



Effect of Quinolinic Acid on Behavior, Morphology, and Expression of Inflammatory/oxidative Status in Rats' Striatum: Is Coenzyme Q₁₀ a Good Protector?

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Abstract

Quinolinic acid (QUIN) is a toxic compound with pro-oxidant, pro-inflammatory, and pro-apoptotic actions found at high levels in the central nervous system (CNS) in several pathological conditions. Due to the toxicity of QUIN, it is important to evaluate strategies to protect against the damage caused by this metabolite in the brain. In this context, coenzyme Q₁₀ (CoQ₁₀) is a provitamin present in the mitochondria with a protective role in cells through several mechanisms of action. Based on these, the present study was aimed at evaluating the possible neuroprotective role of CoQ₁₀ against damage caused by QUIN in the striatum of young Wistar rats. Twenty-one-day-old rats underwent a 10-day pretreatment with CoQ₁₀ or saline (control) intraperitoneal injections and on the 30th day of life received QUIN intrastratial or saline (control) administration. The animals were submitted to behavior tests or euthanized, and the striatum was dissected to neurochemical studies. Results showed that CoQ₁₀ was able to prevent behavioral changes (the open field, object recognition, and pole test tasks) and neurochemical parameters (alteration in the gene expression of IL-1 β , IL-6, SOD, and GPx, as well as in the immunoprotein content of cytoplasmic Nrf2 and nuclear p-Nf- κ β) caused by QUIN. These findings demonstrate the promising therapeutic effects of CoQ₁₀ against QUIN toxicity.

Keywords Quinolinic acid · Coenzyme Q₁₀ · Behavior · Morphological analysis · Gene expression · Nrf2 · p-Nf- κ β

Introduction

The kynurenine pathway is the main degradation pathway for the amino acid tryptophan. This pathway is responsible for the formation of metabolites that participate in

several physiological processes, for example, quinolinic acid (QUIN) (Liang et al. 2022), which is an important N-methyl-D-aspartate (NMDA) receptor agonist found in low concentrations in the brain under physiological conditions. However, in situations of brain injury, its production by microglial cells and activated macrophages increases considerably, possibly leading to central nervous system (CNS) damage (La Cruz et al. 2013; Liang et al. 2022).

Several studies show that the increase in QUIN concentrations is related to neurodegenerative diseases and animal models that use this compound can reproduce brain damage found in Parkinson's and Huntington's diseases (Colle et al. 2012; Antunes Wilhelm et al. 2013; Mor et al. 2021). The neurotoxic effects of QUIN can be observed through cognitive and motor damage (Pierozan et al. 2014) and are caused by several mechanisms of action, such as oxidative and inflammatory changes. QUIN at high levels is responsible for increasing the production of reactive oxygen and nitrogen species and impairs the production of enzymes

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and antioxidant compounds (Guillemin 2012; La Cruz et al. 2013). Furthermore, the increase in the production of this compound may lead to a positive feedback mechanism. The cells (microglial cells and macrophages) that act as inflammatory mediators lead to more production of QUIN, and an increase in its concentration leads to the activation of these cells, which may increase the levels of inflammatory markers in the brain (Kalonias et al. 2011; Guillemin 2012; Braidy and Grant 2017).

Due to neurotoxicity of QUIN, it is necessary to evaluate protection strategies against the damage caused by this compound on the CNS. In this context, coenzyme Q₁₀ (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone, CoQ₁₀) is a compound found in the inner mitochondrial membranes responsible for receiving electrons from complexes I and II and transferring them to complex III, besides being an important component in maintaining the electrochemical gradient of mitochondria (Aaseth et al. 2021). It is present in all cells but is found in high concentrations in the brain, heart, and liver. CoQ₁₀ production can happen endogenously or it can be obtained from the diet, and it is found in two forms in cells: oxidized (ubiquinone) and reduced (ubiquinol). In the form of ubiquinol, it has an important antioxidant role, preventing the oxidation of lipids and proteins and protecting DNA from damage by free radicals. In addition, it is directly related to the activation of anti-inflammatory mechanisms (Aaseth et al. 2021; Pallotti et al. 2022). Recent *in vivo* and *in vitro* studies demonstrate its protective role in a model of neurodegenerative diseases. In addition, clinical studies showed that its supplementation in patients was able to reduce cardiovascular damage (Spindler et al. 2009; El-Aal et al. 2017; Hargreaves et al. 2020; Pallotti et al. 2022).

The present study was aimed at evaluating the possible neuroprotective role of CoQ₁₀ supplementation in an animal model of intrastriatal administration of QUIN, analyzing behavioral, morphological, inflammatory, and oxidative status parameters. Our hypothesis is that CoQ₁₀ is able to prevent damage caused by QUIN in the analysis performed on this study.

Materials and Methods

Animals and Reagents

Twenty-one-day-old male Wistar rats were obtained from the Central Animal House of the Department of Biochemistry of the Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. These animals were maintained under a dark–light cycle and a controlled temperature (22 ± 1 °C) with free access to a water and protein chow. Animals' experimental procedures were performed following the official guidelines as "Principles of Laboratory Animal Care"

(NIH publication 85–23, revised 1996) and Arouca Law (11,794/2008) and were approved by the University's Ethics Committee (CEUA) under project #35,442.

Quinolinic acid, coenzyme Q₁₀, acrylamide, bisacrylamide, SDS, cresyl violet, and other chemical analytical reagents used for analysis were obtained from Sigma-Aldrich, St Louis, MO, USA. Antibodies anti-Nrf2, anti-phospho-NF- κ B, and anti-GFAP were purchased from Abcam, Santa Cruz Biotechnology, and Cell Signaling Technology, respectively.

Pretreatment with Coenzyme Q₁₀

The animals received a daily intraperitoneal injection of CoQ₁₀ from the 21st to the 30th day of life, at a dose of 10 mg per kilogram of animal body weight (with an administration volume of approximately 150 μ L), according to a protocol adapted from Rauscher et al. (Rauscher et al. 2001). Due to its lipophilic character, CoQ₁₀ was initially dissolved with Tween 20 and later with NaCl 0.9% solution, resulting in a homogeneous solution. Control animals received an equivalent volume of saline solution.

Intrastriatal Administration of QUIN

The animals were anesthetized with solution containing thiopental (2.5 mg/kg *i.p.*) and were positioned in a stereotaxic apparatus with the skull exposed. The injections were performed with a Hamilton microsyringe into the right striatum, using the following coordinates: 0.6 mm posterior to the bregma, 2.6 mm lateral to the midline, and 4.5 ventral from dura (Paxinos and Watson 2006). The experiments used 150 nM/0.5 μ L of QUIN or saline-phosphate buffer (PBS), based on previous studies (Pierozan et al. 2014; Ferreira et al. 2020). The correct position of the needle was tested by 0.5 mL of methylene blue injection (4% in saline solution) and carrying out histological analysis. After the surgery, the animals used for behavior tests received tramadol 5 mg/kg subcutaneous twice a day for 72 h. Animals were sacrificed by decapitation without anesthesia 60 min after surgery or behavior analysis, and the striata were dissected and used for biochemical and morphological analysis.

Behavior Analysis

Open Field

Three days after surgery, animals were submitted to the open field test for 2 days (training and test) (adapted from Sanches et al. (Sanches et al. 2013)). This task was used for analyzing motor function, exploratory behavior, and anxiety. The open field apparatus consists of a regular box (50 \times 50 \times 40 cm) virtually divided into 16 squares. Each rat was placed in

the center of the apparatus and their activity was recorded for 10 min and evaluated by mean speed, distance traveled, immobile time, number of line crossing, and percent of the time on the periphery about the total. The camera was placed above the apparatus and ANY-maze software was used to analyze the data.

Novel-Object Recognition

One day after the open field test, animals performed the novel-object recognition, a test used to investigate cognitive processes such as memory and learning (adapted (Ennaceur and Delacour 1988; Pamplona et al. 2009)). This task was performed on the open field apparatus for 2 days (training, test 3 h, and test 24 h). In the training session, a rat was placed on the apparatus with two similar objects and the time exploring each object was recorded for 5 min. To evaluate the short-term memory, the second session followed after 3 h. Rats were placed back on the apparatus with one familiar and one new object. Their time exploring each object was again evaluated for 5 min. After 24 h, the third session was realized, to evaluate the long-term memory, using the same protocol as the second session. The object discrimination index was calculated in the test sessions, as follows: the difference in exploration time divided by the total time spent exploring the two objects $\{[(B - A1)/(A1 + B)]$ where B is the new object and $A1$ is the familiar object}. The objects using were constructed with plastic LEGO blocks. The objects A and B had a different form, but were similar in complexity and had the same color and texture.

