Current Pharmacology Reports (2022) 8:1–19
https://doi.org/10.1007/s40495-021-00273-6

NEUROPHARMACOLOGY (G ASTON-JONES, SECTION EDITOR)

The Impact of Coenzyme Q10 on Neurodegeneration: a Comprehensive Review

Monika Kadian[1] · Garima Sharma[1] · Shivani Pandita[1] · Kritika Sharma[1] · Kanishka Shrivasatava[1] · Neetu Saini[1] · Anil Kumar[1]

Accepted: 4 December 2021 / Published online: 6 January 2022

Abstract
Coenzyme Q10 (CoQ10) is a lipophilic molecule that shares characteristics with nutrients like vitamins and is located in all biological membranes of our body. It acts as a key component for the synthesis of ATP and also a life-sustaining cofactor for complexes I, II, and III of the electron transport chain in the mitochondria. Several reported research studies advocate the use of CoQ10 as a nutritional supplement or along with other therapeutic agents as an aid to preserve or modify the health of aged people and also to eradicate neural health–related problems. Moreover, CoQ10 has been the subject of numerous preclinical and clinical investigations to determine its dosage, safety, and tolerability. This review will summarize CoQ10's background, biochemistry, pharmacokinetics and bioavailability, physicochemical properties, mechanism of action, valuable functions, consequences of deprivation and overconsumption, available marketed formulations, and the impact of CoQ10 therapy in various neurodegenerative diseases based on preclinical and clinical research.

Keywords Coenzyme Q10 · Mitochondrial dysfunction · Neurodegenerative diseases · Oxidative stress · Ubiquinol · Ubiquinone

Introduction

Coenzyme Q10 (CoQ10), an organic lipophilic unit, abundantly located in biological membranes specially in mitochondria (in reduced form—ubiquinol and oxidized form—ubiquinone), was first identified by Frederick C. in Wisconsin (USA, 1957) [1]. Therapeutic usage of CoQ10 emerged firstly from oxidative phosphorylation (OXPHOS) defects and several CoQ10 deficiency ailments where the CoQ10 deficiency was documented clearly. Therefore, these pathological situations gave evidences regarding the efficacy and safety of COQ10 treatment [2]. Several reported studies certified that enhanced ROS production, free-radical generation, altered mitochondrial function (impaired OXPHOS), and oxidative stress engaged with the pathophysiology of various neuron-related or neurodegenerative problems [3]. Furthermore, it is also evidenced that CoQ10 plays an effective role at the level of the mitochondrial electron transport chain functioning as well as acts as a powerful antioxidant and anti-inflammatory agent [4, 5]. Several preclinical and clinical studies have been conducted on CoQ10 till now to find out its dose, safety, and tolerability. This review aims to summarize the CoQ10 background, biochemistry, pharmacokinetics and bioavailability, physicochemical properties, mechanism of action, valuable functions, repercussion of its deprivation and overconsumption, and available marketed formulation and also sums up the impact of CoQ10 therapy in various neurodegenerative diseases conducted through preclinical and clinical studies.

History

Crane and his partners distinguished a unique quinone moiety in the lipid samples of mitochondria [6], in David Green's Laboratory (USA), and called it ubiquinone or CoQ10 as a result of its contribution in ETC. The compound structural constitution of CoQ10 (1958) was presented by Wolf at Merck Laboratories [7], and it was discovered to have a

This article is part of the Topical Collection on *Neuropharmacology*.

The editors would like to thank Dr. Zhengyuan Su for taking the time to review this manuscript.

✉ Anil Kumar
kumaruips@pu.ac.in

[1] Pharmacology Division, University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Study, Panjab University, Chandigarh 160014, India

structure like that of quinone, which was later represented by Morton and partners [8] and named ubiquinone as a sign of its omnipresence in various tissues. Ubiquinone was created as an authentic name of CoQ10 in 1975 based on the Biochemical Nomenclature by the IUPAC-IUB Commission [9]. As of late, the "vitamin Q" term has been foreseen [10] as a result of its different gainful impacts. However, the ubiquinone term is the most satisfactory term for a few reasons: first, it presents a co-enzymatic property as well as acts as a potential anti-oxidative agent in its reduced form; also, it is time to time synthesized in all mammalian tissues and hence not considered as a real vitamin [11]. The primary investigation for the treatment of human infection by coenzyme Q7 was congestive cardiovascular breakdown, and it was done by Prof. Yamamura (Japan, 1963). Moreover, Mellors and Tappel [12, 13] portray that the diminished structure CoQ6 was a significant anti-oxidative agent. Diminished levels of CoQ10 in cardiovascular-related illness of people [14] was archived by Littarru and his co-workers alongside Folkers. The Nobel Prize was awarded to P.D. Mitchell (1978) for his contribution in comprehending and explaining the energy transfer in biological systems by means of the chemiosmotic hypothesis definition, which involves the basic proton drive job of CoQ10 in the energy transfer scheme [15, 16].

Biochemistry

CoQ10 is a lipid-soluble unit with somewhat common characteristics and structural similarity to vitamin K [17]. Chemically, it is known as 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone and located in different biological membranes principally in the middle of the phospholipid bilayer; however, the relative sum contrasts in various organelles. Broadly speaking, the high-energy-demanding cells contain CoQ10 in plentiful amounts such as the brain, heart, liver, and kidney cells' organelle mitochondrial bilayer in both reduced and oxidized forms known as ubiquinol and ubiquinone, respectively, where it controls the rate of energy production by regulating some specific important enzymes in the ETC. Hence, CoQ10 anticipates a potential role in a cell's bioenergetics [18–20]. CoQ10 can support consistent redox cycles and is a phenomenal electron transporter, transporting electrons from reduced nicotinamide-adenine dinucleotide (NADH)-coenzyme-Q oxidoreductase (complex I or C-I) or succinate coenzyme-Q dehydrogenase (C-II) to ubiquinone-cytochrome-C oxidoreductase (C-III), and it is additionally an important moiety of both C-I and C-III[1]. Additionally, CoQ10 can receive electrons from acyl-coenzyme A dehydrogenases and it is a required component in the transport of protons by uncoupling of proteins, hence directing the transition across the mitochondrial membrane [1].

Pharmacokinetics and Bioavailability

Practically, CoQ10 has low water solvency [21] and higher atomic weight, i.e., 863.34 g/mol; consequently, it shows a low bio-availability in people. When we take in CoQ10 through dietary supplements, it is not well absorbed and is present in insufficient levels (Zhang et al., 1995), whereas the documented CoQ10 level in plasma ranges from 0.40 to 1.91 µmol/l (0.34 to 1.65 µg/ml) [22, 23]. As indicated by the bio-pharmaceutical classification system, CoQ10 goes under the class II category which shows it has less dissolvability and high penetrability profile [24].

Physicochemical Properties

CoQ10 is a dull, scentless and yellow to orange crystalline powder, which is sparingly dissolvable in ethanol and water and completely solubilized in di-ethyl-ether. It undergoes deterioration when handled at higher temperatures, i.e., higher than 46 °C. Further, it is light sensitive, so storage should be in a cool and dark place to avoid decomposition upon light irradiation. It is available in three redox structures, totally oxidized (ubiquinone), free radical form (semiquinone), and totally reduced (ubiquinol), and these different structures play different key roles contributing to its chemical properties [11, 25, 26]. Moreover, it has two chemical forms, cis and trans, but naturally, it exists in the trans form. Notwithstanding, with the assistance of fermentation technology, the two structures (cis and trans) can be shaped in a blend (US Patent 2003).

Mechanism of Action and Functions

As it is involved in ATP formation, it affects the function and regulation of the energy demand of all cells within the body, and thus, it seems to be essentially required for the wellness of all body parts. The major role of CoQ10 lies within the powerhouse of the body cell's ETC. CoQ10 acquires electrons from numerous donors such as C-I and C-II, and from the oxidation of branched-chain amino acids and fatty acids to C-III through the mediators including electron transfer factor Q oxidoreductase and flavin-linked dehydrogenases [13, 14]. As shown in Fig. 1, CoQ10 cycles between three interchangeable redox forms such as ubiquinone, semiquinone, and ubiquinol[16]. This Q-cycle inside the mitochondrial matrix is responsible for proton transportation from the matrix to the inter-membrane area, where it generates an electrochemical gradient and ultimately results in ATP formation. The CoQ10 is

