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Nadia Turton, Nathan Bowers, Sam Khajeh, Iain P Hargreaves & Robert A Heaton

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REVIEW

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Coenzyme Q_{10} and the exclusive club of diseases that show a limited response to treatment

Nadia Turton, Nathan Bowers, Sam Khajeh, Iain P Hargreaves and Robert A Heaton

School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool UK

ABSTRACT

Introduction: Coenzyme Q_{10} (CoQ_{10}) is a ubiquitous organic molecule with a significant role in the mitochondrial electron transport chain (ETC). As a result of its role in such an important biological process, $_{CoQ10}$ deficiency has been implicated in the pathogenesis of numerous diseases such as Parkinson's disease (PD) and multiple sclerosis (MS). This has led to multiple attempts to use CoQ_{10} supplementation as a treatment or pre-treatment with varying degrees of success.

Areas covered: The present review will identify evidence of mitochondrial dysfunction in MS, PD and mitochondrial ETC disorders. In addition, the inability of Co_{10} supplementation to elicit significant clinical outcome in these disorders and possible flaws in these studies will be discussed. The databases utilized for this review were the Web of science and PubMed, with inclusive dates (1957–2021).

Expert opinion: A lack of improved neurological outcome in these disorders post treatment with CoQ_{10} may be attributable to the limited ability of CoQ_{10} to cross the blood–brain barrier. Thus, CoQ_{10} alternatives should also be considered. Other factors including time of disease diagnosis, dosage, administration, and duration of CoQ_{10} therapy may have a significant influence on the efficacy of this treatment.

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KEYWORDS
Coenzyme Q_{10}; mitochondrial electron transport chain disorders; multiple sclerosis; Parkinson's disease

1. Introduction

Coenzyme Q_{10} (CoQ_{10}) is the dominant form of ubiquinone found in humans and can be found in almost all cellular membranes [1]. This lipid-soluble molecule is made up of a benzoquinone moiety, with a 10-subunit polyisoprenoid lipid tail [2] (Figure 1). The central benzoquinone ring includes two redox active sites, essential for its cellular function, whereas the polyisoprenoid tail is responsible for the correct positioning in a variety of membranes [2].

The synthesis of CoQ_{10} can be divided into three distinct steps. Firstly, the synthesis of the benzoquinone ring from 4-hydroxybenzoate, followed by the synthesis of the polyisoprenoid tail from acetyl-coenzyme A (CoA) utilizing the mevalonate pathway and finally, the condensation of the two structures to form CoQ_{10} [3]. The condensation step in CoQ_{10} synthesis takes place within the mitochondria and has been suggested to be the rate limiting step in the CoQ_{10} biosynthetic pathway [4].

CoQ_{10} plays a significant role in a number of biochemical pathways within the mitochondrion [2]. However, CoQ_{10}'s principal function is as an electron carrier, exchanging electrons derived from both complex I and II and transferring them to complex III facilitating electron transfer in the mitochondrial electron transport chain (ETC; Figure 2). In addition, CoQ_{10} also functions as an essential lipid-soluble antioxidant within the cell, and because of CoQ_{10}'s ubiquitous nature it not only protects the mitochondrial membrane from free radical induced oxidation, but also that of other organelle membranes together with the plasma membrane [3]. Additionally, CoQ_{10} is also involved in the regeneration of other cellular antioxidants such as vitamin C and E [5]. In a recent study by Heaton, Heales [6] evidence showed that cellular CoQ_{10} concentration can even influence the lysosomal lumen pH, although the mechanism by which this occurs has yet to be elucidated.

In view of coQ_{10}'s functional role, CoQ_{10} has been supplemented in response to three disorders of the central nervous system (CNS), of which they have displayed evidence of mitochondrial dysfunction and oxidative stress [3,7,8]. These disorders include multiple sclerosis (MS), mitochondrial electron transport chain (ETC) disorders and Parkinson's disease (PD). The present review will evaluate the inability of Co_{10} supplementation to elicit significant clinical outcome in these disorders and possible flaws in these studies will be discussed.

1.1. CoQ_{10} Deficiency

CoQ_{10} deficiencies can be divided into two categories, primary and secondary deficiencies [2]. Primary COQ_{10} deficiencies are caused by mutations in the genes directly involved in the biosynthesis of CoQ_{10} [9,10]; whereas secondary deficiencies have been associated with mutations in genes that are indirectly related to CoQ_{10} biosynthesis, or to other non-genetic factors [11].

