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ORIGINAL PAPER

Coenzyme Q_{10} Alleviated Behavioral Dysfunction and Bioenergetic Function in an Animal Model of Depression

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Abstract

Coenzyme Q_{10} (CoQ_{10}) is a natural compound, is involved in the mitochondrial electron transfer chain (ETC) and plays an important pattern in adenosine triphosphate (ATP) production. Amelioration of ATP is related to abnormalities in cognitive function and psychiatric diseases. Previous studies have shown that depression is accompanied by the induction of inflammatory and oxidative stress pathways and amelioration of antioxidant status. In a recent study, we investigated the beneficial effects of CoQ_{10} on behavioral dysfunction and CoQ_{10} level in the rat brain. Therefore, intracerebroventricular (ICV) infusion of a single dose of streptozotocin (STZ, 0.2 mg/mouse) was used in adult male mice to induce depression. The behavioral data revealed a significant difference between the depression and control groups regarding the forced swim test (FST) and splash test results at 24 h following STZ treatment. Also, the validated and accurate high-performance liquid chromatography (HPLC) technique showed decreased CoQ_{10} level in the brain samples of the STZ group, compared to the controls. Our findings revealed that behavioral abnormalities due to STZ target mitochondria and affect energy metabolism and hemostasis, resulting in the initiation of oxidative damage in the brain. Besides, 4-week administration of CoQ_{10} could reverse the depressive like behavior and bioenergetic effects of STZ in the treated groups.

Keywords Coenzyme Q_{10} (CoQ_{10}) · Behavioral assessment · Depression · High performance liquid chromatography (HPLC) · Brain · Mice

Introduction

Depression, as a debilitating neuropsychiatric disorder, is considered as a major health concern in the twenty-first century [1]. A large body of the literature has confirmed the involvement of immunoinflammatory responses and oxidative stress in the pathobiology of depression [1–3]. Despite enormous efforts to surmount the obstacles, limited progress has been made in finding or treating the underlying mechanisms of depression.

Recent evidence suggests that intracerebroventricular (ICV) infusion of streptozotocin (STZ) triggers behavioral abnormalities and mitochondrial dysfunction similar to those observed in depression [1, 4]. The major application of STZ is in diabetes and Alzheimer's disease (AD) modeling in rodents to induce oxidative stress, neuroinflammation, and cellular energy injury [5]. A recent study revealed that ICV infusion of STZ may be a distinctive method for investigating the underlying pathophysiological mechanisms of depression in mice [1, 4, 6, 7]. Recent evidence suggests that ICV infusion of STZ can induce changes in cerebral insulin signaling, while reduced brain glucose metabolism leads to an insulin-resistant brain state, which stimulates cerebral alterations in AD and depression [8].

In addition, ICV injection of STZ induces oxidative damage in the brain and cognitive impairments, such as depressive-like behaviors, Alzheimer-like changes, and memory deficits. Currently, the ICV-STZ model used to ehas been used to evaluation of neuroprotective effects of various compounds including: anti-inflammatory drugs (e.g., cyclooxygenase inhibitors), antidepressants (e.g., fluoxetine), antioxidants (e.g., curcumin, selenium, and apigenin), acetylcholinesterase inhibitors (e.g., donepezil and tacrine), alpha and beta receptor adrenergic antagonists (e.g.,

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carvedilol), and protease inhibitors or type I phosphodiesterase inhibitors (e.g., vinpocetine) [9].

Coenzyme Q_{10} (CoQ_{10}), as an electron carrier, is a strong antioxidant, which has been introduced as a key factor in mitochondrial bioenergy transfer for formation of adenosine triphosphate (ATP) [10–12]. An accumulating body of evidence introduces CoQ_{10} as an important cofactor in the mitochondrial respiratory chain, involved in oxidative phosphorylation and protection against free radical damage [13, 14]. Generally, CoQ_{10} can be found abundantly in the mitochondria, especially in the heart, kidneys, liver, and muscles [15]. Acute and chronic use of CoQ_{10} has not shown any serious adverse effects in human and experimental animals [16]. According to some studies, the reduced content of CoQ_{10} leads to mitochondrial dysfunction, involved in the pathophysiology of several diseases, such as AD, Huntington's disease, Parkinson's disease, hypertension, renal failure, and cardiovascular diseases [12, 17].