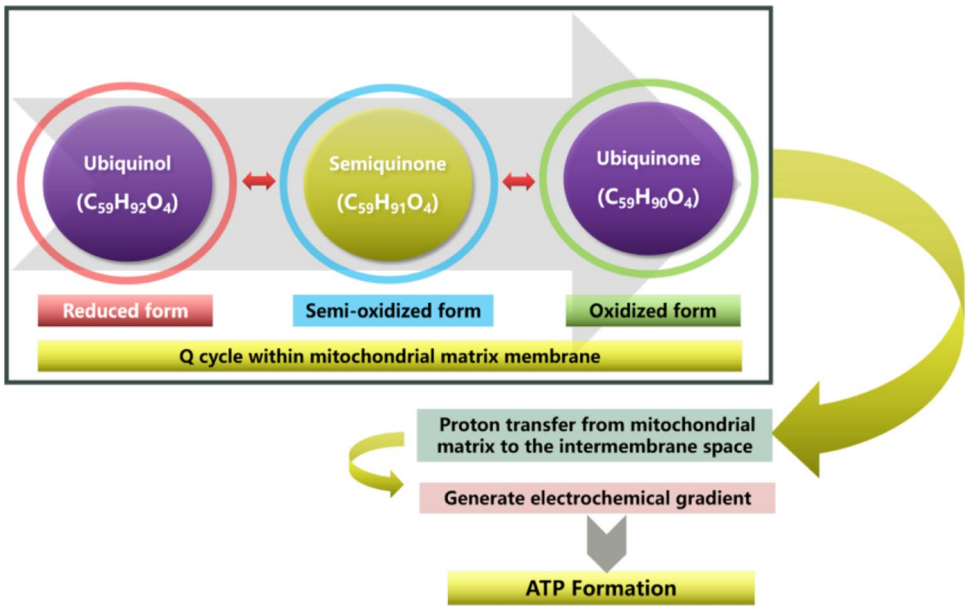

Fig. 1 Three interchangeable redox forms of CoQ10 (ubiquinol—reduced form, ubiquinone—oxidized form, and semiquinone—semi-oxidized form), forming the Q cycle inside the mitochondrial matrix membrane, permits proton movement from the mitochondrial matrix to the inter-membrane space, assisting with the creation of the electrochemical gradient for ATP formation

Table 1 CoQ10: functions within living beings related to the brain

S. no	Functions
Major function: mitochondrial ETC	
1	Acts as a carrier for electrons and protons, as it accepts electrons from different donors like C-I and C-II, and from free fatty- and amino-acid oxidation, and then transfer to the C-III and by this forming a Q cycle This Q cycle is responsible for generating an elctrochemical gradient which further leads to ATP formation
Epigenetic effects	
2	CoQ10 administration plays a role in epigenetics and produces effects in genes engaged with metabolic reactions, cell signaling processes, disease conditions and mutation, phosphorylation, and gene transcription regulation and also demonstrates the role in the transition of gene expression
Antioxidant effect	
3	CoQ10 shows an antioxidant effect by protecting the phospholipids of bio-membranes like the plasma membrane and other cell organelle membranes against peroxidation, which takes place by heightening the enzyme activity of glutathione peroxidase and superoxide dismutase Its oxidized and semi-oxidized structures are additionally responsible for the usage of some other antioxidative units, α-tocopherol (reduced), and ascorbate adding to the oxidation–reduction equilibrium within the cell Thus, it regulates physicochemical properties of the biological membranes
Anti-inflammatory effect	
4	According to Fan et al., CoQ10 supplementation shows marked diminution in markers of inflammation like interleukin-6 (IL-6), C-reactive protein, and tumor necrosis factor alpha (TNF-α) It could exert this effect through reducing nuclear factor-κB (NF-κB)–based gene expression Redox state imbalance and generated reactive oxygen species (ROS) can activate NF-κB and then upregulate the pro-inflammatory cytokine levels
Other	
5	Anti-aging in neurodegenerative diseases Mitophagy and inflammasome modulators Helps in the proper functioning of mitochondrial membrane permeability transition pores Within the inner mitochondrial membrane, it also participates as an essential cofactor for the dihydroorotate dehydrogenase which is required for the synthesis of pyrimidine nucleotide by the oxidation of dihydroorotate to orotate

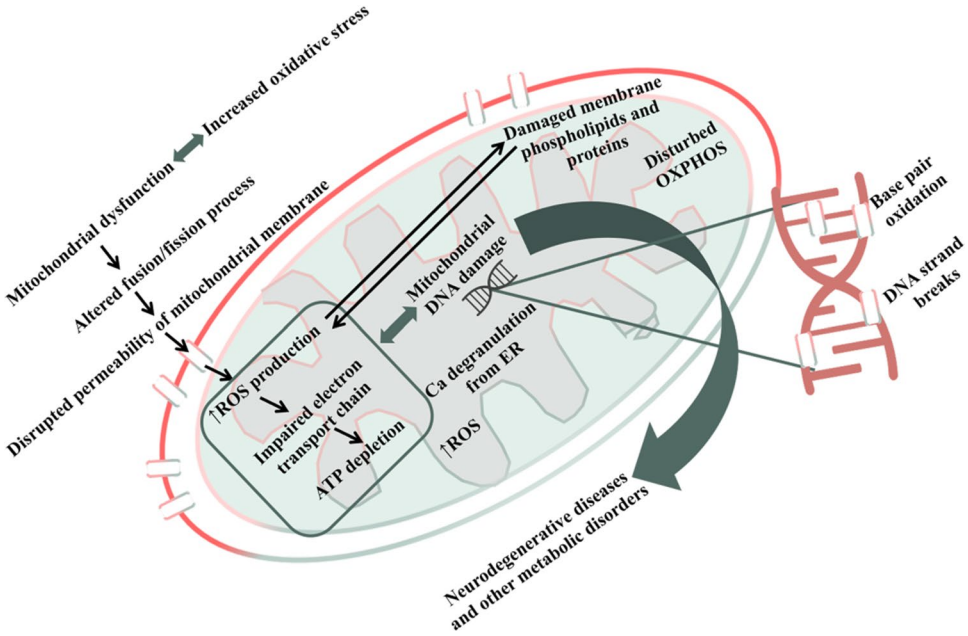

Fig. 2 Schematic view of events responsible for the mitochondrial dysfunction which leads to pathological conditions

also responsible for numerous functions as described in Table 1 [22].

Repercussion of CoQ10 Deprivation and Overconsumption

CoQ10 deficiency syndrome is an infrequent one with different phenotypical representations like encephalopathy, myopathy-associated encephalopathy, neuropathy, and brain muscle wasting with ataxia [5, 27, 28]. CoQ10 deficiency can be brought about by changes or mutation in CoQ genes (PDSS1, PDSS2, CoQ2, and CoQ9) that encrypt proteins of the CoQ synthesis in living systems known as primary deficiency and on other hand deficiency due to the absconds in other mitochondrial capacities which are indirectly associated with the bio-synthesis of CoQ10 known as a secondary deficiency, for example, GLUT1 mutations [5, 28–31]. Moreover, several investigations about the pathophysiology of CoQ10 inadequacy showed diminished activities of mitochondrial complexes, decreased expression of those proteins which were directly or indirectly associated with oxidative phosphorylation, diminished mitochondrial membrane potential, high ROS production, and decreased growth rate. These anomalies turned around mostly with CoQ10 supplementation [5]. The individuals suffering from primary CoQ10 inadequacy show improvement in pathological phenotype, for example, limited the advancement in encephalopathy when the individuals were treated with CoQ10 supplements orally. Ubiquinol has been approved by the European Medicine Agency as an orphan medicine for the management of dysfunction or disorders associated with primary CoQ10 deficiency [29].

Generally, there is no bad consequential effect after CoQ10 supplementation, as supplementation of it through diet does not show any enhancement effect on its biosynthesis within the living system, but there is a defined safety dose for its administration, i.e., 1200 mg/day/person. However, enough high quantity such as 3000 mg/day did not produce any serious bad effect in humans except some moderate effects such as nausea and gastrointestinal upset [3, 31]. But when we talk about chronic administration of CoQ10 in high quantity, the resulting serious effects are yet to be figured out properly as regards the underlying mechanism [3].

Aging: Free Radical Theory and Mitochondrial Dysfunction

Aging is a usual process in living beings, associated with a declined rate of functioning of different organs which is further linked to the marked risk of age-concomitant diseases such as dementia and neurodegenerative disease and many more. A typical hypothetical theory clarifies that the pathophysiologies of aging and neurodegeneration are an imbalance in redox reactions such as ROS generation and the antioxidant mechanism, for example, superoxide dismutase (SOD), reduced glutathione (GSH), glutathione peroxidase (GPx), ascorbic acid and tocopherol levels, and CoQ10, prompting a condition of oxidative stress [2, 32–36].