Due to the plethora of different biochemical functions of COQ_{10}, the clinical consequences resulting from aCoQ_{10} deficiency can have a wide spectrum of presentations. In

CONTACT Robert A Heaton School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, UK r.heaton@2013.ljmu.ac.uk

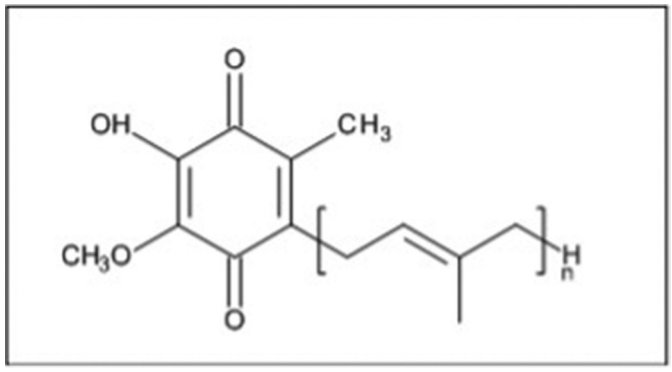

Figure 1. Chemical structure of coenzyme Q_{10} (CoQ_{10}) N = 10.

particular, a CoQ_{10} deficiency results in the impairment of the METC, leading to a reduced cellular ATP production [12]. Primary CoQ_{10} deficiencies are most often reported in tissues with high energy demand such as the CNS [12]. The clinical presentation and severity of primary CoQ_{10} deficiencies can vary drastically ranging from a mild clinical phenotype to a severe infantile presentation which can often be fatal [13].

Secondary CoQ_{10} deficiency typically presents in diseases such as mitochondrial myopathies [14,15], cardiovascular disease [16], type II diabetes [17], chronic kidney disease [18], liver disease and critical illness [19]. In common with a primary CoQ_{10} deficiency the deficit in CoQ_{10} contributes to disease pathophysiology in these disorders by impairing energy metabolism and compromising cellular antioxidant status. As discussed previously, a secondary CoQ_{10} deficiency can be caused by non-genetic factors such as the pharmacological agents, statins [20]. Statins reduce the circulatory levels of low-density lipoprotein (LDL) through the competitive inhibition of the enzyme, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA reductase) (Figure 3) which serves as a major regulatory role in both cholesterol and CoQ_{10} biosynthesis [21]. A number of studies have reported reduced CoQ_{10} status following statin treatment [21]. However, the majority of these studies assessed endogenous CoQ_{10} status in plasma/serum, which may only reflect the decrease in LDL, as LDL is the principal carrier of CoQ_{10} in the circulation [3]. Only a small number of studies have directly measured CoQ_{10} muscle status which is thought to be a more accurate reflection of endogenous CoQ_{10} status [22].

2. Multiple sclerosis

MS is a chronic inflammatory disease of the CNS and currently the most common cause of non-traumatic neurological disability in young adults [23]. While the etiology and pathogenesis of MS still remain to be fully elucidated, research suggests that genetic predisposition and environmental factors trigger the permeation of myelin-specific autoreactive lymphocytes into the CNS, an important causative factor for MS [24–26]. The entry of these lymphocytes into the CNS results in multifocal demyelination, neural and axonal damage, oligodendrocyte loss, blood–brain barrier (BBB) breakdown and oxidative stress [23,27–29]. The clinical presentation of MS includes optic neuritis, diplopia, fatigue, paralysis, paresthesias and cognitive dysfunction [30]. MS can be categorized into four disease states including relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPSM), primary progressive multiple sclerosis (PPMS), and progressive-relapsing multiple sclerosis (RPMS) [31,32]. The majority of MS patients experience RRMS, during which an episode of neurological impairment is followed by partial or complete remission [33,34].

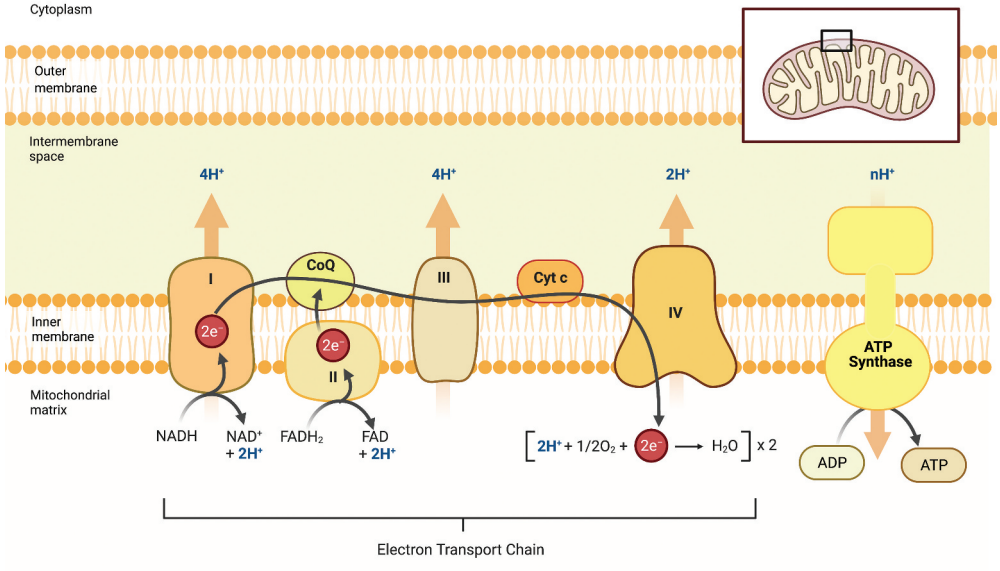

Figure 2. Diagram of electron transport chain (ETC) and ATP synthase illustrating the pumping of H+ ions into the intermembrane space, and how CoQ_{10} augments the passage of electrons. Created using BioRender.com (template provided by Biorender).

