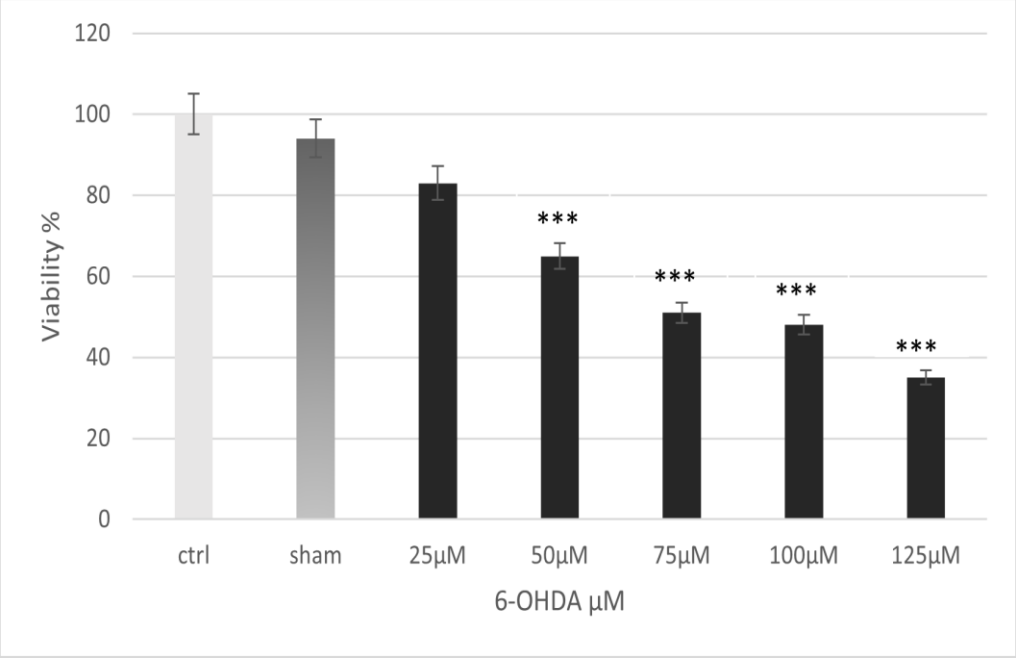


**Figure 1.** MTT assay results. 50 -75 - 100 and 125 µ/mol dosages of 6- Hydroxy dopamine showed a significant toxic effect (***: P<0.001).

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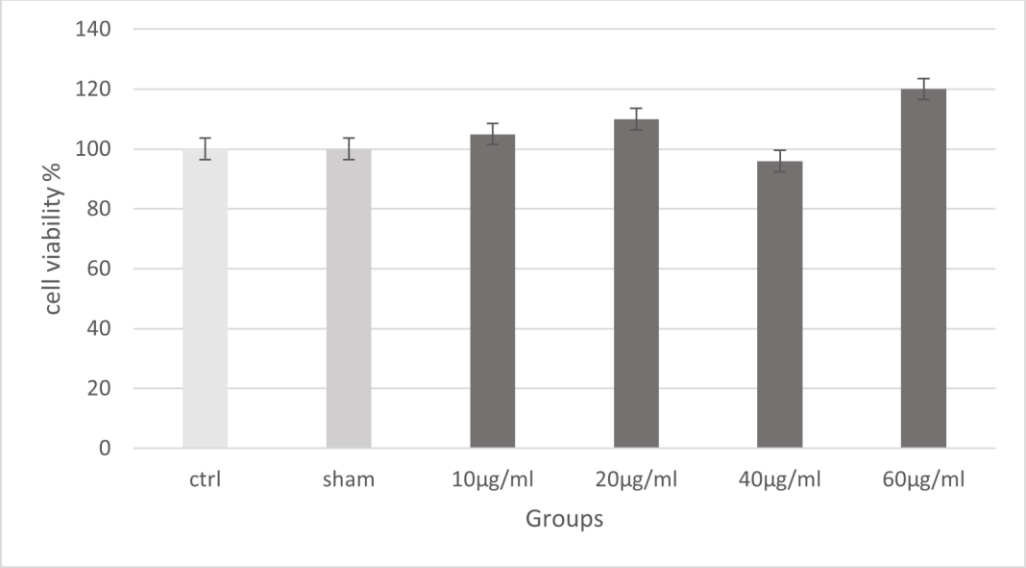


**Figure 2.** Viability of chalcone concentrations (10-20-40-60 µg/ml) on PC12 cells. There was no significant difference between the groups compared to the control group.