Beam Walking

Rats were submitted to the beam walking task to evaluate motor coordination and balance (Carter et al. 2001). In the training session, animals crossed a narrow wooden beam (width 2.5 cm, length 100 cm). The beam was elevated 50 cm above the floor by two acrylic boxes. The animals were placed on one side, with a safe place (a black box) on the other side, encouraging the animals to walk on the beam. In the test session, after 24 h, the mean of crossing time and the mean of errors committed during the crossing were analyzed.

Pole Test

The rats were submitted to the vertical pole test (Ramires Júnior et al. 2021), a task used for measuring bradykinin in models of neurodegeneration diseases. The apparatus consisted of a vertical wooden pole (50 cm in length and 0.8 cm in diameter), wrapped with sticking plaster to increase traction, and mounted on a horizontal support. In the training session, the animals were placed facing down

on the top of the pole, and the latency to climb down the pole was measured. Three trials were performed, and each test had a maximum time of 60 s for the animal to perform the descent. Animals unable to perform the task were guided to the base of the pole. In the test session (after 24 h), the animals were placed head up on the top of the pole. The time to turn head down (latency for the beginning of the movement) and the time to go down and touch the four paws on the floor were recorded.

Morphological Analysis

The animals were anesthetized with thiopental and transcardiac perfused with saline solution (0.9%) followed by paraformaldehyde (4%) with phosphate buffer. Brains were removed and post-fixed for 4 h, then were cryoprotected with 15% and 30% sucrose solution and frozen in liquid nitrogen. Using a cryostat, serial Sects. (20 μm) were obtained of the striatum. For cresyl violet technique (Deniz et al. 2018), sections were rehydrated and stained with 5% cresyl violet (Sigma-Aldrich, St. Louis, MO, USA) for 3 min, dehydrated in increasing concentrations of ethanol followed by xylene, and coverslipped. The number of cells was counted bilaterally in 4 sections per animal, 4 animals/group (area, 531,944 μm^2) using an Olympus BX40 microscope (magnification of $\times 400$). For GFAP immunofluorescence (Segabinazi et al. 2020), sections were washed three times in PBS solution (5 min each wash) followed by PBS-Tx (PBS containing 0.4% Triton X-100) for 10 min and were incubated with BSA 3%. After 30 min, the sections were incubated with monoclonal mouse anti-GFAP antibody (1:300) for 48 h at 4 °C. They were washed with PBS three times and incubated with secondary antibody rabbit anti-mouse IgG conjugated with peroxidase (1:500; Sigma-Aldrich) for 2 h at dark and room temperature. Fluoromount-G Mounting Medium with DAPI (Sigma-Aldrich) was used for mounting the slides evaluated in the fluorescence microscope (Nikon Eclipse E-600, Japan) coupled to a digital camera. The fluorescent labeling to GFAP in each image was evaluated from the mean of the integrated density of three areas of interest (AOIs), each measured 2,458,719 μm^2 , using ImageJ v. 1.80_112 software (IBM, USA). Data are reported as relative density (% of control).

Quantitative Real-Time PCR (RT-qPCR)

Total RNA was isolated from the hippocampus using the TRIzol[®] reagent (Thermo Fisher Scientific, Rockford, IL, USA) according to the manufacturer's instructions. Total RNA was quantified using a ND-1000 spectrophotometer (NanoDrop), and cDNA was synthesized from 1 μg of total RNA using the High-Capacity cDNA Reverse Transcription Kit with RNase Inhibitor (Thermo Fisher Scientific,

Rockford, IL, USA). The HOT FIREPol® Evagreen® qPCR Supermix (Solis Biodyne, Denmark) was used for RT-qPCR to detect double-stranded DNA synthesis. Reactions were carried out in a final volume of 10 μ L, using 2 μ L of diluted cDNA (1:10) and 300 nM each of reverse and forward primers. The following primers were used: I11b 5'-CTATGTCTTGCCCGTGGAG-3' (forward) and 5'-CATCATCCCACGAGTCACA-3' (reverse); I16 5'-CTCCGC AAGAGACTTCCAG-3' (forward) and 5'-CTCCTCTCC GGACTTGTGA-3' (reverse); Tnf 5'-ACAAGCCCGTAG CCCACGTC-3' (forward) and 5'-AGGAGCACGTAGTCG GGGCA-3' (reverse); I110 5'-GCTGGACAACATACT GCTAAC-3' (forward) and 5'-ATTTCCGATAAGGCT TGGCAA-3' (reverse); MCP-1 5'-CCAACCACAGG CTACAGG-3' (forward) and 5'-GCGTCACACTCAAGC TCTG-3' (reverse); CAT 5'-GAGGCAGTGTACTGCAAG TTCC-3' (forward) and 5'-GGGACAGTTCACAGGTAT CTGC-3' (reverse); SOD 5'-GCAGGGCGTCATTCACCT -3' (forward) and 5'-AGACTCAGACCACATAGGGA-3' (reverse); GPx 5'-CAGTTCGGACATCAGGAGAAT-3' (forward) and 5'-AGAGCGGGTGAGCCTTCT-3' (reverse); and Gapdh 5'-GGTGAAGGTCGGTGTGAAC-3' (forward) and 5'-CGTTGATGGCAACAATGTC-3' (reverse). Reactions were performed in a 7500 Fast Real-Time System (Applied Biosystems, Foster City, CA, USA). The relative gene expression was calculated using the comparative cycle threshold (Ct) method ($\Delta\Delta$ Ct) and normalized to the level of the control group. Gapdh was used as the endogenous control, and the results are expressed as relative expression of the gene of interest/Gapdh.

Cytosol and Nucleus Cellular Fractionation and Western Blotting

To obtain cytosolic and nuclear fractions, samples were homogenized in 300 μ L hypotonic lysis buffer (10 mM HEPES (pH 7.9), 1.5 mM $MgCl_2$, 10-mM KCl, 0.5 mM phenylmethylsulfonyl fluoride (PMSF), 1 mM dithiothreitol (DTT), 5 mM NaF, and 1 mM sodium orthovanadate plus protease inhibitor cocktail). Samples homogenates were then lysed with 18 μ L 10% IGEPAL. The homogenates were centrifuged (14,000 \times g, 30 s, 4 $^{\circ}$ C), and supernatants containing the cytosolic fraction were stored at -80° C. The nuclear pellet was resuspended in 200 μ L ice-cold hypertonic extraction buffer (10 mM HEPES (pH 7.9), 0.40 M NaCl, 1.5 mM $MgCl_2$, 10 mM KCl, 0.5 mM PMSF, 1 mM DTT, 5 mM NaF, 1 mM sodium orthovanadate, 0.25 mM EDTA, 25% glycerol plus protease inhibitor cocktail). After 40 min of intermittent mixing, extracts were centrifuged (14,000 \times g, 10 min, 4 $^{\circ}$ C), and supernatants containing nuclear protein were secured. For electrophoresis analysis, aliquot samples were dissolved in 25% (v/v) of a solution containing 40% glycerol, 5% mercaptoethanol,

and 50 mM Tris-HCl, pH 6.8. Western blotting was performed as described (Biasibetti-Brendler et al. 2017). For electrophoresis analysis, the fractions previously prepared were homogenized in 200 μ L of a lysis solution (2 mM EDTA, 50 mM Tris-HCl, pH 6.8, and 4% sodium dodecyl sulfate (SDS)). Then, samples were dissolved 1:1 in Laemmli buffer 2 \times containing 40% glycerol, 5% 2-mercaptoethanol, 50-mM Tris-HCl, pH 6.8, and 10% SDS and boiled for 5 min. Total protein homogenate was separated by 10% SDS-PAGE (30 μ g/lane of total protein) and transferred (Trans-Blot SD Semi-Dry Transfer Cell, Bio-Rad) to nitrocellulose membranes for 1 h at 15 V in transfer buffer (48 mM Trizma, 39 mM glycine, 20% methanol, and 0.25% SDS). The blot was then incubated overnight at 4 $^{\circ}$ C in a blocking solution containing 5% bovine serum albumin (BSA) and the antibodies anti-Nrf2 (1:1000, Abcam) and p-Nf- κ B (1:1000, Santa Cruz Biotechnology). The blot was washed twice for 5 min with T-TBS and twice for 5 min with TBS and incubated with peroxidase-conjugated anti-mouse IgG and anti-rabbit IgG (Cell Signaling Technology), both diluted 1:1000. The blot was developed using a chemiluminescence kit (Immobilon Western Chemiluminescent HRP Substrate, Millipore) and detected by ImageQuant LAS 4000 (GE Healthcare Life Sciences).

Protein Determination and Statistical Analysis

The protein content of samples was determined using BSA as standard, according to Lowry et al. (Lowry et al. 1951).