Figure 3. Schematic diagram of the CoQ_{10} biosynthetic pathway, demonstrating how pharmacological inhibition, such as statin therapy may also influence the synthesis of CoQ_{10}. Adapted from Hargreaves, Duncan [20].

2.1. Mitochondrial dysfunction and oxidative stress in MS

It is becoming increasingly apparent that oxidative stress accompanies neuro-inflammation observed in MS, which can result in secondary mitochondrial dysfunction [35]. This injurious effect upon the mitochondria can result in further reactive oxygen species (ROS) production continuing the cycle of free radical generation, eventually resulting in decreased neuronal ATP production [36,37]. These factors ultimately lead to activation of apoptosis and progressive axon degeneration, which can extenuate to the neuronal body and dendrites and eventually the presynaptic and postsynaptic neurons [38]. Mitochondrial dysfunction has been associated with the disease pathogenesis of MS, since deficiencies in ETC complex IV, citrate synthase (mitochondrial matrix marker) and complex I (NADH dehydrogenase: ubiquinone reductase) activities have been detected in the active lesions of postmortem brain samples taken from chronic MS patients [39]. Similarly, Sadeghian et al. [40] reported that the activity of ETC complex I was selectively compromised in the spinal tissue in a mouse model of the disease (experimental autoimmune encephalomyelitis; EAE), together with an increase in astrocytic phosphofructokinase 2 (PFK2) expression and a shift from oxidative to glycolytic metabolism. These findings accompanied depolarization of the axonal mitochondria and axons themselves,

thus, correlating with neurological deficits. Evidence of mitochondrial dysfunction is relatively unexplored in other tissues; however, Hargreaves et al. [41] reported statistically significant alterations to ETC complex I and complex II/III (succinate: ubiquinone reductase) activities at the pre-symptomatic and asymptomatic stages in spinal cord, jaw muscle and liver tissues of EAE mouse models of MS. ETC complex I has been reported to be the main site of ROS production in the ETC [42]; thus, increased levels of oxidative stress reported in MS patients [43] may be attributable to a decrease observed in complex I activity [39,40]. Additionally, lymphocytes isolated from MS patients were found to have a significant reduction in mitochondrial membrane potential compared to healthy controls [44]. The differences in mitochondrial function identified in this study were proportional to the degree of MS severity, again suggesting mitochondrial dysfunction may contribute to the pathogenesis of disease progression in MS and is not limited to the CNS.

2.2. CoQ_{10} limitations in MS

In view of the evidence of mitochondrial dysfunction and oxidative stress reported in the pre-symptomatic and symptomatic stages of MS, the ETC electron carrier and lipid-soluble antioxidant, CoQ_{10} may be considered as a potential adjunct therapy to control disease progression [15,45]. However, although proven to be beneficial in some cases, several studies have suggested that CoQ_{10} still has some therapeutic limitations in the treatment of MS and this will be outlined in the following section.

Sanoobar et al. [46] demonstrated that CoQ_{10} supplementation had no effect on the activity of the antioxidant enzyme, glutathione peroxidase (GPx) in RRMS patients. In this study, fasting blood samples were taken from 45 subjects with MS before and after a 12-week intervention with CoQ_{10} and a placebo control. However, despite an increase in superoxide dismutase activity (SOD), a decrease in malondialdehyde (MDA; marker of lipid peroxidation) levels and reduced total antioxidant capacity (TAC) levels detected in the CoQ_{10} treated MS patient group, no significant difference in GPx activity was identified between the control and treated groups. Previously, reduced levels of peripheral GPx activity have been reported in MS patients compared to healthy controls [47]. It has been suggested that GPx may make more of a contribution than the antioxidant enzyme, catalase in detoxifying cellular hydrogen peroxide [48]. Thus, in view of the susceptibility of the CNS to ROS induced oxidative damage, CoQ_{10} supplementation does not appear to have the capacity to up-regulate the activity of the vital antioxidant enzyme, GPx in MS, which may therefore limit the ability of CoQ_{10} to delay disease progression [46].