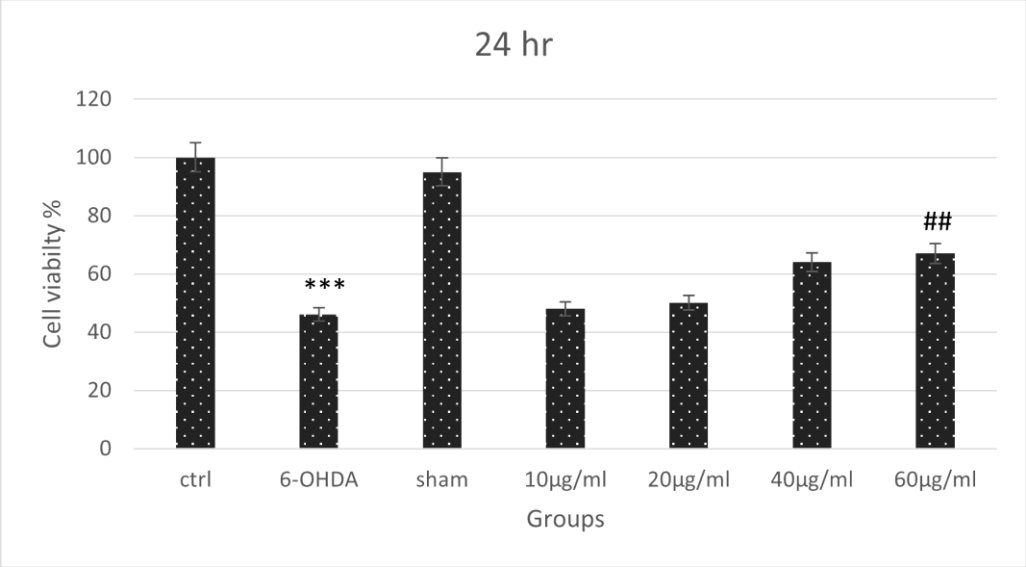


**Figure 3.** The different concentrations of chalcone on the viability of PC12 cells after 6-hydroxy dopamine treatment by MTT assay after 24 hours (***: P<0.001 compared with control). (##: p<0.05 compare with 6-OHDA)

The results of the cell viability after chalcone treatment on the PC12 Parkinson's model are shown in figure 3. The 60 µg/ml concentration significantly increased the viability compared to the 6-OHDA group after 24 hours (P <0.05), while the effects of 10, 20, and 40 µg/ml were not significant (Figure 3).

The viability results of different concentrations of chalcone after 48 hours showed that both dosages of 40 and 60 µg/ml of chalcone significantly prevented the cytotoxicity effect of 6-OHDA, indicating dose-dependent and time-dependent effects of chalcone on PC12 cells (Figure 4).

**ROS Production Results:** The results of the ROS assay showed a significant increase in ROS level in the 6-OHDA group compared to the control group. Treatment of chalcone with 40 and 60µg/ml concentrations significantly decreased ROS levels compared to the 6-OHDA group. This finding showed

