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Quinic Acid Protects Human SH-SY5Y Neuroblastoma Cells Against Amyloid-β Cytotoxicity

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ABSTRACT

Objective: Alzheimer's disease is a progressive, widespread neurodegenerative illness and the most common type of dementia. Although this disease's exact mechanism is unknown, one of the most important factors is the formation of amyloid beta (Aβ) intercellular plaques. Quinic acid (QA) is a polyphenol that has neuroprotective effects because of its antioxidant properties. Our study aimed to investigate the in vitro protective effect of QA on Aβ peptide-induced oxidative neurotoxicity.

Methods: When the plated SH-SY5Y cell density reached 80%, 10 µM retinoic acid was applied for 5 days. Then, 50 µM Aβ1-42 dose was exposed for 48 hours. Then, they were treated with 50, 75 and 100 µM doses of QA. To determine the neuroprotective effect of QA, 3-4.5-dimethyl-thiazolyl-2.5-diphenyltetrazolium bromide (MTT) and the antioxidant-oxidant effects, total antioxidant capacity (TAC)-total oxidant status (TOS) analyses were performed.

Results: Aβ markedly decreased the viability of SH-SY5Y cells, as determined by MTT analysis. Moreover, Aβ decreased the activity of TAC in SH-SY5Y cells (p<.001). QA markedly balanced Aβ-induced TOS generation. Moreover, QA increased the activity of TAC in Aβ-exposed SH-SY5Y cells (p<0.05).

Conclusion: Our findings revealed the neuroprotective effect of QA through the prevention of Aβ-induced neurotoxicity and oxidative stress.

Keywords: Alzheimer's disease, Antioxidant, Neuroblastoma, Quinic acid

Introduction

Alzheimer's disease (AD) is a progressive, widespread neurodegenerative illness and is known as the most common type of dementia (Squitti et al., 2023). Dementia is characterized by the deterioration of cognitive functions and memory, such as learning, language functions, perception, orientation, recall, and personality, which affect a person's daily activities (Cipriani et al., 2020).

Although the pathological mechanism of AD is not known exactly, one of the most important factors leading to this illness is the generation of amyloid beta (Aβ) intercellular plaques, and the other is increased tau phosphorylation (Rajmohan & Reddy, 2017). Additionally, various works have documented the essential role of oxidative stress (OS) in the pathogenesis of this disease (Dhapola et al., 2024). Elevated levels of oxidized proteins, lipid peroxidation end products, and the generation of toxic species such as peroxides may play a role in the development of AD by promoting neurodegeneration and neuronal death (Dhapola et al., 2024; Gella & Durany, 2009). In addition, Aβ oligomers can promote the formation of reactive oxygen species (ROS), which further damage neurons and affect cognitive functions (Mecocci et al., 2018; Cheignon et al., 2018). Therefore, brain cells need an effective antioxidant mechanism to protect against the dangerous OS state in AD patients (Dhapola et al., 2024, Esmaeili et al., 2022).