Data from clinical trials show that CoQ_{10} supplementation decreases mitochondrial abnormalities in neurodegenerative diseases, such as Parkinson's disease and AD [18]. Furthermore, research suggests that CoQ_{10} in myocardial cells can increase the ATP level, as well as the contractile rate [19]. CoQ_{10} supplementation has been shown to be effective in mitochondrial-dependent and neurodegenerative diseases as the main source of reactive oxygen species (ROS) and the most immediate target of oxidative stress [20]. Therefore, low CoQ_{10} concentration in the plasma or tissues is the main biomarker of depression or neuropsychiatric diseases [21, 22]. Based on different analytical techniques in previous studies, high-performance liquid chromatography (HPLC) is a fast and simple technique for measuring CoQ_{10} level in biological fluids and tissues due to its antioxidant potential and modulation of energy-generating properties [23–26].

According to preliminary information on the pathogenesis of depression, we aimed to investigate whether depression induction following 24 h of STZ injection could trigger behavioral dysfunction in treated animals and whether depression and anxiety were related to mitochondrial dysfunction and low CoQ_{10} content in the brain, based on simple, efficient, and reproducible methods.

Materials and Methods

Animals

The male BALB/c mice (20–30 g) were obtained from Pasteur Institute, Tehran, Iran. The mice were kept in standard condition (12:12 h light/dark cycle at 21–23 °C) and were permitted access to food and water ad libitum. This study was conducted in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. It was also approved by the Animal Ethics Committee of Zanjan University of Medical Sciences.

Streptozotocin and Coenzyme Q_{10} treatment

After dissolving STZ (Sigma, St Louis, MO, USA) in normal saline (0.9%), 0.2 mg/4 µL/mouse of the solution was administered to mice via ICV infusion, based on methods described by Haley and McCormick, 1957 and Amiri et al.,2017. The animals were euthanized after STZ infusion. Twenty-four hours after drug injection, the STZ group underwent behavioral and molecular evaluation. In order to eliminate the possible effects of ICV saline, the control group was treated with sterile saline (0.2 mg/4 µL/mouse, ICV) and tested 24 h after injection. The administrative dose of STZ was determined based on previously published data and our pilot studies [1]. Besides, CoQ_{10} (Nature's bounty Pharmaceutical Inc., USA) was dissolved in corn oil (10 mg/kg, P.O.) and administered twice weekly for 4 weeks through gavage (stomach tubes).

Experimental Design

After acclimation, the male mice were randomly divided into four groups of 10 animals: group 1, receiving corn oil as the solvent of CoQ_{10} (sham or control); group 2, receiving CoQ_{10} (10 mg/kg in corn oil, P.O.) twice a week for 28 days (CoQ_{10}); group 3, receiving an ICV injection of STZ at 0.2 mg/4 µL/mouse (equivalent to 8 mg/kg) on the first test day (STZ); and group 4, receiving CoQ_{10} (10 mg/kg) in post-treatment twice a week for 28 days at 24 h after a single dose of STZ-ICV infusion (STZ + CoQ_{10}). At the end of the behavioral experiment, the mice were sacrificed. The brain tissues were harvested and stored at − 80 °C until analysis time to minimize changes in metabolite composition.

Behavioral Test

The experimental tests were done between 9.00 a.m. and 4.00 p.m. and analyzed by researchers who were blind to the experiments in order to avoid bias.

Open-Field Test (OFT)

OPT is used to assess the effects of STZ and CoQ_{10} supplementation on the distance moved (horizontal activity), spent time in central zone and number of rearing (vertical activity) to assess motor function and anxiety-like behaviors as described previously [27]. The mice were placed gently in the central zone of a white opaque Plexiglas box (50 × 50 × 40 cm), which was dimly illuminated. The

animals' behaviors were recorded by a camera for 5 min. The device was cleaned after each test with 70% ethanol.

Forced Swimming Test (FST)

In FST, an inescapable challenge response is determined by recording the immobility time in the last 4–6 min of the test in cylinders (10 × 25 cm), containing 19 cm of water at 23 ± 1 °C. The animal's motionless floating in water and keeping the head above water with negligible movements were considered as immobility behaviors [1].

Splash Test

Grooming behaviors, including nose/face grooming, head washing, and body washing, can be investigated in mice using the splash test, which often represents depressive-like behaviors, such as motivational and self-care difficulties. After spraying sucrose solution (10%) onto the dorsal of the animals, the grooming activity was videotaped for 5 min, based on a previous protocol [28].