One potential therapeutic mechanism of CoQ_{10} is its ability to adjust the immune response [49]. Inflammation is a key contributor to axonal injury in MS, of which anti-inflammatory cytokines are decreased and pro-inflammatory cytokines are increased in the CSF [50,51]. A study by Sanoobar et al. [7] reported that CoQ_{10} supplementation for 12 weeks (500 mg/day) did not alter levels of anti-inflammatory cytokines transforming growth factor-β (TGF- β) and interleukin (IL)-4 in the serum of MS patients compared to the placebo group. Similarly, in an EAE C57BL/6 female adult mouse model study of MS, Soleimani et al. [52] observed no alterations in the levels of IL-4 in the CoQ_{10} treated group compared to the untreated group. TGF- β can suppress T-cell proliferation, macrophage activity and cytotoxic lymphocyte maturation [53]. Similarly, IL-4 inhibits the ability of macrophages to produce TNF-α, IL-1 and IL-6 [54,55]. Both of which have demonstrated protective properties in EAE models [56,57]. However, CoQ_{10} may utilize its anti-inflammatory effects via the inhibition of pro-inflammatory cytokines, as opposed to increasing anti-inflammatory cytokines [7,52]. On the contrary, 12-week CoQ_{10} (200 mg/day) supplementation in RRMS patients treated with interferon beta1a 44 μg (IFN-β1a) demonstrated higher levels of IL-4 in the peripheral blood [58]. However, at present we cannot exclude the possibility that the increase in circulatory IL-4 was the result of IFN-β1a treatment rather than that of CoQ_{10}. The studies discussed also required patient `follow up reports` that exceeded a 3-month intervention to identify meaningful changes over longer periods of time. Additionally, in view of the fact that MS is an inflammatory disease of the CNS, supplementary markers of MS severity should be included e.g magnetic resonance imaging data allow an assessment of the effect of CoQ_{10} supplementation on cerebral function.

Depression and fatigue are common symptoms of MS [59], and therefore, a randomized, double-blinded, placebo-controlled trial was undertaken to assess the effect of a CoQ_{10} supplementation (500 mg/day) on MS-related fatigue over a 12 week period [60]. In the study fatigue symptoms were measured using a fatigue severity scale (FSS). In the CoQ_{10} (500 mg/day) treated patient group a significant decrease in FSS was observed. Similarly, previous studies have observed improved fatigue sensation and physical performance during fatigue-inducing workload trials at high-dose CoQ_{10} (300 mg/day) supplementation [61]. However, these levels of CoQ_{10} may be higher than that achievable with current oral CoQ_{10} formulation and lower doses of CoQ_{10} (100 mg/day) have been shown to have no effect on fatigue during physical workload trials in healthy volunteers, which may translate into the effects of fatigue in MS patients [61]. Furthermore, it should also be considered that larger and long-term follow-up studies are required to confirm the anti-fatigue effects of CoQ_{10} in MS as well as developing more accurate methods of quantifying fatigue severity in MS following CoQ_{10} supplementation. However, it should be noted that the etiology of MS-related fatigue is unknown and may be multifactorial and therefore may require more than one candidate therapy

3. Parkinson's disease

PD is a neurodegenerative disorder that is pathologically characterized by Lewy body formation and striatal dopamine depletion in the Substantia Nigra [8]. Abnormal accumulation of ROS in the neuronal cells of PD patients leads to a reduction in the antioxidant, glutathione. As a result, increased oxidative stress leads to mitochondrial respiratory chain dysfunction, the release of pro-apoptotic mitochondrial proteins and ultimately, cell death [62]. As well as CoQ_{10}'s role in the METC

(Figure 2), reduced CoQ_{10} is also an important antioxidant, protecting the membrane and lipoproteins from ROS [63]. Consequently, the therapeutic efficacy of CoQ_{10} in the treatment of PD has been tested in numerous studies. The following section evaluates the results obtained from some of the key trials that have been conducted, as well as discussing the potential future applications of CoQ_{10} in the treatment of PD.

3.1. CoQ_{10} limitation in PD

Results obtained from a phase II trial indicated that the progression of early-stage PD could be stabilized using oral CoQ_{10} supplementation [64]. In this trial, patients were randomly assigned to a placebo group or CoQ_{10} treatment at dosages of 300, 600, or 1200 mg/d. Disease progression was then measured at one, four, eight, twelve and sixteen months using the Unified Parkinson's Disease Rating Scale (UPDRS). This scale measures the mental and motor capacity of patients, as well as their ability to complete daily living activities and in doing so considers the various clinical features of PD. After eight months, the mean total UPDRS score of patients receiving 300 mg/d and 600 mg/d dosages was similar, but importantly, lower than that of the placebo group, suggesting that CoQ_{10} was effective in slowing disease progression. However, the UPDRS scores of the 1200 mg/d group were not significantly lower than both aforementioned groups, indicating that there is a dosage threshold required for maximum drug efficacy. Following these promising findings, a phase III clinical trial involving 600 patients was conducted using largely the same method [65]. In this trial, treated patients received CoQ_{10} dosages of 1200 mg/d or 2400 mg/d. Despite 1200 mg/d being the highest dosage used in the previous study, the mean change in UPDRS score of treated patients was not significantly lower than that of the placebo group after 16 months. The researchers therefore concluded that CoQ_{10} showed no benefit and should not be used in the treatment of early-stage PD.