As we know, mitochondria are the chief source of ROS formation, so that at the same time it is also vulnerable to ROS damage. The constant supply and aggregation of ROS

Table 2 Impact of CoQ10 therapy in various neurodegenerative diseases

Impact of CoQ10 therapy on Alzheimer's diseases					
Dose	**Subject/animal**	**Study type/design**	**Experimental model and assessed parameters**	**Results**	**References**
CoQ10 (20 mg/kg, i.p.)	Male Goto–Kakizaki (GK diabetic rats) and control Wistar rats	Preclinical study for 7 weeks	$A\beta_{(1-40)}$ model used for inducing mitochondrial dysfunction, checked several mitochondrial parameters such as respiratory indexes, transmembrane potential, ATP levels, and the ability of mitochondria to generate hydrogen peroxide	CoQ10 attenuated the reduction in oxidative phosphorylation and increment in hydrogen peroxide formation, evoked by the neurotoxic peptide	[46]
CoQ10 (10 mg/kg; i.p.) for 3 weeks	Male Wistar rats (480–520 g)	Preclinical study for 3 weeks	ICV-STZ model (1.5 mg/kg in saline, 5 µL/injection site); checked TBARS, GSH, protein carbonyls, ATP, and the enzymatic activities of GR, GPx, AChE, and ChAT. Also performed MWM task and passive avoidance test to assess memory	Increased time spent in target quadrants and decreased escape latency observed in CoQ10-treated rats. CoQ10-treated rats showed an increased GSH level, restored TBARs content and ATP levels significantly. Increased ChAT and decreased AChE activity were also observed in the hippocampus of CoQ10-treated rats. Antioxidant enzyme (GPx and GR) activities decreased and protein carbonyl level increased in the ICV-STZ group were reversed in CoQ10-treated rats	[47]
CoQ10 (2400 mg/kg/day)	Transgenicmice (28 APP/PS1, 28 APP, 28 PS1, and 28 wild types)	Preclinical study for 60 days	APP/PS1 double transgenic mouse model, checked brain atrophy, hemispheric and hippocampal volumes	CoQ10-treated group displayed significantly reduced brain atrophy and increased hemispheric and hippocampal volumes compared to placebo group	[48]
CoQ10 (1200 mg/kg/day)	Aged female transgenic mice (16–17 months old)	Pre-clinical study for 2 months	Transgenic mouse model, checked oxidative parameters like SOD and MDA levels	CoQ10-treated mice showing partially decreased MDA level, upregulated the activity of SOD and decreased Abeta 42 levels	[49]

Table 2 (continued)

Impact of CoQ10 therapy on Alzheimer's diseases

Dose	Subject/animal	Study type/design	Experimental model and assessed parameters	Results	References
CoQ10 supplement	Aged Tg mice (with APP mutation)	Pre-clinical study for 60 days	Transgenic mouse model, checked brain atrophy in vivo	Attenuated brain atrophy assessed by MRI	[5]
CoQ10 (2400 mg/kg/day)	Single Tg mice (APP and Presenilin (PS1)) and double Tg mice (APP/PS1)	Preclinical study on Tg mice and placebo animal groups	Transgenic mouse model, checked brain atrophy	Significantly less atrophy in hemisphere and hippocampus of treated mice as compared to placebo	[5]
CoQ10 (1200 mg/day)	Transgenic mice (overexpressing Alzheimer's presenilin 1-L235P mutation)	Pre-clinical study for 60 days	Transgenic mouse model, checked Abeta plaque and oxidative stress markers	-Partially reduced Abeta production and intracellular Abeta cortical deposits -Restored MDA and SOD levels	[5, 50]
CoQ10 supplement (10 g/kg diet)	C65/Bl6 mice	Preclinical study for 1 month	Checked oxidative parameters	Markedly reduced protein carbonyls	[51]
CoQ10 (0.4% or 2.4% CoQ10 in chow)	TG19959 transgenic mice	Preclinical study for 3 or 5 months	Transgenic mouse model, checked oxidative stress markers, Abeta plaque, and memory loss (MWM task)	-CoQ10 showed reduction in oxidative stress markers and amyloid plaque deposition in both hippocampus and cortex. -CoQ10 also showed improved behavioral performance in MWM task. -Decreased protein carbonyl levels	[5, 52]
CoQ10 (0.5% CoQ10 diet)	Male P301S transgenic mice and female wild-type mice	Preclinical study	Transgenic mouse model, checked locomotor activity, anxiety in open field test, immunohistochemistry for assessing tau phosphorylation (using AT8), and MDA, GSH, and GSSG levels and also checked the activities of enzymes of TCA cycle and ETC	-CoQ10-treated mice showed improved survival and behavioral deficits in the P301S mice. -CoQ10-treated mice exhibited moderate diminution in phosphorylation of tau proteins in the P301S mice, upregulated the key enzymes of ETC, and reduced oxidative stress	[53]
CoQ10 different concentrations used (0, 0.01, 0.1, 1, 10, or 100 μM)	Primary culture of neuron (cortical neurons from SD rats during gestation period)	Preclinical in vitro study	Amyloid $beta_{25–35}$ induced neurodegeneration model used, checked the expression of proteins related to viability of neuron (p85αPI3K, pAkt, pGSK-3beta, and HSTF-1) and also checked the levels of cytochrome c and caspase 3	CoQ10 reduced levels of free radicals dose dependently, also increased the expression levels of proteins associated with neuronal viability and reduced the cytochrome c levels and cleaved caspase 3 levels	[54]

Table 2 (continued)

Impact of CoQ10 therapy on Alzheimer's diseases					
Dose	**Subject/animal**	**Study type/design**	**Experimental model and assessed parameters**	**Results**	**References**
CoQ10 (10 μM) or docosahexaenoic acid (DHA) (30 μM) or vitamin E (50 nM)	Human neuroblastoma M17 cells	Preclinical study (in vitro)	Aβ and zinc induced mitochondrial dysfunction in AD, checked ROS production, inner mitochondrial membrane potential (using JC-1 assay)	DHA exhibited neuroprotective action against zinc-induced mitochondrial dysfunction, but no effect on Aβ neurotoxicity. -CoQ10 exhibited protective action compared to zinc and Aβ-induced modification in mitochondrial function	[55]
CoQ10 different concentrations (1, 2.5, 5, 10, 20, 40 μM)	Neural stem cells (NSCs)	Preclinical study (in vitro)	Aβ (25–35) oligomers induced AD model, checked proliferation activity by BrdU labeling, colony formation assay, and immunoreactivity of Ki-67. Western blot analysis of proteins (p85αPI3K, pAkt(Ser473), pGSK-3β(Ser9), and HSTF-1) related to PI3K pathway	-Restored NSC proliferation observed with CoQ10 compared to Aβ (25–35) oligomer treatment. -Increased expression of protein in western blot analysis was observed in CoQ10-treated groups	[56]
CoQ10 (109 mg/kg/day), or α-tocopherol (250 mg/kg/day) or combination of both	C57BL/6 J male mice	Preclinical studies for 3 and 10 weeks	Young and old mice were used for this study, checked protein carbonyl levels in different brain regions and cognitive and psychomotor functions	CoQ10 or α-tocopherol or combination of both reduced the protein damage as well as improved the psychomotor and cognitive functions in old animals	[57]
Watersoluble formulation of CoQ10 (50 μg/mL)	Healthy female fibroblasts and PS-1 mutated AD patient fibroblasts (PSAF). Experiments were continual with extra PS-1 mutated fibroblasts from male AD patients	Preclinical study (in vitro)	Presenilin-1 (PS-1) mutated cell lines, checked ROS and H_2O_2 levels and also ATP generation	-Water-soluble CoQ10 alleviated noxious effects originated by PS-1 mutations -Water-soluble CoQ10 reduced the levels of ROS and H_2O_2 and increased ATP production, eventually improving the mitochondrial efficiency	[43]

Table 2 (continued)

Impact of CoQ10 therapy on Alzheimer's diseases

Dose	Subject/animal	Study type/design	Experimental model and assessed parameters	Results	References
MitoQ (0.1 μM, 1 μM, 5 μM)	*Caenorhabditis elegans*	Pre-clinical for a week	Abeta toxicity induced in *C. elegans,* checked oxidative stress markers and mitochondrial dysfunction	-MitoQ showed longer survival and retarded paralysis -It also improved decrease of cardiolipin, and protected mitochondrial functioning by affecting complexes IV and I	[58]
CoQ10 (200 mg/kg; orally; daily) or epigallocatechin-3-gallate (EGCG) (10 mg/kg, *i.p.*; every other day) or combination of both	Male SD rats (180–200 g). This study involved normally fed (received 20% casein) and protein malnourished (received 10% casein) rats	Preclinical study for 4 weeks	Aluminum-($AlCl3{\cdot}6H_2O$) induced neurotoxicity (70 mg/kg) model of AD, checked oxidative parameters (SOD, MDA, and TAC), AChE levels, Aβ levels, and histopathological studies	Treatment with CoQ10 or EGCG given preventive action in both normally fed and malnourished rats evidenced by diminished Aβ and AChE levels and MDA levels. Also observed the increase in SOD and TAC. Moreover, combination treatment was more pronounced	[59]
CoQ10 (10 mg/kg for a period of 2 weeks) or electromagnetic fields (EMFs; frequency—50 Hz for 7 h daily over 1 week) or both	36 male Balb/c mice (25–30 g)	Preclinical study for 3 weeks	Trimethyltin hydroxide (TMT; 2.5 mg/kg)–induced hippocampal injury model, checked learning and memory using MWM test, histopathological studies (tunnel assay and Nissl staining), and assessment of apoptotic genes by western blot analysis	CoQ10 or combination of CoQ10 and EMF exhibited improvement in memory task, decline in apoptotic and necrotic cells in Nissl staining, and also upregulation in expression of anti-apoptitic genes in western blot analysis	[60]
Combination of copper nicotinic acid complex (400 μg/kg) and CoQ10 (10 mg/kg)	Male wistar rats (200-280 g)	Preclinical study for 49 days	Aluminum chloride ($AlCl_3$; 100 mg/kg; orally) induced rat model and D-galactose (60 mg/kg) model of AD. Checked plasma ferric reducing ability of plasma, SOD levels, IL-1β levels and aspartate transaminase concentrations	Combination treatment restored the checked parameters to about normal range comparable to those of AD	[61]
CoQ10 supplement (100 mg/kg and 600 mg/kg once a day for 3 months)	Male Wistar rats	Preclinical study on diabetes-induced memory deficit	Streptozotocin (50 mg/kg, i.p.) used to induce diabetes, checked spatial memory by using MWM	High dose of CoQ10 shows an appreciable decrement in escape latency and path traveled as compared to STZ-treated animals	[62]