COQ_{10} Analysis

Tissue Preparation

After 4 weeks of treatment in all groups, the animals' brains were quickly dissected on ice after decapitation and kept at − 80 °C until further analysis. Then, 100 mg of the freeze-clamped brain was homogenized based on previously published protocols [29, 30]. Ethanol and butylated hydroxytoluene(BHT) were added to the samples to remove proteins and prevent autooxidation, respectively. Finally, after evaporation of the organic layer and reconstitution, 200 µL of the sample was injected into the HPLC instrument.

Apparatus and Chromatographic Conditions

For CoQ_{10} analysis, a KNAUER HPLC system (Berlin, Germany) was used, which was coupled with a UV detector (KNAUER, Smartline 2500) at 275 nm. Separation was performed on C_{18} (4.6 × 250 mm; 5 µm) at column oven temperature (25 °C), and then, 100 µL of the sample was injected to HPLC by Hamilton syringe. The mobile phase was consist of ethanol–methanol (80:20 v/v), which was filtered and degassed before use at a flow rate of 1.2 mL/min. In addition, the retention time was 7.2 ± 0.2 min. All the solvents were purchased from Merck Company (Darmstadt, Germany).

Method Validation

Preparation of Standard Solution Calibration Curves

The stock standard solution was prepared by dissolving pure CoQ_{10} in ethanol (1 mg/mL) and stored at − 20 °C. A total of five serial dilutions of standard solutions were prepared in mobile phase within the range 0.625–10 µg/mL. These solutions were stable for 1 week when stored at 4 °C. The calibration curves were plotted by analyzing CoQ_{10} (0.625, 1.25, 2.5, 5, and 10 µg/mL) against the peak height on three consecutive days.

Limits of Quantitation (LOQ) and Detection (LOD)

LOQ and LOD were defined based on the signal-to-noise ratios (3 and 10, respectively), with precision (CV%) of ± 20%.

Accuracy, Precision, and Recovery

For evaluating repeatability (intraday) and reproducibility (interday), the replicated samples (three times), spiked with CoQ_{10} at three levels, were analyzed on the same day and three different days, respectively. Recovery was evaluated by spiking the samples with known concentrations; finally, the level of CoQ_{10} was corrected in the real samples through recovery. The precision of method validation was determined in terms of repeatability by calculating the coefficient of variation percentage (CV%) for three-replicate intraday and interday analyses at three concentrations of CoQ_{10} within CV% of ± 15% as the acceptability criterion.

Stability

The stability of CoQ_{10} was studied in the frozen samples (− 80 °C) after sample extraction during 24 h at room temperature to ensure CoQ_{10} degradation.

Selectivity

Selectivity was investigated at analyte retention times, without any interfering peaks with the CoQ_{10} chromatogram.

Statistical Analysis

Statistical analyses were performed by Graphpad Prism 5 and SigmaPlot. Data are expressed as mean ± standard deviation (SD). Comparisons between the groups

were made using *t* test and one-way analysis of variance (ANOVA), followed by Duncan's multiple range test. *P* value < 0.05 was considered statistically significant.

Results

CoQ_{10} Supplementation Reversed Depressive-Like Behaviors in the Animal Model

The statistical analysis revealed significant differences in terms of FST (F[3, 30] = 56.914; $P < 0.001$) and splash test (F[3, 30], 14.152; $P < 0.001$) between the STZ and control groups. As shown in Fig. 1, the STZ group had a longer immobility time in comparison with the controls ($P < 0.001$). Our findings showed that chronic treatment with CoQ_{10} in the STZ group could remarkably decrease immobility time on FST ($P < 0.001$; Fig. 1).

On the splash test, reduction in the time spent grooming is considered a self-care difficulty and anhedonic in rodents. As shown in Fig. 2, the grooming activity time increased in the STZ + CoQ_{10} and CoQ_{10} groups versus the STZ group ($P < 0.001$), as confirmed by FST. Also, significant differences were observed in grooming time between the STZ and control groups (Fig. 2; $P < 0.001$).

In addition, the number of crossed squares or distance moved by the animals (horizontal activity) was not significantly different between the STZ + CoQ_{10}, CoQ_{10}, STZ, and control groups (F[3, 30] = 3.582; $P = 0.025$; Fig. 3a) and. In other words, chronic treatment with CoQ_{10} had no significant effects on the locomotor activity according to the OFT results. But, the number of rearing (vertical activity)