CoQ_{10} was unable to stabilize PD progression in the study described by Beal, Oakes [65], but further assessment of this potential treatment is not futile. Half of dopaminergic neurons within the substantia nigra of PD patients are damaged before clinical diagnosis [66]. As the average age of participants in this study was 65 years old, it is possible that the neurones of these patients were already significantly damaged prior to treatment with CoQ_{10}, meaning its neuroprotective effects would be limited [67]. The answer to improving its therapeutic efficacy could therefore lie in using novel methods to diagnose the disease earlier. In addition, the loss of glutathione during presymptomatic Parkinson's disease pathogenesis implies that supplementary antioxidants, such as CoQ_{10}, could be advantageous in its treatment [68].

In both of the trials described, the studied populations consisted of a broad range of sporadic PD patients, this means their contrasting findings could have been the result of diverse gene mutations within their respective populations. A number of mutant genes have been linked to familial PD [69], for example, a mutation to the PINK1 gene prevents PINK1 from transferring electrons between complex 1 and CoQ_{10} in the MECT [70]. This mutation would significantly reduce the effectiveness of CoQ_{10} supplementation on disease progression, however, screening for it did not occur during patient selection, meaning the reported null effects of CoQ_{10} in PD may have been skewed. The capacity of CoQ_{10} to reduce oxidative stress could still prove beneficial in treating patients suffering from other forms of the disease and should be investigated further. Both studies reported an increase in mean CoQ_{10} plasma levels from baseline to the last assessment; however, as previously discussed, this is not an entirely accurate way to estimate tissue CoQ_{10} concentrations. In addition, neuronal cells have yet another limiting factor in the BBB permeability restricting the passage of CoQ_{10} into the cells [71]. Whilst creating compounds that can penetrate the BBB still proves difficult to this day, CoQ_{10} analogues that have better water solubility have been produced. Studies by Muthukumaran, Leahy [72] and Sikorska, Lanthier [73] have shown that water-soluble Ubisol-Q10 can stabilize the progression of PD in animal models; however, the positive results obtained from Sikorska, Lanthier [73] are caveated by reports that treatment disruption resulted in continued neuronal degradation. Analogues of CoQ_{10} which possess improved mitochondrial membrane penetration have also been produced [74]. MitoQ consists of CoQ_{10} bound to triphenyl alkyl phosphonium cations, the cations interact with negative mitochondrial membranes and in doing so improve CoQ_{10} uptake [75]. The therapeutic efficacy of MitoQ was tested in a study conducted by Snow, Rolfe [67] where treated patients were given 40 mg or 80 mg dosages of the compound each day for 16 months. Whilst the mean UPDRS score of treated patients did not significantly differ from that of the placebo group, it is possible that late diagnosis of the disease, as well as struggles in getting the compound to cross the BBB hindered the results. If the above-mentioned obstacles can be overcome, water-soluble analogues of CoQ_{10} could still prove beneficial in treating PD. Proposals suggested by Park, Park [76] indicate that the answer to the BBB conundrum is continuous CoQ_{10} in traditional delivery. In their study, PD was induced in rat models using 6-hydroxydopamine. They were then injected with various dosages of CoQ_{10} solution, and their neurodegeneration measured. Measurements used in this study included behavioral and dopaminergic evaluation, as well as neurogenesis, angiogenesis and neuroinflammation analysis. Compared to the placebo group, models treated with high dosage CoQ_{10} solution showed significant improvements in every parameter. These results suggest that convection-enhanced delivery could improve CoQ_{10} therapeutic efficacy and therefore provide the basis for more research into what seems a promising avenue for PD treatment.

4. Mitochondrial electron transport chain disorders

The clinical heterogeneity and unpredictable nature of ETC disorders have not been conducive to the development of effective therapeutic strategies for these diseases. Treatment of these disorders is extremely challenging with no cure as yet in sight. Most patients with ETC disorders are afforded symptomatic treatment to manage the various clinical presentations of the disease. Treatment can also involve therapy aimed at enhancing ETC function as well as reducing

Table 1. Summary of the current clinical trials which have assessed the therapeutic efficacy of CoQ_{10} in the treatment of ETC disorders. Abbreviations: MERRF: mitochondrial encephalopathy and ragged red fibers, MELAS: myoclonic epilepsy and lactic acidosis, CPEO: chronic progressive external ophthalmoplegia, KSS: Kearns Sayre syndrome, NARP: Neuropathy, ataxia, and retinitis pigmentosa. Clinical trials which have assessed the efficacy of CoQ10 in the treatment of ETC disorders.