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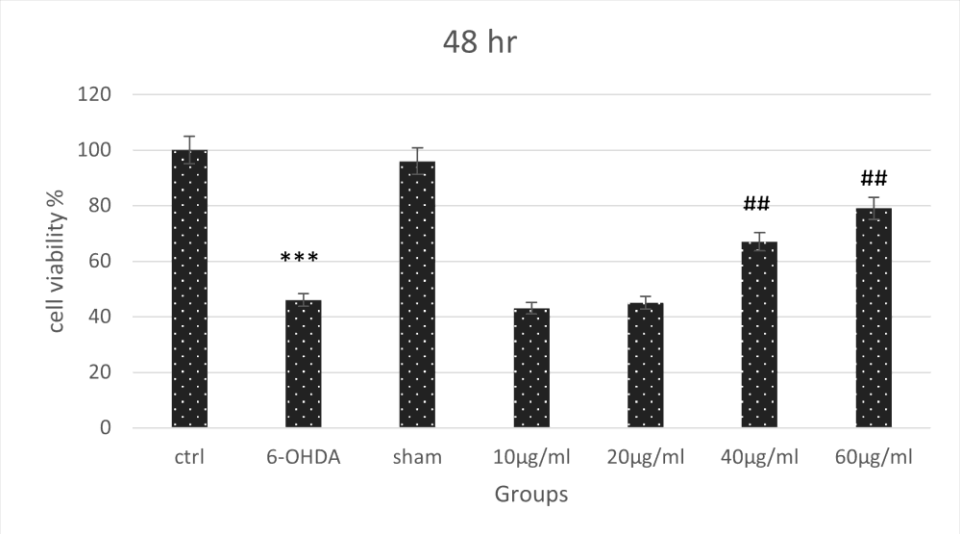


**Figure 4.** The different concentrations of chalcone on the viability of PC12 cells after 6-hydroxy dopamine treatment by MTT assay after 48 hours (***: P<0.001 compared with control). (##: p<0.05 compare with 6-OHDA)

that chalcone could prevent intracellular ROS production following 6-OHDA (Figure 5).

**Western Blotting Results:** Regarding the effectiveness of a 60 µg/ml dosage of chalcone to inhibit ROS production, this dosage was considered to study the expression of the pro-apoptotic proteins. The result of the expression of caspase III protein showed a significant decrease in the 60 µg/ml experimental group compared to the 6-OHDA group (P<0.001). Accordingly, it seems that inhibition expression of caspase III pro-apoptotic protein in PC12 cells Parkinson's model happens following the prevention of ROS production by this concentration of chalcone. (Figure 6)

Western blotting results of D2-like receptor expression showed no significant difference compared to the 6-OHDA group (Figure 7). However, P53 expression was significantly reduced compared to the 6-OHDA group (###:P<0.001). Thus, chalcone inhibited pro-apoptotic proteins but did not affect receptor expression (Figure 8).

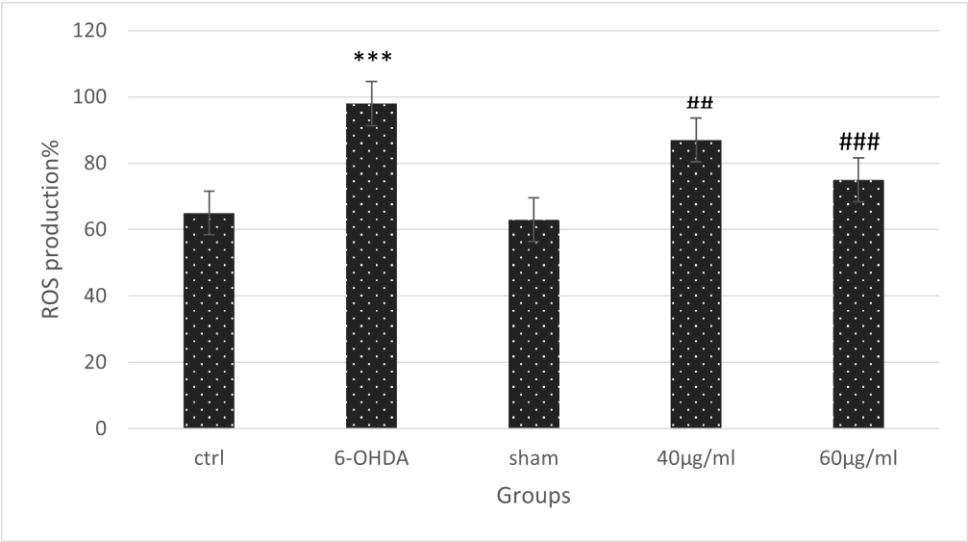


**Figure 5.** Percentage of ROS production of different concentrations (40,60 µg/ml) of chalcone after 48 hours. (***: P<0.001 compared to control and ##: P<0.05 compared to 6-OHDA).

