Journal of Clinical and Medical Research

ISSN: 2582-4333
Nagashima D, et al., 2022- J Clin Med Res
Research Article

Effect of Coriander on H_2O_2-induced Oxidative Stress in PC12 Cells

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Abstract

Objective: Coriander (*Coriandrum sativum*), a member of the Apiaceae family of plants, is traditionally used as a spice and medicinal plant which has anti-aging, anti-inflammatory, and anti-anxiety effects and is used for the treatment of diabetes. The present study aimed to investigate the effects of coriander on H2O2-induced neurotoxicity in PC12 cells.

Methods: PC12 cells were cultured in Dulbecco's modified Eagle's medium, and the effects of various treatments were analyzed using cytotoxicity assay, morphological evaluation of neurite outgrowth, and western blotting.

Results: The cytotoxicity assay showed increased levels of LDH in cells treated above 10^{-5} M H_2O_2, however there was no significant change in the coriander administration group. Morphological evaluation showed significantly increased neurite outgrowth in the nerve growth factor (NGF) treatment group after 72 h. Treatment of NGF-stimulated cells with H_2O_2 reversed the effect of NGF on neurite outgrowth, which returned to the levels of the control group. Simultaneous administration of H_2O_2, NGF and 0.1 or 0.01 μg/mL of coriander significantly increased neurite outgrowth after 72 h. Western blot showed that phosphorylated ERK levels were significantly increased in the NGF group compared with H_2O_2+NGF group, and no significant differences were found compared to the H_2O_2+NGF+0.1 μg/mL coriander administration group.

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Received Date: 06-30-2022

Accepted Date: 07-12-2022

Published Date: 07-30-2022

Citation: Nagashima D, Matsubara C, Mizukami N, Nakagawa N, Furukawa M, Toho M, et al. Effect of Coriander on H2O2-induced Oxidative Stress in PC12 Cells. J Clin Med Res. 2022;4(3):1-10.
DOI: https://doi.org/10.37191/Mapsci-2582-4333-4(3)-115

Conclusion: Coriander reversed the reduction in neurite outgrowth following treatment of NGF-stimulated PC12 cells with H_2O_2. This suggests that coriander may help prevent oxidative stress-induced neurodegeneration.

Keywords: Coriander; PC12 cells; H_2O_2; Nerve growth factor; Neurite outgrowth.

Introduction

Coriander (*Coriandrum sativum*), a member of the Apiaceae family of plants, is extensively cultivated in North Africa, Central Europe, and Asia, although it originated in the Mediterranean region. Coriander possesses nutritional and medicinal properties [1]. Traditionally, coriander has been used as a spice and medicinal plant because of its anti-aging, anti-inflammatory, and anxiolytic effects, and for the treatment of diabetes [2-4]. Recent studies have shown that coriander detoxifies food and removes toxic mineral residues. [5]. Furthermore, a study of heavy metal-intoxicated animals showed encouraging results as chelation and of toxicity reduction following treatment with coriander [6]. Moreover, it has been shown to protect nerve cells by suppressing oxidative stress in Alzheimer's disease (AD) animal models [7,8].

AD is a progressive neurodegenerative disorder with core symptoms, including disorientation, memory impairment, and executive dysfunction. The pathogenesis of AD involves the overproduction of β-amyloid (Aβ) in the central nervous system, which leads to aggregation and accumulation of tau protein and depletion of a group of enzymes involved in the production of acetylcholine [9]. Aβ- and tau-containing neurofibrils progressively spread in the cholinergic nerves of the septal hippocampus and basal forebrain cortex [9]. As a result of these processes, cholinergic and noradrenergic axons degenerate, and subsequent memory impairment progresses with hippocampal atrophy [10]. Pharmacological treatment of this disease includes neurotransmitter replacement, enhanced release or suppression of degradation, and synaptic receptor stimulation/blockade, with limited efficacy. The antioxidant effect of coriander is expected to protect against neurodegenerative, aging, and lifestyle-related diseases; however, the mechanism has not been clearly elucidated. Previous studies have reported that treatment of senescence-accelerated mouse-prone 8 (SAMP8) mice with coriander significantly ameliorated aging-induced memory decline [11]. Therefore, the present study investigated the effect of coriander on H_2O_2-induce neurotoxicity in rat pheochromocytoma (PC12) cells.