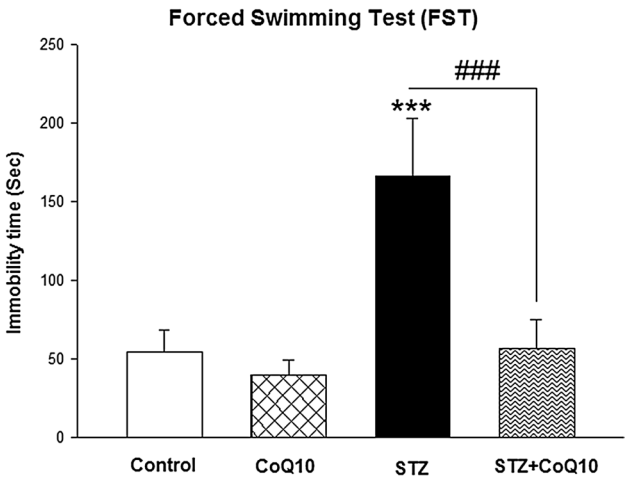

Fig. 1 Effects the chronic administration of CoQ_{10} on behavioral alteration in the FST. Values are expressed as the mean ± SD and were analyzed using one-way ANOVA followed by Tukey's post hoc test. ***P < 0.001 compared with control group. ##P < 0.001 compared with STZ-received mice (n = 8–10)

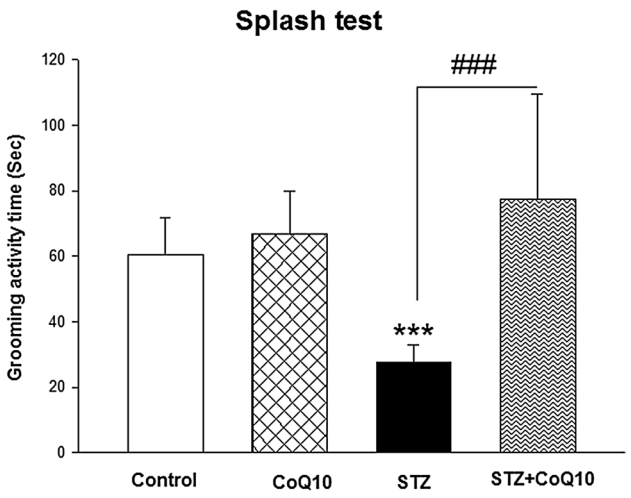

Fig. 2 Effects the chronic administration of CoQ_{10} on self-care behavior in the splash test .Values are expressed as the mean ± SD and were analyzed using one-way ANOVA followed by Tukey's post hoc test. ***P < 0.001 compared with control group. ##P < 0.001 compared with STZ-received mice (n = 8–10)

decreased in the STZ and STZ + CoQ_{10} groups versus the control group ($P < 0.001$), to evaluation of anxiety-like behaviors. In addition, CoQ_{10} caused no significant changes in horizontal and vertical activities in the OFT in control mice (P > 0.05, Fig. 3a, b). Statistical analysis demonestrated that STZ + CoQ_{10} group considerably increased the number of rearing activity (vertical activity) of the OF apparatus in comparison with STZ administration group (P < 0.05; Fig. 3b). Also, spent time in central zone between four investigated animal groups were not significantly difference similar to horizontal activity [F[3, 30] = 2.737; $P = 0.061$; Fig. 3c].

Performance Characteristics of the Proposed Method

According to the literature, optimized chromatographic conditions were used, and the following analytical characteristics were determined: (1) precision and accuracy; (2) calibration data; (3) linearity of calibration curve; (4) LOQ and LOD; (5) selectivity and stability; and (6) analysis of real samples.

Precision and Accuracy

Table 1 presents the results of inter- and intra-day precision and accuracy tests following three-replicate injections of the spiked sample at low, medium, and high concentrations. The results showed higher inter- and intra-day accuracies of 97–105% and 89–101%, respectively. The inter- and intra-day precisions (CV%) were below 10% for all the spiked or

