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Neuroprotective Effects of Morin Against Acrylamide-Induced Cytotoxicity in PC12 Cells

Shabnam Shahsavand[1], Simin Joharinia[2;] *, Iraj Javadi[3], Reza Ghasemi[4], Atefeh Shirinzadeh Feizabadi[5,*,]*

1. Department of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran
2. North Khorasan University of Medical Sciences, Bojnurd, Iran
3. Department of Toxicology, Shahreza Branch, Islamic Azad University, Shahreza, Iran
4. Department of Cardiology, School of Medicine, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran
5. Department of Anesthesiology, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran

* ***Corresponding author:*** Simin Joharinia, North Khorasan University of Medical Sciences, Bojnurd, Iran.E-mail: Joharinia.s@gmail.com

** ***Corresponding author:*** Atefeh Shirinzadeh Feizabadi, Department of Anesthesiology, Torbat Heydariyeh University of Medical Sciences, Torbat Heydariyeh, Iran.E-mail: at_shirinzadeh@yahoo.com

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Abstract

Background: Acrylamide (ACR) is widely used in industry and is also formed in carbohydrate-rich foods during high-temperature cooking processes. The neurotoxicity of ACR in humans and animals is well established, and multiple mechanisms have been proposed to mediate its toxic effects. Among these, oxidative stress and apoptosis pathways have gained considerable attention in recent years. Morin, a bioactive flavonoid found in mulberry, has demonstrated neuroprotective properties, particularly due to its antioxidant and anti-apoptotic activities.

Objective: The present study aimed to evaluate ACR-induced neurotoxicity and the potential protective effects of morin in an in vitro model using PC12 cells.

Methods: PC12 cells were pretreated with various concentrations of morin (25–400 µM) for 24 hours, followed by exposure to ACR (4.5 mM, IC_{50} value) for another 24 hours. Cell viability was assessed by MTT assay. Apoptosis was evaluated by flow cytometry using the Sub-G1 peak method, and intracellular reactive oxygen species (ROS) levels were measured using DCF-DA.

Results: ACR induced cytotoxicity in a concentration-dependent manner (IC_{50} = 4.5 mM) and significantly increased both apoptotic cell percentage (to 21.25 ± 1.32%; $p < 0.001$) and ROS levels ($p < 0.001$) compared to control. Pretreatment with morin significantly attenuated ACR-induced cytotoxicity in a concentration-dependent manner ($p < 0.001$), reduced apoptosis (to 5.17 ± 0.86%; $p < 0.001$), and decreased ROS production ($p < 0.001$). Morin alone showed no cytotoxicity and reduced basal ROS levels ($p < 0.001$).

Conclusion: Oxidative stress and apoptosis play key roles in ACR-induced neurotoxicity. Morin exerts neuroprotective effects by reducing intracellular ROS production and, consequently, lowering apoptosis levels, thereby significantly mitigating ACR-induced neuronal damage.

Keywords: Acrylamide, Morin, Oxidative stress, apoptosis.

1. Background

Acrylamide (ACR, 2-propenamide, C_3H_5NO) is a white, odorless crystalline solid soluble in water, ethanol, ether, and chloroform (1, 2). The acrylamide monomer is widely used in chemical industries, water purification, papermaking, textile manufacturing, and scientific research (3, 4). Acrylamide also forms

