REVIEW ARTICLE

Unlocking the Potential of Coenzyme Q10: From Cellular Energy to Clinical Applications

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Abstract

Coenzyme Q10 (CoQ10) is a naturally occurring, lipid-soluble compound crucial for cellular energy production and antioxidant defense. Structurally composed of a benzoquinone ring and a polyisoprenoid side chain, CoQ10 resides within cell membranes, particularly in mitochondria. It plays a key role in the mitochondrial electron transport chain, facilitating ATP generation. Beyond energy production, CoQ10 protects cells from oxidative stress and supports the regeneration of other antioxidants like vitamins C and E. It is also involved in various metabolic pathways, including cholesterol synthesis, lysosomal function, and inflammation regulation. Although the body synthesizes CoQ10, its levels decline with age and can be reduced by certain diseases and medications, notably statins. This decline contributes to mitochondrial dysfunction, especially in metabolically active tissues such as muscle, brain, and retina. Ubidecarenone is the pharmaceutical form of CoQ10, often used in supplements. It has shown therapeutic potential in conditions involving oxidative stress, mitochondrial dysfunction, and statin-induced myopathy. Despite its low toxicity and good tolerability, CoQ10's clinical use faces challenges, particularly related to its bioavailability and ability to reach target tissues like the brain or retina. Although supplementation shows promise in improving oxidative stress markers, consistent clinical benefits in conditions such as neurodegenerative diseases remain inconclusive. Interactions with drugs like warfarin and certain chemotherapeutics also require caution. Future research should focus on improving delivery systems, determining optimal dosing, and establishing clear guidelines for its therapeutic use. Enhanced formulations may help unlock CoQ10's full potential in treating age-related and chronic diseases more effectively.

Keywords: coenzyme Q10, free radical, antioxidant, ubidecarenone, mitochondria, chronic diseases
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Introduction

Coenzyme Q10

Coenzyme Q10 (CoQ10) is a lipid-soluble molecule characterized by a benzoquinone core and a 10-unit polyisoprenoid side chain, which anchors it within the lipid bilayers of various cell membranes[1] (Figure 1). The redox-active sites of CoQ10 are located within its benzoquinone ring, enabling its role in cellular energy production and antioxidant defense. CoQ10 has been extensively studied since it was first described in 1955. Although often described as a vitamin-like compound, it is not classified as a vitamin since it is synthesized by multiple human tissues. Its biosynthesis involves three key steps: the formation of the benzoquinone ring from 4-hydroxybenzoate, derived from tyrosine or phenylalanine; the production of the polyisoprenoid side chain from acetyl-coenzyme A (CoA) via the mevalonate pathway; and the final assembly of these components to form the functional CoQ10 molecule[1].

Finally, the two structures are combined to form coenzyme Q10. The benzoquinone ring structure is further modified by hydroxylation, methylation, and decarboxylation to form CoQ10[2]. The biosynthesis process for coenzyme Q10 has many possible rate-limiting stages, such as the polyisoprenoid chain synthesis (via HMG-CoA reductase) and the condensation of the polyisoprenoid chain and benzoquinone ring (through prenyltransferase)[3].

CoQ10 is a vital enzyme playing a crucial role in ATP production by acting as a cofactor for cellular enzymes. It is involved in many important cellular processes, most notably in the mitochondria but also in other parts of the cell[4]. During oxidative phosphorylation, CoQ10 is an essential component of the mitochondrial electron transport chain (mtETC), responsible for transporting electrons from complexes I and II to complex III (Figure 2). In addition to its role as a cofactor of dihydroorate dehydrogenase, it participates in the control of the mitochondrial permeability transition pore, the metabolism of fatty acids, pyrimidines, and mitochondrial uncoupling proteins[5]. Coenzyme Q10 (CoQ10) is a crucial lipid-soluble antioxidant that prevents oxidative stress (OS) caused by free radicals[2]. It protects cellular membranes, including mitochondrial and extra-mitochondrial, such as the Endoplasmic reticulum, Golgi apparatus, peroxisomes and lysosomes[6].