The data were analyzed by two-way analysis of variance (ANOVA) followed by post hoc Tukey's test. Values of $p < 0.05$ were considered statistically significant. Data were evaluated for normality by the Shapiro-Wilk test. No outliers were excluded. All analysis and plots were performed using GraphPad Prism 8.0 software program on a compatible computer.

Results

Initially, behavioral analyses were performed. The first task performed was the open field; Fig. 1 shows that the group that received the QUIN injection had an increase in the average speed (A), the distance traveled (B), and the number of line crossings (C), in addition to a decrease in the percentage of time exploring the periphery about the total (E) ($F(1,35) = 6.269$, $p < 0.05$; $F(1,35) = 5.636$, $p < 0.05$; $F(1,35) = 4.649$, $p < 0.05$; and $F(1,35) = 7.388$, $p < 0.05$, respectively). Pretreatment with CoQ₁₀ was able to prevent the alteration of these parameters caused by QUIN ($F(1,35) = 11.08$, $p < 0.01$; $F(1,35) = 9.923$, $p < 0.01$; $F(1,35) = 14.52$, $p < 0.001$; and $F(1,35) = 7.468$, $p < 0.01$, respectively). There was

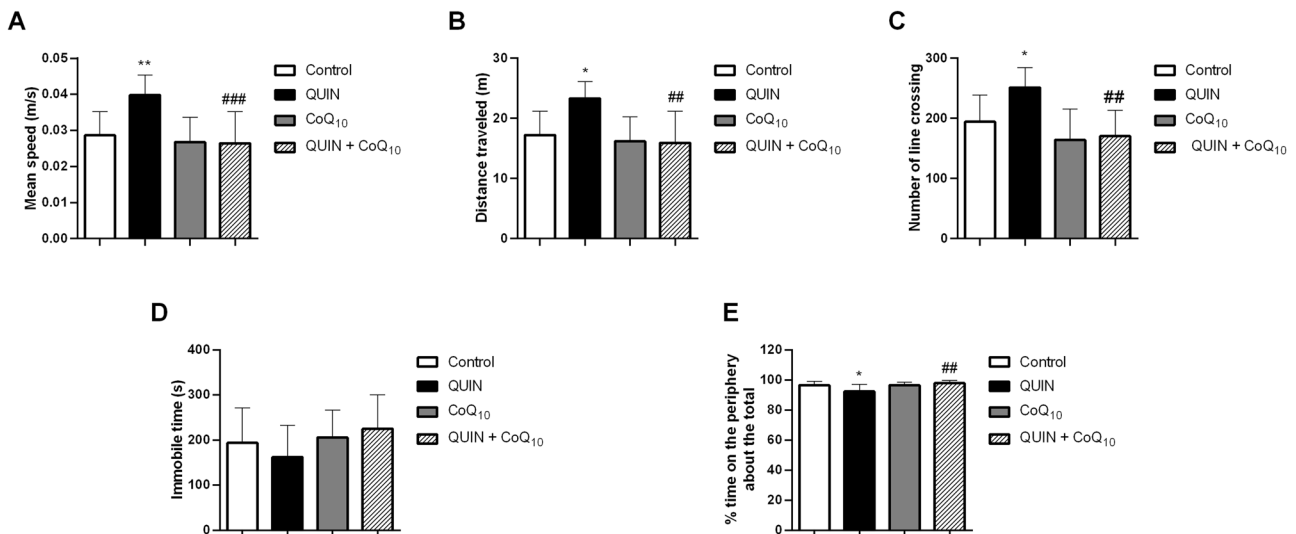


Fig. 1 Protective effect of CoQ₁₀ on QUIN-treated striatum on open field task: mean speed (A), distance traveled (B), number of line crossings (C), immobile time (D), and percent time on the periphery about the total (E). Results are expressed as mean ± SD of *n* = 9

animals per group. **p* < 0.05 and ***p* < 0.01 compared to the control group; ##*p* < 0.01 and ###*p* < 0.001 compared to the QUIN group (two-way ANOVA followed by Tukey’s post hoc test)

no significant variation in the assessment of the immobile time of the animals during the test (D) (*p* > 0.05).

After 24 h, the animals were submitted to the object recognition task (Fig. 2). The tests performed 3 h (b) and 24 h

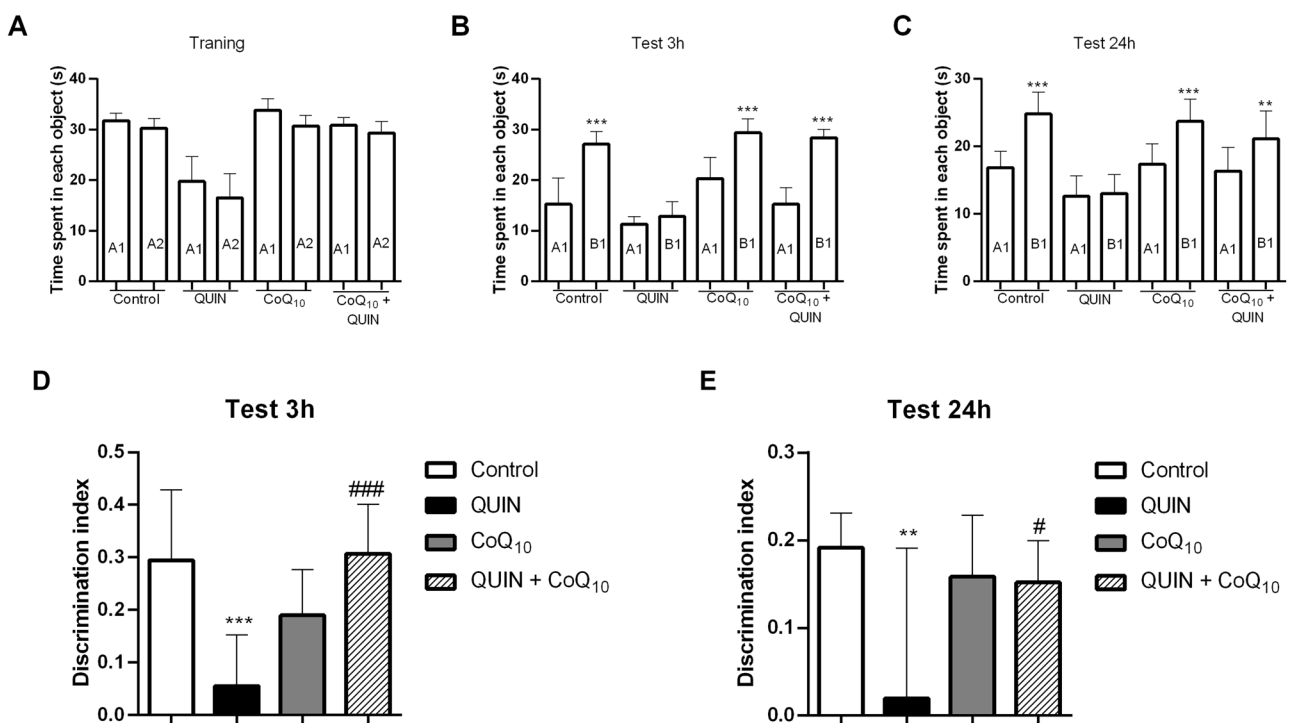


Fig. 2 Effect of CoQ₁₀ on QUIN-treated striatum on novel-object recognition task: time spent in each object on training (A), time spent in each object on test 3 h after training (B), time spent in each object on test 24 h after training (C), discrimination index in test 3 h after training (D), and discrimination index in test 24 h after training

(E). Results are expressed as mean ± SD of *n* = 9 animals per group. ***p* < 0.01 and ****p* < 0.001 compared to the control group; #*p* < 0.05 and ###*p* < 0.001 compared to the QUIN group (two-way ANOVA followed by Tukey’s post hoc test)

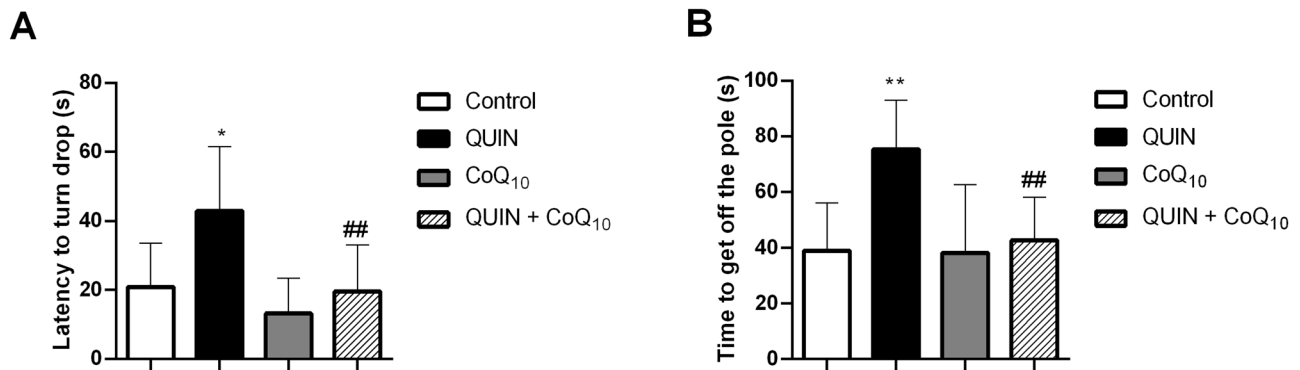


Fig. 3 Protective effect of CoQ₁₀ on QUIN-treated striatum on the pole test: latency to turn drop (A) and time to get off the pole (B). Results are expressed as mean \pm SD of $n=9$ animals per group.