Table 2 (continued)

Impact of CoQ10 therapy on Alzheimer's diseases

Dose	Subject/animal	Study type/design	Experimental model and assessed parameters	Results	References
CoQ10 (50 mg/kg/day orally, for 3 weeks pre- and after, of the Aβ administration)	Male Wistar rats	Preclinical study on impaired synaptic plasticity	Aβ (1–42) used for inducing AD, checked MDA, TAC, TOS, LTP, and histopathological studies	CoQ10 reduces the effects of Aβ on LTP, decreases MDA and TOS, and increases TAC. Reduced Aβ plaque in CoQ10 group, confirmed by Congo Red staining in rat's brain	[63]
CoQ10 (500 mg/kg;orally) or photobiomodulation (PBM) (810 nm transcranial laser) or both, for 2 weeks after surgery	Adult male Balb/c mice (approx 20 to 25 g)	Preclinical study for 8 weeks	D-Galactose (500 mg/kg; *s.c.*) model of aging and bilateral occlusion of the common carotid artery (BCCAO) model used to induced transient cerebral ischemia. Checked cognitive functions and also checked ROS and ATP levels, mitochondrial activity and inflammatory biomarkers	-CoQ10 or PBM or combination of two improved spatial and episodic memory. -CoQ10 or PBM or both lowered ROS levels, enhanced ATP formation and mitochondrial activity. Reduced TNF-α. iNOS, and IL-1β levels were also observed	[64]
Omega-3 (500 mg/kg) or CoQ10 (10 mg/kg) or combination of both for 30 days	Wistar rats (120 g, 6 to 8 weeks old)	Preclinical study for 30 days	Hypercholesterolemia-induced AD model of rats, checked oxidative parameters (LPO, NO, GSH), antioxidant activity of GST, GPx, and AChE. Also assessed the ACh, Aβ 42, and TNF-α levels in rats brain	Individually or in combination, these agents alleviated the mental oxidative stress and neuroinflammation, and presented restoredneuronal functioning of cholinergic system	[65]
CoQ10 (500 µg/well)	Neuron culture prepared from pregnant C57BL/6 J mice (2 months old; 20–25 g)	Preclinical study (in-vitro)	Sevoflurane anesthesia induced cognitive deficiency (6 days old mice). Checked or measured ATP, SOD, mRNA expression of ApoE (full-length, fragments and its total protein), phosphorylated-tau, and neuroinflammatory markers	Anesthesia represented significant reduction in SOD activity and ATP levels; however, enhanced mRNA expression of ApoE (full-length, fragments and its total protein), phosphorylated-tau and neuroinflammatory markers. However, CoQ10 reversed the expression of these factors	[66]

Table 2 (continued)

Impact of CoQ10 therapy on Alzheimer's diseases					
Dose	**Subject/animal**	**Study type/design**	**Experimental model and assessed parameters**	**Results**	**References**
Vitamin E (100 mg/kg, orally) or CoQ10 (200 mg/kg, orally) or combination of both	Male SD rats (220–250 g)	Preclinical study for 8 weeks	Chronic cerebral hypoperfusion-induced neurodegeneration rat model for AD. Checked learning and memory by MWM task and performed histopathological studies	CoQ10 alone or in combination with vitamin E showed reduced escape latency and distance traveled as compared to the untreated induced AD group. But there was no significant difference in time spent in target quadrants and hippocampal viable pyramidal cells among all groups of the study	[67]
CoQ10 (400 mg compounded as wafer; 2 wafers 3 times a day with meal)	75 participants out of which 25 receive CoQ10 wafers	Clinical trial (phase-I, double-blind, placebo-controlled)	Checked safety, tolerability and impact influence on oxidative biomarkers	No influence on CSF biomarkers related to amyloid or tau pathology	NCT00117403 [51, 68]
Idebenone (90 mg for 1 year or 120 mg for 2 years)	450 patients with AD	Clinical trial for 2 years	Monitor Alzheimer's disease assessment scale (ADAS)-total score	Patients showing improved ADAS-total score upon 6 months on high dosage	[69]
Idebenone (30 mg, 90 mg) or placebo for 6 months	300 patients with AD	Clinical trial for 6 months	Monitor ADAS-total score	Patients showing improved ADAS-total score upon 6 months on high dosage	[69]
Idebenone (120 mg or 240 mg or 360 mg) or placebo for 1 year	536 patients with AD	Clinical trial for 1 year	Monitor ADAS-cognitive score	Patients showing no differences among groups	[69]
Ubiquinol (200 mg/day)	128 subjects (52/group)	Randomized controlled trial in healthy elderly	Checked primary outcomes at 90-day treatment on cognitive performance using CogTrack battery tests and secondary outcomes monitored across 30-, 60-, and 90-day time points, which included treatment effects on an extent of mood and cognitive outcomes and biochemical outcomes	This study provided a valuable clinical data respective to the effectivity of ubiquinol and helpful in figuring out the accelerating productiveness and quality of life in these subjects and similar age group	ANZCTRN1261800184126870
Impact of CoQ10 therapy on amyotrophic lateral sclerosis					
CoQ10 powder (200 mg/kg/day formulated in rat chow)	Male SD rats (12 months old) for 2 months and follow-up study with same dose in Fisher 344 rats (24 months old) for 1 month and transgenically modified mice overexpressing a human Cu/Zn superoxide dismutase (SOD1) mutation	Pre-clinical study	Transgenic mouse model of familial ALS and 3-nitropropionic (NP) acid for inducing lesions. Analyzed the mortality rate in transgenic mice and also checked the 3-NP-induced lesions in rats	CoQ10 markedly attenuated striatal lesions, significantly increased life span, and also increased brain mitochondrial concentration	[70]

Table 2 (continued)

Impact of CoQ10 therapy on Alzheimer's diseases					
Dose	**Subject/animal**	**Study type/design**	**Experimental model and assessed parameters**	**Results**	**References**
MitoQ (500 μM concentration twice a week)	Transgenic ALS mice	Pre-clinical study	Transgenic ($SOD1^{G93A}$) mouse model of ALS used, checked mitochondrial respiration, grip strength, neuronal viability, astro-gliosis, and nitrosative and oxidative stress	Declined deterioration of mitochondrial function within quadriceps muscles and spinal cord in MitoQ-treated groups. Also showed marked reduction in nitroxidative markers and pathological signs of spinal cord and recovery in neuromuscular junctions	[71]
CoQ10 (1200, 1800, 2400, 3000 mg/day)	31 participants	Clinical trial	Checked the safety, tolerability, and CoQ10 plasma availability	CoQ10 (3000 mg/day) found to be safe, good tolerance, and plateau phase achieved in between 2400 and 3000 mg/day	[72]
Impact of CoQ10 therapy on Friedreich's ataxia					
Idebenone phase 1A (10 mg/kg to max. 75 mg/kg), phase 1B (60 mg/kg, three times a day in divided doses for a period of 1 month)	Phase 1A—78 subjects and phase 1B—15 subjects with FA	Clinical trial	Monitored the tolerance and safety level of idebenone dosage	Higher doses result in proportionate availability increment within plasma and it was given a good tolerance	[73]
Idebenone (different doses such as 5, 15, and 45 mg/kg)	48 patients	Clinical trial (randomized double-blind, placebo-controlled) for 6 months	Checked neurological function and doses tolerability	Higher-dose treatment generally exhibited good tolerance and resulted in improved neurological action	[73]
Idebenone (450 or 900 mg/day ($n=22$) and 1350 or 2250 mg/day ($n=24$) or placebo ($n=24$))	70 pediatric patients	Clinical trial (randomized, double-blind, placebo-controlled) for 6 months	Monitor ataxia score	No significant results were found	[73]

Table 2 (continued)

