Toxicology International
DOI: 10.18311/ti/2026/v33i3/49772
INFORMATICS JOURNALS
eISSN: 0976-5131 | Vol 33(3), 2026 | pp. 513-526

# Coenzyme Q10 Nanoparticles Supplementation Prevents the Monocrotophos-Induced Mitochondrial Dysfunctions in Brain Tissues of Rats

**Amit Kumar[1], Jatin Phogat[1], Aakash Chaudhary[2] and Vijay Kumar[1*]**

*[1]Department of Biochemistry, Maharshi Dayanand University, Rohtak - 124001, Haryana, India; vksiwach.biochem@mdurohtak.ac.in*

*[2]Department of Zoology, Maharshi Dayanand University, Rohtak - 124001, Haryana, India*

## Abstract

Monocrotophos (MCP), an organophosphate pesticide, is frequently used in agricultural fields. MCP-induced oxidative stress can result in mitochondrial dysfunction, a well-renowned contributor to neurodegenerative disorders. This study evaluated Coenzyme Q10 Nanoparticles (CoQ10 NPs) neuroprotective efficacy against MCP-induced mitochondrial impairment in rat brain tissues. This study utilised male albino rats grouped (N=5) as: control; low dos CoQ10 NPs (50 mg/kg b. wt); high dose CoQ10 NPs (100 mg/kg b. wt); MCP-exposed (4.5 mg/kg b. wt); low dose of CoQ10 NPs + MCP treated group (50 mg and 4.5 mg/kg b. wt); and high dose of CoQ10 NPs + MCP treated group (100 mg and 4.5 mg/kg b. wt, respectively). CoQ10 NPs were administered orally 3 hours prior to MCP. Function of the mitochondrial Electron Transport Chain (ETC) was evaluated by spectrophotometric assays of complex I (NADH dehydrogenase), complex II (succinate dehydrogenase) and complex IV (cytochrome c oxidase) activities. Semi-quantitative Reverse Transcription-Polymerase Chain Reaction (RT-PCR) was used to assess the changes in the expression of mitochondrial subunit genes (ND1, ND2, COX1, COX2, COX4), antioxidant gene (MnSOD), and mitochondrial biogenesis regulators, Peroxisome Proliferator- Activated Receptor Gamma Coactivator (PGC-1α), Nuclear Respiratory Factor (NRF-1, NRF-2), Transcription Factor (Tfam). MCP exposure significantly inhibited the activities of complexes I, II and IV and down-regulated the expression of messenger Ribonucleic Acid (mRNA) levels of mitochondrial subunit and biogenesis-associated genes, which suggested that the activities of the ETC were impaired and mitochondrial biogenesis was impaired. Co-administration of CoQ10 NPs, especially at the high dose, had a highly significant effect on the restoration of complex activity and re-establishment of the transcriptional profile of mitochondrial and biogenesis genes towards control levels. Finally, CoQ10 NPs effectively prevented MCPs-induced mitochondrial dysfunction in rat brain through a mechanism that involved reduction in oxidative stress and recovery of ETC subunits and PGC-1α/NRF/Tfam-mediated biogenesis signalling, thus suggesting their potential as a translational therapeutic approach to organophosphate-induced neurotoxicity.

**Major Findings:** MCP (4.5 mg/kg) significantly impaired mitochondrial ETC complexes leading to mitochondrial dysfunction via downregulated PGC-1α/NRF-1/NRF-2/Tfam biogenesis axis in rat brain. High-dose CoQ10 NPs (100 mg/kg) effectively prevented MCP-induced mitochondrial dysfunction primarily by reducing oxidative stress and reactivating ETC subunits and PGC-1α/NRF/Tfam-mediated biogenesis signalling, supporting their potential as a translational therapeutic approach against organophosphate neurotoxicity.

**Keywords:** Coenzyme Q10 Nanoparticles, Mitochondrial Biogenesis, Mitochondrial Dysfunction, Monocrotophos, Neurotoxicity

## 1. Introduction

In the modern era, several chemical pesticides are utilised to control the unbridled increasing graph of pests in agricultural fields, and it is a matter of concern that Organophosphates (OP) account for more than 50% of total pesticides available in open markets. OP are extremely toxic causing harm to the health of non-target living organisms like birds, fish, and mammals, including human beings. Accidental exposure to these harmful OP

**Article Received on:** 12.05.2025 **Revised on:** 26.06.2026. **Accepted on:** 01.07.2026

**Author for correspondence*

through any route results in various kinds of symptoms such as nausea, diarrhoea, abdominal cramps, vomiting, headache, dizziness, blurred vision, lacrimation, salivation, sweating, and mydriasis[1-5].

MCP is commonly available in the market with the brand name "Azodrin." Due to its extreme utilisation, MCP persists in the environment and makes humans more vulnerable to chronic exposure to it[6-8]. Monocrotophos, popularly known as "bird poison", is highly toxic to birds, domestic and non-domestic animals, including mammals, because of which it is banned in several Western countries, including the United States of America (USA) and the United Kingdom (UK), as well as across several African nations. On the contrary, this dreadful pesticide is massively utilised in Asian countries including India. It is important to mention that dermal contact with MCP results in localised perspiration and involuntary muscular spasms in living organisms. Similarly, inhalation causes respiratory distress resulting in sudden shortness of breath, chest discomfort, wheezing, sneezing, and intense chest tenderness. The acute poisoning of MCP induces cytotoxic abnormalities, axonal degeneration, and central and peripheral neuropathy[1,9-11].

MCP intoxication can produce free radical-mediated oxidative damage to the brain, which is very susceptible to it. It is a well-acknowledged fact that mitochondria are the principal source of cellular energy. Additionally, the ETC involves a variety of enzyme complexes found in mitochondria. If there is a structural flaw in any of these complexes, the ETCoverall functions are altered, which in turn causes oxidative stress-mediated mitochondrial cytopathy[12-15]. Previous studies have shown that MCP administration induces mitochondrial alteration via reducing the complexes' activity and downregulation of ND2, ND1 (complex I subunits), COX4, and COX1 (complex IV subunit) mRNA expression in liver and brain tissues of rats, indicating the emergence of oxidative stress-mediated mitochondrial dysfunctioning[16,17].

In a recent study, organophosphate exposure has been shown to induce neuroinflammation, amyloidogenic processing and progressive damage of cells in the brain, which are mechanisms linked to Alzheimer-like neurodegeneration[18]. A comprehensive review by Farkhondeh *et al.*, 2020, brought mitochondrial dysfunction and generation of Reactive Oxygen Species (ROS) together as a unifying mechanism in the neurotoxicity of OP in one view[19]. Simultaneously, intoxication by MCP is reported to directly affect the activities of the mitochondrial complexes in the liver[20] and causes region-specific oxidative damage in the frontal cortex, hippocampus, and cerebellum of intoxicated rats, indicating that the brain is more sensitive to this pesticide[21].

MCP poisoning causes oxidative stress, which modifies the mRNA expression of genes linked to mitochondrial biogenesis, hence influencing the signalling pathways of mitochondrial biogenesis[22]. The peroxisome proliferator-activated receptor gamma-coactivator-1α (PGC-1α) is a key component of the mitochondrial biogenesis pathway that modulates the mRNA expression of NRF-2 and NRF-1, and transcription factors via alteration in the mRNA expression of mitochondrial transcription factor A (Tfam) in cells[23]. Several published research reports have demonstrated that the administration of MCP stimulates the downregulation of Tfam, NRF-1, PGC-1α, and NRF-2 mRNA, resulting in altered mitochondrial biogenesis in the brain[22-24], and in hepatocytes in a rat model[17].

One essential endogenous antioxidant found in all mammalian cells is coenzyme Q10. It acts as a mobile oxidoreductive component in the mitochondrial ETC that shuttles both protons and electrons. Because of its high antioxidant capacity, it maintains cellular homeostasis and metabolism, and functions as a neuroprotectant, preventing apoptosis and maintaining integrity in brain tissues[25]. Recently, the therapeutic role of CoQ10 was shown in a wide range of neurodegenerative and psychiatric diseases, recognising its beneficial effects as related to mitochondrial bioenergetic restoration and antioxidant defence[26]. The clinical potential of native CoQ10, however, is limited by its lipophilicity and poor Blood–Brain Barrier (BBB) permeability[27]. Nanoparticulate formulation has therefore developed into a strategic solution, as solid lipid nanoparticles of CoQ10 can significantly improve the biopharmaceutical performance in the brain[28], and nanoparticles can effectively reduce pesticide-induced mitochondrial dysfunction and apoptosis in rat tissues[29]. Coenzyme Q10 has low bioavailability, poor gastrointestinal absorption, and requires high dosages to produce clinical benefits. These issues can be addressed with the use of coenzyme Q10 nanoparticles (CoQ10 NPs). A previous study has demonstrated that CoQ10 NPs exhibit hepatoprotective properties against dichlorvos-induced toxicity in rat liver tissues and hepatic cell lines[22]. There is a lack of data demonstrating the neuroprotective impact of CoQ10 NPs against MCP-induced mitochondrial dysfunction.