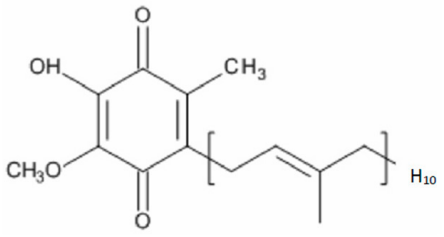

Figure 1: The chemical structure of CoQ10 (Crane, 2001)

CoQ10 not only directly functions as an antioxidant, but it also plays a role in the regeneration of vitamin C and vitamin E, which are also antioxidants[3]. Coenzyme Q10 also plays a role in inflammation mediation (has anti-inflammatory properties), metabolism of cholesterol[7,35], lysosomal pH regulation[8], sulphide metabolism (as sulphide quinone oxidoreductase cofactor)[9], and in the metabolism of amino acid (as choline dehydrogenase and proline dehydrogenase cofactor, respectively, in biosynthesis of glycine and proline/arginine, respectively)[10,11]. Evidence suggests that coenzyme Q10 directly influences the expression of several genes[12]. There are two forms of coenzyme Q10—ubiquinone and ubiquinol—and their continuous interconversion is essential to the correct functioning of the molecule[13].

The precise daily requirement for CoQ10 is still uncertain, although it has been approximated to be around 500 mg/day. This estimation is calculated on basis of a total body pool of 2000 mg and an average tissue turnover period of four days[14]. The body obtains a little quantity of CoQ10 (about 5 mg) from the daily food[15], while the majority of the daily need is produced internally. CoQ10 is synthesised in several tissues, with especially elevated concentrations seen in the kidney, heart, skeletal muscle, and liver[16]. Considering the CoQ10 levels in tissues (measured in grammes per gramme of tissue) along with the weight of organs, it is evident that the liver is the primary location for CoQ10 production in the body. Aging is linked to a decline in CoQ10 levels and heightened oxidative stress. Peak production is typically achieved at roughly 25 years of age, following which there is a gradual drop. By the age of 65, production levels are around 50% of what they were at age 25[17].

Deficiency in CoQ10 primarily affects metabolically active tissues such as skeletal muscle, the brain, and the retina. CoQ10 levels are diminished not only due to the process of ageing, but also as a result of specific medications, mainly statins, and several disorders[2]. In addition, due to its several crucial functions in cellular metabolism, a deficit of CoQ10, whether resulting from ageing, pharmaceutical medicines, or sickness, can have significant impacts on an individual's health.

The beneficial effects of CoQ10 have been reported in the treatment of chronic diseases. Retinal diseases and neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and Friedreich's ataxia, are characterized by increased oxidative stress, which the diminished CoQ10 levels fail to counterbalance. While animal studies suggest that CoQ10 supplementation may be beneficial for these conditions, its clinical application in humans presents several challenges, particularly in ensuring safe and effective delivery to affected tissues[18]. AD does not show significant improvement with CoQ10 supplementation, likely due to the limited efficacy of oral formulations. However, synthetic alternatives like Idebenone have demonstrated potential in neurodegenerative diseases, including AD, though further research is required to establish their effectiveness. The existence of various formulations, from the use of ubiquinol or ubiquinone to new analogues such as Ubisol-Q10 or Qter®, which vary in their bioavailability and effectiveness, makes it difficult to compare studies and reach a clear conclusion on the clinical use of CoQ10[19]. Additional studies are necessary to better understand the interplay between aging, CoQ10, and disease development. Existing research indicates that high-dose CoQ10 supplementation provides positive effects in retinal diseases, whereas its impact on neurodegenerative disorders is less evident[20].

Despite evidence of improvements in oxidative stress markers, the direct clinical benefits remain uncertain. A