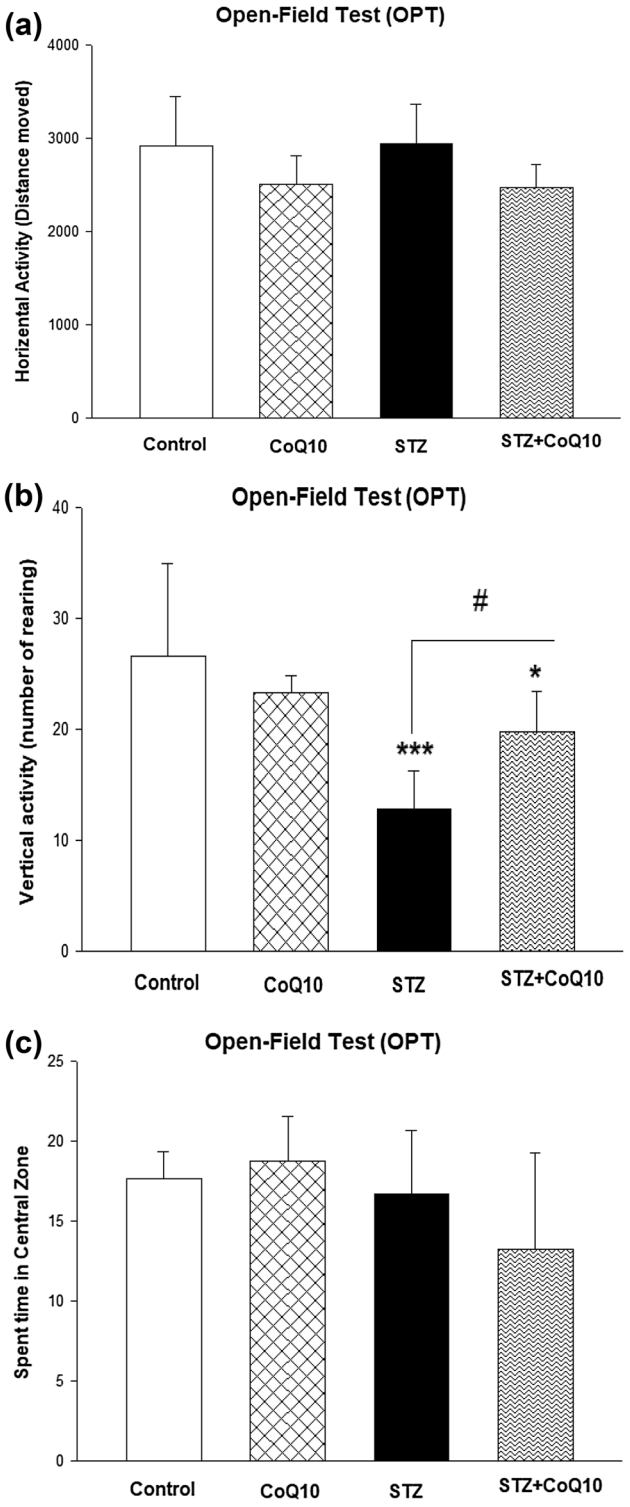

Fig. 3 Effects the chronic administration of CoQ_{10} on **a** distance moved; **b** rearing number; **c** spent time in central zone in the OFT. Values are expressed as the mean ± SD and were analyzed using one-way ANOVA followed by Tukey's post hoc test (n = 8–10)

quality control (QC) samples of brain tissues (acceptable range ± 15%). The average recovery was above 88%, while the relative SDs (RSDs) were below 10%.

Limit of Detection (LOD) and Limit of Quantification (LOQ)

The LOD and LOQ values for CoQ_{10} were 160 and 237 ng/mL, respectively, which represent the high sensitivity of the proposed method.

Linearity

The results exhibited the linearity of the method for CoQ_{10} within the desired range (0.625–10 µg/mL). A good correlation was found between CoQ_{10} peak heights and concentrations in several standard calibration curves ($r^2 = 0.991$) with < 3% CV% at each concentration.

Selectivity

The recorded chromatograms were free of endogenous interference peaks after extracting and analyzing the blank and spiked samples, based on the described method (Fig. 4).

Stability

The stability of the solvent (standard solutions) and matrix (purified extracts) was confirmed if variability in the assay results was less than 10% of the baseline. When stored at an ambient temperature, no significant reduction was observed in the desired concentrations of the standard and spiked samples after 6 h extraction, respectively; this inhibited any degradation of the analyte in the suggested period (Table 2). Furthermore, the stability of the column was evaluated by calculating the retention time of the standard solution, which was determined to be 7.2 ± 0.2 min.

Measurement of CoQ_{10} in Real Samples

There was a significant difference in the level of CoQ_{10} ($P < 0.001$) between the STZ and control groups (Fig. 5). There was also a significant difference in the brain CoQ_{10} level between the STZ + CoQ_{10} and CoQ_{10} groups ($^{\Phi}P < 0.05$). Besides, the findings suggested a significant difference in CoQ_{10} level between the STZ + CoQ_{10} and control groups ($P < 0.001$), suggesting a relative reversal in CoQ_{10} concentration due to chronic oral administration of CoQ_{10} supplementation.