Despite these advances, a critical research gap remains. The neuroprotective potential of CoQ10 NPs when exposed to MCP-induced mitochondrial dysfunction in brain tissues has not been studied systematically so far. The neuroprotective potential of CoQ10 NPs against MCP-induced mitochondrial dysfunction in brain tissue has not been studied systematically yet. Moreover, no study has yet investigated whether CoQ10 NPs can simultaneously restore mitochondrial ETC complex activities and reprogramme the transcriptional landscape of mitochondrial biogenesis-related genes (PGC-1α/NRF-1/NRF-2/Tfam) in the brain following exposure to MCP. To fill this gap, in the present study, we have investigated the neuroprotective effect of CoQ10 NPs against mitochondrial dysfunction caused by MCP in rat brain tissues, both on the activities of ETC complexes and transcription regulation of mitochondrial subunit and biogenesis genes. We proposed that CoQ10 NPs would mitigate the mitochondrial dysfunction induced by MCP by increasing the activity of ETC complexes I, II and IV and by inducing the mRNA expression of mitochondrial subunit genes (ND1, ND2, COX1, COX2, COX4), the antioxidant gene Manganese Superoxide Dismutase (MnSOD) and the biogenesis regulators (PGC-1α, NRF-1, NRF-2, Tfam). This would provide a mechanistic basis for the use of CoQ10 NPs as a potential clinically applicable therapeutic candidate for organophosphate neurotoxicity. Thus, our research study demonstrated the therapeutic effects of CoQ10 NPs in MCP-mediated mitochondrial dysfunction and biogenesis in rat brains.

# 2. Materials and Methods

## 2.1 Chemicals and Reagents

Coenzyme Q10, MCP, Total RNA Isolation (TRI®) reagent, agarose, acetone, and methanol were obtained from Sigma-Aldrich, St. Louis, Missouri, USA. Cytochrome c oxidase was obtained from SRL, Mumbai, India. RevertAid™ cDNA synthesis kit, dNTPs, master mix, DNA markers and DNA Taq polymerase were obtained from Fermentas, Germany. All glassware and plasticware were purchased from Borosil Glass Works Ltd., Mumbai, India, and Tarson's Products Pvt. Ltd., India.

## 2.2 Preparation of CoQ10 NPs

The synthesis of CoQ10 NPs was done using the method reported by Sun *et al.*[24]. Briefly, 30mg of CoQ10 was dissolved in 3ml of absolute ethanol in a sterile 100ml beaker. The prepared solution was blended drop by drop in 27ml of Double-Distilled Water (DDW) under homogenising conditions using a Glass Dounce Homogenizer at 14,000 rpm for 15 sec. To obtain the fine suspensions of CoQ10 NPs, the solution was homogenised for 30 cycles on microfluidics high shear homogeniser at 3500 bar pressure. Finally, the fine suspension of CoQ10 NPs was collected in a fresh beaker. The details of preparation and characterisation of synthesised CoQ10 NPs have been published earlier[25].

## 2.3 Ethical Approval

Approximately 8-week-old male albino rats (weighing 140-180 grams) were procured from Disease Free Small Animal House LUVAS (Hisar). The animals at the Animal House Facility of Maharshi Dayanand University in Rohtak were acclimatised to normal daylight and temperature conditions for one week. The experimental procedure was duly approved by the Institutional Animal Ethics Committee (IAEC) (No. 210-19, dated 14-11-2019).

## 2.4 Experimental Design

A total of 30 rats were categorised into six distinct categories, with each consisting of five animals:

**Control Group:** This group of rats was administered the same volume of normal saline as the MCP-exposed rats.

**CoQ10 NPs Treated Group I:** Oral gavage was utilised to administer a single dose of CoQ10 NPs (50 mg/kg b. wt) to the rats in this group.

**CoQ10 NPs Treated Group II:** Oral gavage was utilised to administer a single dose of CoQ10 NPs (100 mg/kg b. wt) to the rats in this group.

**MCP Treated Group:** Oral gavage was utilised to administer a single dose (0.25 % of $LD_{50}$) of MCP (4.5mg/kg b. wt) mixed along with DW.

**CoQ10 NPs and MCP Exposed Group:** One dose of MCP (4.5 mg/kg b. wt) and one dose of CoQ10 NPs (50 mg/kg b. wt) were administered orally to the rats in this group. The CoQ10 NPs were administered 3 hrs prior to MCP administration.

**CoQ10 NPs and MCP Exposed Group:** The rats in this group were given a single dosage of CoQ10 NPs (100mg/kg b. wt) and a single dosage of MCP (4.5mg/kg b. wt).

The selection of the dosage of CoQ10 NPs and MCP was based on previously published research articles[22,24,26].

Rats were sacrificed after the treatment; the entire brain was removed and submerged in ice-chilled normal saline solution (0.9% w/v). One part of the brain tissue homogenate was utilised for semi-quantitative RT-PCR analysis, while the rest was used to analyse mitochondrial complex activities.

## 2.5 Mitochondria Sample Preparation

Whole brain tissue was homogenised in a 10% brain homogenising buffer containing 10mM of EGTA, 250mM of sucrose, and 10mM of Tris-HCl (pH 7.6). After centrifugation, the prepared homogenate was spun at 1000×g for 15 minutes; the supernatant was collected in a fresh Eppendorf and the mitochondrial pellet was separated by centrifuging the supernatant again for 10 minutes at 13000×g at 4°C. The collected pellets were washed in brain homogenising buffer and spun again for 10 minutes at 13000×g. The pellet was finally dissolved in the same homogenising medium and used for the study of mitochondrial complex activity.

## 2.6 Mitochondrial Complexes Activity Assays

### *2.6.1 NADH Dehydrogenase Activity Assay*

The enzymatic activity of this complex was evaluated using the process described by Prakash *et al.*,[27]. In a sterile reaction cuvette, 0.1ml Nicotinamide Adenine Dinucleotide Hydrogen (NADH) (6mM) dissolved in glycine buffer (2mM), 0.ml cytochrome c (10.5mM), 0.25ml glycyl glycine buffer (0.2M, pH 8.5), 2.4ml distilled water, sodium bicarbonate (0.2M), and 0.02ml brain mitochondrial pellets were added. The absorbance was measured using an Ultraviolet (UV)-vis spectrophotometer at 550nm for two minutes. The kinetic activity was expressed in terms of nmol NADH oxidised $min^{-1}mg^{-1}$ protein.

### *2.6.2 Succinate Dehydrogenase Activity Assay*

The activity of the succinate dehydrogenase enzyme complex was evaluated using the method reported by Prakash *et al.*,[27]. Briefly, 0.025ml of brain mitochondrial pellet was mixed in a reaction tube consisting of 0.2ml of succinic acid (0.6M), 0.3ml of BSA (1%), 1.75ml of DDW, 1.5ml of sodium phosphate buffer (0.2M, pH 7.8), and 0.025ml of potassium ferricyanide (0.03M). The absorbance was recorded at 420nm for 2 min using a UV-Vis spectrophotometer. This assay's kinetic activity was expressed as nmol succinate oxidised $min^{-1}$ $mg^{-1}$ protein.

### *2.6.3 Cytochrome c Oxidase Activity Assay*

The complex IV assay activity was recorded by using the protocol reported by Prakash *et al.*,[27]. Briefly, in a fresh test tube, 0.01ml of brain mitochondrial pallet was mixed with a reaction mixture containing 0.7ml of phosphate buffer (75mM) and 0.1ml of reduced cytochrome c (0.3mM). Then, the absorbance was recorded using a

**Table 1.** Primer sequences used for RT-PCR quantification of mitochondrial subunits and MnSOD involved in mitochondrial functions

| Gene | Product Size | Direction | Sequence |
|---|---|---|---|
| ND1 | 150bp | Forward | TGGCCTTCCTCACCCTAGTA |
| | | Reverse | AGGTGGTTAGAGGGCGTATG |
| ND2 | 225bp | Forward | TCATCAGTCTTTGTTGGCGC |
| | | Reverse | TCATGCGAGTGAGAGTGTGT |
| COX1 | 174bp | Forward | CACATGAGCAAAAGCCCACT |
| | | Reverse | ACGGCCGTAAGTGAGATGAA |
| COX2 | 218bp | Forward | ACAAGACGCCACATCACCTA |
| | | Reverse | GTAGGGAGGGAAGGGCAATT |
| COX4 | 250bp | Forward | GACTACCCCTTGCCTGATGT |
| | | Reverse | ACACGTAGCTCTTCTCCCAG |
| MnSOD | 198bp | Forward | CTGAGGAGAGCAGCGGTCGT |
| | | Reverse | CTTGGCCAGCGCCTCGTGGT |

UV-vis spectrophotometer at 550nm. Finally, the results were represented as nmol cytochrome c oxidised $min^{-1}$ $mg^{-1}$ protein.