Methods

Materials and methods

Cell culture and chemicals

The PC12 cells were purchased from RIKEN BRC (Ibaraki, Japan). They were cultured in Dulbecco's modified Eagle's medium (D-MEM; Wako Pure Chemical Industries, Ltd. Osaka, Japan) supplemented with 10% heat-inactivated fetal bovine serum (FBS; #S00EO10002, biowest Co., Ltd., Nuaillé,

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France) at 37 °C and 5% CO_2 in a humidified incubator. Coriander (#202107021, Choko Co., Ltd., Tokyo, Japan) was dissolved in distilled water and sterilized using a 0.22 μm filter (Millipore Corporation, Billerica, MA, USA). H2O2 was diluted in distilled water before use.

Determination of appropriate concentration

Concentrations of H_2O_2 and coriander were determined using a lactate dehydrogenase (LDH) cytotoxicity assay. Briefly, cells were seeded (1×103 cells/well) in an untreated 96-well plate. Then, they were treated with 0.1–1000 μM H_2O_2 and 0.001–10 μg/mL coriander for 24 h. Cytotoxicity was evaluated using the Cytotoxicity LDH Assay Kit-WST (Dojindo Laboratories, Kumamoto, Japan) following the manufacturer's protocols. Optical density (OD) at 490 nm was measured using a microplate reader (infinite F50, TECAN Japan., Co., Ltd., Kanagawa, Japan).

Morphological evaluation of cell outgrowth

PC12 cells were treated with 50 ng/mL of nerve growth factor (NGF) and/or 1×10^{-6} M H_2O_2, 0.01 or 0.1 μg/mL coriander for a maximum of 72 h incubation. The cells were treated with 0.5 μg/mL ascorbic acid (AA) as a positive control. Digital images of five random fields were obtained using a phase-contrast inverted microscope (BZ-X800, KEYENECE, Osaka, Japan) equipped with a camera at 24 and 72 h after treatment with NGF, H_2O_2, AA, or coriander. The details for each group are presented in Table 1. Morphological evaluation was performed using our previous method [12]. Briefly, it was performed using the neurocyte image analyzer software (Kurabo Industries Ltd., Osaka, Japan), and three parameters were evaluated: neurite length (Length), neurite segment (Joint), and neurite branching (Passage). Experiments were conducted in 2-3 wells per group, and more than three times.

	control	NGF	H_2O_2	AA	C 0.1	C 0.01
NGF (50 ng/mL)	(-)	(+)	(+)	(+)	(+)	(+)
H_2O_2 (1×10^{-6} M)	(-)	(-)	(+)	(+)	(+)	(+)
AA (0.5 μg/mL)	(-)	(-)	(-)	(+)	(-)	(-)
coriander (0.1 μg/mL)	(-)	(-)	(-)	(-)	(+)	(-)
coriander (0.01 μg/mL)	(-)	(-)	(-)	(-)	(-)	(+)

Table 1: Details of each group which used in morphological experiment. NGF: Nerve growth factor, AA: Ascorbic acid, C: Coriander.

Western blot analysis

To understand the mechanism of action of coriander in oxidative stress-induced neurotoxicity, ERK and phosphorylated ERK levels were analyzed using western blotting. Samples (n=5 in each group) containing 10 μg cell protein were prepared as described in our previous study [13]. The protein extraction procedure is shown in Figure 1, and the details for each treatment group are shown in Table 2. Briefly, H_2O_2 and/or coriander were pre-administered for 1 h, and then NGF was added for 30 min. Distilled water was added to the

control group and the H_2O_2 group. Protein concentrations were determined using a Micro BCA Protein Kit (Thermo Fisher Scientific Inc.). For the analyses, 12% Mini-PROTEAN TGX Precast Gels (Bio-Rad Laboratories, Hercules, CA, USA) and polyvinylidene fluoride (PVDF) membranes (Millipore Corporation, Billerica, MA, USA) were used. Non-specific binding was blocked using Tris-buffered saline with 0.1% Tween-20 (TBS-T) and 5% bovine serum albumin (Wako Pure Chemical Industries, Ltd. Osaka, Japan) for 1 h at room temperature. The membranes were then washed with 0.1% TBS-T (three times, 5 min each) and incubated overnight at 4 °C with primary antibodies against ERK and phosphorylated ERK (Cell Signaling Technology, Inc., MA, USA). Immunoreactive bands were detected using horseradish peroxidase-conjugated secondary antibody (Cell Signaling Technology). Protein bands were visualized using ECL reagents and an Amersham Imager 680 (Global Life Science Technologies Japan Co., Ltd., Tokyo, Japan). Images were analyzed using the ImageJ software (freely available from the National Institutes of Health, Bethesda, MD, USA). Protein expression levels were normalized to the levels of β-actin protein.