in carbohydrate-rich foods heated above 120°C, such as potato chips, French fries, biscuits, and coffee, primarily via the Maillard reaction, though formation mechanisms remain incompletely understood (5, 6). Heat-processed foods, especially fried potato products (e.g., French fries and potato chips), coffee, and bakery items, are the primary dietary sources and contribute substantially to total acrylamide exposure in the general population (3, 7). Major human health concerns include potential carcinogenicity and neurotoxic effects. In 1994, the International Agency for Research on Cancer (IARC) classified acrylamide as "probably carcinogenic to humans" (Group 2A) (8). Neurotoxicity is a primary consequence of ACR exposure, affecting the central and peripheral nervous systems (9-11). ACR neurotoxicity appears well-documented in humans and laboratory animals, manifesting as sensory, autonomic, and motor deficits (12). Additionally, ACR induces structural changes in neurofilament distribution, neuronal and astrocyte apoptosis, and demyelination (13, 14). Human evidence remains limited, but ACR reportedly causes ataxia, skeletal muscle weakness, weight loss, and axon degeneration in the peripheral and central nervous systems (9, 11). Epidemiological studies indicate that long-term occupational exposure leads to acute, subacute, and chronic poisoning (15, 16). Mechanisms of ACR neurotoxicity are debated but involve impaired axonal transport, conjugation with reduced glutathione (GSH), metabolism to glycidamide via cytochrome P450 (CYP2E1), DNA adduct formation, decreased CNS levels of noradrenaline, dopamine, and 5-hydroxytryptamine, altered postsynaptic dopamine receptor affinity and density, and oxidative stress, which plays a significant role in neurotoxicity progression (12). Furthermore, ACR-induced neurotoxicity in Wistar rats leads to lipid peroxidation and reduced antioxidant capacity in the nervous system (2, 12). PC12 cells, a rat pheochromocytoma-derived line with dopaminergic characteristics, serve as a widely used in vitro neuronal model for studying ACR neurotoxicity; they differentiate into neuron-like cells upon nerve growth factor stimulation and reliably recapitulate ACR-induced oxidative stress, apoptosis, cytotoxicity, ROS elevation, and mitochondrial dysfunction observed in vivo (2, 12, 13).

In recent years, natural compounds have garnered attention for treating neurological diseases (17- 20). Flavonoids, diphenylpropane compounds found in fruits, vegetables, and juices (18-20), exhibit diverse biological and pharmacological activities (21). Morin hydrate (3,5,7,2′,4′-pentahydroxyflavone), a yellow crystalline polyphenolic compound, occurs in Castanea sativa (sweet chestnut), Prunus dulcis (almond), Morus alba L. (white mulberry), and other fruits (22). It serves widely as a food supplement and in traditional herbal medicine (18). Morin hydrate demonstrates beneficial pharmacological effects, including free radical scavenging (23, 24), xanthine oxidase inhibition (25), and anti-inflammatory actions (26), as well as DNA protection against free radical damage, inhibition of low-density lipoprotein oxidation, and anticancer properties (20). Its antioxidant and anti-inflammatory activities play key roles in therapeutic processes for disorders associated with oxidative stress (27, 28). Morin, highly hydroxylated, exerts potent antioxidant effects in vitro and attenuates ROS formation in neuronal models, contributing significantly to its neuroprotective effects (29).

2. Objective

The present study aimed to evaluate ACR-induced neurotoxicity and the potential protective effects of morin in an in vitro model using PC12 cells.

3. Methods

Chemicals:

Morin hydrate (CAS No. 654055-01-3) was supplied by Sigma-Aldrich (St. Louis, MO, USA).

Acrylamide (CAS No. 79-06-1) was purchased from Merck (Darmstadt, Germany). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; CAS No. 298-93-1) was obtained from Sigma-Aldrich (Steinheim, Germany). Fetal bovine serum (FBS) and RPMI-1640 medium were purchased from Gibco (Grand Island, NY, USA).

Cell culture:

PC12 cells (rat pheochromocytoma cell line) were obtained from Mashhad University of Medical Sciences (Mashhad, Iran). Cells were cultured in RPMI-1640 medium supplemented with 10% (v/v) heat-inactivated FBS, 100 U/mL penicillin, and 100 µg/mL streptomycin at 37°C in a humidified 5% CO_2 atmosphere. Medium was changed every 2–3 days. At 70–80% confluence, cells were subcultured using 0.25% trypsin-EDTA. Cell viability (>95%) was confirmed by trypan blue exclusion.

All experiments were conducted in triplicate (n = 3 independent experiments). Acrylamide (ACR) stock was prepared in PBS; morin in DMSO (final concentration <0.1%). The IC_{50} of ACR after 24 h was 4.5 mM.