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Although various pharmacological agents are currently known for their ability to treat AD, a more powerful or definitive treatment method has not yet been identified (Peng et al., 2023). Therefore, studies have been conducted to control the symptoms of this disease and slow its progression (Peng et al., 2023, Nelson & Tabet, 2015). Among these, research on the use of medicinal plants with antioxidant and anti-inflammatory features has become the focus of attention (Bordoloi et al., 2024). Phenolic-based natural compounds have been used for the treatment and reduction of progression of AD (González et al., 2019). The widespread use of phenolic products has made them a very popular treatment due to less toxicity and fewer side effects (Kim et al., 2019). Studies have confirmed the advantages of phenolic products such as resveratrol, quercetin (Ahmed et al., 2017), vitamins C and E, melatonin, curcumin, luteolin (Lee et al., 2013), rosmarinic acid and huperzine A in the treatment of AD (Laurent et al., 2014, Bui & Nguyen, 2017). Many polyphenol compounds show their activity by blocking the oligomer formation of Aβ1–40 and Aβ1–42, as well as tau in vitro (Na et al., 2017, Ono et al., 2020, Cao et al., 2020). Quinic acid (QA) is a polyphenol found in various plants and microorganisms (Liu et al., 2024). QA cannot be synthesized by mammals, including humans. This molecule, taken through the diet, helps in the synthesis of tryptophan and nicotinamide in the gastrointestinal tract, which ultimately contributes to DNA repair (Pero et al., 2009). Notably, in the literature, QA has neuroprotective features because of its antioxidant properties (Liu et al., 2024, Li et al., 2024). Furthermore, while the ability of natural products to penetrate the blood–brain barrier is restricted, previous experimental results suggest that QA can cross the blood–brain barrier for neuroprotection (Park et al., 2024). There are a limited number of works in the literature investigating the protective effect of QA against AD, and more detailed research is needed. Our study aimed to investigate the in vitro protective effect of QA on Aβ peptide-induced oxidative neurotoxicity.

Methods

Cell culture procedure

In this study, the SH-SY5Y cell line was obtained from American Tissue Cell Culture (ATCC) to establish an in vitro AD model. The cells were grown in 25 cm2 flasks in DMEM containing 1% L-glutamine, 10% FBS, and 1% penicillin/streptomycin (Sigma–Aldrich, Massachusetts, USA) in a 5% CO2 incubator. The cells were passaged with EDTA when they covered 80% of the flask (Kovalevich & Langford, 2013). SH-SY5Y cells were differentiated with 10 µM retinoic acid (Cayman Chemical, USA) for 5 days before QA application (Lee et al., 2015). Differentiated cells were exposed to fresh medium containing 50 µM Aβ1-42 (Cayman Chemical, USA) and incubated for 48 h (Celik Topkara et al., 2022). Then, doses of QA 50, 75, and 100 µM were administered (Murugesan et al., 2020).

Biochemical analysis

Cell viability was determined via the MTT method on the basis of colorimetric measurements. MTT solution (Sigma–Aldrich, Massachusetts, USA) was added to the wells according to the kit protocol and instructions. Afterwards, the cells were incubated in a 37°C CO2 incubator for 3 h. After incubation, the formazan precipitate was dissolved by adding 150 µL of DMSO, and the absorbance value was read at 480 nm (BioTek Instruments, Vermont, USA).

To determine oxidative stress, total antioxidant capacity (TAC)-total oxidant status (TOS) levels in the samples were determined via the automatic measurement method developed by Erel and commercially available kits (Rel Assay Diagnostics, Gaziantep, Türkiye) (Erel, 2004; Erel, 2005).

Statistical analysis

Statistical comparisons of multiple groups were assessed using one-way ANOVA and post hoc Tukey test using IBM SPSS (Armonk, NY, USA) version 23.0 software. In this study, P values less than .05 ($p<.05$) and .001 ($p<.001$) were considered statistically significant. We considered significant as this indicated that the observed results were unlikely to be due to chance. The data were expressed as mean (SD), which allowed us to show the mean value for each group along with the variation or spread of the data around the mean.

Results

The neuroprotective effect of QA against Aβ-induced cytotoxicity in SH-SY5Y cells

Compared with control treatment, treatment with 50 µM Aβ for 48 hours markedly decreased cell viability (55%) ($p<0.001$). However, treatment with QA (50, 75, and 100 µM) reversed Aβ-induced cell death in a concentration-dependent manner compared with that in the Aβ group (65%, 78%, and 97%, respectively) (Figure 1) ($p<0.05$).