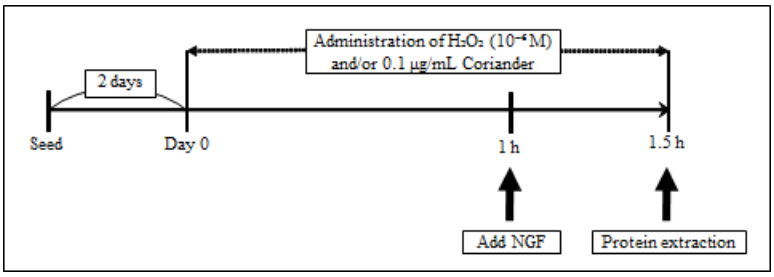

Figure 1: Experimental schedule of protein extraction for western blot.

	control	NGF	H_2O_2	NGF+H_2O_2	NGF+H_2O_2+C
NGF (50ng/mL)	(-)	(+)	(-)	(+)	(+)
H_2O_2 (1×10^{-6} M)	(-)	(-)	(+)	(+)	(+)
coriander (0.1μg/mL)	(-)	(-)	(-)	(-)	(+)

Table 2: Details of each group which used in western blot experiment. NGF; Nerve growth factor, C; Coriander.

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Comparisons between multiple administration groups and the corresponding controls in each experiment were performed using one-way analysis of variance (ANOVA) followed by Dunnett's test and Tukey's multiple group comparison test. Statistical analyses were performed using the SPSS software version 28.0 (IBM Corp., NY, USA). Differences were considered statistically significant at probability (p) values <0.05.

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Results

Changes in LDH levels. The appropriate concentrations for administration to PC12 cells were determined by the LDH assay, which was used to evaluate H_2O_2 and coriander cytotoxicity. Treatment of PC12 cells with 0.001–10 μg/mL coriander for 24 h showed no cytotoxicity; however, exposure to 1×10^{-7}–10^{-3} M of H_2O_2 for 24 h showed a significant increase in 10-3 to 10^{-5} M groups, compared with 10^{-6} to 10^{-7} M groups (Figure 2). In the following experiments, 10-6 M H_2O_2 was used. Coriander was used at 0.1 and 0.01 μg/mL because the researchers were interested in examining the effects of the lower concentrations in this study.

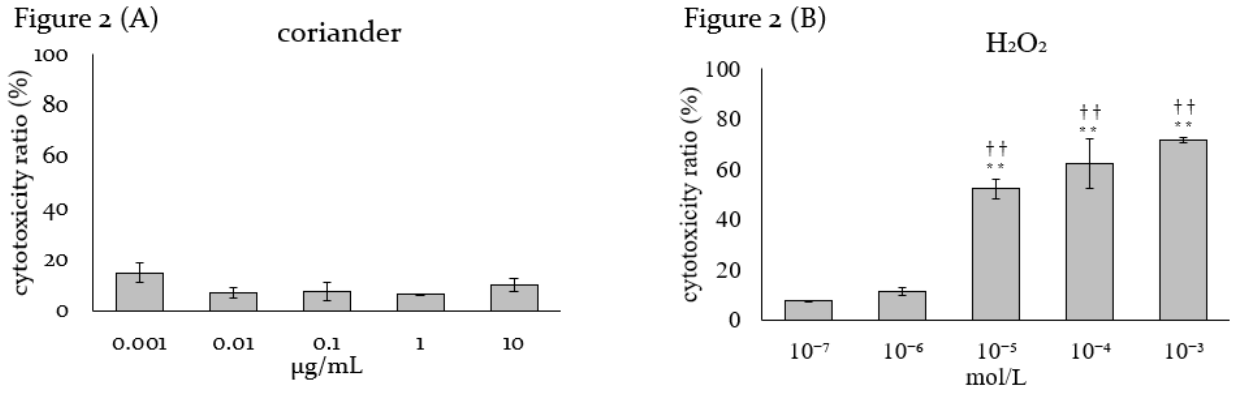

Figure 2: Cytotoxicity ratio of Coriander (A) and H_2O_2 (B) using an LDH assay kit. Data values are presented as mean ± standard deviation (SD). $^{**}p<0.01$, compared with the 10^{-7} M; ††$p<0.01$, compared with the 10^{-6} M.