### *2.6.4 Isolation of Total RNA and Analysis of Gene Expression*

TRI reagent was used to extract the total RNA from brain tissue. The NanoDrop spectrometer was used to estimate the total amount of RNA. For all samples, absorbance was recorded at two wavelengths, 260nm and 280nm. A 260/280 absorbance ratio greater than 1.8 was taken as an acceptable value. The Revert Aid 1st Strand cDNA Synthesis Kit was used to reverse-transcribe the total RNA into 20µL of cDNA. Semi-quantitative RT-PCR analysis was performed on cDNA products using a gradient thermal cycler (PEQ LAB, Erlangen, Germany). The specific set of primer sequences used to perform this study is shown in Table 1 and Table 2.

## 2.7 Statistical Analysis

The mean ± S.D. from five separate tests was used to express the results. The Least Significant Difference (LSD) test was used with IBM SPSS Statistics® (version 25) software to evaluate the difference between means at a significance level of $p<0.05$.

# 3. Results

## 3.1 Effects of MCP and CoQ10 NPs Treatment on Complex I Activity in Rat Brain

Complex I convert NADH to ubiquinone and contributes to the movement of protons within the mitochondrial membrane. Acute MCP administration led to a significant reduction in Complex I activity compared to control rats. Complex I activity was significantly restored when low

**Table 2.** Primer sequence used for RT- PCR quantification of biogenesis-related factors involved in mitochondrial functions

| Gene | Product Size | Direction | Sequence |
|---|---|---|---|
| β-actin | 213bp | Forward | TTGCCCTAGACTTCGAGCAA |
| | | Reverse | AGACTTACAGTGTGGCCTCC |
| PGC-1α | 240bp | Forward | AGCCTCTTTGCCCAGATCTT |
| | | Reverse | GCAATCCGTCTTCATCCACC |
| NRF-1 | 186bp | Forward | ACATACTCAACTCCACGGCA |
| | | Reverse | ATGTGGCTCTGAGTTTCCGA |
| NRF-2 | 163bp | Forward | TGTCAGCTACTCCCAGGTTG |
| | | Reverse | ATCAGGGGTGGTGAAGACTG |
| Tfam | 152bp | Forward | GATCATGACGAGTTCTGCCG |
| | | Reverse | AGAACTTCACAAACCCGCAC |

**Table 3.** Effect of CoQ10 NPs administration on MCP exposure-induced mitochondrial complex activity

| Groups | Complex I Activity (nmol NADH oxidised/ min/mg protein) | Complex II activity (nmol succinate oxidised/ min/mg protein) | Complex IV activity (nmol cytochrome c oxidised/ min/mg protein) |
|---|---|---|---|
| **Control** | 78.87 ± 2.31 | 82.91 ± 9.57 | 85.12 ± 5.46 |
| **CoQ10 NPs LD** | 77.70 ± 2.68$^{NS}$ | 79.06 ± 8.69 $^{NS}$ | 84.95 ± 4.00 $^{NS}$ |
| **CoQ10 NPs HD** | 78.11 ± 2.70$^{NS}$ | 80.04 ± 9.55 $^{NS}$ | 83.61 ± 5.63 $^{NS}$ |
| **MCP** | 56.43 ± 5.61 $^{a}$ *** | 58.51 ± 4.43 $^{a}$*** | 61.11 ± 4.22 $^{a}$*** |
| **MCP+CoQ10 NPs LD** | 61.94 ± 3.32 $^{b}$ * | 64.73 ± 4.66 $^{NS}$ | 67.23 ± 4.14 $^{NS}$ |
| **MCP+CoQ10 NPs HD** | 70.67 ± 2.97 $^{b}$ *** | 70.47 ± 6.84 $^{b}$ * | 75.95 ± 6.02 $^{b}$ *** |

N=5 for all treatments. All data are expressed as mean ± S.D. The **NS**- denoted data are not significantly different from each other.**a** significantly different from control ($p<0.05$). **b** significantly different from the MCP-exposed group ($p<0.05$). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ set as significance difference.

and high concentrations of CoQ10 NPs were administered before treatment of the MCP to rats. On the other hand, neither high nor low dosages of CoQ10 NPs given alone had a negative impact on Complex I activity as compared to control rats (Table 3).

## 3.2 Effects of MCP and CoQ10 NPs Treatment on Complex II Activity in Rat Brain

Complex II is a membrane-anchored molecule that aids in the transport of electrons from succinate to ubiquinone in the ETC. When compared to control rats, acute MCP exposure dramatically reduced complex II activity in brain tissue. This decreased Complex II activity was significantly restored with pre-treatment with a high dose of CoQ10 NPs in MCP-intoxicated rats. However, when rats exposed to MCP were treated with a low dose of CoQ10 NPs, the activity of Complex II did not decrease significantly as compared to the group exposed to MCP. CoQ10 NP delivered alone, both low and high dosages, did not affect Complex II activity compared to the control group (Table 3).