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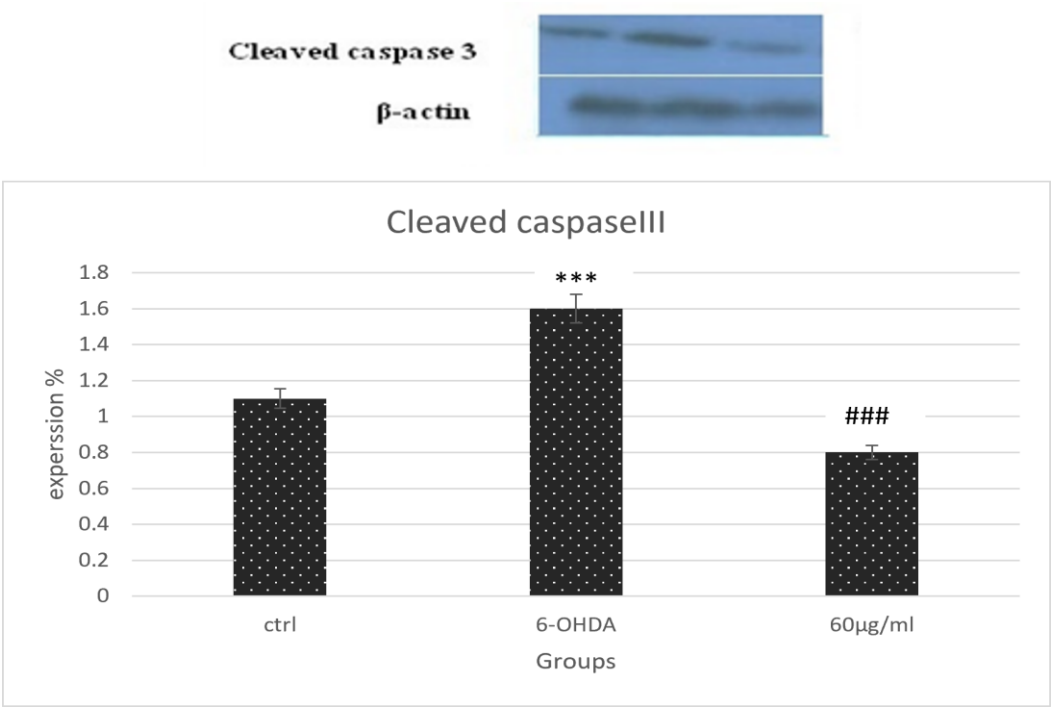


**Figure 6.** Result of Western blotting of caspase III expressions (***: P<0.001 compared to control and ###: P<0.001 compared to 6-OHDA).

## Discussion

PD is the second most common neurodegenerative disease (21). In PD, dopaminergic neurons in SN degenerate with unknown mechanisms (2, 22, 23). The current treatments for most neurodegenerative diseases, including PD, are still not effective (10, 11).

In PD, treatments are conservative, mainly focusing on replacing and restoring the lost dopamine (10, 11). None of these therapies could completely inhibit the progression of the disease (10, 11). Targeting the mechanisms attributed to dopaminergic neuron death in SN could help find more effective treatments. The findings of our study showed that chalcone could decrease the death rate of dopaminergic neurons in an in vitro model of PD.