Coriander ameliorated reduction of H2O2-induced neurite outgrowth

Changes in neurite outgrowth length, Joint, and Passage are shown in Figure 1. At 24 h, NGF single administration significantly increased Joint, and Passage compared with the control group. Simultaneous administration of NGF and H_2O_2 significantly suppressed Joint compared with the NGF administration alone. Simultaneous administration of NGF, H_2O_2, and AA significantly increased Joint compared to that in the control group. Simultaneous administration of NGF, H_2O_2, and coriander at 0.1 μg/mL and 0.01 μg/mL significantly increased Length, Joint, and Passage compared to the control group. Moreover, simultaneous administration of NGF and H2O2 significantly increased the Length, and Joint and Passage compared to the control group. At 72 h, NGF single administration significantly increased the Length, Joint, and Passage, compared with the control.

Simultaneous administration of NGF and H2O2 significantly suppressed the Length, Joint and Passage, compared with NGF single administration. Simultaneous administration of NGF, H_2O_2, and AA significantly increased the Length, Joint, and Passage, compared with the control group. Simultaneous administration of NGF, H_2O_2, and 0.1 and 0.01 μg/mL coriander significantly increased the Length, Joint, and Passage, compared to the control group. In addition, the simultaneous

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administration of NGF and H_2O_2 significantly increased the Length, Joint, and Passage, compared to the control group.

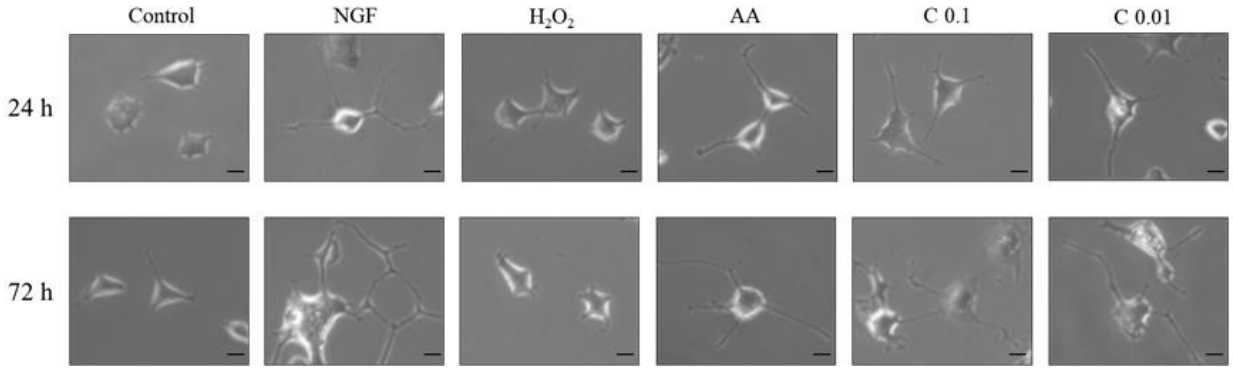
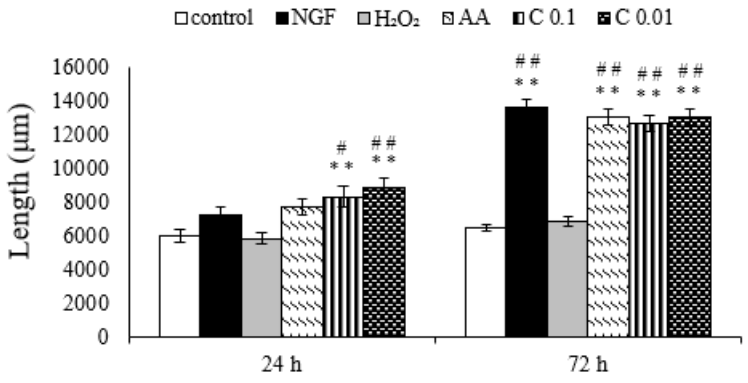
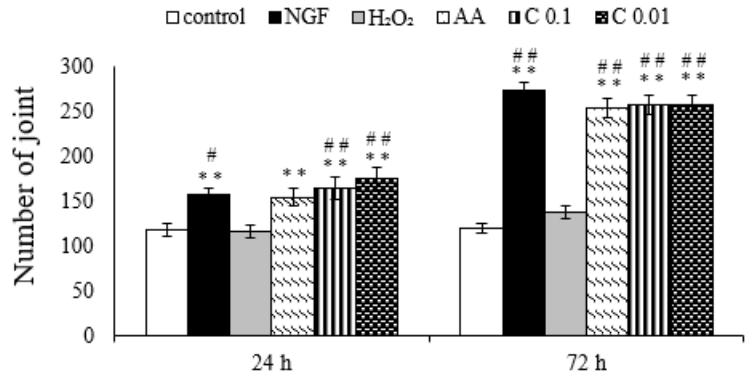