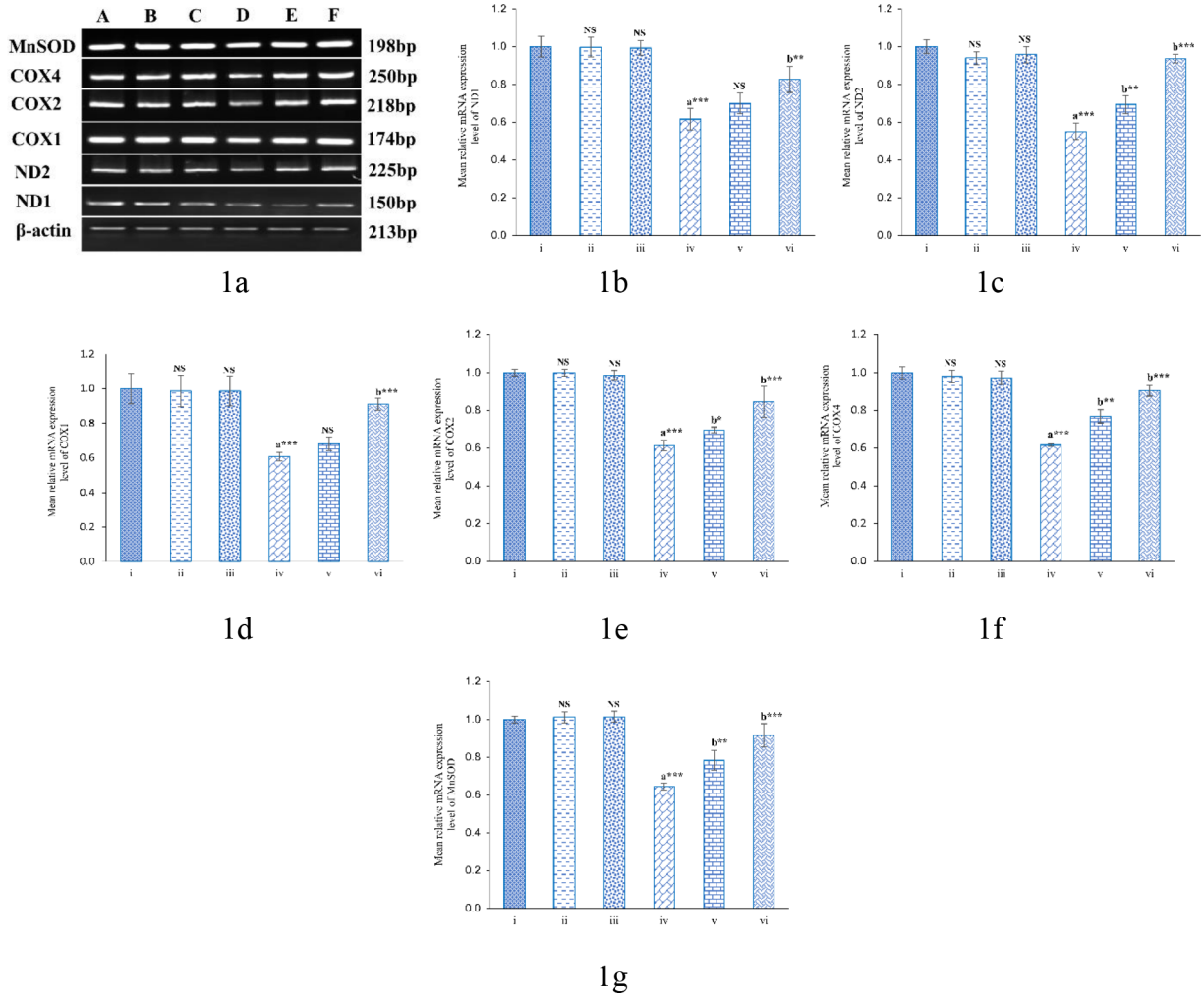



**Figure 1.** Effect of CoQ10 NPs treatment on mitochondrial subunit-related genes in MCP-exposed brain tissue of rats. **a**) Representative image of mRNA expression of ND1, ND2, COX1, COX2, COX4, and MnSOD. Mean relative mRNA expression of **b)** ND1, **c)** ND2, **d)** COX1, **e)** COX2, **f)** COX4, and **g)** MnSOD genes with respect to β-actin. Where, (i) control; (ii) CoQ10 NPs LD treated; (iii) CoQ10 NPs HD treated; (iv) MCP-exposed; (v) CoQ10 NPs LD and MCP co-treated; and (vi) CoQ10 NPs HD and MCP co-treated. NS denotes data are not significantly different from each other. The values are represented as mean ± S.D. (N = 3). **a** as compared to the control group; **b** as compared to the MCP-exposed group. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ set as significance difference

### 3.3 Effects of MCP and CoQ10 NPs Treatment on Complex IV Activity in Rat Brain

Complex IV is the terminal enzyme involved in the ETC. It is involved in Adenosine Triphosphate (ATP) production through the reduction of molecular oxygen. Exposure to MCP significantly reduced the complex IV activity in comparison to a control group of rats. Rats treated with a high dosage of CoQ10 NPs along with MCP showed enhanced complex IV activity. The administration of CoQ10 NPs at a lower dose along with MCP did not significantly increase complex IV activity in comparison to the MCP-administered rats. Nevertheless, when comparing the control group of rats to those treated with low or high doses of CoQ10 NPs, there was no significant change in complex IV activity (Table 3).

### 3.4 Effects of MCP Exposure and CoQ10 NPs Administration on mRNA Expression of Mitochondrial Function-Related Genes in Rat Brain

Biochemical analysis of mitochondrial complexes revealed that MCP exposure may have affected ETC functions. A semi-quantitative RT-PCR evaluation of PGC-1α and its downstream target genes, along with important mitochondrial complex subunits, was performed to further study the effects of CoQ10 NPs administration on MCP exposure-mediated mitochondrial functioning (Figure 1a). Our results showed that MCP-exposed rats had considerably downregulated ND1 and ND1 mRNA expression compared with controls. In MCP-intoxicated rats, low and high dosages of CoQ10 NPs restored ND1 and ND2 mRNA expression more than in MCP-exposed rats. The low- and high-dose CoQ10 NPs treated group alone had equivalent ND1 (Figure 1b) and ND2 (Figure 1c) mRNA expression to the control group.

The COX subunits are associated with complex IV and regulate the mitochondrial respiration efficacy inside the mitochondria. COX1 and COX2 are subunits encoded in the mitochondria, whereas COX4 is encoded in the nucleus. The reduced activity of these complexes might be interlinked with altered transcriptional expression of COX subunits. In comparison to control rats, acute exposure to MCP markedly reduced the expression of the COX4, COX1, and COX2 subunits. The administration of a low dosage of CoQ10 NPs in the MCP-exposed group non-significantly increased the COX1 subunit mRNA expression in comparison to MCP-treated animals. Rats

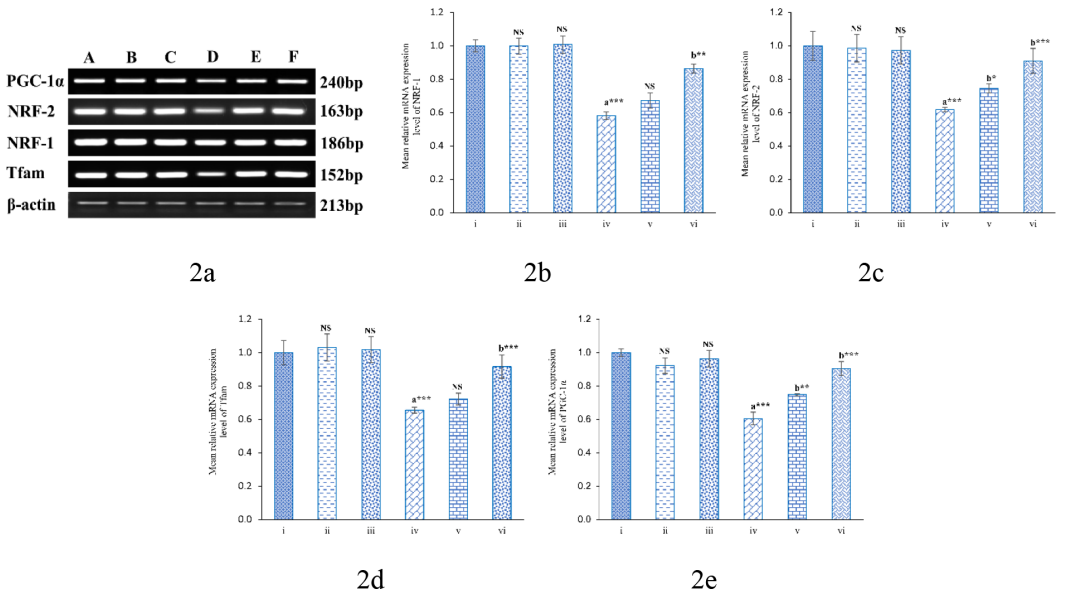



**Figure 2.** Effect of CoQ10 NPs treatment on mitochondrial biogenesis-related genes in MCP-exposed brain tissue of rats. (**a**) Representative image of mRNA expression of mitochondrial biogenesis-related factors Tfam, NRF-1, NRF-2 and PGC-1α. Mean relative mRNA expression of NRF-1 **(b)**, NRF-2 **(c)**, Tfam **(d)**, and PGC-1α **(e)** genes with respect to β-actin
(i) control; (ii) CoQ10 NPs LD treated; (iii) CoQ10 NPs HD treated; (iv) MCP-exposed; (v) CoQ10 NPs LD and MCP co-treated; and (vi) CoQ10 NPs HD and MCP co-treated. NSdenotes data are not significantly different from each other. The values are represented as mean ± S.D. (N = 3). [a] as compared to the control group; [b] as compared to the MCP-exposed group. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ set as significance difference

intoxicated with a high dose of CoQ10 NPs along with MCP showed a significant upregulation of the mRNA of COX1, COX4, and COX2 subunits. Nonetheless, the group that received both high and low dosages of CoQ10 NPs alone had comparable COX1(Figure 1d), COX2 (Figure 1e), and COX4 (Figure 1f) subunit expression to the control group.

MnSOD is a prime mitochondrial gene that regulates the ROS levels inside the mitochondria. Our study also demonstrated that MnSOD expression was downregulated by MCP treatment. In comparison to the MCP-intoxicated group, MnSOD mRNA expression was considerably recovered by the administration of both low and high dosages of CoQ10 NPs. Pre-treatment with both dosages of CoQ10 NP alone did not alter MnSOD mRNA expression compared to control rats (Figure 1g).

By controlling a number of downstream processes, PGC-1α is a key transcriptional factor that alters mitochondrial activity. This study demonstrated that acute exposure to MCP significantly downregulated the NRF-2, Tfam, PGC-1α and NRF-1 mRNA expression in comparison to the control group of rats (Figure 2a). The depletion in the levels of PGC-1α and associated factors suggested mitochondrial dysfunction and decreased mitochondrial biogenesis following acute MCP exposure. Administration of a high dose of CoQ10 NPs reversed the expression of PGC-1α, NRF-1, Tfam, and NRF-2 in the MCP-exposed group. There was a non-significant change in the expression of these genes in the low-dose CoQ10 NPs co-treated group. Conversely, neither low nor high dosages of CoQ10 NPs alone altered the expression of the NRF-1(Figure 2b), PGC-1α (Figure 2e), Tfam (Figure 2d) and NRF-2 (Figure 2c) genes compared to the control group.