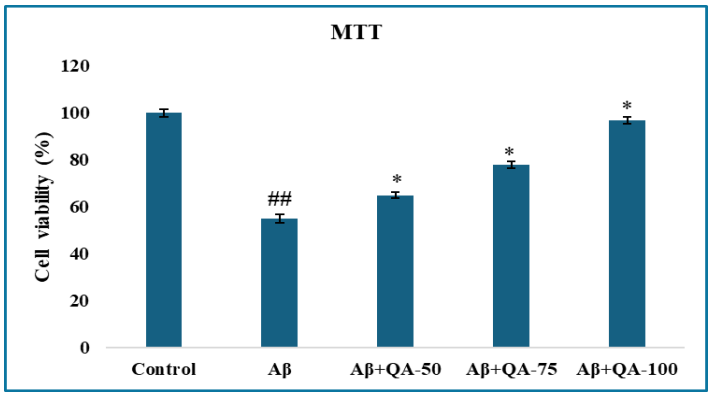

Figure 1. Protective effects of QA against Aβ-induced death in SH-SY5Y cells. ##p<0.001 vs the control group, *p<0.05 vs the Aβ group.

Protective effect of QA on oxidative stress-induced Aβ-induced cytotoxicity in SH-SY5Y cells

We performed a TOS test on the basis of H2O2 equiv/mmol L-1 (Figure 2). Aβ (12 H2O2 mmol/L) significantly increased oxidant TOS levels in the cell culture supernatant (p<0.001). However, treatment with QA (50, 75, and 100 µM) increased the levels of TOS excited by Aβ in a dose-dependent manner (10, 9, and 7 H2O2 equivalents/mmol L-1, respectively) (p<0.05).

We appraised the TAC level on the basis of Trolox equiv/mmol L-1 (Figure 2). Aβ decreased the level of TAC in SH-SY5Y cells by 7 Trolox equiv/mmol L-1 (p<0.001). However, treatment with QA (50, 75, and 100 µM) decreased the levels of TAC produced by Aβ in a dose-dependent manner (9, 11, and 13 Trolox equiv/mmol L-1, respectively) (p<0.05).

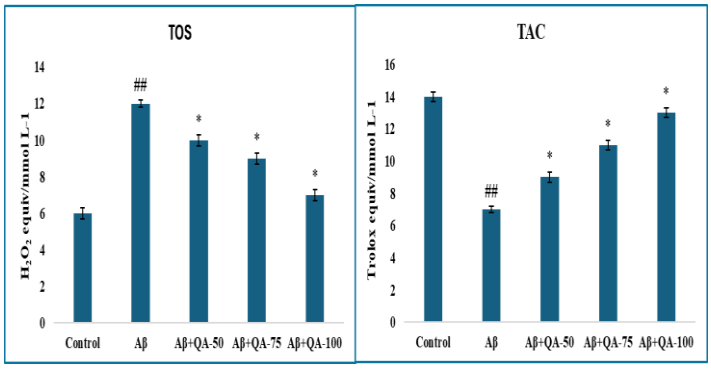

Figure 2. The effects of QA on OS-connected biomarkers in Aβ-excited SH-SY5Y cells. ##p<0.001 vs the control group, *p<0.05 vs the Aβ group.

Discussion

This report aimed to demonstrate the possible protective role of QA on oxidative stress in SH-SY5Y cells treated with Aβ, a neurotoxic protein responsible for the pathogenesis of AD. SH-SY5Y cells are among the most common cell lines employed to create a cellular AD model in vitro to investigate Aβ neurotoxicity, as they display many of the biochemical and functional properties of neurons (Zafeer et al., 2018). Therefore, we preferred to use the SH-SY5Y cell line to create an AD model in our research. In addition, according to our in vitro findings in the present study, the reduction in cell viability in the AD-induced group was prevented by QA, and the viability rate increased; thus, QA had a neuroprotective effect.