Treatment groups:

- ACR alone: 25, 50, 100, 200, 400 µg/mL (24 h) for dose-response.
- Morin alone: 25–400 µg/mL (24 h) to assess toxicity.
- Protective effect: Pretreatment with morin (25–400 µg/mL) for 24 h, followed by ACR (4.5 mM) for 24 h.
- Additional groups for apoptosis and ROS assays: Control (vehicle), ACR alone (4.5 mM), morin alone (100 or 400 µg/mL), and morin + ACR combinations.

Cell viability:

Cell viability was determined using the MTT reduction assay. PC12 cells were seeded at 1.5 × 10^4 cells/well in 96-well plates and incubated for 24 h to allow attachment.ACR cytotoxicity was assessed by exposing cells to ACR (25, 50, 100, 200, and 400 µg/mL) for 24 h; the IC_{50} was calculated to be 4.5 mM. These doses were selected to establish a full dose-response curve, as standard in neurotoxicity studies. Morin alone was tested at the same concentrations (25–400 µg/mL) for 24 h to confirm the absence of intrinsic toxicity; doses were based on the literature and preliminary data showing safety in this range. To evaluate neuroprotective effects, cells were pretreated with morin (25–400 µg/mL) for 24 h, followed by ACR (4.5 mM) for another 24 h. Pretreatment was chosen (rather than simultaneous or post-treatment) to simulate preventive conditions and allow morin to activate antioxidant and anti-apoptotic mechanisms prior to ACR-induced damage.

Following treatment, MTT (0.5 mg/mL) was added, and the mixture was incubated for four h at 37°C. Formazan crystals were dissolved in DMSO, and absorbance was read at 540 nm (reference 590 nm) using an ELISA reader. Viability was expressed as a percentage of control. Experiments were performed in triplicate (n = 3).

Measurement of ROS (Reactive oxygen species):

Intracellular ROS levels were measured using the 2′,7′-dichlorofluorescin diacetate (DCF-DA) fluorescent probe. DCF-DA is a non-fluorescent compound that diffuses into cells, where it is deacetylated by cellular esterases to DCFH and subsequently oxidized by ROS to the highly fluorescent dichlorofluorescein (DCF). Cells were seeded and treated as described in the experimental groups (Section 2.3). After 24 h treatment, DCF-DA was added to a final concentration of 10 µM and incubated for 30 min at 37°C in 5% CO_2. The medium was removed, the cells were washed twice with PBS, and then trypsinized. Fluorescence intensity was immediately measured by flow cytometry (Partec™) using excitation at 485 nm and emission at 530 nm (FL-1 channel). (30).

The studied groups were:

Ⅰ) control (vehicle: PBS only),

Ⅱ) Pretreatment with morin (25–400 µg/mL) for 24 h followed by ACR (4.5 mM),

Ⅲ) ACR alone (4.5 mM, 24 h),

Ⅳ) Morin alone (400 µg/mL, highest concentration).

Experiments were performed in triplicate (n = 3).

Detection of apoptotic cells with flow cytometry:

Apoptotic cells were identified by PI staining of treated cells, followed by flow cytometry to detect the sub-G1 peak. The following subgroups were examined in the sub-G1 method: Ⅰ) Control cells with (PBS) solvent. Ⅱ) Cells exposed to different concentrations of morin (25, 50, 100, 200, and 400 µg / ml) and ACR (4.5 mM concentration) for 24 hours, Ⅲ) Cells exposed to ACR with a concentration of 4.5 mM for 24 hours, and Ⅳ) Cells were exposed only to the best concentration of morin (100 µg / ml). At the end of the exposure time, the supernatant was collected, and then 750 µl of PI solution (0.1% sodium citrate and 0.1% Triton X-100) was added. Incubation was performed for 30 minutes, and then the contents of the plates were added to the tubes. Fluorescence rate was evaluated by Partec TM flow cytometry at 488 nm induction and 585 nm (FL-2 filter).