Study		Possible flaws in study
1.	In the study by Bresolin, et al. [92] 44 mitochondrial patients (CPEO, KSS and MERRF) were treated CoQ10 (2 mg/kg/day) for 6 months. 54% of patients following CoQ10 treatment were found to have a 35% decrease in plasma lactate levels post exercise. These were deemed •responders however following a further 3 months of Colo treatment no differences were found between the •responders' and the placebo group.	In the study, serum CoQ10 levels were reported as: 0.93 nmol/L (pre CoQ10 supplementation) and 1.33 nmol/L (post CoQ10 supplementation). The general serum/plasma ref range is reported as: 0.48–1.8 PM [13,931. The level of CoQ10 only increased by approximately 1.4-fold following CoQ10 supplementation. Possibly due to the poor bioavailability of the COQ10 formulation used. Low dosage of CoQ10 used (2 mg/kg/day).
2.	In the study by Chen, et al. [94] patients with mitochondrial encephalomyopathies (M ERRF, MELAS, CPEO) were treated with CoQ10 (160 mg/day) for 3 months. A significant improvement in the global M RC score which is used for grading the muscle strength was noted in patients together with a nonsignificant decrease in plasma lactate levels post exercise. Patient serum CoQ10 levels were decreased below control levels, 0.6–0.98 PM (patient); 0.57–1.83 gM (control range). Following 3 months of CoQ10 therapy the serum CoQ10 level of patients increased to 3.46 PM (3.5–5fold increase, approximately).	Low dosage of CoQ10 used (160 mg/day). No details oftype of CoQ10 formulation were provided. Short duration trial (3 months). Patient fatigability was not significantly improved.
3.	In the study by Glover, et al. [95] 30 patients with MRC diseases (MELAS, CPEO, NARP, LHON) were treated with CoQ10 (1200 mg/day) for 60 days. CoQ10 used in the study was a Q gel; Tishcon, New York. Following CoQ10 treatment, only a significant decrease in plasma lactate levels were observed post exercise in patients, no other clinical benefit noted.	The plasma CoQ10 status of the MRC patients showed no evidence of a CoQ10 deficiency (mean plasma COQ10 status of patients: 1.15 gM). Since these patients may not have an underlying CoQ10 deficiency, they may not be expected to show any clinical improvement following CoQ10 supplementation [96]. Short duration trial (60 days).

increased ROS generation typically associated with ETC impairment. In light of the prospect that supplementation with CoQ_{10} may increase the efficiency of electron transfer through the ETC in patients with disorders of the ETC, CoQ_{10} supplementation is one of the regular therapeutic strategies used in specialist clinical centers [3]. However, at present there is a paucity of high-level evidence supporting the use of CoQ_{10} in the treatment of patients with ETC disorders. However, a number of case studies have reported evidence of an increase in strength, accelerated post exercise recovery and an improvement in oxygen consumption in patients following CoQ_{10} supplementation [77]. The most consistent finding, however, following Co_{10} therapy appears to be at the biochemical level, with a decrease in plasma lactate levels being reported following supplementation [78].

4.1. CoQ_{10} limitations in ETC disorders

Presently, only a limited number of clinical trials have assessed the efficacy of CoQ10 as a treatment for mitochondrial disease (Table 1). The results of these studies have demonstrated no overall clinical benefit and mostly included patients with ETC disorders with variable clinical phenotypes and genotypes. This makes it difficult to draw definite conclusions on the responsiveness of COQ10 therapy on particular patient groups. Although no benefit in any of the outcomes was observed in two trials [79] evidence of improvement in muscle strength [80] and following exercise, a decrease in plasma lactate levels was reported [81] was reported. It has been suggested that the duration of the study and the dose of COQ10 administrated are both factors that may compromise the therapeutic efficacy of CoQ10 in clinical trials [82,83]. The lack of clinical trials that have assessed the effectiveness of CoQ10 for the treatment of mitochondrial disease can be attributed to the difficulty in recruiting a sufficient number of patients and the relatively high cost of conducting the trials themselves. Furthermore, the reasons for the refractory nature of the neurological sequelae associated with ETC dysfunction to CoQ10 supplementation may be a consequence of the relatively poor ability of CoQ10 to cross the BBB. Animal studies have suggested that CoQ10 supplementation can be transported across the BBB [A, B] (whats A and B). However, it is yet to be established whether the degree of CoQ10 uptake observed in these animal studies would be sufficient to restore cerebral ETC function.