Impact of CoQ10 therapy on Alzheimer's diseases

Dose	Subject/animal	Study type/design	Experimental model and assessed parameters	Results	References
Impact of CoQ10 therapy on Huntington's disease					
CoQ10 supplement (1% CoQ10 within diet or its combination with 2% creatine)	Male C57BL/6 mice (25–30 g, 3 months old), male Lewis rats (250–300 g, 3 months old), and male R6/2 HD mice	Preclinical study	For PD: MPTP model, for HD: 3-NP model and R6/2 transgenic mouse model, checked dopamine levels, MDA levels, LPO levels, α-synuclein accumulation, glutathione homeostasis	-Combination treatment showed cumulative neuroprotective actions on dopamine reduction in striatum, significant reduction in LPO levels, and α-synuclein aggregation in substantia nigra pars compacta neuronal cells of MPTP-treated animals. -Also ascertained reduction in striatal lesion in the 3-NP-treated rats and also noted the restored glutathione homeostasis, reduced level of LPO and DNA oxidative damage. -Combination treatment in the transgenic R6/2, produced additive neuroprotective action by better motor activity and prolonged aliveness	[74]
CoQ10 (600 mg/day)	10 participants	Clinical trial	Checked safety, tolerability, efficacy of CoQ10	CoQ10 found to be risk-free and exhibited good tolerance	[75]
CoQ10 (360 mg/day)	18 participants	Clinical trial	Checked the changes in levels of lactate within brain (using NMR technique)	CoQ10 attenuated lactate levels within brain cortex	[44]
Impact of CoQ10 therapy on multiple sclerosis					
CoQ10 (500 mg/day)	48 patients (4 male, 44 female) CoQ10 500 mg/day (=24) or placebo ($n=24$)	Clinical trial (randomized, double-blind, placebo-controlled) for 12 weeks	Checked MDA, SOD, and GPx activity and also total antioxidant capacity	Significant increase in SOD activity and decrease in MDA levels in CoQ10-treated subjects as compared to control. However, no significant effect was found for GPx and total antioxidant capacity	[76]
MitoQ (100 nmol/mouse and 2 µmol/mouse), intraperitoneal injections two times a week	Experimental autoimmune encephalomyelitis (EAE) mouse and C57BL/6 mice used for normal control (10 weeks old)	Pre-clinical study for 3 weeks	EAE mouse model used for MS	Reduced inflammatory markers of EAE, attenuated spinal cord neuronal harm, axonal swelling and oxidative stress markers	[77]

Table 2 (continued)

Impact of CoQ10 therapy on Alzheimer's diseases					
Dose	**Subject/animal**	**Study type/design**	**Experimental model and assessed parameters**	**Results**	**References**
CoQ10 supplement (500 mg/day)	48 patients CoQ10 500 mg/day ($n=24$) or placebo ($n=24$)	Clinical trial (randomized, double-blind, placebo-controlled) for 12 weeks	Checked fatigue symptoms by means of fatigue severity scale and assessed depressive symptoms by means of Beck depression inventory	Improved fatigue and depression in patients with multiple sclerosis	[77]
Impact of CoQ10 therapy on Parkinson's disease					
CoQ10 supplement (1% CoQ10 within diet or its combination with 2% creatine)	Male C57BL/6 mice (25–30 g, 3 months old), male Lewis rats (250–300 g, 3 months old) and male Male R6/2 HD mice	Preclinical study	For PD: MPTP model, for HD: 3-NP model and R6/2 transgenic mouse model, checked dopamine levels, MDA levels, LPO levels, α-synuclein accumulation, glutathione homeostasis	-Combination treatment showed cumulative neuroprotective actions on dopamine reduction in striatum, significant reduction in LPO levels, and α-synuclein aggregation in substantia nigra pars compacta neuronal cells of MPTP-treated animals -Also ascertained reduction in striatal lesion in the 3-NP-treated rats and also noted the restored glutathione homeostasis, reduced level of LPO and DNA oxidative damage -Combination treatment in the transgenic R6/2, produced additive neuroprotective action by better motor activity and prolonged aliveness	[74]
Ubisol-Q10 (nanomicellar formulation of coenzyme Q10) (stock solution of CoQ10 (50 mg/ml) prepared in water, and three different doses of CoQ10 used in this study- 30 mg, 6 mg, or 3 mg/kg/day)	Male C57BL/6 mice (8–10 weeks old, weighed 22–25 g)	Preclinical study for different time periods 28, 45, and 56 days	MPTP mouse model of PD, checked degeneration of nigrostriatal pathway, dose efficacy of CoQ10, and standardization of subchronic MPTP model (5 daily injections)	Outcome of the study was that Ubisol-Q10 intervention could stop, but not reversed the present current neurodegeneration in MPTP-treated mice	[78]
CoQ10 (400, 600, 800 mg/day)	15 participants	Clinical trial	Checked safety level, tolerance, plasma profile of CoQ10	Risk-free and good tolerance	[79]
CoQ10 (300, 600, 1200 mg/day) and placebo	80 participants	Clinical trial	Checked the changes in UPDRS for period of 16 months	The significant linear graph found with CoQ10 and mean change in UPDRS	[80]
CoQ10 (360 mg/day) and placebo	28 participants	Clinical trial	Checked UPDRS and color vision	Decreased UPDRS with CoQ10 against baseline	[81]

Table 2 (continued)

Impact of CoQ10 therapy on Alzheimer's diseases					
Dose	**Subject/animal**	**Study type/design**	**Experimental model and assessed parameters**	**Results**	**References**
CoQ10 (1000, 1500 mg/day)	12 participants	Clinical trial	Performed motor tasks and checked part II UPDRS	Motor task improvement exhibited in CoQ10-treated subjects against baseline	[82]
CoQ10 (1200, 1800, 2400, 3000 mg/day)	17 participants	Clinical trial	Checked safety, tolerability, plasma CoQ10 levels, UPDRS	-Safe and well tolerated. Plasma levels plateau between 2400 and 3000 mg/day -No change was found in motor UPDRS	[83]
Nanoparticular CoQ10 (300 mg/day or 100 mg 3 times a day)	131 patients with PD (placebo—$n=67$; CoQ10—$n=64$)	Clinical trial (multicenter, placebo-controlled, randomized, stratified, double-blind, parallel-group, single-dose clinical trial)	Checked whether nanoparticular CoQ10 safe and tolerated or not	Nanoparticular CoQ10 (300 mg/day)found to be safe and well tolerated	NCT00180037 [84]
Impact of CoQ10 therapy on progressive supranuclear palsy					
CoQ10 (2400 mg/day)	61 participants received CoQ10 2400 mg or placebo	Clinical trial (multicenter, randomized, placebo-controlled, double-blind) for 12 months	Checked effectiveness in disease progression by PSPRS, UPDRS, ADL, Mini-mental state examination, also checked the safety and tolerability	Well-tolerated, CoQ10 (even high doses) did not significantly improve PSP symptoms or disease progression	NCT00382824 [85]

AChE acetylcholinesterase, *ADAS* Alzheimer's disease assessment scale, *ADL* activities of daily living, *BCCAO* bilateral occlusion of common carotid artery, *ChAT* choline-acetyl transferase, *EAE* experimental autoimmune encephalomyelitis, *EGCG* epigallocatechin-3-gallate, *EMF* electromagnetic field, ETC electron transport chain, *GPx* glutathione peroxidase, *GR* glutathione reductase, *GST* glutathione-s-transferase, *GSH* reduced glutathione, *HD* Huntington's disease, *HSTF-1* heat shock transcription factor, *ICV-STZ* intracerebroventricular-streptozotocin, *IL-1β* interleukin-1 beta, *IL-6* interleukin-6, *LPO* lipid peroxidation, *LTP* long-term potentiation, *MDA* malondialdehyde, *MWM* Morris water maze, *NO* nitric oxide, *3-NP* nitropropionic acid, *NSCs* neural stem cells, *pGSK-3β* phosphorylated glycogen synthase kinase-3 beta, *PBM* photobiomodulation, *PSPRS* progressive supranuclear palsy rating scale, *ROS* reactive oxygen species, *SOD* superoxide dismutase, *TAC* total antioxidant capacity, *TBARS* thiobarbituric acid reactive substances, *TMT* trimethyltin hydroxide, *TNF* tumor necrosis factor, *TOS* total oxidant status, *UPDRS* unified Parkinson's disease rating scale

Table 3 Different formulations of CoQ10 present in the market[32]