Statistical analysis

Flow cytometry data were analyzed using WinMDI software. Results were expressed as mean ± standard deviation (SD) from three independent experiments (n = 3). The IC_{50} value was calculated using GraphPad Prism software (version 6). Statistical comparisons were performed using InStat software, with one-way analysis of variance (ANOVA) followed by the Tukey-Kramer post hoc test. Due to the small sample size (n = 3) typically used in cell-based studies and the visual inspection of data indicating approximate normality, parametric tests were applied as commonly accepted in similar published works. A p-value < 0.05 was considered statistically significant.

4. Results

Effect of ACR in PC12 cells: Exposure of PC12 cells to increasing concentrations of ACR (equivalent to approximately 0.35–5.6 mM, prepared as 25–400 µg/mL stock solutions) for 24 h resulted in a significant, concentration-dependent reduction in cell viability (Figure 1). The IC_{50} value for ACR was determined as 4.5 mM. Viability decreased markedly at higher concentrations ($p < 0.01$ and $*p < 0.001$ versus control), confirming ACR's potent cytotoxic effects.

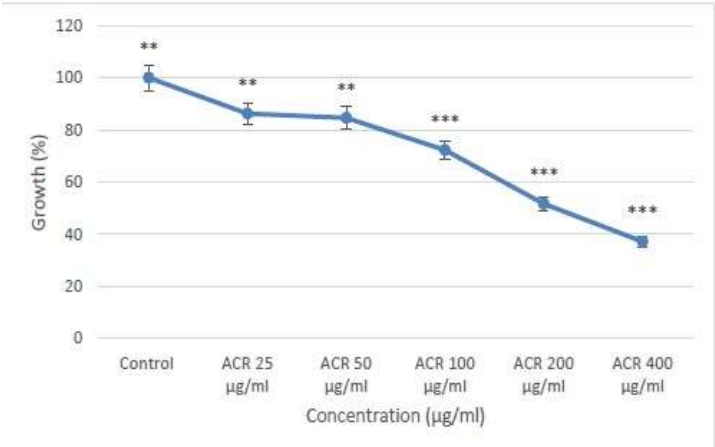


Figure 1. Cells were exposed to various concentrations of ACR for 24 h. Data are mean ± SD from 3 independent experiments (n=6). **p < 0.01 and ***p < 0.001 vs. control (Tukey-Kramer test).

Effect of Morin on PC12 cells:

To establish the non-toxic concentration range of morin, PC12 cells were exposed to morin (25–400 µg/mL) for 24 h. Morin

exhibited no cytotoxicity at any tested concentration. At 25 and 400 µg/mL, viability was comparable to the control ($p > 0.05$). However, 100 and 200 µg/mL caused a mild but significant increase in cell viability (**$p < 0.01$ versus control), likely reflecting enhanced metabolic activity rather than toxicity (Figure 2).

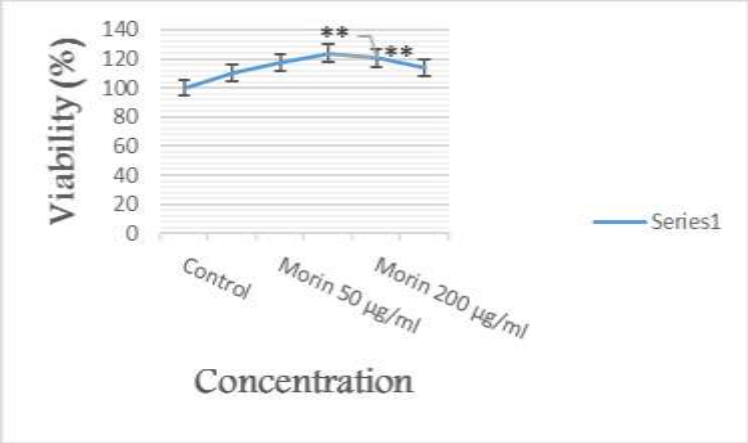


Figure 2. Effect of morin on PC12 cell viability. PC12 cells were exposed to morin (25–400 µg/mL) for 24 h. Viability was assessed by MTT assay. Data are mean ± SD (n = 3). **p < 0.01 vs. control group (Tukey-Kramer test).