(c) after training showed that control animals spent more time exploring the new object (B1), while animals QUIN-treated explored the familiar object (A1) and the new object (B1) at the same time. CoQ₁₀ per se did not cause changes when compared to the control. CoQ₁₀ was able to prevent changes in the tests performed 3 and 24 h after training, as observed in the discrimination index (Fig. 2d, e) ($F(1.38)=29.73$, $p<0.001$; $F(1.38)=8.080$, $p<0.01$, respectively).

In the pole test (Fig. 3), we observed that animals that received QUIN injections showed a significant increase in latency time to initiate movement (A) and also in descent time (B) when compared to control animals ($F(1.31)=8.691$, $p<0.01$ and $F(1.31)=10.27$, $p<0.01$, respectively). Pretreatment with CoQ₁₀ was able to prevent these changes ($F(1.31)=10.35$, $p<0.01$ and $F(1.31)=6.879$, $p<0.01$, respectively). No significant changes were found in the parameters evaluated in the beam walking test (Fig. 4a, b, $p<0.05$).

To evaluate inflammatory and oxidative changes, the gene expression of cytokines, chemokines, and antioxidant enzymatic defenses was analyzed. Figure 5 shows that the administration of QUIN was able to increase the expression of TNF- α

* $p<0.05$ and ** $p<0.01$ compared to the control group; ## $p<0.01$ compared to the QUIN group (two-way ANOVA followed by Tukey's post hoc test)

(A), IL-1 β (B), IL-6 (C), and MCP-1 (E) ($F(1.16)=5.574$, $p<0.05$; $F(1.16)=5.023$, $p<0.05$; $F(1.16)=6.516$, $p<0.05$; and $F(1.16)=7.70$; $p<0.05$, respectively), and CoQ₁₀ per se was able to alter the expression of TNF- α and MCP-1 ($F(1.16)=22.64$, $p<0.01$; $F(1.16)=17.07$, $p<0.01$). CoQ₁₀ prevented the alteration of IL-1 β completely and IL-6 partially ($F(1.16)=4.967$ and $F(1.16)=0.03$, respectively), in addition to causing an increase in TNF- α , IL-10, and MCP-1 when compared to control ($F(1.16)=22.64$, $p<0.01$; $F(1.16)=38.64$, $p<0.001$; and $F(1.16)=32.42$, $p<0.001$, respectively).

In Fig. 6, we observed that the administration of QUIN led to a decrease in the expression of CAT (A), SOD (B), and GPx (C) enzymes when compared to the control ($F(1.14)=33.35$, $p<0.01$; $F(1.18)=24$, $p<0.01$; and $F(1.20)=6.267$, $p<0.05$, respectively) and that CoQ₁₀ prevented the decrease found in the expression of SOD and GPx ($F(1.18)=43.40$, $p<0.001$ and $F(1.20)=5.027$, $p<0.05$, respectively).

We evaluated the immunocontent levels of transcription factors Nrf2 and p-Nf- κ B in the cytosolic and nuclear fractions of the striatum of treated animals (Fig. 7). We observed that QUIN administration decreased cytoplasmic Nrf2 (A) and nuclear p-Nf- κ B (D) immunocontent when compared

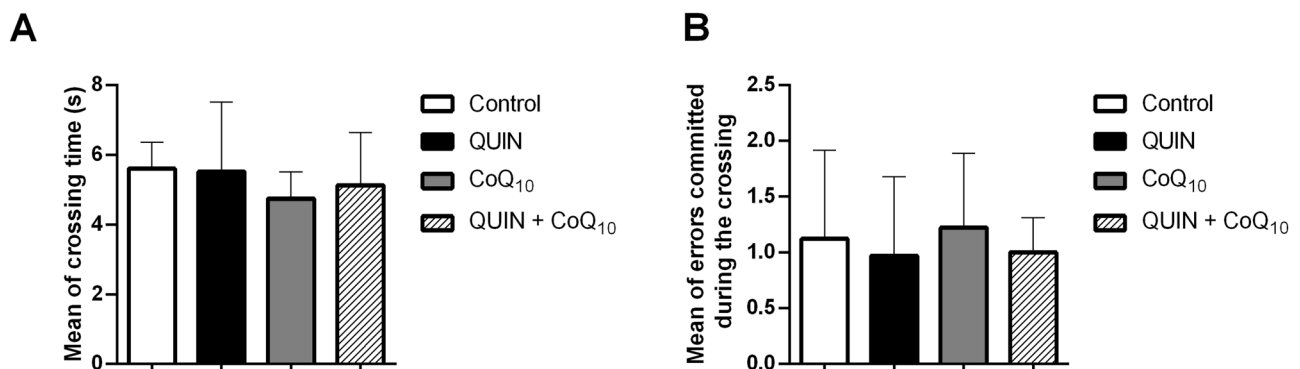


Fig. 4 Effect of CoQ₁₀ on QUIN-treated striatum on the beam walking test: mean of crossing time (A) and mean of errors committed during the crossing (B). Results are expressed as mean \pm SD of $n=9$ animals per group (two-way ANOVA followed by Tukey's post hoc test)

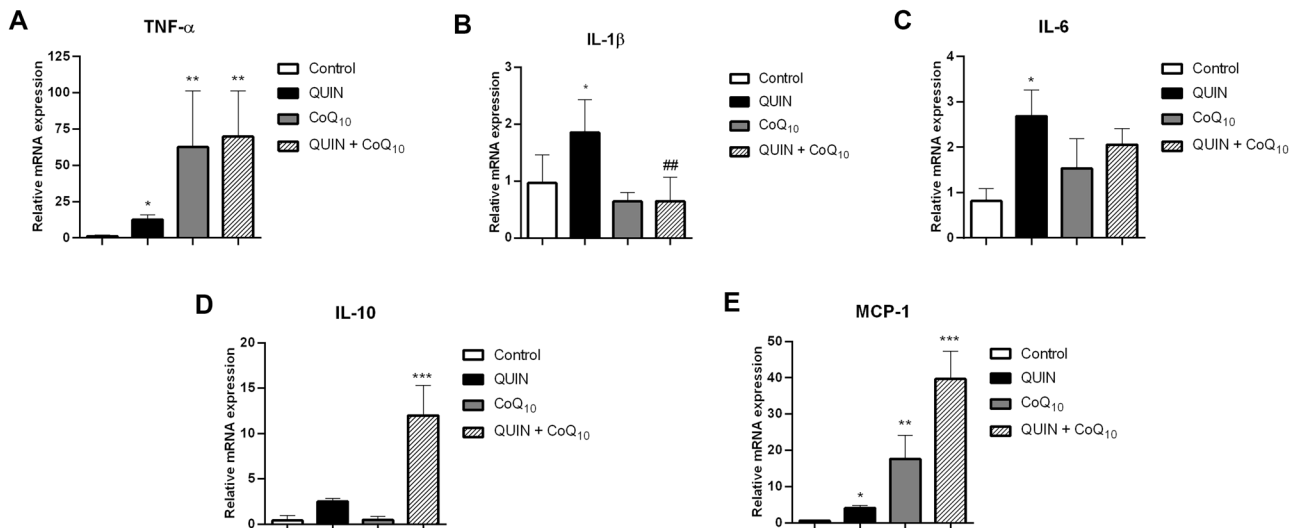


Fig. 5 Protective effect of CoQ₁₀ on QUIN-treated striatum on gene expression of inflammatory markers: TNF- α (A), IL-1 β (B), IL-6 (C), IL-10 (D), and MCP-1 (E). Results are expressed as mean \pm SD of

$n=5$ animals per group. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ compared to the control group; ## $p < 0.01$ compared to the QUIN group (two-way ANOVA followed by Tukey's post hoc test)

to control ($F(1.16) = 6.33$, $p < 0.01$ and $F(1.12) = 4.596$, $p < 0.05$, respectively). Pretreatment with CoQ₁₀ was able to prevent the alteration of Nrf2 and partially prevent the alteration of p-Nf- κ B ($F(1.16) = 6.254$, $p < 0.01$ and $F(1.12) = 1.922$, respectively). CoQ₁₀ per se did not cause significant changes when compared to the control.