S. no	Formulation name	Types of preparation	Manufacturing company
1	Bio-Quinon®	Soyabean oil emulsion, soft gelatin soyabean oil emulsion	Pharma Nord ApS
2	Colloidal-Q10	Colloidal-Q10	Vesifact AG
3	Commercial CoQ10	Solubilisate 1, solubilisate 2, oil-based formulation, formulation 1, formulation 3	Pharma Nord ApS
4	CoQ10	Soy lecithin emulsion, vegetable oil emulsion	Blackmores, Kordel's, Thompson's
5	CoQ10 powder	Powder	Tishcon
6	Kaneka QH™	Rapeseed oil, soy lecithin emulsion	Kaneka
7	LiQ-10	Nanodispersion	Tishcon
8	MitoQ	Veg capsules	MitoQ limited
9	NanoSolve	Soybean phospholipid emulsion	Lipoid GmbH
10	Opti-CoQ10	Fish oil emulsion	Good Health
11	PureSorb-Q™	Water-soluble powder	Nishi Pharma
12	P40 tablets	Oil-based formulation	Nishi Pharma
13	Q-Gel®	Solubilisate	Tishcon
14	Q-Sorb CoQ10	Rice bran oil emulsion	Radiance
15	Q-Nol™	Solubilized	Tishcon
16	Q_{10} Vital® liquid	Water suspension	Valens Int
17	Q_{10} Vital® powder	Powder	Valens Int
18	UbiQGel®	Solubilized	Tishcon
CoQ10 combinations			
19	Amoguard	Capsule	A S Pharmaceutical (India) Pvt. Ltd
20	BIO-Q-Forte	Tablet	Sanat Products Ltd
21	Cardio-PRO	Oral powder	British Biologicals (Criticare)
22	Colred	Oral powder	British Biologicals (Criticare)
23	COQ	Soft gel capsules	Uni. Medicare
24	COQ Forte	Soft gel capsules	Uni. Medicare
25	Coqueen	Tablet	East West Pharma
26	Coqueen Plus	Capsule	East West Pharma
27	Encar	Tablet	Xeno Pharmaceuticals Pvt. Ltd
28	Enphene	Tablet	Xeno Pharmaceuticals Pvt. Ltd
29	EN-Q 100	Capsule	Xeno Pharmaceuticals Pvt. Ltd
30	EN-Q 300	Capsule	Xeno Pharmaceuticals Pvt. Ltd
31	Fertiwork	Tablet	Acinom Healthcare
32	HI-Q 300, HI-Q Plus TAB, HI-Q TAB	Film-coated tablet	Biomiicron Pharma India Pvt. Ltd
33	Hyrase	Capsule	Bionova
34	I-10	Capsule	Invision Medi Sciences Pvt. Ltd
35	Lenova-M	Tablet	Intra Labs India Pvt. Ltd
36	MAC-Q10	Tablet	Macleods Pharmaceuticals Ltd. (Osteva)
37	M-GAM	Film-coated tablet	Glenmark Pharmaceuticals Ltd. (G&G)
38	Paternia	Capsule	Zydus Cadila Healthcare Ltd. (Nutriva)
39	Q-Star	Soft gel capsule	Intra Labs India Pvt. Ltd. (Inventure)
40	Q-Star CL	Tablet	Intra Labs India Pvt. Ltd. (Inventure)
41	Quantus, Quantus-100	Soft gel capsule	Rowez Life Sciences Pvt. Ltd
42	Rqual-Gold	Soft gel capsule	Genesis Biotec Inc
43	ZY-10 Active, ZY-10 Forte	Soft gel capsule	Indchemie Health Specialities Pvt. Ltd

is fundamental to "the free radical theory of aging" [37, 38], in spite of the fact that the gathering of ROS has a significant effect such as strand breaks, base pair oxidation, harm in locales coding for ETC proteins, and also harm in the different structures of the basic unit of life like phospholipid bilayers and proteins, which prompted the dysregulation

of ETC, deficient ATP formation, and further excess ROS generation [34, 39–41] and impaired oxidative phosphorylation (OXPHOS). Thus, electrons spilling from disturbed oxidative phosphorylation respond with oxygen to shape the free radical superoxide species, which further effects the mitochondrial dynamic with impaired fission adding to mitochondrial broadening and ultimately reduction in ATP formation [2, 33, 42]. Significant proof backs the connection between ROS aggregation and mitochondrial dysfunction prompting aging and other neurological problems (Fig. 2).

Brain Anomalies and CoQ10

Any unusual thing that happens within the brain is responsible for impaired function and damaged normal features and structure of the brain resulting in abnormal conditions, which leads to various pathologies, neurodegenerative diseases being one of them.

All of the neurodegenerative diseases share a common link involving impaired mitochondrial functions and energy production and oxidative stress. Exaggerated ROS production, free radical generation, and impaired OXPHOS are believed to be engaged with pathophysiologies of various neuron-related problems [3], for example, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Friedreich's ataxia (FA), Huntington's disease (HD), multiple system atrophy, multiple sclerosis (MS), Parkinson's disease (PD), progressive supranuclear palsy (PSP), and other neurodegenerative disorders. CoQ10 is a potential antioxidant with anti-inflammatory and mitochondrial function restorative characteristics, and has been recommended for examination as a possible neuroprotective treatment in various neurological diseases [3, 43–45]. Moreover, various pre-clinical studies have been conducted by various researchers in different labs proving the beneficial effects of CoQ10 in neurodegeneration and other brain-related disorders mainly by restoring mitochondrial capability, diminishing oxidative stress by maintaining or regulating oxidative stress marker levels, redox cycle, and energy balance. Here, we provide a brief note on pre-clinical and clinical studies on CoQ10 in the area of neurological disorder research and the different formulations available in the market, in tabulated form (Tables 2 and 3).

Conclusion

The current review study exhibited evidence that CoQ10 was risk free and well tolerated by volunteers or subjects with neurological disorders in different pre-clinical studies and clinical trials. We can say that the neuroprotection provided by CoQ10 is due to its antioxidant property. A large-scale and long-term follow-up survey or scrutiny would be needful to corroborate neuroprotection and the underlying mechanism of CoQ10 in various neurodegenerative disorders.

Acknowledgements We gratefully acknowledge the support provided by the Indian Council of Medical Research (ICMR), New Delhi, India [ICMR-SRF grant (No. 45/35/2018-PHA/BMS) and ICMR-RA grant (No. 3/1/90/Neuro/2018-NCD-I)].

Declarations

Conflict of Interest All other authors declare no conflict of interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Martelli A, Testai L, Colletti A, Cicero AFG. Coenzyme Q10: clinical applications in cardiovascular diseases. Antioxidants. 2020;9(4):1–26. https://doi.org/10.3390/antiox9040341.
2. De-Barcelos IP, Haas RH. CoQ10 and aging. Biology. 2019;8(2):1–22. https://doi.org/10.3390/biology8020028.
3. Gutierrez-Mariscal FM, Ubero-Serrano EM, Villalba JM, Lopez-Miranda J. Coenzyme Q10: from bench to clinic in aging diseases, a translational review. CritRevFood Sci Nutr. 2019;59(14):2240–57. https://doi.org/10.1080/10408398.2018.1442316.
4. Geromel V, Rotig A, Munnich A, Rustin P. Coenzyme Q10 depletion is comparatively less detrimental to human cultured skin fibroblasts than respiratory chain complex deficiencies. Free Radic Res. 2002;36(4):375–9. https://doi.org/10.1080/10715760290021216.
5. Spindler M, Beal MF, Henchcliffe C. Coenzyme Q10 effects in neurodegenerative disease. Neuropsychiatr Dis Treat. 2009;2009(5):597–610. https://doi.org/10.2147/ndt.s5212.
6. Crane FL, Hatefi Y, Lester RL, Widmer C. Isolation of quinine from beef heart mitochondria. BiochimBiophysActa. 1957;25(1):220–1. https://doi.org/10.1016/0006-3002(57)90457-2.
7. Wolf DE, Hoffman CH, Trenner MR, Arison BH, Shunk CH, Linn BO. Coenzyme Q, structure studies on the coenzyme Q group. J Am Chem Soc. 1958;80(17):4750–2.
8. Festenstein GN, Heaton FW, Lowe JS, Morton RA. A constituent of the unsaponifiable portion of animal tissue lipids (X... 272 m,u.). Biochem J. 1995;59(4):558–66. https://doi.org/10.1042/bj0590558.
9. IUPAC-IUB. Commission on biochemical nomenclature- nomenclature of quinones with isoprenoid side-chains. EurJ Biochem. 1975;53:15–8.
10. Folkers K. Heart failure as a dominant deficiency of coenzyme Q10 and challenges for future clinical research on coenzyme Q10. J Clin Invest. 1993;71(8):S51–4. https://doi.org/10.1007/bf00226840.
11. Ernster L, allner GD. Biochemical, physiological and medical aspects of ubiquinone function. Biochim Biophys Acta. 1995;1271(1):195–204. https://doi.org/10.1016/0925-4439(95)00028-3.
12. Mellors A, Tappel AL. Quinones and quinols as inhibitors of lipid peroxidation. Lipids. 1966;1:282–4. https://doi.org/10.1007/BF02531617.
13. Mellors A, Tappel AL. The inhibition of mitochondrial peroxidation by ubiquinone and ubiquinol. J Biol Chem. 1966;241(19):4353–6.
14. Littarru GP, Ho L, Folkers K. Deficiency of coenzyme Q10 in human heart disease, Part I and II. IntJ Vit Nutr Res. 1972;42(2):291.