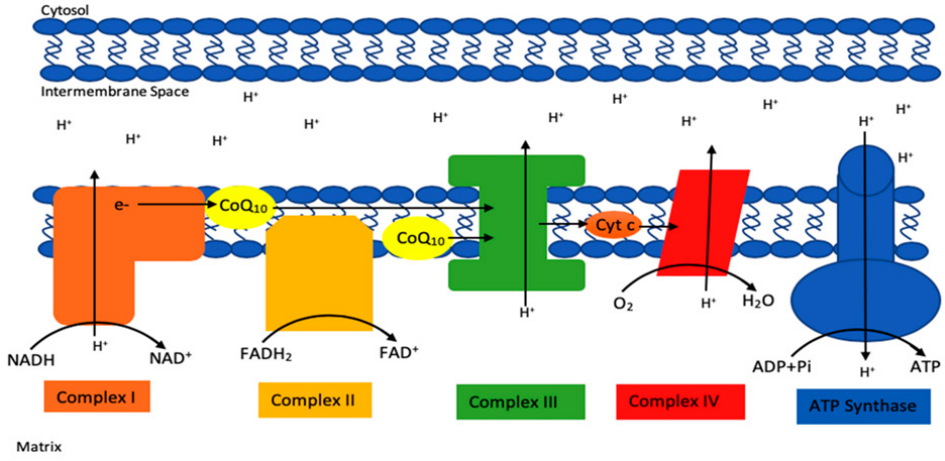

Figure 2: Illustration of the mitochondrial electron transport chain (METC) showing the role of coenzyme Q10 as an electron carrier (Crane, 2001)

consensus needs to be reached about the optimal dose for its therapeutic use with different diseases, since discrepancies in its effects are observed between different studies. A key limitation is the bioavailability of CoQ10, particularly its ability to cross the blood-brain barrier when administered orally or reach the retina through topical application[21].

Ubidecarenone

Ubidecarenone is a market preparation of CoQ10. Mitochondrial dysfunction is a crucial molecular event that leads to the development of cachectic myopathy[22,23]. More precisely, the deterioration of mitochondria is proposed as a precursor to muscle wasting in cachexia[24] making it a crucial focus for early intervention in treatment. Hence the possible role of Ubidercarenone in preventing myopathy. Ubidecarenone functions as a crucial electron carrier in the mitochondrial electron transport chain (mtETC) during oxidative phosphorylation that safeguards both the mitochondrial and extra-mitochondrial cellular membranes from oxidative stress caused by free radicals[25].

Ubidecarenone (Coenzyme-Q10) supplementation also ameliorates muscle symptoms related to use of statins, therefore Ubidecarenone supplementation could be done to benefit patients experiencing statin induced myopathy[26].

Ubidecarenone supplementation is generally safe and well tolerated. Toxicity of Ubidecarenone is low and serious side effects have not been reported. Gastrointestinal side effects such as abdominal pain and passage of soft feces are the most commonly documented side effects[27]. Plasma levels of Ubidecarenone reach a plateau at around 2400 mg/day.[28] Ubidecarenone supplementation upto 3600 mg/day was safely tolerated in patients of Huntington's disease as well as healthy controls.[29]

Ubidecarenone has some structural similarity to Vitamin K and it may increase the metabolism of warfarin through selective interaction with cytochrome P450 enzymes[30]. Theophylline may also be affected by Ubidecarenone supplementation, since it is also metabolized by cytochrome P450 enzymes. In fact, animal studies found altered theophylline pharmacokinetic parameters with Ubidecarenone coadministration[31]. As a potent antioxidant, it may confer an increased protection to oxidative stress and therefore, it may reduce the efficacy of certain pro-oxidant chemotherapeutic treatments such as Cisplatin, doxorubicin, and bleomycin[32]. Since Ubidecarenone may have an antihypertensive effect leading to decrease of arterial pressure when co-administered with antihypertensive drugs. Therefore, monitoring is advised[33]. The antihypertensive effect of the drug is probably based on a diminution of peripheral resistance[34].

Conclusion

Coenzyme Q10 (CoQ10) is a vital lipid-soluble molecule with essential roles in cellular energy production, antioxidant defense, and various metabolic processes. Its declining levels with age and certain medical conditions highlight the need for supplementation, particularly in mitochondrial dysfunction and oxidative stress-related diseases. While CoQ10 has shown promise in treating chronic conditions, challenges remain regarding its bioavailability, optimal dosage, and clinical efficacy. Further research is required to establish standardized therapeutic guidelines and improve delivery mechanisms. Advancements in CoQ10 formulations may enhance its clinical applications, ultimately providing more effective interventions for neurodegenerative, cardiovascular, and metabolic disorders.

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Conflict of Interest

The authors certify that they do not have any conflicts of interest regarding this research.

Statement

Our study has not been published elsewhere nor has it been submitted simultaneously for publication elsewhere.

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