With regard to morphological parameters, no significant results were observed in the labeling of neurons with cresyl violet and in the immunoccontent of GFAP in the striatum of rodents submitted to QUIN (Table 1 and Fig. 8). In Fig. 8, we have the representative images of the evaluation of the GFAP immunoccontent. The count of neurons labeled with cresyl violet was performed directly under the microscope.

Discussion

Quinolinic acid is a compound formed by the kynurenine pathway, which is found at high concentrations in the CNS in pathological situations (Stone 1993). The increase in

QUIN has been observed in neurodegenerative diseases, schizophrenia, amyotrophic lateral sclerosis, and others. This metabolite can cause cellular damage by several mechanisms, such as alterations in redox homeostasis, mitochondrial damage, production of pro-inflammatory markers, and activation of apoptotic pathways (Behan et al. 1999; Santamaría et al. 2001; Lugo-Huitrón et al. 2011; Guillemín 2012; Kalonia et al. 2012). In this context, it is important to research molecules capable of preventing the damage caused by QUIN in the CNS. In this context, CoQ₁₀ is a provitamin present in the inner mitochondrial membrane that has antioxidant and anti-inflammatory characteristics (Aaseth et al. 2021; Pallotti et al. 2022). Previous studies show that in addition to participating in the electron transport chain, it may regenerate the cellular antioxidant defenses, preventing damage to proteins, lipids, and DNA, and also modulate the release of pro-inflammatory cytokines and apoptotic cascade proteins (Sas et al. 2007; Cornelius et al. 2017; El-Aal et al. 2017). Therefore, the objective of this work was to evaluate the

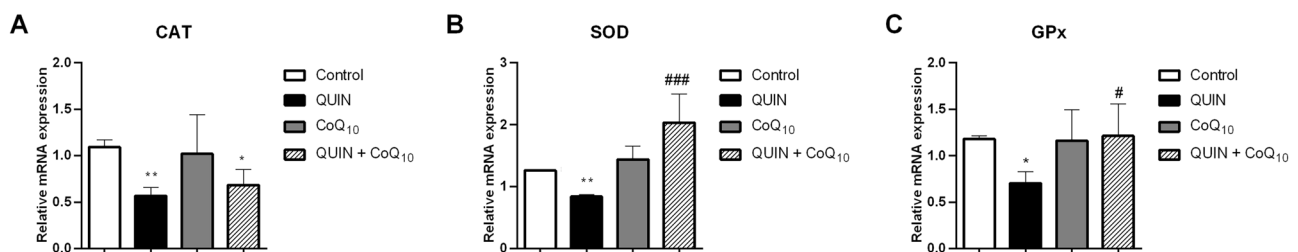


Fig. 6 Effect of CoQ₁₀ on QUIN-treated striatum on gene expression of oxidative markers: CAT (A), SOD (B), and GPx (C). Results are expressed as mean \pm SD of $n=5$ animals per group. * $p < 0.05$ and

** $p < 0.01$ compared to the control group; # $p < 0.05$ and ### $p < 0.001$ compared to the QUIN group (two-way ANOVA followed by Tukey's post hoc test)

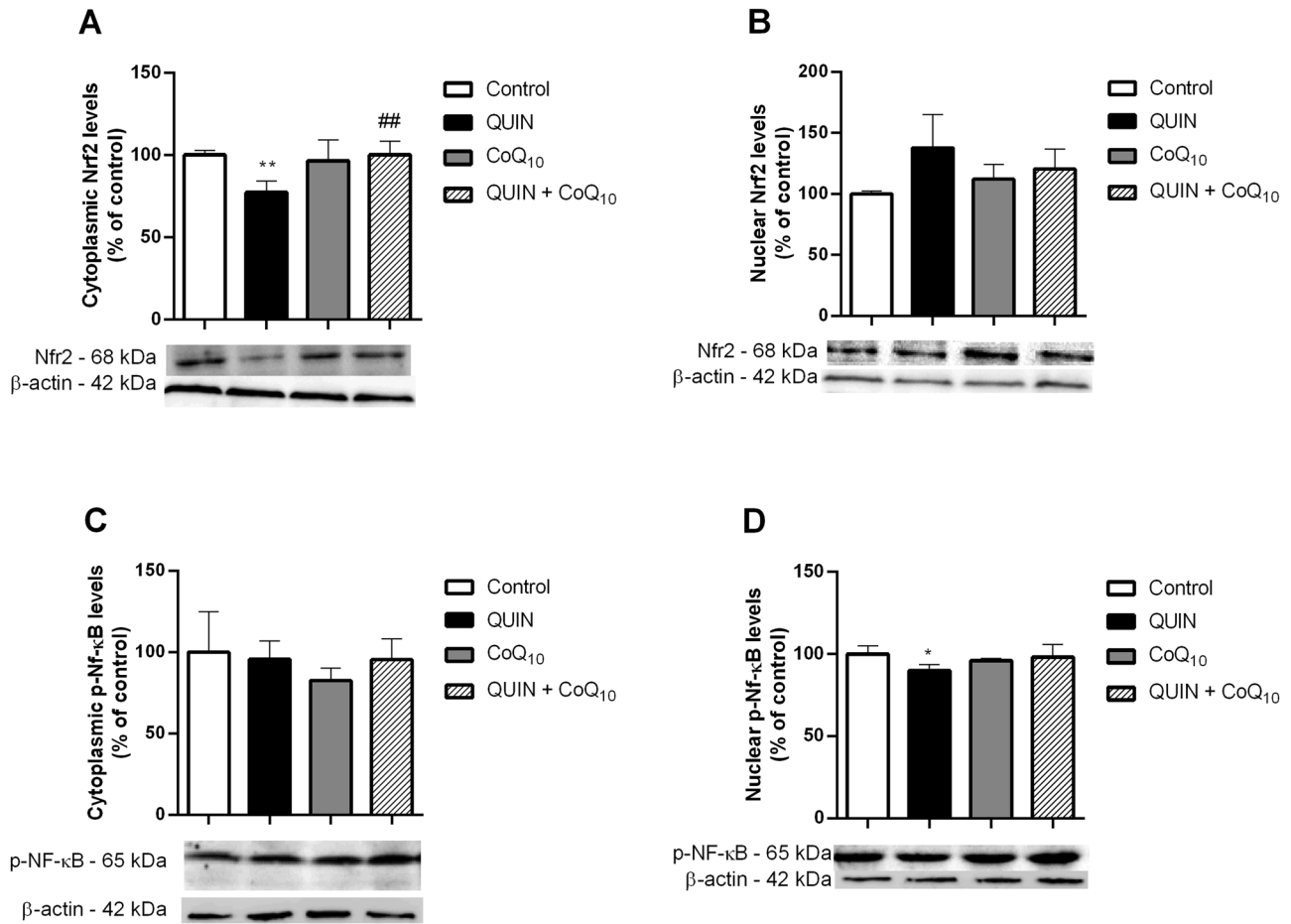


Fig. 7 Protective effect of CoQ₁₀ in cytoplasmic (A) and nuclear (B) Nrf2 levels and cytoplasmic (C) and nuclear (D) p-Nf-κβ levels on QUIN treatment. Results are expressed as mean ± SD of n=6 experi-

ments per group. **p* < 0.05 and ***p* < 0.01 compared to the control group; ##*p* < 0.01 compared to the QUIN group (two-way ANOVA followed by Tukey’s post hoc test)

possible neuroprotective role of CoQ₁₀ on behavioral, morphological, inflammatory, and oxidative status parameters in young Wistar rats submitted to intrastriatal administration of QUIN.

Initially, we tested the effect of QUIN on behavioral tasks. These results, corroborating previous studies, demonstrate difficulties in the animals’ habituation to the apparatus and behavior with characteristics of anxiety (Antunes Wilhelm et al. 2013). There was no significant difference in the assessment of immobile time.