## 4. Discussion

Monocrotophos is an extremely prevalent and cost-effective pesticide that finds extensive applications globally. Notably, India is the biggest producer and consumer of this chemical pesticide. Monocrotophos is one of the most broadly used and toxic organophosphate pesticides, especially in South Asia. Its tendency to cause oxidative stress, neuroinflammation, and mitochondrial bioenergetic collapse is well documented[18-19]. Acute and chronic intoxication of this pesticide induces the generation of oxidative stress via inhibition of AChE activity and exerts adverse effects on many organs of animals, including the brain, liver, kidney, and other vital organs[1,3,15,24]. MCP-induced oxidative stress modifies enzyme activity, lowers endogenous antioxidants, and promotes neuronal inflammation and mitochondrial dysfunction, resulting in multi-organ toxicity and severe genetic abnormalities that may be fatal[29-32]. Exposure to MCP induces disruptions in metabolism and creates changes in the homeostasis of cells, both of which are indicators of neurotoxicity[21]. The present study directly shows that acute exposure to MCP (4.5 mg/kg b. wt) markedly inhibits the catalytic activities of mitochondrial complexes I, II and IV in rat brain tissues and at the same time reduces the expression of mRNA for mitochondrial subunit genes (ND1, ND2, COX1, COX2, COX4), antioxidant gene MnSOD and biogenesis regulators (PGC-1α, NRF-1, NRF-2, Tfam). All the enzymatic activities of the ETC complexes were significantly improved after Pre-treatment with CoQ10 NPs, especially at the dose of 100 mg/kg, which also had a significant effect on the transcriptional profile of the genes involved in mitochondrial subunit assembly and biogenesis.

Recent investigations on the protection against pesticide damage have demonstrated the neuroprotective properties of several natural antioxidants[33-34]. A growing body of evidence indicates that antioxidative dietary supplements are beneficial against oxidative stress[11,17,30,35]. Coenzyme Q10 is a widely recognised electron acceptor co-factor in mitochondrial respiration. In addition to its bioenergetic function, it possesses potent scavenging capabilities against free radicals[36]. Many previous research studies have demonstrated that CoQ10 is protective against neurotoxicity, oxidative damage, and cardiotoxicity induced by rotenone, Adriamycin, and $H_2O_2$[37-39]. Treatment with CoQ10 NPs instead of simple coenzyme Q10 might reduce some major problems faced in antioxidant supplementation, like improvement of membrane permeability, limited bioavailability, fast metabolism, stability, efficiency, effectiveness, and better solubility in both hydrophilic and lipophilic medium[40-41]. All these facts ensure better solubility and high bioavailability and concentration of supplements inside the cells[22].

The increased oxidative stress resulting from MCP exposure may alter the mitochondrial functions in the brain tissues of rats. It is widely acknowledged that oxidative stress generation is correlated with mitochondrial dysfunction[17,42-44]. Mitochondria are the most important cellular organelles because they generate energy, regulate

oxidative metabolism, and maintain homeostasis inside the cells. Several evidences suggest that mitochondria are the primary organelles affected by pesticide exposure[45-46]. Several studies have demonstrated a connection between changes in mitochondrial complex function and oxidative stress[16,17,42]. The results of our research indicated that the activities of complexes I, II, and IV were significantly diminished in comparison to the control rats. Any alterations in complex I activity indicate that electron transport and proton translocation in mitochondria are disrupted[43,47]. The decrease in the activity of complex II revealed that there was an aberration in proton translocation, which can alter the ionic gradient which is essential for the normal functioning of mitochondria. Complex IV is an essential component of mitochondrial respiration that helps with proton pumping and enables the transport of electrons from cytochrome c to oxygen. The reduction in the activity of complex IV strongly suggested that oxygen is not properly utilised by mitochondria. Many previous studies have shown that lipid membrane damage can degrade the components of ETC and impede the flow of electrons and translocation of protons, hence altering mitochondrial complexes' activity[14,15,48-51]. The results of the current study are consistent with those of prior investigations showing that rats exposed to MCP have a decrease in respiratory chain enzymes and an increase in ROS[47].

The decrease in complex I (NADH dehydrogenase) activity in MCP exposure is similar to the one reported in arsenic-impacted rats' brain, where the researchers suggested that the decreased activity was due to the oxidative damage of the iron–sulphur clusters of the complex[27]. Likewise, hydroxytyrosol, a polyphenolic antioxidant, is also reported to reverse the impairment of complexes I and IV in the brain of arsenic-challenged rats, to a similar extent as was observed in the present study with CoQ10 NPs [50]. The paradigm further expands to include direct effects of aluminium-induced oxidative stress on complex IV (cytochrome c oxidase) and the dysregulation of PGC-1α [17]. Taken together, these reports support our idea that oxidative stress due to xenobiotic exposure is a common upstream mechanism leading to dysfunction of the ETC, and that lipid-soluble antioxidants, including CoQ10 NPs, can improve the integrity of the ETC, as they are able to reduce mitochondrial ROS and maintain electron flow.

The administration of a high dose of CoQ10 NPs in MCP-intoxicated rats significantly recovered the activities of these complexes in comparison to the MCP-exposed group of rats, suggesting the ameliorative potential of CoQ10 NPs against pesticide toxicity conditions. Administration of a low dose of CoQ10 NPs in the co-exposed group non-significantly increased the activities of complexes II and IV and significantly restored the complex I activity, in contrast with the MCP-intoxicated group. Various previous investigations have established that supplementation with antioxidants can mitigate the decline of oxidative stress and enhance the functionality of ETS enzymes in rodent brains and liver tissues subjected to various toxic exposures[5,16,17,25,50]. In this study, alterations in the activities of mitochondrial complexes may be attributable to alterations in their constituent subunits. Several proteins that mediate mitochondrial and cellular activity are encoded by the mitochondrial subunits. The mitochondrial DNA encodes the ND1, ND2, COX1, and COX2 subunits, while nuclear DNA encodes COX4. These complex subunits are essential for oxygen utilisation and oxidative phosphorylation. The findings of this study showed that acute exposure to MCP downregulated the expression of COX1, COX2, COX4, ND1 and ND2 subunit mRNAs when compared to control rats. Findings suggest that the downregulated gene expression of certain mitochondrial subunits might also be responsible for the decreased activities of mitochondrial complexes. These findings corroborate previous research findings showing that oxidative changes of ETC complex subunits lead to the loss of complexes functioning in the kidney mitochondria of aged mice[14]. Many earlier studies have also depicted that the mRNA expression of mitochondrial complex subunits was significantly reduced in rats exposed to metal poisoning[27,51].

The reduction of ND1, ND2, COX1, COX2, COX4, and MnSOD mRNA after MCP exposure is similar to Singh *et al.*[20], who showed that the same mitochondrial subunit transcripts were reduced in rat liver after exposure to MCP and could be restored by N-acetylcysteine[20]. Dhillon *et al.*[21] also observed that complex I and IV subunits were decreased by MCP-induced oxidative stress, and lipid peroxidation was increased while glutathione was decreased in the frontal cortex and hippocampus. In our study, transcriptional upregulation of these transcripts through the use of CoQ10 NPs indicates that CoQ10 NPs can not only be an antioxidant within the ETC at a one-to-one ratio, but can also lift the oxidative repression of the transcriptional machinery responsible for the production of the complex I and IV subunits. This dual

antioxidant –transcriptional mode of action is reinforced by the simultaneous restoration of MnSOD, an important mitochondrial antioxidant enzyme regulated by the Nrf2/ARE pathway.

The decreased mRNA expression of these subunits was significantly reversed by the administration of both high and low dosages of CoQ10 NPs in the co-exposed group in comparison to the MCP-exposed group. These findings suggest that the antioxidative efficacy of CoQ10 NPs might be responsible for reviving the functioning of mitochondria at biochemical and molecular levels. Several previous studies are in line with the results of our study and have shown that the administration of different antioxidant supplements could restore the altered mRNA of mitochondrial complex subunits in the brain tissue of rats[51]. Further, the expression of PGC-1α and related factors was assessed to correlate the significance of biogenesis factors in mitochondrial dysfunction. It is mentioned that PGC-1α is a transcriptional co-activator that is highly expressed in metabolically active tissues[52]. In response to mitochondrial oxidative stress, it neutralises ROS, triggers apoptosis, and co-regulates several other transcription factors[53]. Moreover, many antioxidant genes, including UCP-2, NRF-1, MnSOD, and NRF-2, are directly regulated by the action of PGC-1α at the transcriptional level. PGC-1α binds to NRF-2 and NRF-1 transcription factors and activates respiratory complex subunits[15,52]. These NRFs bind to COX4 subunits and regulate the gene expression of cell proliferation-related factors. NRF-1 transcription factor modulates the expression of the nuclear-encoded subunits of all five ETC complexes by modulating transcriptional regulators such as Tfam, whereas NRF-2 selectively increases the expression of COX4 subunits. In addition to this, reduced mRNA expression of PGC-1α is also associated with the downregulation of certain mitochondrial subunits because it has a direct role in mitochondrial biogenesis[15]. Tfam is also another important key regulator of mitochondrial transcription that increases the level of replication and transcription of mitochondrial DNA.