Oxidative stress is a pathological factor that plays a role in the death of dopaminergic neurons in PD (8). Different studies in patients with PD showed a decrease in the glutathione (GSH)/oxidized glutathione (GSSH) (GSH/GSSH) ratio, an increase in lipid peroxidation, and an increase in DNA oxidation (24-26). Oxidative stress is one of the main causes of apoptosis in PD (8, 26). The major cell death pathway seems to be either caspase III or other pathways leading to caspase III activation (8). Therefore, reducing oxidative stress or preventing caspase III activations can help prevent the progression of the disease (27).

Chalcones, the metabolites belonging to the flavonoid family, have significant antioxidant activity (28). This activity is mainly based on the oxidation and reduction properties of hydroxyl, phenolic, and other structural bonds between different parts of their chemical structure (28-30).

The antioxidant property of chalcone is meaningly higher than vitamins E and C (31). With its anti-apoptotic properties, chalcone reduces the activity of caspase III and BCL2-associated X protein (Bax) (28). It increases the activity of the anti-apoptotic protein B-cell lymphoma 2 (Bcl2) (28).

In addition, it has been shown that chalcone could increase the expression of glutathione-related enzymes at the transcriptional level (32). Chalcone has also been shown to have a strong regulatory effect on young erythrocytes' superoxide dismutase (SOD) enzyme following oxidative stress (28).

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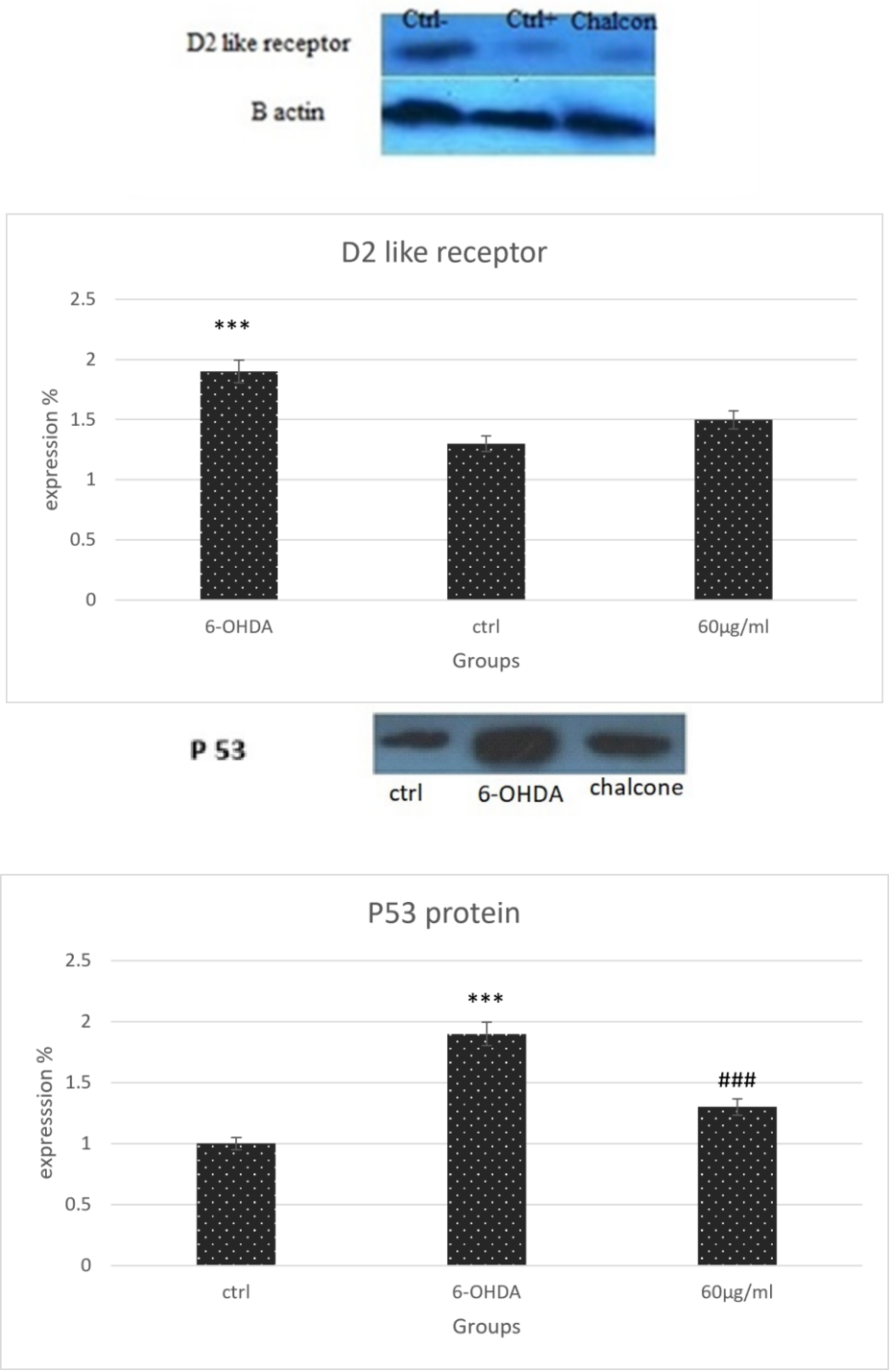