Figure 3: Representative PC12 cells images at 24 h and 72 h after treatment of each material. Bar=20 μm. NGF, nerve growth factor; AA, ascorbic acid; C, coriander.





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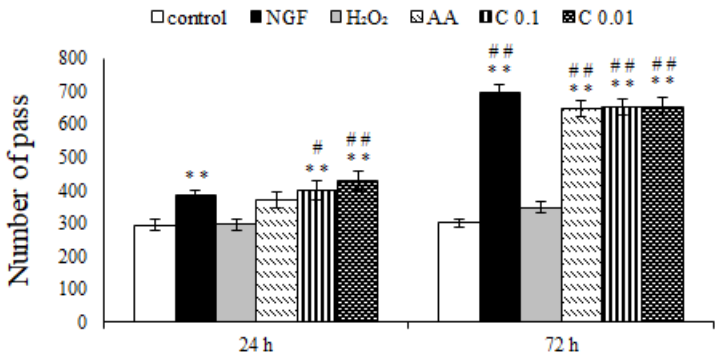
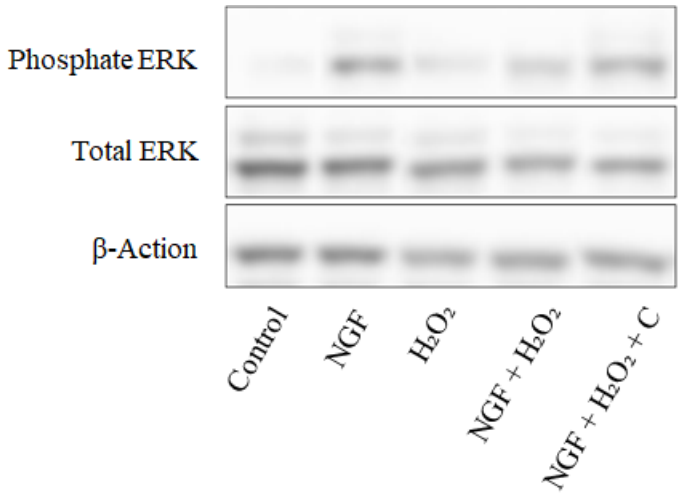


Figure 4: The morphological evaluation, including Length (A), Joint (B) and Passage (C), at 24 and 72 h after treatments. Data values are presented as mean ± standard deviation (SD). $^{**}p<0.01$, compared with the control; #p<0.05, compared with the H_2O_2; ##p<0.01, compared with the H_2O_2. NGF, nerve growth factor; AA, ascorbic acid; C, coriander.

Western blot analysis

To understand the anti-oxidative effects of coriander, the researchers performed western blot analysis to determine total ERK and phosphorylated ERK protein levels. Phosphorylated ERK expression was significantly increased by NGF compared with that in the control group. Moreover, compared with the H2O2 group, phosphorylated ERK levels were significantly increased in the NGF group. Simultaneous administration of H2O2 and NGF significantly increased the levels of phosphorylated ERK compared with the single administration of H2O2. Simultaneous administration of H2O2, NGF, and 0.1 μg/mL significantly increased the levels of phosphorylated ERK compared to the control and H2O2 group.