The master transcriptional coactivator of mitochondrial biogenesis is the peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), which regulates NRF-1 and NRF-2, which ultimately regulate Tfam-mediated transcription and replication of the mitochondrial genome[4,16]. The observed MCP-induced downregulation of this axis is consistent with previous studies that demonstrated that organophosphate-induced ROS affects PGC-1α signalling, leading to reduced biogenesis[17,21]. Some previous studies have demonstrated a strong link between the expression levels of Tfam, PGC-1α, and NRF-1 in PC12 cells[20]. Furthermore, they also showed that NRF-1-mediated transcriptional control is necessary for maintaining mitochondrial mass and mtDNA copy number during serum deprivation via Tfam expression[54]. In addition, many previous studies have also shown that the targeted disruption of NRFs causes early embryonic mortality in animals[54-56]. Consistent with our results, previous research studies have revealed that oxidative stress reduces PGC-1-mediated mitochondrial biogenesis through its downstream targets under toxic conditions that affect the brain and liver tissues of rats[16,57]. Treatment with a high dose of CoQ10 NPs significantly upregulated the mRNA expression of PGC-1α and other downstream targets in a co-treated group of rats. However, treatment with a low dose of CoQ10 NPs in the MCP-intoxicated group was not effective in restoring the mRNA expression of many genes. The acute MCP intoxication might consistently increase high levels of oxidative stress, which might significantly reduce the expression of mitochondrial biogenesis-related factors, which could not be reversed by the low dose of CoQ10 NPs treatment.

Alterations in mitochondrial activities have the potential to stimulate the formation of ROS and inhibit the activity of the antioxidant defence system both at cellular and subcellular levels. MnSOD is a necessary antioxidant which prevents mitochondrial oxidative stress by neutralising superoxide radicals generated during ETC. The reduction in the mRNA expression of the MnSOD gene is a crucial sign of oxidative stress that leads to pathophysiological changes in mitochondria[14,58]. The results of our study have shown that exposure to MCP decreased both mRNA and protein expression of MnSOD as compared to the control group. This suggests that MCP exposure might reduce the activity of MnSOD by reducing its transcription and protein synthesis. Several prior investigations have demonstrated that a reduction in MnSOD mRNA is a contributing factor to oxidative stress inside the mitochondria, resulting in mitochondrial dysfunctions[17,27,51]. The expression of MnSOD mRNA was significantly increased in rats treated with MCP when high doses of CoQ10 NPs were administered. Some previous studies have also shown similar results, in which supplementation of different antioxidants was shown to neutralise the oxidative stress induced by toxic conditions

via elevating the MnSOD mRNA and protein expression in liver and brain tissues of rats[17,21]. However, the treatment with a low dose of CoQ10 NPs failed to restore the MnSOD expression in MCP-exposed rats, suggesting generation of high oxidative stress and low efficacy of CoQ10 NPs against it. Hence, it can be speculated that CoQ10 NPs may stabilise the functions of mitochondrial complexes and maintain transcriptional levels of mitochondrial subunits by reducing the formation of free radicals.

Interestingly, the high dose of CoQ10 NPs (100 mg/kg b.wt) showed significant effects on the return of PGC-1α, NRF-1, NRF-2, and Tfam transcript levels as well as ETC complex activities compared to the low dose (50 mg/kg b.wt). This dose-dependence is mechanistically explicable on two grounds: (i) the higher intracellular CoQ10 concentration will result in more complete reduction of mitochondrial ROS, thereby offsetting the redox-sensitive repression of PGC-1α; and (ii) sufficient cerebral bioavailability of CoQ10, a challenge that conventional CoQ10 cannot consistently achieve due to BBB constraints but can be more readily achieved with the higher nanoparticulate dose, consistent with the enhanced brain delivery profile reported for nanoparticulate CoQ10 formulations[59-60]. Taken together, our results suggest that CoQ10 NPs in cooperation exert a neuroprotective effect against the mitochondrial dysfunction induced by MCP, which involves a two-step process: (i) direct antioxidant effects that neutralise ROS produced by MCP, and (ii) activity as transcriptional modulators that restore the expression of both mitochondrial subunit genes and re-engage the PGC-1α/NRF/Tfam biogenesis axis. Native CoQ10 (CoQ10) is limited by its intrinsic bioavailability and BBB penetration, which is overcome by the nanoparticulate formulation that allows intracerebral delivery at translationally meaningful doses[37,61]. These mechanistic insights suggest CoQ10 NPs as a rational therapeutic candidate for OP neurotoxicity.

## 5. Conclusion

Based on the present study, acute exposure to MCP (4.5 mg/kg b.wt) significantly impairs the function of mitochondria in the brain tissues by decreasing the activities of the ETC complexes (complexes I, II, and IV) and also by downregulating the expression of the genes encoding the mitochondrial subunits (ND1, ND2, COX1, COX2 and COX4), the antioxidant gene MnSOD, and the biogenesis regulators (PGC-1α, NRF-1, NRF-2, and Tfam). Pre-treatment with CoQ10 NPs (especially at a high dose; 100mg/kg b.wt) significantly normalised these parameters towards the control level. The mechanism underlying the action of the CoQ10 NPs on the mitochondrial damage induced by the MCP is apparently coordinated by two actions: (i) direct antioxidant scavenging of ROS in the inner mitochondrial membrane, which preserves the integrity of the ETC complexes; and (ii) transcriptional modulation, establishing re-expression of mitochondrial subunit genes and reactivation of the PGC-1α/NRF/Tfam biogenesis signalling axis. Long-term recovery after the acute exposure window or protein-level expression of the genes investigated, however, was not assessed in this study. Future studies are needed to extend the findings of these models to chronic models of MCP exposure, include molecular quantification using Western blot, and evaluate behaviour and neurocognitive outcomes to firmly translate these molecular findings to functional neuroprotection. Therefore, CoQ10 NPs could be a promising therapeutic approach for the prevention of MCP-induced neurotoxicity and further study, both preclinical and clinical, is warranted as a mitochondria-targeted neuroprotective treatment.

## 6. Acknowledgement

The authors are highly thankful to the Central Instrumentation Facility of Maharshi Dayanand University, Rohtak, Haryana - 124001 (India).

## 7. References

1. Choksi KB, Nuss JE, Boylston WH, Rabek JP, Papaconstantinou J. Age-related increases in oxidatively damaged proteins of mouse kidney mitochondrial electron transport chain complexes. Free Radic Biol Med. 2007; 43(10):1423-1438. https://doi.org/10.1016/j.freeradbiomed.2007.07.027 PMid:17936188 PMCid:PMC2080815.
2. Devi S, Singh J, Kumar V, Malik V. Monocrotophos-induced biochemical and histopathological alterations in the kidney tissues of mice. Chem Biol Lett. 2019; 6(2):39-45.
3. Dhillon T, Verma A, Kumar V. N-acetylcysteine elevates Nrf-2/ARE-regulated antioxidant response and mitochondrial biogenesis in different brain regions of monocrotophos-exposed rats. Res J Biotechnol. 2022; 17(11):63. https://doi.org/10.25303/1711rjbt63072
4. Gleyzer N, Vercauteren K, Scarpulla RC. Control of mitochondrial transcription specificity factors (TFB1M and TFB2M) by nuclear respiratory factors (NRF-1 and