The low bioavailability of some of the CoQ10 formulations used in these trials together with their low treatment doses or short durations may have contributed to the ambiguity in the results of the clinical trials (Table 1) [80,84,85]. CoQ10 doses typically in the range of 5–50 mg/kg/day are recommended in the treatment of patients with primary COQ10 deficiency and soluble forms are recommended instead of tablet forms, due to their higher bioavailability [86]. At present, however, there is no consensus on what dosage of CoQ10 is appropriate to administer to patients with other forms of ETC dysfunction. However, a dosage of at least 5 mg/kg/day is suggested [87]. Importantly, there is evidence of secondary CoQ10 deficiency associated with patients with ETC disorders, linked to a mutation in a gene not specifically involved in the CoQ10 biosynthetic pathway; in some cases, these patients have been shown to be more responsive to CoQ10 therapy and have shown significant clinical improvement post CoQ10 supplementation [88]. Moreover, this demonstrates the importance of determining the CoQ_{10} status prior to treatment, in order to identify any subgroups of patients with ETC disorders who may be more responsive to therapy [89]. It should also be noted that additionally to its supposed ability to improve electron transport in the ETC, the therapeutic efficacy associated with CoQ_{10} in the treatment of mitochondrial disease may also be the result of its potent lipid soluble antioxidant capacity [78].

In light of their increased absorption, the use of both gel and oil-based formulations has been recommended over the use of conventional tablet formulations in patients with ETC disorders [90]. In a study by Martinefski, Samassa [91] it was reported that liquid emulsion improved the bioavailability of CoQ_{10} with respect to solid formulations. Currently, there is considerable debate as to whether formulations of ubiquinol rather than the ubiquinone form of CoQ_{10} have a better absorption from the gastrointestinal tract (GI). It has been reported that absorption of ubiquinol is three to four times higher than CoQ_{10} in the GI [91,92]. However, because during absorption in the GI CoQ_{10} undergoes reduction to ubiquinol, the suggested increased bioavailability of the ubiquinol formulations may be due to the matrix in which the ubiquinol is held in rather than its redox state.

5. Conclusion

A number of studies have highlighted evidence of mitochondrial dysfunction in the pathophysiology of MS, PD and ETC disorders. Thus, is view of CoQ_{10}'s significant role in the ETC, it may be deemed a potential therapeutic strategy in response to the aforementioned disorders. However, in some cases CoQ_{10} has demonstrated an inability to elicit significant neurological outcome in MS, PD and ETC disorders and this has been discussed in the present review.

Although there is an abundance of evidence indicating the ability of CoQ_{10} to slow and even limit disease pathogenesis, there are certain diseases in which CoQ_{10} supplementation has only demonstrated a limited therapeutic benefit to patients. The factors that may contribute to the limited therapeutic efficacy of CoQ_{10} are at present uncertain, but the paucity of hospital centers that are able to assess the endogenous CoQ_{10} status of patients and therefore indicate evidence of an underlying CoQ_{10} deficiency should be taken into consideration. Furthermore, CoQ_{10} assessments are most often determined based on serum or plasma surrogates, which may not reflect endogenous levels. This may influence the ability of CoQ_{10} supplementation to impact the progression of the disease, because the severity of the CoQ_{10} deficiency may be masked by the use of inappropriate surrogates for endogenous CoQ_{10} determination. In addition, a late diagnosis of a CoQ_{10} deficiency may result in irreversible disease progression and a limited response to CoQ_{10} supplementation. Other important factors to consider which may influence the clinical response to CoQ_{10} supplementation are the type of CoQ_{10} formulation employed and the dosage used, as these factors will influence the absorption and bioavailability of CoQ_{10}. Furthermore, the use of synthetic analogues of CoQ_{10} capable of passing through the BBB may also be a consideration.

In conclusion, it is currently uncertain why CoQ_{10} supplementation may be ineffective in the treatment of the diseases discussed in this review and further studies may be required in order to establish appropriate quinone treatment protocols.

6. Expert opinion

In the present review, the inability of CoQ_{10} to augment significant improvements in the pathophysiology and clinical outcome of three disorders of CNS was discussed. In some cases, CoQ_{10} treatment appeared to elicit little or no improvement on disease pathophysiology; however, this in part may reflect the paucity of information currently available and the limited number of studies assessing the therapeutic efficacy of CoQ_{10} in the treatment of CNS disorders which is certainly the case for MS [93]. Furthermore, the inclusion of supplementary markers of disease severity should also be considered in clinical studies such as, magnetic resonance imaging data to enable an accurate assessment of the effect of CoQ_{10} supplementation on cerebral activity in these CNS disorders.