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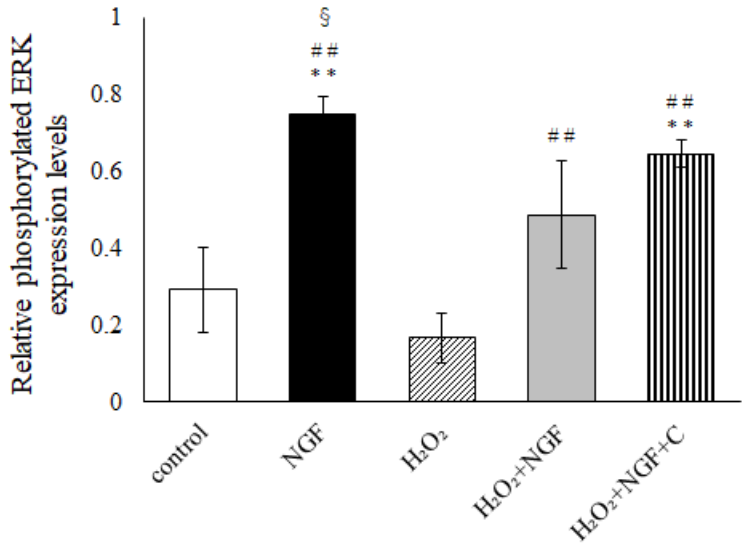

Figure 5: (A) Results of western blot analysis for phosphorylated ERK and total ERK in PC12 cells, (B) ratio of relative levels. Changes relative ratio of phosphorylated ERK to total ERK were investigated using western blot analysis. β-action served as a loading reference. Relative protein levels are expressed as the mean ± SD. **p<0.01, compared with the control; ##p<0.01, compared with the H_2O_2; §p<0.05, compared with the H_2O_2+NGF group. NGF: nerve growth factor; C: coriander.

Discussion

The main results of the present study were that administration of NGF, H2O2, and coriander induced, in PC12 cells, the following changes: (1) H_2O_2 was not cytotoxic at concentrations below 10^{-6} M. Coriander was not cytotoxic at any concentration in the range of 0.001–10 μg/mL, (2) a significant increase in neurite outgrowth in cells treated with 50 ng/mL NGF for 72 h was noted, (3) the neurite outgrowth effect of NGF was suppressed by 10^{-6} M H_2O_2, (4) the inhibition of neurite outgrowth following treatment with H_2O_2 was reversed in the presence of 0.1 and 0.01 μg/mL coriander, (5) the recovery of neurite outgrowth by coriander involved an increase in the expression of phosphorylated ERK.

The mitogen-activated protein kinase (MAPK) pathway is involved in NGF-induced neurite outgrowth [14]. NGF binding the NGF receptor TrkA activates MAPK signaling pathways, including the PLC-γ, PI3K, p38MAPK, JNK, and ERK signaling pathways, leading to neural differentiation and cell proliferation. MAPK has been shown to regulate complex signaling pathways related to cell proliferation and apoptosis [15]. Western blot analysis revealed a significant increase in the ratio of phosphorylated ERK to total ERK after NGF stimulation for 30 min compared to the control and H_2O_2 group. Moreover, compared with the H_2O_2+NGF group, phosphorylated ERK levels were significantly increased in the NGF single administration group. This suggests that H_2O_2 pretreatment suppressed phosphorylated ERK levels. However, the simultaneous administration of coriander did

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not result in a significant change compared with the NGF treatment. Therefore, NGF increased the expression of phosphorylated ERK, H_2O_2 decreased its levels, and coriander recovered the levels of phosphorylated ERK. Based on these results, concluded that coriander was not directly involved in increasing phosphorylated ERK but may reduce H_2O_2-induced oxidative stress.

Morphological evaluation showed that the administration of H_2O_2 reduced neurite outgrowth. It has been reported that H2O2 activates the apoptotic pathway by permeating the cell membrane and increasing intracellular Ca2+ concentration, causing cytotoxicity [16,17]. In contrast, the antioxidant effect of AA is known to reduce cytotoxicity related to H2O2-induced oxidative stress [18]. The present study showed that, similar to AA, the administration of coriander improved neurite outgrowth and may have reduced oxidative stress.

There are limitations in the present study. First, cell viability was not evaluated. This problem could be solved by the cytotoxicity ratio; however, further experiments are required to investigate cell proliferation. Second, the present study did not evaluate major neural differentiation markers such as those comprising the neurofilament family and GFAP. Third, the lack of data on the mechanisms is a limitation of this study. Therefore, this is a preliminary study on the anti-oxidative effect of coriander, and further studies are required to determine whether treatment with coriander affects oxidative stress-induced neurotoxicity.

Conclusion

Coriander reversed the reduction in neurite growth under conditions of H_2O_2-induced oxidative stress in NGF-stimulated PC12 cells. Oxidative stress is known to contribute to the development of AD, and the results of the present study suggest that daily intake of coriander may help prevent neurodegenerative diseases.

Conflict of interest statement

The authors declare no conflicts of interest.

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