NRF-2) and PGC-1 family coactivators. Mol Cell Biol. 2005; 25(4):1354. https://doi.org/10.1128/MCB.25.4.1354-1366.2005 PMid:15684387 PMCID: PMC548005.
5. Gundi VAKB, Reddy BR. Degradation of monocrotophos in soils. Chemosphere. 2006; 62(3):396. https://doi.org/10.1016/j.chemosphere.2005.04.076 PMid:15978655.
6. Huang Y, Shi T, Luo X, Xiong H, Min F, Chen Y, Xie M. Determination of multi-pesticide residues in green tea with a modified QuEChERS protocol coupled to HPLC-MS/MS. Food Chem. 2019; 275:255. https://doi.org/10.1016/j.foodchem.2018.09.094 PMid:30724195.
7. Ibrahim AAE. Cytogenetic studies on the effect of insecticide Monocrotophos in mouse somatic and germ cells. Cytologia. 2005; 70(4):385. https://doi.org/10.1508/cytologia.70.385
8. Karumuri SB, Singh H, Naqvi S, Mishra A, Flora SJS. Impact of chronic low-dose exposure of monocrotophos in rat brain: Oxidative/nitrosative stress, neuronal changes and cholinesterase activity. Toxicol Rep. 2019; 6:1295. https://doi.org/10.1016/j.toxrep.2019.11.005 PMid:31867220 PMCID: PMC6906705.
9. Kazi AI, Oommen A. The effect of acute severe monocrotophos poisoning on inhibition, expression and activity of acetylcholinesterase in different rat brain regions. Neurotoxicology. 2012; 33(5):1284. https://doi.org/10.1016/j.neuro.2012.07.010 PMid:22903060.
10. Krause KH, van Thriel C, de Sousa PA, Leist M, Hengstler JG. Monocrotophos in Gandaman village: India school lunch deaths and need for improved toxicity testing. Arch Toxicol. 2013; 87(10):1877. https://doi.org/10.1007/s00204-013-1113-6 PMid:23943209.
11. Malik V, Singh J, Kumar A, Kumar V. Protective effect of coenzyme Q10 nanoparticles against monocrotophos-induced oxidative stress in kidney tissues of rats. Biologia. 2021. https://doi.org/10.1007/s11756-021-00732-x
12. Mandal M, Jaiswal P, Mishra A. Curcumin-loaded nanoparticles reversed monocrotophos-induced motor impairment and memory deficit: Role of oxidative stress and intracellular calcium level. J Drug Deliv Sci Technol. 2020; 56:101559. https://doi.org/10.1016/j.jddst.2020.101559
13. Mehndiratta MM. Neurological mitochondrial cytopathies. Neurol India. 2002; 50(2):162.
14. Mehndiratta MM, Aggarwal P. Neurological mitochondrial cytopathies in children. Indian Pediatr. 2000; 37(11):1175.
15. Ramjiawan A, Bagchi RA, Albak L, Czubryt MP. Mechanism of cardiomyocyte PGC-1α gene regulation by ERRα. Biochem Cell Biol. 2013; 91(3):148. https://doi.org/10.1139/bcb-2012-0080 PMid:23668787.
16. Rius-Pérez S, Torres-Cuevas I, Millán I, Ortega ÁL, Pérez S. PGC-1α, Inflammation, and Oxidative Stress: An integrative view in metabolism. Oxid Med Cell Longev. 2020; 452696. https://doi.org/10.1155/2020/1452696 PMid:32215168 PMCID: PMC7085407.
17. Sharma DR, Sunkaria A, Wani WY, Sharma RK, Kandimalla RJL, Bal A, Gill KD. Aluminium-induced oxidative stress results in decreased mitochondrial biogenesis via modulation of PGC-1α expression. Toxicol Appl Pharmacol. 2013; 273(2):365. https://doi.org/10.1016/j.taap.2013.09.012 PMid:24084166.
18. Yadav B, Kaur S, Yadav A, Verma H, Kar S, Sahu BK, Pati KR, Sarkar B, Dhiman M, Mantha AK. Implications of organophosphate pesticides on brain cells and their contribution toward progression of Alzheimer's disease. J Biochem Mol Toxicol. 2024; 38(3):e23660. https://doi.org/10.1002/jbt.23660 PMid:38356323.
19. Farkhondeh T, Mehrpour O, Forouzanfar F, Roshanravan B, Samarghandian S. Oxidative stress and mitochondrial dysfunction in organophosphate pesticide-induced neurotoxicity and its amelioration: A review. Environ Sci Pollut Res. 2020; 27(20):24799-24814. https://doi.org/10.1007/s11356-020-09045-z PMid:32358751.
20. Singh J, Phogat A, Kumar V, Malik V. N-acetylcysteine ameliorates monocrotophos exposure-induced mitochondrial dysfunctions in rat liver. Toxicol Mech Methods. 2022; 32(9):686. https://doi.org/10.1080/15376516.2022.2064258 PMid:35403558.
21. Dhillon T, Kumar A, Kumar V. Neuroprotective effect of N-acetylcysteine against monocrotophos-induced oxidative stress in different brain regions of rats. Appl Biochem Biotechnol. 2022; 194(9):4049-4065. https://doi.org/10.1007/s12010-022-03967-9 PMid:35587328.
22. Eftekhari A, Ahmadian E, Azami A, Johari-Ahar M, Eghbal MA. Protective effects of coenzyme Q10 nanoparticles on dichlorvos-induced hepatotoxicity and mitochondrial/lysosomal injury. Environ Toxicol. 2018; 33(2):167. https://doi.org/10.1002/tox.22505 PMid:29143438.
23. Singh S, Kumar V, Kanwar R, Wani AB, Gill JPK, Garg VK, Ramamurthy PC. Toxicity and detoxification of monocrotophos from ecosystem using different approaches: A review. Chemosphere. 2021; 275:130051. https://doi.org/10.1016/j.chemosphere.2021.130051 PMid:33676273.
24. Sun J, Wang F, Sui Y, She Z, Zhai W, Wang C, Deng Y. Effect of particle size on solubility, dissolution rate, and oral bioavailability: Evaluation using coenzyme Q10 as naked nanocrystals. Int J Nanomedicine. 2012; 7:5733. https://doi.org/10.2147/IJN.S34365 PMid:23166438 PMCid:PMC3500035.
25. Amit K, Jagjeet S, Ritu S, Vijay K. Coenzyme Q10 nanoparticles prevent monocrotophos exposure-mediated neurotoxicity by attenuating histological alterations in rats. Res J Chem Environ. 2022; 26(12):13. https://doi.org/10.25303/2612rjce13023.

26. Devadasu VR, Wadsworth RM, Kumar MNV. Protective effects of nanoparticulate coenzyme Q10 and curcumin on inflammatory markers and lipid metabolism in streptozotocin-induced diabetic rats: A possible remedy to diabetic complications. Drug Deliv Transl Res. 2011; 1(6):448. https://doi.org/10.1007/s13346-011-0041-3 PMid:25786365.
27. Prakash C, Soni M, Kumar V. Biochemical and molecular alterations following arsenic-induced oxidative stress and mitochondrial dysfunction in rat brain. Biol Trace Elem Res. 2015; 167(1):121. https://doi.org/10.1007/s12011-015-0284-9 PMid:25764338.
28. Yaduvanshi SK, Ojha A, Pant SC, Lomash V, Srivastava N. Monocrotophos-induced lipid peroxidation and oxidative DNA damage in rat tissues. Pestic Biochem Physiol. 2010; 97(3):214. https://doi.org/10.1016/j.pestbp.2010.02.004.
29. Dwivedi N, Flora SJS. Concomitant exposure to arsenic and organophosphates on tissue oxidative stress in rats. Food Chem Toxicol. 2011; 49(5):1152. https://doi.org/10.1016/j.fct.2011.02.007 PMid:21349312.
30. Nidheesh T, Salim C, Rajini PS, Suresh PV. Antioxidant and neuroprotective potential of chitooligomers in *Caenorhabditis elegans* exposed to monocrotophos. Carbohydr Polym. 2016; 135:138. https://doi.org/10.1016/j.carbpol.2015.08.055 PMid:26453861.
31. Ali SJ, Rajini PS. Effect of monocrotophos, an organophosphorus insecticide, on the striatal dopaminergic system in a mouse model of Parkinson's disease. Toxicol Ind Health. 2016; 32(7):1153. https://doi.org/10.1177/0748233714547733 PMid:25227224.
32. Arora DK. Effect of monocrotophos (an organophosphate) on liver of albino rat: Histochemical and biochemical studies. J Pharmacogn Phytochem. 2019; 8(4S):95.
33. Phogat A, Singh J, Kumar V. Berberine mitigates acetamiprid-induced hepatotoxicity and inflammation via regulating endogenous antioxidants and NF-κB/TNF-α signalling in rats. Environ Sci Pollut Res Int. 2023; 30(37):87412. https://doi.org/10.1007/s11356-023-28279-1 PMid:37421530.
34. Phogat A, Singh J, Sheoran R, Hasanpuri A, Chaudhary A, Bhardwaj S, *et al*. Berberine attenuates acetamiprid exposure-induced mitochondrial dysfunction and apoptosis in rats via regulating the antioxidant defence system. J Xenobiotics. 2024; 14(3):1079. https://doi.org/10.3390/jox14030061 PMid:39189176 PMCid: PMC11348026.
35. Li S, Cao C, Shi H, Yang S, Qi L, Zhao X, Sun C. Effect of quercetin against mixture of four organophosphate pesticides-induced nephrotoxicity in rats. Xenobiotica. 2016; 46(3):225. https://doi.org/10.3109/00498254.2015.1070443 PMid:26226520.
36. Papucci L, Schiavone N, Witort E, Donnini M, Lapucci L, Tempestini A, *et al*. Coenzyme Q10 prevents apoptosis by inhibiting mitochondrial depolarization independently of its free radical scavenging property. J Biol Chem. 2003; 278(30). https://doi.org/10.1074/jbc.M302297200 PMid:12736273.
37. Li L, Du J, Lian Y, Zhang Y, Li X, Liu Y, Wu T. Protective effects of coenzyme Q10 against hydrogen peroxide-induced oxidative stress in PC12 cell: The role of Nrf2 and antioxidant enzymes. Cell Mol Neurobiol. 2016; 36(1):103. https://doi.org/10.1007/s10571-015-0224-4 PMid:26072159 PMCID: PMC11482346.
38. Moon Y, Lee KH, Park JH, Geum D, Kim K. Mitochondrial membrane depolarization and the selective death of dopaminergic neurons by rotenone: Protective effect of coenzyme Q10. J Neurochem. 2005; 93(5):1199. https://doi.org/10.1111/j.1471-4159.2005.03112.x PMid:15934940.
39. Ohhara H, Kanaide H, Yoshimura R, Okada M, Nakamura M. A protective effect of coenzyme Q10 on ischemia and reperfusion of the isolated perfused rat heart. J Mol Cell Cardiol. 1981; 13(1):65. https://doi.org/10.1016/0022-2828(81)90229-7 PMid:7253030.
40. Won R, Lee KH, Lee BH. Coenzyme Q10 protects neurons against neurotoxicity in hippocampal slice culture. Neuroreport. 2011; 22(14):721. https://doi.org/10.1097/WNR.0b013e32834acb8d PMid:21849914.
41. Okudan N, Belviranlı M, Sezer T. Potential protective effect of coenzyme Q10 on doxorubicin-induced neurotoxicity and behavioral disturbances in rats. Neurochem Res. 2022; 47(5):1280. https://doi.org/10.1007/s11064-021-03522-8 PMid:34978671.
42. Orrenius S, Gogvadze V, Zhivotovsky B. Mitochondrial oxidative stress: implications for cell death. Annu Rev Pharmacol Toxicol. 2007; 47:143. https://doi.org/10.1146/annurev.pharmtox.47.120505.105122 PMid:17029566.
43. Sandhir R, Sood A, Mehrotra A, Kamboj SS. N-acetylcysteine reverses mitochondrial dysfunctions and behavioral abnormalities in 3-nitropropionic acid-induced Huntington's disease. Neurodegener Dis. 2012; 9(3):145. https://doi.org/10.1159/000334273 PMid:22327485.
44. Owumi SE, Akomolafe AP, Imosemi IO, Odunola OA, Oyelere AK. N-acetyl cysteine co-treatment abates perfluorooctanoic acid-induced reproductive toxicity in male rats. Andrologia. 2021; 53(5):e14037. https://doi.org/10.1111/and.14037 PMid:33724529.
45. Liu Q, Wang Q, Xu C, Shao W, Zhang C, Liu H, Gu A. Organochloride pesticides impaired mitochondrial function in hepatocytes and aggravated disorders of fatty acid metabolism. Sci Rep. 2017; 7(1):46339. https://doi.org/10.1038/srep46339 PMid:28397872 PMCid: PMC5387717.
46. Akbar SM, Sharma HC, Jayalakshmi SK, Sreeramulu K. Methylparathion- and carbofuran-induced mitochondrial dysfunction and oxidative stress in *Helicoverpa armigera*