The aforementioned diseases are accompanied by evidence of mitochondrial dysfunction and oxidative stress [39,43]. Additionally, some studies have reported evidence of tangible improvements in mitochondrial functioning post treatment with CoQ_{10} [46]. Thus, in view of the important role CoQ_{10} plays as an electron carrier in the ETC and as a potent antioxidant, we cannot at present exclude the potential for CoQ_{10} to elicit significant enhancement of mitochondrial functioning in the CNS disorders discussed in this review [15,45]. However, a lack of improved neurological outcome post treatment with CoQ_{10} may be attributable to the limited ability of CoQ_{10} to cross the BBB [94]. There is still uncertainty about the transports of CoQ_{10} across the BBB in humans and to date, no studies to date have yet assessed the transport of CoQ_{10} across the human BBB. Animal studies, however, have shown a degree of CoQ_{10} transport across the BBB. In a study by Matthews, Yang [95] a 30% increase in cerebral cortex CoQ_{10} and coenzyme Q9 (CoQ_9; predominant ubiquinone species in rat) was reported following oral supplementation of 12-month -old Sprague-Dawley rats with CoQ_{10} (200 mg/kg) for 2 months. Additionally, in a study by Smith, Matson [96] it was reported high-dose supplementation (1000–5000 mg/kg) led to a significant increase in CoQ_{10} concentrations in the brain of mice models. Yet, it is unclear whether this increase in CoQ_{10} status following supplementation would be sufficient to replenish an underlying cerebral CoQ_{10} deficiency. An in vitro study assessing the transport of CoQ_{10} across the BBB has reported that the uptake of CoQ_{10} via the Receptor for Advanced glycation end products (RAGE) and SR-B1 (scavenger Receptor) correlates with an efflux via the low-density lipoprotein receptor (LDLR) transporters, demonstrating that CoQ_{10} transcytosis occurs in both directions, resulting in no 'net' transport across the BBB [94]. In view of this, administration of LDLR inhibitors or the stimulation of the luminal activity of SR-B1 transporters in conjunction with CoQ_{10} supplementation may be an appropriate method to enhance the CNS uptake of exogenous CoQ_{10}. Alternatively, the short-chain analog of CoQ_{10}, idebenone which has been reported to readily cross the BBB [97] should also be considered as an alternative means of targeting the ETC dysfunction and oxidative stress associated with the CNS disorder discussed in this review. Idebenone administration has been reported to improve oxidative metabolism in patients with the CNS mitochondrial syndrome, MELAS [98]. Therefore, idebenone may be an appropriate alternative to CoQ_{10} in the treatment of MS, PD and ETC disorders, although it should be noted that this therapy may be disease dependent. Furthermore, idebenone treatment has been reported to induce oxidative stress in

in vitro studies and exacerbate disease presentation in a patient with a primary deficiency in CoQ_{10} biosynthesis and therefore caution should always be exercised before replacing CoQ_{10} with idebenone in therapeutic regime of patients [15].

Factors such as the time of disease diagnosis, dosage, administration, and duration of CoQ_{10} therapy may have a significant influence on the efficacy of this treatment. For example, the studies discussed in this review generally lacked long-term follow-up reports that exceeded 3-months to identify significant changes with CoQ_{10} intervention over longer periods of time [58]. Thus, we cannot at present exclude the possibility that there may be possible long-term beneficial effects associated with CoQ_{10} therapy. In addition, the studies discussed used a range of CoQ_{10} dosages; however, at present there is no consensus on the appropriate dosage of CoQ_{10} required to elicit significant clinical benefit to the patient. Doses as high as 2400 mg/day are being administered in the treatment of PD [99]. However, doses exceeding this level may result in a block of GI absorption and split dosing is recommended for patient administration [100,101]. Additionally, primary CoQ_{10} deficiencies if diagnosed at the early stage of the disease have been widely reported to be responsive to CoQ_{10} supplementation with accompanying clinical improvement being observed [102]. However, the stage of the disease may be important when CoQ_{10} supplementation is initiated, as if this occurs after irreversible organ damage has occurred no therapeutic efficacy may be elicited even in cases of primary CoQ_{10} deficiency [10].

It should also be noted that evidence of an underlying deficit in CoQ_{10} status has been observed among some patients with ETC disorders and PD [103,104]. Thus, it would be anticipated that these patients may be more responsive to CoQ_{10} supplementation, and this should be considered upon administration. In view of this, the level of CoQ_{10} in patients should be assessed prior to administration to determine which patients may benefit from CoQ_{10} intervention. Interestingly, a deficit in serum COQ_{10} levels was not reported in MS patients [105]. This may justify why MS patients in some cases do not respond to this therapy [7]. In addition to this, the stage of the disease progression when CoQ_{10} is administered may be of importance, as patients with early-stage disease (prior to irreversible CNS damage) may be more responsive to CoQ_{10}.

Other dietary preferences and supplementation taken in response to MS, PD and ETC disorders may influence the absorption of CoQ_{10}. For example, high-dose vitamin E administration may compete with CoQ_{10} for GI absorption [106], resulting in lower plasma CoQ_{10} levels and these factors should all be taken into consideration prior to supplementing CoQ_{10} in these disorders. The beneficial effect of CoQ_{10} on these disorders although not clearly demonstrated cannot at present be excluded at this juncture. Further studies are required addressing the points raised in this section before the therapeutic potential of CoQ_{10} in the treatment of MS, PD and ETC disorders can be finally discounted.

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