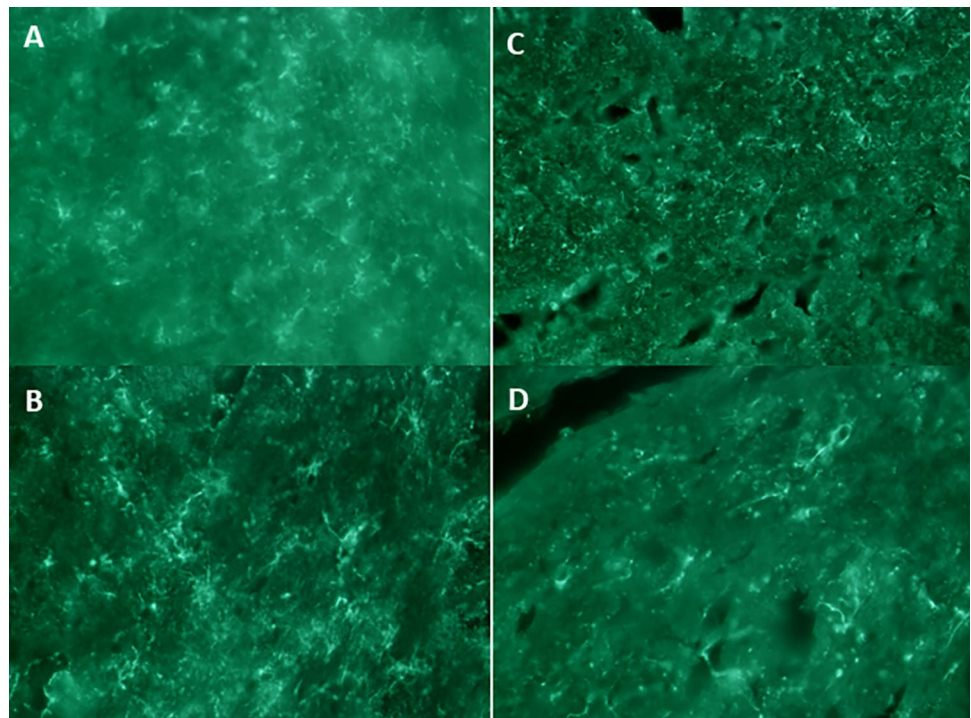
Next, we evaluated the performance of animals on short- and long-term memory with the object recognition, indicating short-term memory impairment in QUIN-treated rats. This effect may be related to the action of QUIN on NMDA receptors, as these receptors are directly involved in the formation of memories (Silveira et al. 2022).

In the evaluation of the pole test, we observed that the animals treated with QUIN presented a longer latency time for the turn and the descent of the apparatus in comparison to the control animals. These results are indicative of

Table 1 Effect of CoQ₁₀ on QUIN-treated striatum on morphological parameters

	Control		QUIN		CoQ ₁₀		QUIN + CoQ ₁₀	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Mean of neurons/μm ²								
Right striatum	99.1333	7.094599	102.85	15.6805	90.4	14.6879	76.9	11.84961
Left striatum	99.6667	16.00042	91.35	20.3564	87.25	16.6015	62.65	10.26499
GFAP optical densitometry								
Right striatum	0.07263	0.003607	0.07679	0.01268	0.06767	0.01806	0.08091	0.022362
Left striatum	0.08082	0.04627	0.10199	0.01502	0.06112	0.03176	0.10788	0.031442

Fig. 8 Representative images of the effect of CoQ₁₀ on QUIN-treated striatum in the evaluation of GFAP content: **a** control group, **b** QUIN group, **c** CoQ₁₀ group, and **d** CoQ₁₀+QUIN group



bradykinesia, a condition that causes slowness in voluntary movements and is indicative of neurological damage (Braidy et al. 2010; Braidy and Grant 2017). In the beam walking test, which evaluates the motor coordination and balance, significant alterations were not found.

We also observed a significant decline in the animals' habituation, anxious-like behavior, short-term and long-term memory changes, and bradykinesia characteristics, which have already been shown in previous studies (Pierozan et al. 2014; Jamwal et al. 2017; Achenbach et al. 2020; Wiprich and Bonan 2021; Purushothaman and Sumathi 2022). Pre-treatment with CoQ₁₀ showed to be efficient in preventing the behavioral damage found. Previous studies demonstrate that the use of CoQ₁₀ in neurodegenerative diseases has protective potential. This is possibly due to the modulation of the activity of proteins present in plasticity and cell survival, in addition to antioxidant action, since the increase of reactive species in cells is directly related to cognitive damage (Andalib et al. 2019; Omid et al. 2019; Ghasemloo et al. 2021a; Salama and Elgohary 2021; Okudan et al. 2022).

In the morphological evaluations performed by staining with cresyl violet and GFAP immunocontent, no alterations caused by QUIN or by treatment with CoQ₁₀ were found. We observed that despite the toxicity of QUIN, in our study, this compound was not able to cause changes in the quantity of striatal neurons and astrocytes when compared to the control group, suggesting that the damage caused by QUIN observed in our study was possibly due to its effects on cell signaling pathways and not by the decrease of viable cells

in the tissue. Also, CoQ₁₀ also did not change the cellular content evaluated.

In this work, we evaluated the gene expression of the following inflammatory markers: TNF- α , MCP-1, IL-1 β , IL-6, and IL-10. TNF- α and MCP-1 are acute inflammatory phase cytokines. They have multiple functions, maintaining the pro-inflammatory status of tissues but also performing the function of recruiting and activating defense cells. From these initial stimuli, pro-inflammatory cytokines, such as IL-1 β and IL-6, and anti-inflammatory cytokines, such as IL-10, are released by cells (Rauf et al. 2022).

Our results demonstrated that treatment with QUIN altered the gene expression of inflammatory markers. There was a significant increase in the expression of TNF- α , IL-1 β , IL-6, and MCP-1. These results corroborate previous studies that demonstrate the pro-inflammatory profile of this metabolite (Lugo-Huitrón et al. 2013; Braidy and Grant 2017; Jamwal et al. 2017; Ferreira et al. 2020). In the pre-treatment with CoQ₁₀, total prevention of IL-1 β alteration and partial prevention of IL-6 alteration are observed. These two cytokines are classic pro-inflammatory mediators, and their increase is directly related to the maintenance of inflammation, which can lead to metabolic alterations and cell death. Due to the protective action of CoQ₁₀, possibly the pro-inflammatory status and cellular damage are reduced (Yousef et al. 2019; Salama and Elgohary 2021). We found an increase in IL-10 gene expression only in the CoQ₁₀+QUIN group. This anti-inflammatory cytokine is considered one of the best defense mechanisms of immune

cells to contain excessive inflammation. The increase in its production is dependent on toxic stimuli to the tissues, such as the administration of a classically pro-inflammatory molecule such as QUIN. Possibly for this reason, we observed an increase in IL-10 expression only in the CoQ10+QUIN group (Yousef et al. 2019; Porro et al. 2020).

Surprisingly, pretreatment with CoQ₁₀ was not able to prevent the increase in TNF- α and MCP-1 gene expression. It is important to consider that both, TNF- α and MCP-1, in addition to their classic effects, are also considered acute inflammatory markers, being responsible for the signaling processes and recruitment of proteins and cells to act in the inflammatory cascade. As they are proteins released in the early stages of inflammation, their increase even in the group treated with CoQ₁₀ may be related to the fact that this is an acute study. Chronic studies with exposure to CoQ₁₀ and/or inflammatory agents demonstrate a different profile from that observed in our study. In an animal model of metabolic syndrome developed for 8 weeks (Onaolapo et al. 2021), CoQ₁₀ treatment was effective in reducing TNF levels as well as in a model of aging (Srivastava et al. 2022). Therefore, our study opens perspectives for a better understanding of the action of CoQ₁₀ in the initial stages of inflammatory processes.

Taken together, the results of gene expression assessments of inflammatory markers confirm the toxic action of QUIN, which leads to increased expression of classic pro-inflammatory markers (Ferreira et al. 2020). Furthermore, considering all the results involving CoQ₁₀, we observed that it prevents the expression of classic pro-inflammatory cytokines, activates the expression of the anti-inflammatory cytokine IL-10, and can infer that it maintains the expression of acute inflammatory mediators for the recruitment of other proteins to react to the previous installed inflammatory process (Ghasemloo et al. 2021b; Moatti and Cohen 2021).

In addition, we observed a decrease in the nuclear immunocent of p-Nf- κ b in the treatment with QUIN. Nf- κ b is an important transcription factor responsible for modulating the expression of proteins related to inflammatory processes, recruitment, proliferation, and cell survival. A decrease in the content of this factor may be related to the maintenance of the inflammatory status since there is a decrease in the production of proteins and enzymes essential for the process. We observed a partial prevention in the treatment with CoQ₁₀, which may be related to an improvement in the processes of reaction to inflammation and cell survival, demonstrating the beneficial effects of CoQ₁₀ in an acute model of damage (Moatti and Cohen 2021).