(*Noctuidae: Lepidoptera*). Pestic Biochem Physiol. 2012; 103(1):31. https://doi.org/10.1016/j.pestbp.2012.02.005.
47. Masoud A, Kiran R, Sandhir R. Impaired mitochondrial functions in organophosphate-induced delayed neuropathy in rats. Cell Mol Neurobiol. 2009; 29(8):1245. https://doi.org/10.1007/s10571-009-9420-4 PMid:19517227 PMCID: PMC11506266.
48. Zhang JG, Tirmenstein MA, Nicholls-Grzemski FA, Fariss MW. Mitochondrial electron transport inhibitors cause lipid peroxidation-dependent and -independent cell death: protective role of antioxidants. Arch Biochem Biophys. 2001; 393(1):87. https://doi.org/10.1006/abbi.2001.2486 PMid:11516165.
49. Bhatti JS, Bhatti GK, Reddy PH. Mitochondrial dysfunction and oxidative stress in metabolic disorders: A step towards mitochondria-based therapeutic strategies. Biochim Biophys Acta Mol Basis Dis. 2017; 1863(5):1066. https://doi.org/10.1016/j.bbadis.2016.11.010 PMid:27836629 PMCID: PMC5423868.
50. Soni M, Prakash C, Sehwag S, Kumar V. Protective effect of hydroxytyrosol in arsenic-induced mitochondrial dysfunction in rat brain. J Biochem Mol Toxicol. 2017; 31(7):e21906. https://doi.org/10.1002/jbt.21906 PMid:28225195.
51. Soni M, Prakash C, Dabur R, Kumar V. Protective effect of hydroxytyrosol against oxidative stress mediated by arsenic-induced neurotoxicity in rats. Appl Biochem Biotechnol. 2018; 186(1):27. https://doi.org/10.1007/s12010-018-2723-5 PMid:29497947.
52. Sharma P, Singh R, Jan M. Dose-dependent effect of deltamethrin in testis, liver, and kidney of Wistar Rats. Toxicol Int. 2014; 21(2):131. https://doi.org/10.4103/0971-6580.139789 PMid:25253921 PMCid:PMC4170553.
53. Kashyap MP, Singh AK, Siddiqui MA, Kumar V, Tripathi VK, Khanna VK, Pant AB. Caspase cascade regulated mitochondria-mediated apoptosis in monocrotophos-exposed PC12 cells. Chem Res Toxicol. 2010; 23(11):1663. https://doi.org/10.1021/tx100234m PMid:20957986.
54. Uittenbogaard M, Baxter KK, Chiaramello A. The neurogenic basic helix-loop-helix transcription factor NeuroD6 confers tolerance to oxidative stress by triggering an antioxidant response and sustaining the mitochondrial biomass. ASN Neuro. 2010; 2(2):e00034. https://doi.org/10.1042/AN20100005 PMid:20517466 PMCid: PMC2874871.
55. Ristevski S, O'Leary DA, Thornell AP, Owen MJ, Kola I, Hertzog PJ. The ETS transcription factor GABPα is essential for early embryogenesis. Mol Cell Biol. 2004; 24(13):5844. https://doi.org/10.1128/MCB.24.13.5844-5849.2004 PMid:15199140 PMCID: PMC480913.
56. Cameron RB, Beeson CC, Schnellmann RG. Development of therapeutics that induce mitochondrial biogenesis for the treatment of acute and chronic degenerative diseases. J Med Chem. 2016; 59(23):10411. https://doi.org/10.1021/acs.jmedchem.6b00669 PMid:27560192 PMCID: PMC5564430.
57. Halder S, Nasrin F, Chandra Shill M, Shuma ML, Sultan MZ, Reza MS. Improved biopharmaceutical performance of coenzyme Q10 through solid lipid nanoparticles for enhanced brain delivery. Scientifica. 2025; 2025(1):9034181. https://doi.org/10.1155/sci5/9034181 PMID: 40551809 PMC ID: PMC12185197.
58. Middlemore-Risher ML, Adam BL, Lambert NA, Terry AV. Effects of chlorpyrifos and chlorpyrifos-Oxon on the dynamics and movement of mitochondria in rat cortical neurons. J Pharmacol Exp Ther. 2011; 339(2):341. https://doi.org/10.1124/jpet.111.184762 PMid:21799050 PMCID: PMC3199992.
59. Mantle D, Hargreaves I. Coenzyme Q10 and the blood-brain barrier: an overview. J Clin Med. 2025; 14(8):2748. https://doi.org/10.3390/jcm14082748 PMid:40283578 PMCID: PMC12027549.
60. Halder S, Nasrin F, Chandra Shill M, Shuma ML, Sultan MZ, Reza MS. Improved biopharmaceutical performance of coenzyme Q10 through solid lipid nanoparticles for enhanced brain delivery. Scientifica. 2025; 2025(1):9034181. https://doi.org/10.1155/sci5/9034181 PMID: 40551809 PMC ID: PMC12185197.
61. Ebrahimi A, Kamyab A, Hosseini S, Ebrahimi S, Ashkani-Esfahani S. Involvement of coenzyme Q10 in various neurodegenerative and psychiatric diseases. Biochem Res Int. 2023; 2023(1):5510874. https://doi.org/10.1155/2023/5510874 PMID: 37946741 PMC ID: PMC10632062.

## Author Contribution

**V.K.** conceptualised the idea of this manuscript; **A.K.**, **A.C.** and **J.P.** jointly conducted the experimental work. **A.K.** and **V.K.** jointly completed the software handling and statistical analysis. **A.K.** prepared and reviewed the manuscript. **V.K.** and **A.K.;** and conducted the final editing.


| Access this journal online | |
|---|---|
| **Website:** https://informaticsjournals.com/journals/toxi/home | **Quick Response Code** |