Table 1 Intra-day and inter-day accuracy and precision for three levels of QC samples (n = 3)

Spiked level (μg/mL)	Intra-day			Inter-day		
	Mean measured (μg/mL) ± SD	Precision (CV %)	Accuracy (%)	Mean measured (μg/mL) ± SD	Precision (CV %)	Accuracy (%)
1	0.98 ± 0.10	9.20	97.70	0.89 ± 0.06	7.03	88.81
5	5.25 ± 0.48	9.10	105.01	4.88 ± 0.54	8.96	97.67
10	9.77 ± 0.75	7.72	97.70	10.10 ± 0.73	7.20	101.03

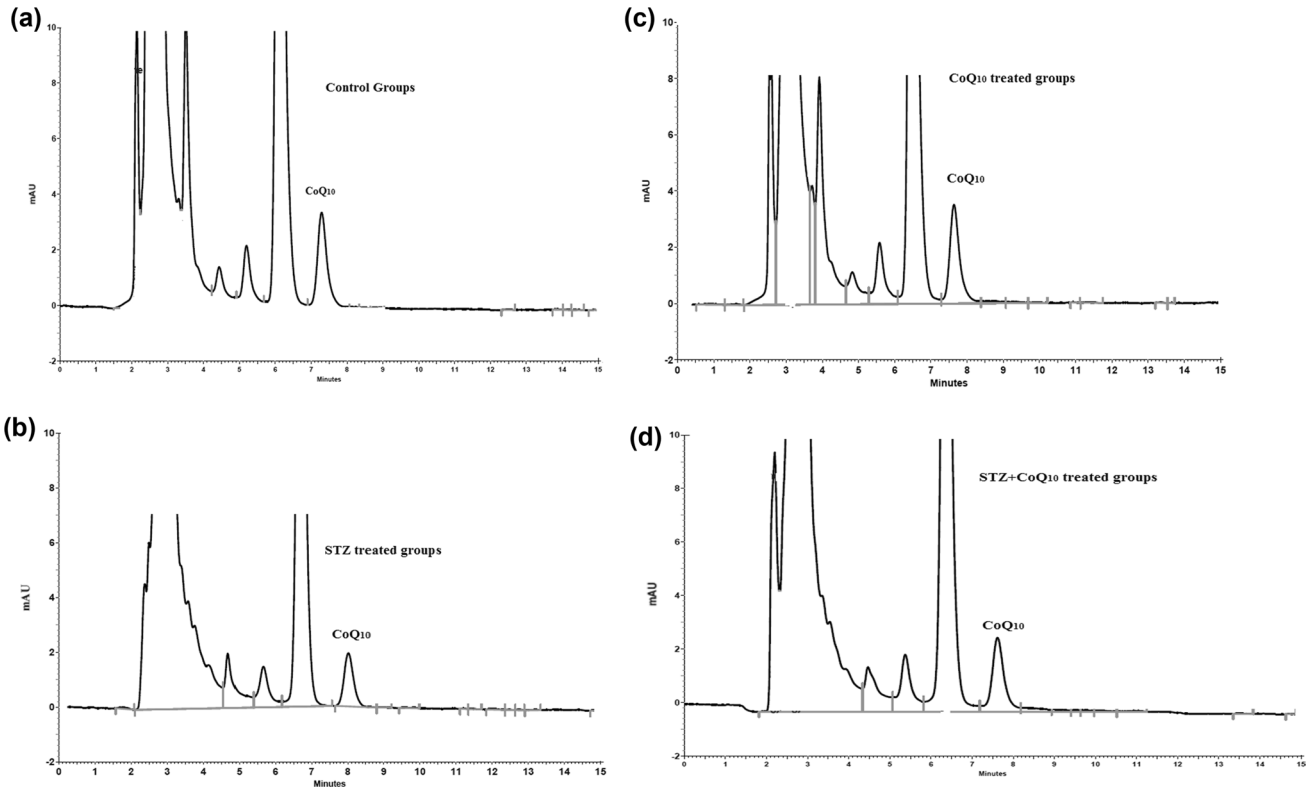

Fig. 4 HPLC chromatograms of CoQ_{10} concentration in different treated groups: **a** control, **b** STZ, **c** CoQ_{10}, **d** STZ + COQ_{10}

Table 2 Comparison of the stability at three QC levels for Co Q_{10} after 24 h at − 80 °C and 6 h at ambient temperature in tissue extracted solution and mobile phase respectively

Initial concentration (μg/mL)	Stability (%)	(CV %)
1 μg/mL (standard)	97.8	7.77
5 μg/mL (standard)	102.3	6.01
10 μg/mL (standard)	99.4	5.31
1 μg/mL (spiked sample)	96.8	5.17
5 μg/mL (spiked sample)	102.2	7.86
10 μg/mL (spiked sample)	96.4	6.27