In the evaluation of antioxidant enzymes, QUIN significantly altered the gene expression of CAT, SOD, and GPx. Previous studies had already shown that QUIN reduces the enzymatic activity of antioxidants, corroborating with its toxic role (Tasset et al. 2010; Kubicova

et al. 2013; Ferreira et al. 2018, 2020). Regarding the pre-treatment with CoQ₁₀, we observed prevention in the SOD and GPx expression, as expected by the antioxidant potential of this compound (Komaki et al. 2019; Aaseth et al. 2021; Ferreira et al. 2022; Pallotti et al. 2022). The change in CAT expression was not prevented by CoQ₁₀. In the evaluation of Nrf2 immunocent, we observed a decrease in cytoplasmic levels in the presence of QUIN, and this effect is prevented by pretreatment with CoQ₁₀. Nrf2 is an important transcription factor, responsible for stimulating the gene expression of antioxidant and anti-inflammatory defenses (Colín-González et al. 2014; Ferreira et al. 2018). Our results corroborate several studies that have already demonstrated the high antioxidant potential of CoQ₁₀ and its effective action on inflammatory processes in the initial/acute phase. (Abiri and Vafa 2021).

In conclusion, this study demonstrated a neuroprotective effect of CoQ₁₀ on the damage caused by QUIN administration, including protection against changes on behavioral and neurochemical (inflammatory and oxidative) parameters, which makes supplementation with CoQ₁₀ an interesting therapeutic alternative, although more studies are necessary to elucidate the mechanisms involved.

Author Contribution FSF: conceptualization, methodology, formal analysis, investigation, data curation, writing original draft, writing, review, and editing; OVRJ, TMS, JSS, BFD, VSA, RCS, and LEBS: methodology and technical help; ATSW: conceptualization, methodology, resources, data curation, writing original draft, writing, review, editing, supervision, project administration, and funding acquisition.

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Declarations

Conflict of Interest The authors declare no conflict of interest.

References

- Aaseth J, Alexander J, Alehagen U (2021) Coenzyme Q10 supplementation – in ageing and disease. *Mech Ageing Dev* 197:111521. <https://doi.org/10.1016/j.mad.2021.111521>
- Abiri B, Vafa M (2021) Impact of coenzyme Q10 on inflammatory biomarkers and its role in future therapeutic strategies. *Clin Nutr ESPEN*
- Achenbach J, Thiels C, Lücke T, Saft C (2020) Clinical manifestation of juvenile and pediatric hd patients: a retrospective case series. *Brain Sci.* <https://doi.org/10.3390/brainsci10060340>
- Andalib S, Mashhadi-Mousapour M, Bijani S, Hosseini MJ (2019) Coenzyme Q 10 alleviated behavioral dysfunction

- and bioenergetic function in an animal model of depression. *Neurochem Res* 44:1182–1191. <https://doi.org/10.1007/s11064-019-02761-0>
- Antunes Wilhelm E, Ricardo Jesse C, Folharini Bortolatto C, Wayne Nogueira C (2013) Correlations between behavioural and oxidative parameters in a rat quinolinic acid model of Huntington's disease: protective effect of melatonin. *Eur J Pharmacol* 701:65–72. <https://doi.org/10.1016/j.ejphar.2013.01.007>
- Behan WM, McDonald M, Darlington LG, Stone TW (1999) Oxidative stress as a mechanism for quinolinic acid-induced hippocampal damage: protection by melatonin and deprenyl. *Br J Pharmacol* 128:1754–1760. <https://doi.org/10.1038/sj.bjp.0702940>
- Biasibetti-Brendler H, Schmitz F, Pierozan P et al (2017) Hypoxanthine induces neuroenergetic impairment and cell death in striatum of young adult Wistar rats. *Mol Neurobiol* 1–9. <https://doi.org/10.1007/s12035-017-0634-z>
- Braidy N, Grant R (2017) Kynurenine pathway metabolism and neuro-inflammatory disease. *Neural Regen Res* 12:39–42
- Braidy N, Grant R, Adams S, Guillemain GJ (2010) Neuroprotective effects of naturally occurring polyphenols on quinolinic acid-induced excitotoxicity in human neurons. *FEBS J* 277:368–382. <https://doi.org/10.1111/j.1742-4658.2009.07487.x>
- Carter RJ, Morton J, Dunnett SB (2001) Motor coordination and balance in rodents. In: *Current Protocols in Neuroscience*
- Colín-González AL, Luna-López A, Königsberg M et al (2014) Early modulation of the transcription factor Nrf2 in rodent striatal slices by quinolinic acid, a toxic metabolite of the kynurenine pathway. *Neuroscience* 260:130–139. <https://doi.org/10.1016/j.neuroscience.2013.12.025>
- Colle D, Hartwig JM, Antunes Soares FA, Farina M (2012) Probucool modulates oxidative stress and excitotoxicity in Huntington's disease models in vitro. *Brain Res Bull* 87:397–405. <https://doi.org/10.1016/j.brainresbull.2012.01.003>
- Cornelius N, Wardman JH, Hargreaves IP et al (2017) Evidence of oxidative stress and mitochondrial dysfunction in spinocerebellar ataxia type 2 (SCA2) patient fibroblasts: effect of coenzyme Q10 supplementation on these parameters. *Mitochondrion* 34:103–114. <https://doi.org/10.1016/j.mito.2017.03.001>
- Deniz BF, Confortim HD, Deckmann I et al (2018) Folic acid supplementation during pregnancy prevents cognitive impairments and BDNF imbalance in the hippocampus of the offspring after neonatal hypoxia-ischemia. *J Nutr Biochem*. <https://doi.org/10.1016/j.jnutbio.2018.06.008>
- El-Aal SAA, El-Fattah MAA, El-Abhar HS (2017) CoQ10 augments rosuvastatin neuroprotective effect in a model of global ischemia via inhibition of NF- κ B/JNK3/Bax and activation of Akt/FOXO3A/Bim cues. *Front Pharmacol* 8. <https://doi.org/10.3389/fphar.2017.00735>
- Ennaceur A, Delacour J (1988) A new one - trial test for neurobiological studies of memory in rats. 1 " Behavioral data. *Behav Brain Res* 31:47–59. [https://doi.org/10.1016/0166-4328\(88\)90157-X](https://doi.org/10.1016/0166-4328(88)90157-X)
- Ferreira FS, Biasibetti-Brendler H, Pierozan P et al (2018) Kynurenic acid restores Nrf2 levels and prevents quinolinic acid-induced toxicity in rat striatal slices. *Mol Neurobiol* 1–12. <https://doi.org/10.1007/s12035-018-1003-2>
- Ferreira FS, Dos Santos TM, Ramires Junior OV et al (2022) Quinolinic acid impairs redox homeostasis, bioenergetic, and cell signaling in rat striatum slices: prevention by coenzyme Q10. *Neurotox Res*. <https://doi.org/10.1007/s12640-022-00484-9>
- Ferreira FS, Schmitz F, Marques EP et al (2020) Intra-striatal quinolinic acid administration impairs redox homeostasis and induces inflammatory changes: prevention by kynurenic acid. *Neurotox Res*. <https://doi.org/10.1007/s12640-020-00192-2>
- Ghasemloo E, Mostafavi H, Hosseini M et al (2021a) Neuroprotective effects of coenzyme Q10 in Parkinson's model via a novel Q10/miR-149-5p/MMPs pathway. *Metab Brain Dis* 36:2089–2100. <https://doi.org/10.1007/s11011-021-00795-4>
- Ghasemloo E, Oryan S, Bigdeli MR et al (2021b) The neuroprotective effect of microRNA-149-5p and coenzyme Q10 by reducing levels of inflammatory cytokines and metalloproteinases following focal brain ischemia in rats. *Brain Res Bull*. <https://doi.org/10.1016/j.brainresbull.2021.01.013>
- Guillemin GJ (2012) Quinolinic acid, the inescapable neurotoxin. *FEBS J* 279:1356–1365
- Hargreaves I, Heaton RA, Mantle D (2020) Disorders of human coenzyme q10 metabolism: an overview. *Int J Mol Sci*
- Jamwal S, Singh S, Gill JS, Kumar P (2017) L-Theanine prevent quinolinic acid induced motor deficit and striatal neurotoxicity: reduction in oxido-nitrosative stress and restoration of striatal neurotransmitters level. *Eur J Pharmacol* 811:171–179. <https://doi.org/10.1016/j.ejphar.2017.06.016>
- Kalonia H, Kumar P, Kumar A (2011) Attenuation of proinflammatory cytokines and apoptotic process by verapamil and diltiazem against quinolinic acid induced Huntington like alterations in rats. *Brain Res* 1372:115–126. <https://doi.org/10.1016/j.brainres.2010.11.060>
- Kalonia H, Mishra J, Kumar A (2012) Targeting neuro-inflammatory cytokines and oxidative stress by minocycline attenuates quinolinic-acid-induced huntington's disease-like symptoms in rats. *Neurotox Res* 22:310–320. <https://doi.org/10.1007/s12640-012-9315-x>
- Komaki H, Faraji N, Komaki A et al (2019) Investigation of protective effects of coenzyme Q10 on impaired synaptic plasticity in a male rat model of Alzheimer's disease. *Brain Res Bull* 147:14–21. <https://doi.org/10.1016/j.brainresbull.2019.01.025>
- Kubicova L, Hadacek F, Chobot V (2013) Quinolinic acid: neurotoxin or oxidative stress modulator? *Int J Mol Sci* 14:21328–21338. <https://doi.org/10.3390/ijms141121328>
- La Cruz VPD, Carrillo-Mora P, Santamaría A (2013) Quinolinic acid, an endogenous molecule combining excitotoxicity, oxidative stress and other toxic mechanisms. *Int J Tryptophan Res* 5:1–8
- Liang Y, Xie S, He Y et al (2022) Kynurenine pathway metabolites as biomarkers in Alzheimer's disease. *Dis Markers*
- Lowry OH, Rosebrough NJ, Farr AL, Randall RJ (1951) Protein measurement with the Folin phenol reagent. *J Biol Chem* 193:265–275. [https://doi.org/10.1016/0304-3894\(92\)87011-4](https://doi.org/10.1016/0304-3894(92)87011-4)
- Lugo-Huitrón R, Blanco-Ayala T, Ugalde-Muñiz P et al (2011) On the antioxidant properties of kynurenic acid: free radical scavenging activity and inhibition of oxidative stress. *Neurotoxicol Teratol* 33:538–547. <https://doi.org/10.1016/j.ntt.2011.07.002>
- Lugo-Huitrón R, Ugalde Muñiz P, Pineda B et al (2013) Quinolinic acid: an endogenous neurotoxin with multiple targets. *Oxid Med Cell Longev*. <https://doi.org/10.1155/2013/104024>
- Moatti A, Cohen JL (2021) The TNF- α /TNFR2 pathway: targeting a brake to release the anti-tumor immune response. *Front Cell Dev Biol*
- Mor A, Tankiewicz-Kwedlo A, Krupa A, Pawlak D (2021) Role of kynurenine pathway in oxidative stress during neurodegenerative disorders. *Cells*
- Okudan N, Belviranlı M, Sezer T (2022) Potential protective effect of coenzyme Q10 on doxorubicin-induced neurotoxicity and behavioral disturbances in rats. *Neurochem Res* 47:1280–1289. <https://doi.org/10.1007/s11064-021-03522-8>
- Omidi G, Karimi SA, Rezvani-Kamran A et al (2019) Effect of coenzyme Q10 supplementation on diabetes induced memory deficits in rats. *Metab Brain Dis*. <https://doi.org/10.1007/s11011-019-00402-7>
- Onaolapo OJ, Omotoso SA, Olofinnade AT, Onaolapo AY (2021) Anti-inflammatory, anti-oxidant, and anti-lipemic effects of daily dietary coenzyme-Q10 supplement in a mouse model of metabolic