15. Mitchell M. Coupling of phosphorylation to electron and hydrogen transfer by a chemiosmotic type of mechanism. Nature. 1961;191:144–8.
16. Mitche llM. Chemiosmotic coupling in oxidative and photosynthetic phosphorylation. BiolRev Cambridge Philosophical Soc. 1966;41(3):445–502.
17. Folkers K. Survey on the vitamin aspects of coenzyme Q. Int J Vit Nutr Res. 1969;39(3):334–52.
18. Folkers K, Vadhanavikit S, Mortensen SA. Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10. ProcNatl Acad SciUSA. 1985;82(3):901–4. https://doi.org/10.1073/pnas.82.3.901.
19. MortensenSA Vadhanavikit S, Folkers K. Deficiency of coenzyme Q10 in myocardial failure. Drugs Exptl Clin Res. 1984;X:497–502.
20. Folkers K, Watanabe T, Kaji M. Critique of coenzyme Q in biochemical and biomedical research and in ten years of clinical research on cardiovascular disease. Mol Med. 1977;2:431–60.
21. Ondarroa M, Sharma SK, Quinn PJ. Solvation properties of ubiquinone-10 in solvents of different polarity. Biosci Rep. 1986;6(9):783–96. https://doi.org/10.1007/BF01117101.
22. Garrido-Maraver J, Cordero MD, Oropesa-Avila M, Vega AF, De la Mata M, Pavon AD, et al. Clinical applications of coenzyme Q10. Front Biosci. 2014;19:619–33.
23. BhagavanHN ChopraRK. Coenzyme Q10: absorption, tissue uptake, metabolism and pharmacokinetics. Free Radical Res. 2006;40(5):445–53. https://doi.org/10.1080/10715760600617843.
24. Barakat A, Shegokar R, Dittgen M, Muller RH. Coenzyme Q10 oral bioavailability: effect of formulation type. JPharm Invest. 2013;43(6):431–51. https://doi.org/10.1007/s40005-013-0101-4.
25. James AM, Smith RAJ, Murphy MP. Antioxidant and pro-oxidant properties of mitochondrial coenzyme CoQ10. ArchBiochem Biophy. 2004;423(1):47–56. https://doi.org/10.1016/j.abb.2003.12.025.
26. Battino M, Ferri E, Gorini A, Villa RF, Huertas JFR, Fiorella P, et al. Natural distribution and occurrence of coenzyme Q homologues. MembBiochem. 1990;9(3):179–90. https://doi.org/10.3109/09687689009025839.
27. Quinzii CM, Lopez LC, Naini A, DiMauro S, Hirano M. Human CoQ10 deficiencies. BioFactors. 2008;32(1–4):113–8.
28. DiMauro S, Quinzii CM, Hirano M. Mutations in coenzyme Q10 biosynthetic genes. JClinInvest. 2007;117(3):587–9.
29. Hernández-Camacho JD, Bernier M, López-Lluch G, Navas P. Coenzyme Q10 supplementation in aging and disease. Front Physiol. 2018;9(44):1–11. https://doi.org/10.3389/fphys.2018.00044.
30. Desbats MA, Morbidoni V, Silic-Benussi M, Doimo M, Ciminale V, Cassina M, et al. The COQ2 genotype predicts the severity of coenzyme Q10 deficiency. HumMol Genet. 2016;25(19):4256–65. https://doi.org/10.1093/hmg/ddw257.
31. Yubero D, O'callaghan M, Montero R, Ormazabal A, Armstrong J, Espinos C, et al. Association between coenzyme Q10 and glucose transporter (GLUT1) deficiency. BMC Pediatr. 2014;14:284. https://doi.org/10.1186/s12887-014-0284-5.
32. Maurya PK, Noto C, Rizzo LB, Rios AC, Nunes SOV, Barbosa DS, et al. The role of oxidative and nitrosative stress in accelerated aging and major depressive disorder. Prog Neuro-Psychopharmacol Biol Psychiatry. 2016;65:134–44. https://doi.org/10.1016/j.pnpbp.2015.08.016.
33. Barja G. Mitochondrial oxygen consumption and reactive oxygen species production are independently modulated: implications for aging studies. Rejuv Res. 2007;10(2):215–24. https://doi.org/10.1089/rej.2006.0516.
34. Brunk UT, Terman A. The mitochondrial-lysosomal axis theory of aging: accumulation of damaged mitochondria as a result of imperfect autophagocytosis. Eur JBiochem. 2002;269(8):1996–2002. https://doi.org/10.1046/j.1432-1033.2002.02869.x.
35. Sohal RS, Mockett RJ, Orr WC. Mechanisms of aging: an appraisal of the oxidative stress hypothesis. Free Radic Biol Med. 2002;33(5):575–86. https://doi.org/10.1016/S0891-5849(02)00886-9.
36. Miquel J. An update on the oxygen stress-mitochondrial mutation theory of aging: genetic and evolutionary implications. Exp Gerontol. 1998;33(1–2):113–26. https://doi.org/10.1016/S0531-5565(97)00060-0.
37. Schniertshauer D, Gebhard D, Bergemann J. Age-dependent loss of mitochondrial function in epithelial tissue can be reversed by coenzyme Q10. JAging Res. 2018;5:6354–80. https://doi.org/10.1155/2018/6354680.
38. Harman D. The biologic clock: the mitochondria? J Am Geriatr Soc. 1972;20(4):145–7. https://doi.org/10.1111/j.1532-5415.1972.tb00787.x.
39. Krutmann J, Schroeder P. Role of mitochondria in photoaging of human skin: the defective powerhouse model. J Investig Dermatol Symp Proc. 2009;14(1):44–9. https://doi.org/10.1038/jidsymp.2009.1.
40. Demple B, Harrison L. Repair of oxidative damage to DNA: enzymology and biology. Annu Rev Biochem. 1994;63:915–48. https://doi.org/10.1146/annurev.bi.63.070194.004411.
41. Clayton DA, Doda JN, Friedberg EC. The absence of a pyrimidine dimer repair mechanism in mammalian mitochondria. ProcNatlAcadSciUSA. 1947;71(7):2777–81. https://doi.org/10.1073/pnas.71.7.2777.
42. Halliwell B. The wanderings of a free radical. Free RadicBiol Med. 2009;46(5):531–42. https://doi.org/10.1016/j.freeradbiomed.2008.11.008.
43. Ma D, Stokes K, Mahngar K, Domazet-Damjanov D, Sikorska M, Pandey S. Inhibition of stress induced premature senescence in presenilin-1 mutated cells with water soluble coenzyme Q10. Mitochondrion. 2014;17:106–15. https://doi.org/10.1016/j.mito.2014.07.004.
44. Koroshetz WJ, Jenkins BG, Rosen BR, Beal MF. Energy metabolism defects in Huntington's disease and effects of coenzyme Q10. Ann Neurol. 1997;41(2):160–5. https://doi.org/10.1002/ana.410410206.
45. Shults CW, Haas RH, Passov D, Beal MF. Coenzyme Q10 levels correlate with the activities of complexes I and II/III in mitochondria from parkinsonian and nonparkinsonian subjects. Ann Neurol. 1997;42(2):261–4. https://doi.org/10.1002/ana.410420221.
46. Moreira PI, Santos MS, Sena C, Nunes E, Seica R, Oliveira CR. CoQ10 therapy attenuates amyloid h-peptide toxicity in brain mitochondria isolated from aged diabetic rats. Exp Neurol. 2005;196(1):112–9. https://doi.org/10.1016/j.expneurol.2005.07.012.
47. Ishrat T, Khan MB, Hoda MN, Yousuf S, Ahmad M, Ansari MA, et al. Coenzyme Q10 modulates cognitive impairment against intracerebroventricular injection of streptozotocin in rats. BehavBrain Res. 2006;171(1):9–16. https://doi.org/10.1016/j.bbr.2006.03.009.
48. Li G, Jack CR, Yang X, Yang ES. Diet supplement CoQ10 delays brain atrophy in aged transgenic mice with mutations in the amyloid precursor protein: an in vivo volume MRI study. BioFactors. 2008;32(1–4):169–78. https://doi.org/10.1002/biof.5520320120.
49. Yang X, Yang Y, Li G, Wang J, Yang ES. Coenzyme Q10 attenuates β-amyloid pathology in the aged transgenic mice with Alzheimer presenilin 1 mutation. JMol Neurosci. 2008;34(2):165–71. https://doi.org/10.1007/s12031-007-9033-7.
50. Yang X, Dai G, Li G, Yang ES. Coenzyme Q10 reduces β-amyloid plaque in an APP/PS1 transgenic mouse model of Alzheimer's disease. J Mol Neurosci. 2010;41(1):110–3. https://doi.org/10.1007/s12031-009-9297-1.
51. Villalba JM, Parrado C, Santos-Gonzalez M, Alcain FJ. Therapeutic use of coenzyme Q10 and coenzyme Q10-related compounds