Different studies have shown that OS plays a main role in the etiopathogenesis of AD (Dhapola et al., 2024; Gella & Durany, 2009; Mecocci et al., 2018; Cheignon et al., 2018). Previous studies have revealed high intracellular ROS concentrations and reduced superoxide dismutase activity and glutathione peroxidase antioxidant enzyme levels after the treatment of SH-SY5Y cells with Aβ (Zhang et al., 2019; Ji et al., 2019). In another report on Aβ-induced cytotoxicity in SH-SY5Y cells, the amount of ROS in the cells markedly increased as a result of Aβ treatment compared with that in the control group (He et al., 2023). In this report, a TOS measurement was performed to evaluate oxidant levels. Our experimental results revealed that the TOS level was greater in the Aβ-treated group than in the control group. There are many types of oxidant molecules. One-by-one measures of these oxidants increase the cost. Therefore, in the present study, all the ROS were determined via TOS analysis (Erel, 2005). In line with the literature, our findings indicated that the TOS level was high in the Aβ group, indicating that the antioxidant defense system is inadequate for protecting neurons against Aβ. In addition, detecting alterations in antioxidant levels in neuronal injury caused by oxygen radicals is one of the frequently preferred methods. TAC is exploited to prevent the cumulative antioxidative effects of all antioxidants in organisms (Erel, 2004). In the present study, TAC levels decreased in parallel with increasing TOS levels in SH-SY5Y cells treated with Aβ. However, QA, which affects Aβ-related damage in SH-SY5Y cells, markedly suppressed the level of TOS, an oxidative stress marker, in the AD group, revealing that QA exhibited antioxidant effects in the in vitro AD model. In addition, the elevation in TAC levels with QA application, which decreased with Aβ application in cells, indicates that QA also induces an increase in cumulative antioxidant activation to eliminate the toxic effects of free radicals.

Antioxidants are compounds that can scavenge free radicals in the human body. QA inhibits hydroxyl radical

formation and is considered an antioxidant for lipid peroxidation (Hwang et al., 2009). Caffeoyl conjugates and carboxy-methyl forms of QA showed inhibitory activity on lipid peroxidation in rat liver microsomes (Góngora et al., 2003). Experiments on mice have shown that QA has neuroprotective effects on dementia (Liu et al., 2020). In addition, QA derivatives have shown neuroprotective effects against β-amyloid peptide and neurotrophic activity in PC12 cells (Soh et al., 2003). In addition, QA has been found to have anti-inflammatory properties by inhibiting the pro-inflammatory transcription factor called nuclear factor kappa B (Pero et al., 2009). Studies have shown that 3,4-di-O-caffeoylquinic acid is effective in treating or preventing neurodegenerative diseases associated with oxidative stress. It is thought to be a potential therapeutic agent (Kim et al., 2005). In our study, QA increased cell viability and improved OS parameters at the cellular level in an in vitro AD model, suggesting that QA probably has protective effects by suppressing neuronal oxidative damage. These findings were also consistent with previous studies reporting that QA has a neuroprotective effect by exerting an antioxidant effect (Liu et al., 2020, Li et al., 2024).

Conclusion and Recommendations

Our findings suggest that QA has neuroprotective properties by preventing neuronal cell death caused by oxidative stress induced by AB and restoring TAC levels. These properties of QA may be useful in improving therapeutic protection as well as in the treatment of neurodegenerative diseases such as AD. In this study, the beneficial effects of QA on Aβ-induced neurotoxicity in SH-SY5Y cells in terms of cell viability and OS were reported. However, further studies are needed to precisely determine the mechanism by which QA exerts neuroprotection.

Ethics Committee Approval: Ethical approval isn't necessary because commercially present cell lines are used in an in vitro study.
Informed Consent: Since it is an in vitro study, participant consent is not required.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept – BC, YY; Design- BC, YY; Materials – BC, YY; Data Collection and/or Processing–BC, YY; Analysis and/or Interpretation – BC, YY; Literature Search –BC, YY; Writing Manuscript– BC, YY; Critical Review – BC, YY; Other–YY.
Conflict of Interest: The authors have no conflicts of interest to declare.
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