Discussion

Depression is a common mental disorder worldwide, with harmful effects on the quality of life and cognitive function [31]. Various studies have reported the multifactorial pathophysiology of depression, involving decreased brain monoamine, functional abnormalities in neurotransmitter receptors, dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis (cortisol), increased oxidative stress, increased level of proinflammatory cytokines [e.g., interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and NF-κB], and increased nitric oxide level versus reduced BDNF [32]. In this regard, a recent study introduced CoQ_{10} sufficiency as a hallmark of depression, which is related to oxidative stress pathways.

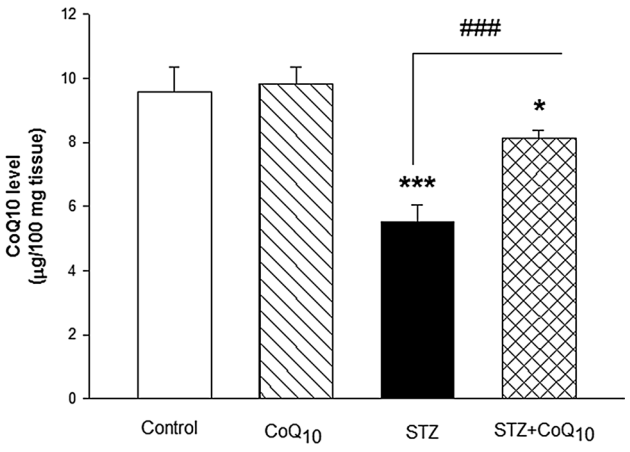

Fig. 5 Therapeutic effects of chronic administration of CoQ_{10} and STZ on CoQ_{10} concentration in the brain. Values are expressed as the mean ± SD and were analyzed using one-way ANOVA followed by Tukey's post hoc test. *P < 0.05; ***P < 0.001 compared with control group. ###P < 0.001 compared with STZ-received mice (n = 4–6)

CoQ_{10} is naturally involved in the electron transport chain (ETC), which accepts and donates electrons from mitochondrial complex I and complex II. It can be used as a useful drug in treating a variety of disorders, such as neurodegenerative disorders, diabetes, cancer, muscular dystrophy, male infertility, and cardiovascular diseases [12].Although CoQ_{10} is found in different organelles, its highest concentrations are observed in the mitochondria of the heart, kidneys, liver, and brain [15]. Preclinical and clinical data have shown that CoQ_{10} does not cause serious adverse effects in humans and experimental animals [16]. Therefore, we aimed to investigate the therapeutic role of CoQ_{10} in the amelioration of cognitive dysfunction and biochemical changes in the brain of ICV-STZ rats.

Previous studies have presented controversial results regarding CoQ_{10} supplementation and its effects on mitochondria. In human studies, CoQ_{10} administration could protect the mitochondria against ROS overproduction and oxidative stress [33]. Other studies have also reported the positive effects of CoQ_{10} (300 and 500 mg/day) on relapsing–remitting multiple sclerosis and coronary artery disease [13, 34, 35]. Robust evidence suggests low plasma CoQ_{10} level as a hallmark in the pathophysiology of depression and neurodegenerative diseases [21, 36]. On the other hand, chronic treatment with CoQ_{10} supplementation modulates cognitive impairments in learning and memory tests in Alzheimer's rats [18]. Our results confirmed an enhancement in immobility time and a reduction in grooming activities on FST in the STZ group, which has been indicated as behavioral despair and a major symptom of depression [37]. Furthermore, chronic usage of CoQ_{10} had no significant effects on the horizontal activities and center square duration of the STZ treated group on OFT, compared to the controls ($P > 0.05$), indicating no interference of STZ or CoQ_{10} in behavioral movement changes. But the number of rearing was decreased by ICV administration of STZ indicating co-occurance of anxiety with depression in animals. Althugh, CoQ_{10} could reversed the frequency of rearing for relative improving of the anxiolytic behavior in STZ + CoQ_{10} treated mice. Besides, supplementation with CoQ_{10} (10 mg/kg, i.p.) for 4 weeks in STZ-injected mice showed significant changes in depressive-like behaviors on the FST and splash tests, compared to STZ-treated animals (depressed animals). The present results confirm the therapeutic effects of CoQ_{10} on improving cognitive dysfunctions. Furthermore, chronic use of CoQ_{10} in mice had no significant effects on the horizontal activities of the STZ group on OFT, compared to the controls ($P > 0.05$), indicating no interference of STZ or CoQ_{10} in behavioral movement changes. We confirmed the involvement of oxidative stress and inflammation in cognitive impairments by introducing a depressive-like animal model [2].