Effect of Morin on ACR-induced cytotoxicity in PC12 cells:

Pretreatment with morin (25–400 µg/mL) for 24 h significantly attenuated ACR-induced cytotoxicity in PC12 cells in a concentration-dependent manner (Figure 3). The strongest protection was observed at 100 and 200 µg/mL (###$p < 0.001$ versus ACR-only group). Lower concentrations (25 and 50 µg/mL) provided moderate protection, while 400 µg/mL showed less pronounced effects.

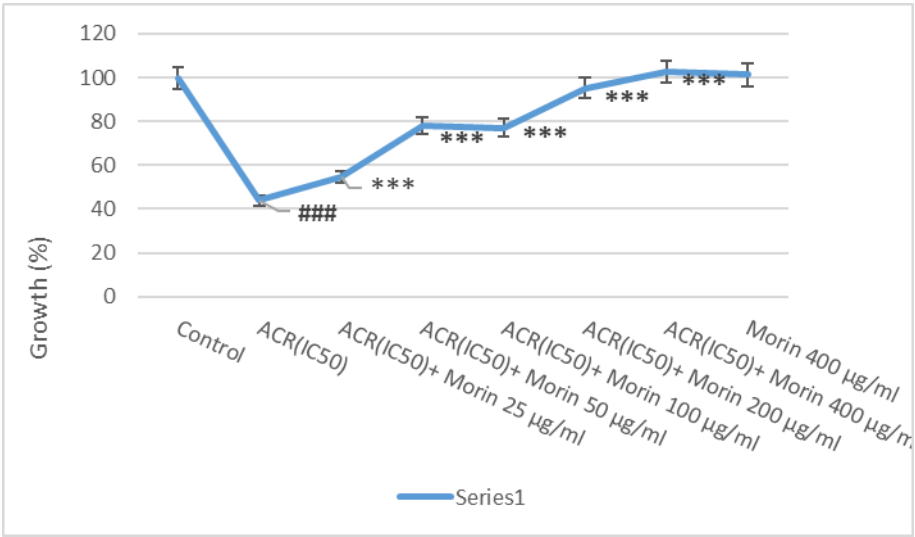


Figure 3. Protective effect of morin against acrylamide (ACR)-induced cytotoxicity in PC12 cells. PC12 cells were pretreated with morin (25, 50, 100, 200, or 400 µg/mL) for 24 h, followed by exposure to ACR (4.5 mM) for an additional 24 h. Cell viability was assessed using the MTT assay. Data are expressed as mean ± SD from three independent experiments (n = 3). ***p < 0.001 compared with control group; ###p < 0.001 compared with ACR-only group (one-way ANOVA followed by Tukey-Kramer post-hoc test).

Phase-contrast micrographs showing morphological changes in PC12 cells after 24 h treatment. (A) Control cells showing normal neuronal morphology with extended neurites. (B) Cells exposed to ACR (4.5 mM, IC_{50} concentration) exhibited cell shrinkage, loss of neurites, and reduced cell density. (C) Cells pretreated with morin (optimal

concentration) prior to ACR exposure, displaying preserved morphology similar to the control. Images were captured at 400× magnification (Figure 4).