and formulations. Expert Opin Investig Drugs. 2010;19(4):535–54. https://doi.org/10.1517/13543781003727495.
52. Dumont M, Kipiani K, Yu F, Wille E, Katz M, Calingasan NY, et al. Coenzyme Q10 decreases amyloid pathology and improves behavior in a transgenic mouse model of Alzheimer's disease. JAlzheimers Dis. 2011;27(1):211–23. https://doi.org/10.3233/JAD-2011-110209.
53. Elipenahli C, Stack C, Jainuddin S, Gerges M, Yang L, Starkov A, et al. Behavioral improvement after chronic administration of coenzyme Q10 in P301S transgenic mice. JAlzheimers Dis. 2012;28(1):173–82. https://doi.org/10.3233/JAD-2011-111190.
54. Choi H, Park HH, Seong H, Koh NYC, Yu HJ, Park J, et al. Coenzyme Q10 protects against amyloid beta-induced neuronal cell death by inhibiting oxidative stress and activating the P13K pathway. Neurotoxicology. 2012;33(1):85–90. https://doi.org/10.1016/j.neuro.2011.12.005.
55. Sadli N, Barrow CJ, McGee S, Suphioglu C. Effect of DHA and coenzyme Q10 against Aβ- and zinc-induced mitochondrial dysfunction in human neuronal cells. Cell Physiol Biochem. 2013;32(2):243–52. https://doi.org/10.1159/000354433.
56. Choi H, Park HH, Lee KY, Choi NY, Yu HJ, Lee YJ, et al. Coenzyme Q10 restores amyloid beta-inhibited proliferation of neural stem cells by activating the PI3K pathway. Stem Cells Dev. 2013;22(15):2112–20. https://doi.org/10.1089/scd.2012.0604.
57. Shetty RA, Forster MJ, Sumien N. Coenzyme Q (10) supplementation reverses age-related impairments in spatial learning and lowers protein oxidation. Age (Dordr). 2013;35(5):1821–34. https://doi.org/10.1007/s11357-012-9484-9.
58. Fang-Ng L, Gruber J, Cheah IK, Goo CK, Cheong WF, Shui G, et al. The mitochondria-targeted antioxidant MitoQ extends lifespan and improves healthspan of a transgenic Caenorhabditis elegans model of Alzheimer disease. Free RadicBiolMed. 2014;71:390–401. https://doi.org/10.1016/j.freeradbiomed.2014.03.003.
59. Ali AA, Ahmed HI, Khalil MG, Alwakeel AI, Elfotuh KA. Comparative study on the influence of epigallocatechin-3-gallate and/or coenzyme Q10 against Alzheimer's disease induced by aluminium in normally-fed and protein malnourished rats. J Alzheimers Dis Parkinsonism. 2016;6(3):1–10. https://doi.org/10.4172/2161-0460.1000240.
60. Soleimani M, Golab F, Alizadeh A, Rigi S, Samani ZN, Vahabzadeh G, et al. Evaluation of the neuroprotective effects of electromagnetic fields and coenzyme Q10 on hippocampal injury in mouse. J Cell Physiol. 2018;234(10):18720–30. https://doi.org/10.1002/jcp.28512.
61. Qusti SY, Balgoon M, Alzahrani ES, Elsawi N, Alotaibi NA. Role of combined administration of copper-nicotinic acid complex and coenzyme Q10 against aluminium chloride-induced oxidative stress in rat brain. Pharmacophore. 2018;9(1):19–29.
62. Omidi G, Karimi SA, Rezvani-Kamran A, Monsef A, Shahidi S, Komaki A. Effect of coenzyme Q10 supplementation on diabetes induced memory deficits in rats. MetabBrain Dis. 2019;34(3):833–40. https://doi.org/10.1007/s11011-019-00402-7.
63. Komaki H, Faraji N, Komaki A, Shahidi S, Etaee F, Raoufi S, et al. Investigation of protective effects of coenzyme Q10 on impaired synaptic plasticity in a male rat model of Alzheimer's disease. Brain ResBull. 2019;147:14–21. https://doi.org/10.1016/j.brainresbull.2019.01.025.
64. Salehpour F, Farajdokht F, Mahmoudi J, Erfani M, Farhoudi M, Karimi P, et al. Photobiomodulation and coenzyme Q10 treatment attenuate cognitive impairment associated with model of transient global brain ischemia in artificially aged mice. Front Cell Neurosci. 2019;13(74):1–17. https://doi.org/10.3389/fncel.2019.00074.
65. Fouad GI. Combination of omega 3 and coenzyme Q10 exerts neuroprotective potential against hypercholesterolemia-induced Alzheimer's-like disease in rats. Neurochem Res. 2020;45(5):1142–55. https://doi.org/10.1007/s11064-020-02996-2.
66. Yang M, Lian N, Yu Y, Wang Y, Xie K, Yu Y. Coenzyme Q10 alleviates sevoflurane-induced neuroinflammation by regulating the levels of apolipoprotein E and phosphorylated tau protein in mouse hippocampal neurons. Mol Med Rep. 2020;22(1):445–53. https://doi.org/10.3892/mmr.2020.11131.
67. Azimi M, Ashour AE, Fuaat AA, Mohamed WMY. Neuroprotective effects of co-administration of coenzyme Q10 and vitamin-E in chronic cerebral hypoperfusion-induced neurodegeneration in rats. Int JNutrPharmacol NeurolDis. 2020;10(2):35–42. https://doi.org/10.4103/ijnpnd.ijnpnd_79_19.
68. Galasko DR, Peskind E, Clark CM, Quinn JF, Ringman JM, Jicha GA, et al. Antioxidants for Alzheimer disease. Arch Neurol. 2012;69(7):836–41. https://doi.org/10.1001/archneurol.2012.85.
69. Mecocci P, Polidori MC. Antioxidant clinical trials in mild cognitive impairment and Alzheimer's disease. Biochim Biophys Acta. 2012;1822(5):631–8. https://doi.org/10.1016/j.bbadis.2011.10.006.
70. Matthews RT, Yang L, Browne S, Baik M, Beal MF. Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. Proc Natl Acad Sci USA. 1998;95(15):8892–7. https://doi.org/10.1073/pnas.95.15.8892.
71. Miquel E, Cassina A, Martínez-Palma L, Souza JM, Bolatto C, Rodríguez-Bottero S, et al. Neuroprotective effects of the mitochondria-targeted antioxidant MitoQ in a model of inherited amyotrophic lateral sclerosis. Free Radic Biol Med. 2014;70:204–13. https://doi.org/10.1016/j.freeradbiomed.2014.02.019.
72. Ferrante RJ, Browne SE, Shinobu LA, Bowling AC, Baik MJ, MacGarvey U, et al. Evidence of increased oxidative damage in both sporadic and familial amyotrophic lateral sclerosis. J Neurochem. 1997;69(5):2064–74. https://doi.org/10.1046/j.1471-4159.1997.69052064.x.
73. Orsucci D, Mancuso M, Ienco EC, LoGerfo A, Siciliano G. Targeting mitochondrial dysfunction and neurodegeneration by means of coenzyme Q10 and its analogues. Curr MedChem. 2011;18(26):4053–64. https://doi.org/10.2174/092986711796957257.
74. Yang L, Calingasan NY, Wille EJ, Cormier K, Smith K, Ferrante RJ, et al. Combination therapy with coenzyme Q10 and creatine produces additive effects in models of Parkinson's and Huntington's disease. J Neurochem. 2009;109(5):1427–39. https://doi.org/10.1111/j.1471-4159.2009.06074.x.
75. Feigin A, Kieburtz K, Como P, Hickey C, Claude K, Abwender D, et al. Assessment of coenzyme Q10 tolerability in Huntington's disease. Mov Disord. 1996;11(3):321–3. https://doi.org/10.1002/mds.870110317.
76. Sanoobar M, Eghtesadi S, Azimi A, Khalili M, Jazayeri S, Gohari MR. Coenzyme Q10 supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with relapsing–remitting multiple sclerosis. Int J Neurosci. 2013;123(11):776–82. https://doi.org/10.3109/00207454.2013.801844.
77. Mao P, Manczak M, Shirendeb UP, Reddy PH. MitoQ, a mitochondria-targeted antioxidant, delays disease progression and alleviates pathogenesis in an experimental autoimmune encephalomyelitis mouse model of multiple sclerosis. Biochim Biophys Acta. 2013;1832(12):2322–31. https://doi.org/10.1016/j.bbadis.2013.09.005.
78. Sikorska M, Lanthier P, Miller H, Beyers M, Sodja C, Zurakowski B, et al. Nanomicellar formulation of coenzyme Q10 (Ubisol-Q10) effectively blocks ongoing neurodegeneration in the mouse 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine model: potential use as an adjuvant treatment in Parkinson's disease. Neurobiol Aging. 2014;35(10):2329–46. https://doi.org/10.1016/j.neurobiolaging.2014.03.032.

79. Shults CW, Beal MF, Fountain D, Nakano K, Hass RH. Absorption, tolerability, and effects on mitochondrial activity of oral coenzyme Q10 in parkinsonian patients. Neurology. 1998;50(3):793–5. https://doi.org/10.1212/WNL.50.3.793.
80. Shults CW, Oakes D, Kieburtz K, Beal MF, Hass R, Plumb S, et al. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol. 2002;59(10):1541–50. https://doi.org/10.1001/archneur.59.10.1541.
81. Muller T, Buttner T, Gholipour AF, Kuhn W. Coenzyme Q10 supplementation provides mild symptomatic benefit in patients with Parkinson's disease. Neurosci Lett. 2003;341(3):201–4. https://doi.org/10.1016/S0304-3940(03)00185-X.
82. Horstink MW, Van-Engelen BG. The effect of coenzyme Q10 therapy in Parkinson disease could be symptomatic. Arch Neurol. 2003;60(8):1170–2. https://doi.org/10.1001/archneur.60.8.1170-a.
83. Shults CW, Beal MF, Song D, Fountain D. Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease. Exp Neurol. 2004;88(2):491–4. https://doi.org/10.1016/j.expneurol.2004.05.003.
84. Storch A, Jost WH, Vieregge P, Spiegel J, Greulich W, Durner J, et al. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q10 in Parkinson disease. ArchNeurol. 2007;64(7):938–44. https://doi.org/10.1001/archneur.64.7.nct60005.
85. Apetauerova D, Scala SA, Hamill RW, Simon DK, Pathak S, Ruthazer R, et al. CoQ10 in progressive supranuclear palsy, a randomized, placebo-controlled, double-blind trial. NeurolNeuroimmunolNeuroinflam. 2016;3(5):1–9. https://doi.org/10.1212/NXI.0000000000000266.