The anti-inflammatory effects of CoQ_{10} are associated with the reduced expression of NF-KB and TNF-α genes against lipopolysaccharide-induced depression in animal models [38]. Besides, deficiency in CoQ_{10} in animal depression models induces greater inflammatory responses and more damage and neurodegeneration in the brain [39, 40]. Based on the oxidative stress theory, inconsistency between ROS production and antioxidant system serves a key function in the pathogenesis of depression [18, 41, 42]. Therefore, production of large amounts of ROS in the brain, as a rich source of polyunsaturated fatty acids (PUFA), increases the brain sensitivity to oxidative stress and neurodegenerative diseases, following the attack of free radicals on proteins, nucleic acids, and lipid membranes, besides disruption of cellular function [43].The increased level of ROS in the cells is accompanied by the reduced level of antioxidants, such as reduced glutathione (similar to CoQ_{10}), in tissues or cells [44]. Besides, insulin deficiency or insulin-receptor desensitization is another mechanism in the brain, affecting behavioral function and decreasing energy metabolism and acetylcholine in neurons [45].

Our pilot study before CoQ_{10} measurements showed biochemical changes in the brain, such as reduced glutathione level and increased malondialdehyde, indicating the involvement of oxidative stress in cognitive dysfunction through prevention of ATP synthesis. Therefore, CoQ_{10} level in the brain, as determined by a simple, accurate and validated HPLC method. Overall, extraction methods can contribute to effective and rapid separation of CoQ_{10} from the mouse brain. The current analytical method can save efforts in monitoring CoQ_{10} in different biological samples and help investigate the effects of other drugs and compounds in the evaluation of CoQ_{10} level. Our findings showed that STZ-ICV reduced CoQ_{10}

level in the brain, and post-treatment with CoQ_{10} could increase the level of CoQ_{10}, compared to STZ-treated groups; nevertheless, it could not completely return to the normal or control level. It is hypothesized that low water solubility and relatively large molecular weight of CoQ_{10} lead to its poor absorption through oral administration (P.O.) [46]. Besides, the longer period of treatment and daily use of CoQ_{10} seem to completely reverse CoQ_{10} concentration for inducing robust antioxidant effects. On the other hand, CoQ_{10} is majorly involved in mitochondrial ETC between complex III and complex IV during ATP production. Amelioration of CoQ_{10} in depressive-like animal models induces mitochondrial dysfunction and excessive hydrolysis of ATP, improves the level of protons, and results in conversion from pyruvate to lactate in the equilibrium reaction as the main criterion of mitochondrial dysfunction [47].

The positive effects of CoQ_{10} on endothelial function in patients with coronary artery disease showed enhancement of the endothelium-bound activity of extracellular superoxide dismutase, without any changes in oxidative stress or inflammatory markers [48]. Another study suggested the significant effects of CoQ_{10} therapy on patients with a history of myocardial infarction, who had low flavin mononucleotide levels and high lactate/pyruvate ratios at baseline [49]. On the other hand, Ochoa et al. [22] showed the protective effects of CoQ_{10} against aging-related oxidative stress and mitochondrial dysfunction in the hearts of rats fed for 24 months with a PUFA-rich diet. Similar to cardiovascular diseases, depression is related to low blood levels of antioxidants, such as serum zinc, vitamin E, vitamin C, tryptophan, tyrosine, glutathione peroxidase, and albumin [50].

Our findings revealed that 4 weeks of CoQ_{10} supplementation relatively reversed mitochondrial dysfunction. It seems that not only the antioxidant activity of CoQ_{10}, but also interference of CoQ_{10} in decreasing mitochondrial ROS in ETC, helps improve CoQ_{10} concentration. Finally, the present results showed that depression is accompanied by CoQ_{10} deficiency, and oral CoQ_{10} supplementation enhances mitochondrial bioenergetics and produces neuroprotective effects via elevating mitochondrial and tissue CoQ_{10} levels in depressive-like animal models. It is assumed that reduced CoQ_{10} concentration is significantly related to treatment resistance or recurrence of depression. Also, CoQ_{10} may be a useful treatment option for neurodegenerative diseases.

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Compliance with Ethical Standards

Conflict of interest There is no conflict of interest in this study.

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