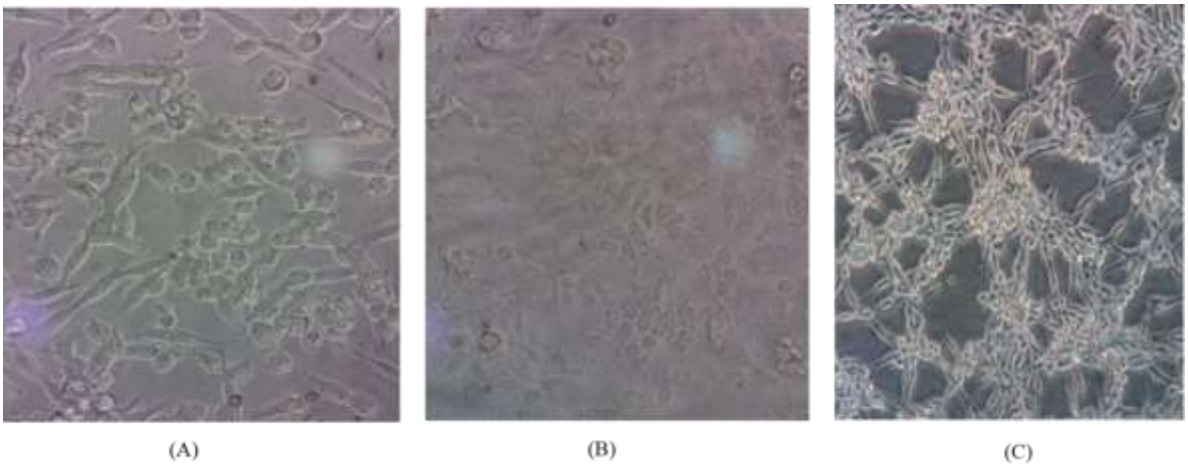
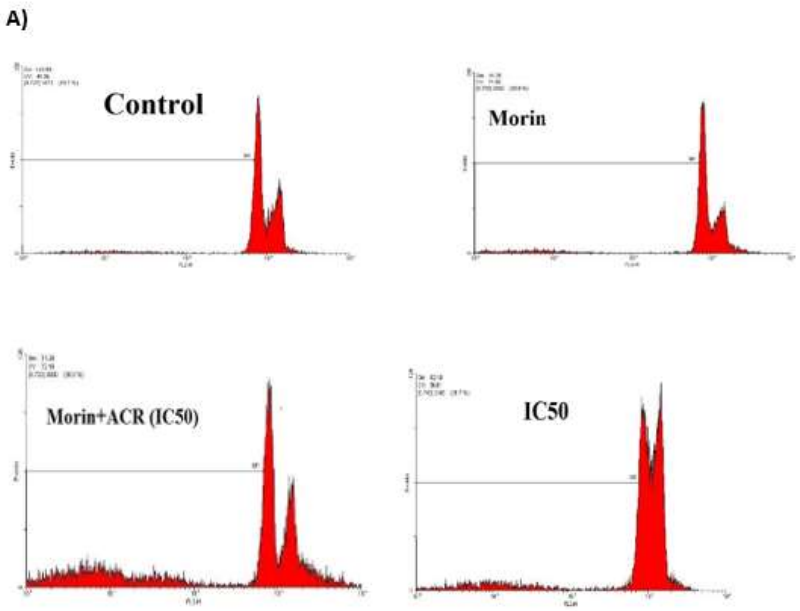


Figure 4. Representative microscopic images of PC12 cells.

Effect of Morin on ACR-induced apoptosis (Sub-G1 analysis):

Flow cytometry demonstrated a significant increase in apoptotic cells after ACR exposure ($p < 0.001$). Pretreatment with morin substantially decreased the Sub-G1 apoptotic population, with 100 µg/mL restoring values to levels close to those of the control. Morin alone also reduced basal apoptosis (Figure 5).