**Figure 7.** Western blotting results of D2-like receptor expression did not show a significant difference compared to the negative control group. However, P53 expression was significantly reduced compared to the positive control group. Thus, chalcone inhibited pro-apoptotic proteins but did not affect receptor expression (***: P<0.001).

6-OHDA and other neurotoxins induce dopaminergic neuron death through the activation of apoptosis signal-regulating kinase 1 (ASK1) (33). There are reports of the efficacy of herbal compounds, including chalcones, in preventing inflammatory responses (34, 35). Chalcone polyphenolic compounds have also been shown to inhibit mRNA expression of inflammatory cytokines such as interleukin (IL)-1B

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and tumor necrosis factor (TNF) (34-36). A similar inflammatory process can occur in human cell lines (36). Lee et al. reported that lutein, a plant flavonoid, inhibits Jun N-terminal kinase (JNK), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), phosphatidylinositol-3 kinase (PI3K), mitogen-activated protein kinase (MEK), and Ak strain transforming (Akt) (37). One of the possible mechanisms of the effect of chalcones in decreasing the toxic effect of 6-OHDA is probably through the inhibition of neuronal inflammation (18).

Our study showed that 6-OHDA increased ROS production, P53, and caspase III activation, which were deceased following chalcone treatment.

Transcription factor P53 is a protein that increases in the brain after exposure to various neurotoxins and can regulate the transcription of genes involved in apoptosis (38). In the cell cycle, following DNA damage, this factor arrests the cell cycle and induces apoptosis (38). Studies have shown that P53 activates caspase III. Several post-translational changes occur among the members of the Bcl2 family that alter their function (39). For example, Bc12 phosphorylation inhibits its ability to prevent apoptosis. Bcl2 dephosphorylation, on the other hand, enhances its function (39). The same event also happens for P53 (40). Following activation, the P53 protein induces extensive cellular responses, leading to cell cycle arrest and apoptosis (40). Treatment with 6-OHDA leads to the phosphorylation of p53 in Serine 15, which induces DNA damage (41). Western blot analysis has demonstrated a significant increase in phosphorylated p53 levels after exposure to 6-OHDA (42). Our results showed that chalcone could reduce the level of P53 activation, resulting in reduced neuronal apoptosis.

## Conclusion

Chalcone could play an important role in reducing the death of dopaminergic neurons following 6-OHDA toxicity. Chalcone compounds reduced 6-OHDA-induced degradation by reducing ROS production, P53, and caspase III activations. Accordingly, chalcone can be considered an effective agent for reducing neuronal damage caused by mechanisms leading to PD. Prospective clinical studies are necessary to determine the safety and efficacy of chalcone derivatives in patients with PD.

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## Conflicts of Interest

The authors declare that they have no conflict of interest.

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