- syndrome. *Antiinflamm Antiallergy Agents Med Chem*. <https://doi.org/10.2174/1871523020666210427111328>
- Pallotti F, Bergamini C, Lamperti C, Fato R (2022) The roles of coenzyme Q in disease : direct and indirect involvement in cellular functions
- Pamplona FA, Pandolfo P, Savoldi R et al (2009) Environmental enrichment improves cognitive deficits in spontaneously hypertensive rats (SHR): relevance for attention deficit/hyperactivity disorder (ADHD). *Prog Neuro-Psychopharmacol Biol Psychiatry* 33:1153–1160. <https://doi.org/10.1016/j.pnpbp.2009.06.012>
- Paxinos G, Watson C (2006) *The rat brain in stereotaxic coordinates sixth edition* by. Acad Press 170:547612. [https://doi.org/10.1016/0143-4179\(83\)90049-5](https://doi.org/10.1016/0143-4179(83)90049-5)
- Pierozan P, Fernandes CG, Dutra MF et al (2014) Biochemical, histopathological and behavioral alterations caused by intrastriatal administration of quinolinic acid to young rats. *FEBS J* 281:2061–2073. <https://doi.org/10.1111/febs.12762>
- Porro C, Cianciulli A, Panaro MA (2020) The regulatory role of IL-10 in neurodegenerative diseases. *Biomolecules*
- Purushothaman B, Sumathi T (2022) 5,6,7 Trihydroxy flavone armoured neurodegeneration caused by quinolinic acid induced huntington's like disease in rat striatum - reinstating the level of brain neurotrophins with special reference to cognitive-socio behaviour, biochemical and histopathol. *Neurosci Res*. <https://doi.org/10.1016/j.neures.2021.08.003>
- Ramires Júnior OV, da Alves B, S, Barros PAB et al (2021) Nanoemulsion improves the neuroprotective effects of curcumin in an experimental model of Parkinson's disease. *Neurotox Res*. <https://doi.org/10.1007/s12640-021-00362-w>
- Rauf A, Badoni H, Abu-Izneid T et al (2022) Neuroinflammatory markers: key indicators in the pathology of neurodegenerative diseases. *Molecules*
- Rauscher FM, Sanders RA, Watkins JB (2001) Effects of coenzyme Q10 treatment on antioxidant pathways in normal and streptozotocin-induced diabetic rats. *J Biochem Mol Toxicol* 15:41–46. [https://doi.org/10.1002/1099-0461\(2001\)15:1%3c41::AID-JBT5%3e3.0.CO;2-Z](https://doi.org/10.1002/1099-0461(2001)15:1%3c41::AID-JBT5%3e3.0.CO;2-Z)
- Salama A, Elgohary R (2021) L-Carnitine and Co Q10 ameliorate potassium dichromate -induced acute brain injury in rats targeting AMPK/AKT/NF- κ B. *Int Immunopharmacol*. <https://doi.org/10.1016/j.intimp.2021.107867>
- Sanches EF, Arteni NS, Nicola F et al (2013) Early hypoxia-ischemia causes hemisphere and sex-dependent cognitive impairment and histological damage. *Neuroscience* 237:208–215. <https://doi.org/10.1016/j.neuroscience.2013.01.066>
- Santamaría A, Galván-Arzate S, Lisý V et al (2001) Quinolinic acid induces oxidative stress in rat brain synaptosomes. *NeuroReport* 12:871–874. <https://doi.org/10.1097/00001756-200103260-00049>
- Sas K, Robotka H, Toldi J, Vécsei L (2007) Mitochondria, metabolic disturbances, oxidative stress and the kynurenine system, with focus on neurodegenerative disorders. *J Neurol Sci* 257:221–239. <https://doi.org/10.1016/j.jns.2007.01.033>
- Segabinazi E, Gasperini NF, Faustino AM et al (2020) Comparative overview of the effects of aerobic and resistance exercise on anxiety-like behavior, cognitive flexibility, and hippocampal synaptic plasticity parameters in healthy rats. *Brazilian J Med Biol Res Rev Bras Pesqui medicas e Biol*. <https://doi.org/10.1590/1414-431X20209816>
- Silveira JS, Ramires Júnior OV, Schmitz F et al (2022) Folic acid supplementation during pregnancy alters behavior in male rat offspring: nitrative stress and neuroinflammatory implications. *Mol Neurobiol*. <https://doi.org/10.1007/s12035-022-02724-7>
- Spindler M, Flint Beal M, Henchcliffe C (2009) Coenzyme Q10 effects in neurodegenerative disease. *Neuropsychiatr Dis Treat* 5:597–610
- Srivastava P, Verma AK, Arya JK, Rizvi SI (2022) Modulatory effect of exogenous coenzyme Q10 on redox and inflammatory biomarkers during aging in rats. *Biol Futur*. <https://doi.org/10.1007/s42977-022-00140-5>
- Stone TW (1993) Neuropharmacology of quinolinic and kynurenic acids. *Pharmacol Rev* 45:309–379
- Tasset I, Pérez-De La Cruz V, Elinos-Calderón D et al (2010) Protective effect of tert-butylhydroquinone on the quinolinic-acid-induced toxicity in rat striatal slices: role of the Nrf2-antioxidant response element pathway. *Neurosignals* 18:24–31. <https://doi.org/10.1159/000243650>
- Wiprich MT, Bonan CD (2021) Purinergic signaling in the pathophysiology and treatment of Huntington's disease. *Front Neurosci*
- Yousef AOS, Fahad AA, Moneim AEA et al (2019) The neuroprotective role of coenzyme Q10 against lead acetate-induced neurotoxicity is mediated by antioxidant, anti-inflammatory and anti-apoptotic activities. *Int J Environ Res Public Health*. <https://doi.org/10.3390/ijerph16162895>

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