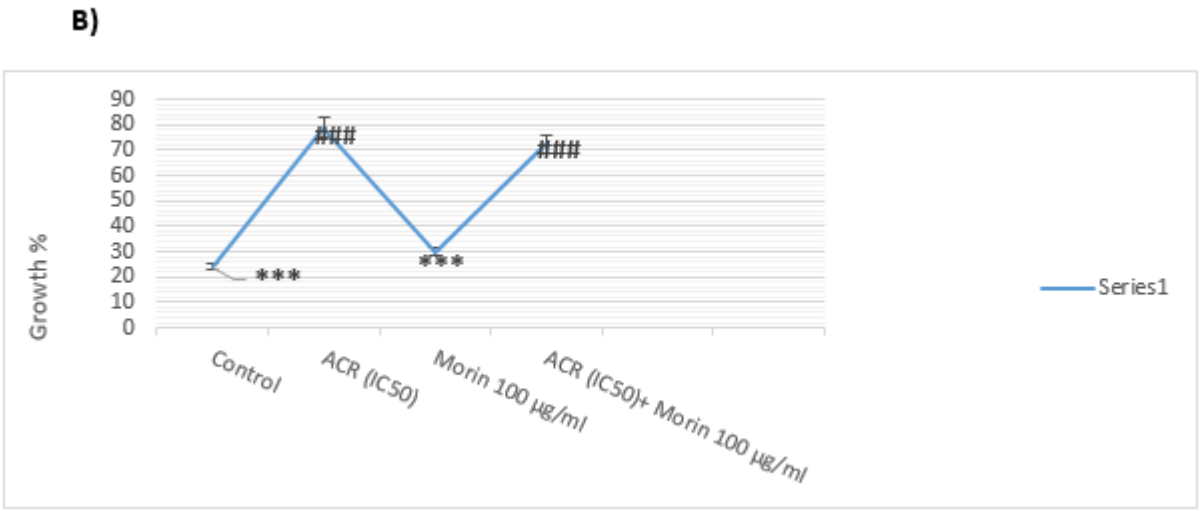


Figure 5. Effect of morin on ACR-induced apoptosis in PC12 cells (Sub-G1 analysis). Representative flow cytometry histograms of PI-stained cells. From top left to bottom right: control, ACR (4.5 mM), morin alone (100 µg/mL), morin Pretreatment + ACR. Sub-G1 peak indicates apoptotic cells. (B) Percentage of sub-G1 population. Data are mean ± SD (n = 3). ***p < 0.001 vs. control; ##p < 0.01, ###p < 0.001 vs. ACR-only (Tukey-Kramer test).

Effect of Morin on ACR-Induced ROS Production:

ACR (4.5 mM) significantly increased intracellular ROS levels compared with control ($p < 0.001$). Pretreatment with morin reduced ACR-induced ROS production in a concentration-dependent manner ($p < 0.05$ and $p < 0.001$ versus the ACR-only group). The most pronounced reductions were observed at 100 and 200 µg/mL morin. Morin alone (especially at 400 µg/mL) also decreased basal ROS levels ($p < 0.001$ versus control), consistent with its antioxidant properties (Figure 6).

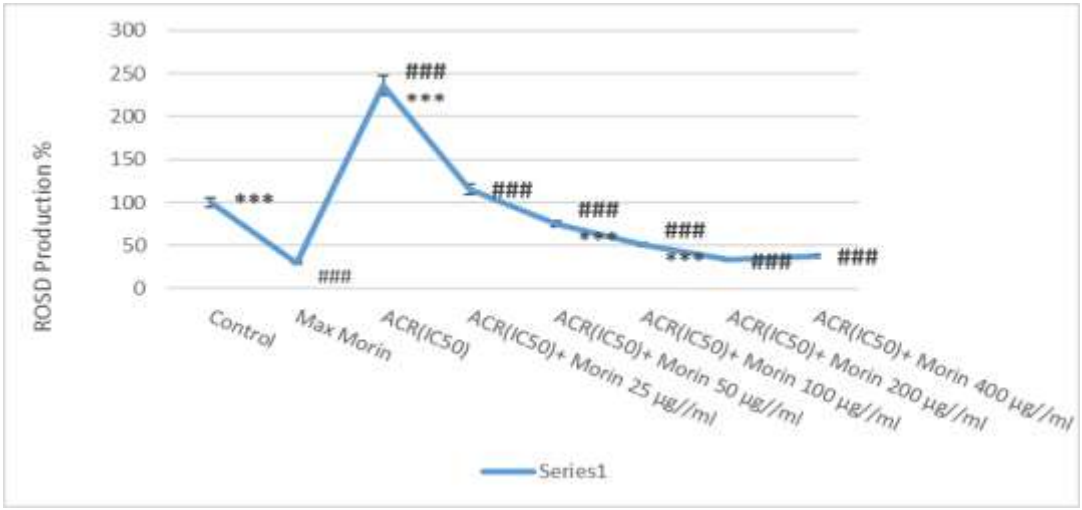


Figure 6. Effect of morin on ACR-induced intracellular ROS production in PC12 cells.

Cells were pretreated with morin (25–400 µg/mL) for 24 h, followed by ACR (4.5 mM) for 24 h. ROS levels were measured by flow cytometry using DCF-DA fluorescence. Data are expressed as mean ± SD (n = 3). *p < 0.001 versus control group; ###p < 0.001 versus ACR-only group (Tukey-Kramer test).

5. Discussion

The neurotoxic effects of acrylamide (ACR) have been extensively documented in

both in vivo and in vitro models, with oxidative stress and apoptosis identified as central mechanisms (9-12). Increased reactive oxygen species (ROS) generation and subsequent lipid peroxidation in nervous tissue have been consistently linked to ACR-induced damage (2, 12). Consequently, ACR-exposed PC12 cells represent a well-established model for screening potential neuroprotective agents with antioxidant and anti-apoptotic properties (2, 13, 31-39).

Exposure to ACR (0.35–5.6 mM) for 24 h reduced PC12 cell viability in a concentration-dependent manner, with an IC_{50} value of 4.5 mM. This finding aligns with previous reports in PC12 and SH-SY5Y cells, in which ACR concentrations in the millimolar range induced comparable cytotoxicity via oxidative stress and mitochondrial dysfunction (2, 12, 13, 36-42).

ACR exposure significantly elevated intracellular ROS levels and increased the sub-G1 cell population, indicating enhanced apoptosis. These results are in agreement with earlier studies demonstrating ACR-induced ROS overproduction, lipid peroxidation, and DNA fragmentation in neuronal cells (2, 12, 14, 43).

Pretreatment with morin markedly suppressed both ROS generation and apoptotic cell death. The reduction in sub-G1 population (from approximately 21% to 5%) further supports morin's anti-apoptotic action, potentially through inhibition of caspase activation or preservation of mitochondrial integrity, as reported in related models (44- 46).

Pretreatment with morin (25–400 µg/mL) significantly attenuated ACR-induced cytotoxicity, with the most pronounced protection observed at 100 and 200 µg/mL. Similar neuroprotective effects of morin have been reported in other neuronal models. For instance, morin reduced ROS-mediated neuroinflammation and mitochondrial superoxide production in high-glucose-exposed Neuro2A cells by activating Nrf2 and inhibiting NF-κB (47). Additionally, morin inhibited ROS formation, caspase-3 activation, and apoptosis in MPP+-intoxicated PC12 cells (48). The concentration-dependent protection observed in the present study is consistent with these findings, suggesting that morin's polyphenolic structure enables effective ROS scavenging and modulation of apoptotic pathways.

Morin alone slightly reduced basal ROS levels and apoptosis, consistent with its intrinsic antioxidant capacity (23, 36). Although direct comparisons are limited by differences in experimental conditions (e.g., exposure duration, cell differentiation state), the protective concentrations of morin used here overlap with those reported to be effective in other oxidative stress models (47, 48). No conflicting results were identified in the literature regarding morin's neuroprotective role; however, variations in efficacy may arise from differences in ACR exposure protocols or cell line-specific responses.

Limitations of the study include reliance on a single cell line (undifferentiated PC12 cells) and the Use of DCF-DA and sub-G1 analysis as primary markers of oxidative stress and apoptosis, respectively. Complementary assays, such as measurement of antioxidant enzyme activities (e.g., SOD, catalase) or lipid peroxidation products (e.g., MDA), as well as specific caspase activity or TUNEL staining, could provide additional mechanistic insights. Furthermore, in vivo validation remains necessary to confirm translational relevance.

6. Conclusion

The results demonstrate that morin exerts neuroprotective effects against ACR-induced toxicity in PC12 cells, primarily by suppressing ROS production and inhibiting apoptosis. These findings support further

investigation of morin as a potential therapeutic agent in ACR-related neurotoxicity.

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Author contributions: Sh.Sh.: Contributed to the conception of the work, revising the draft, approving the final version of the manuscript, and agreeing on all aspects of the work; S. J.: Contributed to the conception and design of the study, drafting of the manuscript and critical revision, and approval of final version I.J., R.Gh, and A.Sh.F.: Contributed to the conception and design of the study, critical revision, and approval of the manuscript's final version.

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