A Critical Review Based on Coenzyme Q10 (Coq10)

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Abstract

The FDA has not approved Coenzyme Q10 (CoQ10) for any medical condition. However, it is widely available as a dietary supplement over-the-counter and is advised by both general care physicians and specialists. Because of its role in ATP production, CoQ10 has an impact on the performance of all cell types, particularly those with a high energy demand, making it vital for the health of all body tissues. This review was designed to emphasize on the CoQ10- chemistry, pharmacokinetics, signaling pathways, pharmacological potentials and mode of action behind diverse their activity. Coenzyme Q10 is also called as ubiquinone with a 10-isoprenoid-unit side chain. Some animals' kinetic curves for coenzyme Q10 developed additional peaks between hours 7 and 24 after drug administration. Over the course of 48 hours, 8.3% of radioactivity in the urine was recovered, consisting of a mixture of conjugated and unbound metabolites, tentatively recognised as Q acid I and Q acid II [2,3 dimethoxy-5-methyl-6-(30-carboxypropyl)-1,4-benzoquinone] in free and conjugated forms, respectively. Coenzyme Q10 is found helpful in formation of ATP and shows anti-oxidant effect. It is also used in cure or prophylaxis of cardiovascular disease- hypertension cancer (breast, lungs), chronic kidney disease, Periodontal disease, mitochondrial diseases, radiation harm, obesity, diabetes, parkinson's disease, AIDS, gastric ulcers, allergies, renal failure, muscular dystrophy, neurodegenerative disorder, polycystic ovarian syndrome, inherited ataxia, lower the anticoagulant efficacy of warfarin, and ageing. Therefore, supplementing with CoQ10 appears to increase mitochondrial activity and provide antioxidant property for organs and tissues damaged by a variety of pathophysiological diseases. Many novel researches are needed to evaluate and confirm its numerous activities and draw a proposed mode of action for different pharmacological potentials.

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INTRODUCTION

The FDA has not approved Coenzyme Q10 (CoQ10) for any medical condition. However, it is widely available as a dietary supplement over-the-counter and is advised by both general care physicians and specialists. Reduced circulating levels of CoQ10 have been linked to disorders such neurodegenerative diseases, fibromyalgia, migraine, diabetes, cancer, mitochondrial diseases, muscle diseases, and heart failure. Many studies have been conducted under the assumption that boosting systemic CoQ10 levels in such conditions would allow for the correct functioning of CoQ10-dependent activities (Sood & Keenaghan, 2021). Coenzyme Q10 is a benzoquinone that occurs naturally and plays a role in electron transport in mitochondrial membranes. Coenzyme Q10 is an endogenous antioxidant that has been found to be deficient in patients with a variety of cancers. Limited research has revealed that coenzyme Q10 may help women with breast cancer regress their tumours. It also shows immunostimulatory property (PubChem Compound Summary for CID 5281915, Coenzyme Q10, 2022).

Mode of action

Because of its role in ATP production, CoQ10 has an impact on the performance of all cell types, particularly those with a high energy demand,

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making it vital for the health of all body tissues. CoQ10 is the only endogenously generated lipid-soluble antioxidant that effectively protects proteins, lipids, and DNA from oxidation. Although part of CoQ10's benefits may be connected to a gene induction pathway, its clinical applications are based on its essential involvement in mitochondrial energy metabolism and well-known antioxidant capabilities. This lipid is now linked to a number of other key functions (Garrido-Maraver et al. 2014).

Chemistry

Coenzyme Q10 is a ubiquinone with a 10-isoprenoid-unit side chain. All isoprenyl double bonds in the naturally occurring isomer are in the E- configuration. It functions as a metabolite in humans, as well as a ferroptosis inhibitor and antioxidant (PubChem Compound Summary for CID 5281915, Coenzyme Q10, 2022).

Molecular formula: C59H90O4
Physical state: Solid
Melting point: 50-52ºC
Molecular weight: 863.3

Synonyms:

Coenzyme Q10, ubidecarenone, 303-98-0, ubiquinone-10, CoQ10, Ubiquinone 50, Neuquinon, Justquinon, Neuquinone, Emitolon, Heartcin, Inokiten, Terekol, Udekinon, Ubiquinone, Ubiquinone Q10, Coenzyme Q, Vitamin Q, NSC 140865, Q 199, Ube-Q, C59H90O4, API-31510, Q 10AA etc.

The Q coenzymes are a more frequent name for them. Most eukaryotic cells contain the coenzyme Q10 (CoQ10), which is involved in electron transport and cell respiration. Many statin users take 100 mg or more of CoQ10 per day as a nutritional supplement since cholesterol-lowering statins deplete the body's CoQ10. Some doctors recommend taking ubiquinol instead of ubiquinone because it may be better absorbed by the body (Q10-ACS, 2009).

Pharmacokinetics and toxicity

Some animals' kinetic curves for coenzyme Q10 developed additional peaks between hours 7 and 24 after drug administration. The liver absorbs oil-soluble coenzyme Q10 from the gut and removes it from circulation. The enterohepatic circulation phenomena appear to be reflected in the additional peaks of coenzyme Q10 concentration seen in humans and guinea pigs. As a result, because of its superior absorption, increased plasma concentrations, and hence improved bioavailability, solubilized coenzyme Q10 is clearly preferred. This is consistent with published results showing that plasma concentrations of coenzyme Q10 are 2-2.5 times higher with solubilized forms during long-term oral therapy, and bioavailability is 3-6 times higher than with powder (Kalenikova et al. 2008).

There were no deaths or unpleasant incidents in any of the groups. Throughout the treatment period, all male and female dogs in the 1200 and 1800 mg/kg per d groups had stools containing test-like material on a regular basis. The emission of unabsorbed test articles in faeces was assumed to be the cause. In the 1800 mg/kg per day group, mucous stool was seen occasionally in 1 male and 1 female. In the 1200 mg/kg per day group, 1 male and 3 females vomited, while in the 1800 mg/kg per day group, all males and 3 females vomited. Vomitus with test article-like substance was found in 1 female in the 1200 mg/kg per day group and 3 males in the 1800 mg/kg group, in the first 6 weeks (Yerramilli-Rao et al. 2012).

Adverse effects

- Coenzyme Q10 is found in the human body naturally. CoQ10 supplements are generally well taken, with only minor and uncommon side effects such as stomach discomfort, nausea, vomiting, and diarrhoea being reported.
- Doses of 100 mg or more per day have been linked to minor sleeplessness in some people.
- Some patients receiving 300 mg or more per day had elevated liver enzymes, but no liver damage was documented.
- Supplementation up to 1200 mg/day has been demonstrated to be tolerable.
- Dizziness, photophobia, irritability, headache, heartburn, increased involuntary movements, and weariness have all been reported as rare side effects.

Pharmacokinetics and its metabolites

Because CoQ10 is a lipophilic chemical, it is absorbed in the same way that lipids are. CoQ10

appears to have a similar absorption mechanism to vitamin E, a lipid-soluble nutrient. oQ10 absorption is enhanced when lipids are present. Because of its water insolubility, poor lipid solubility, and relatively large molar mass, orally administered CoQ10 has a low absorption efficiency. In one study, only around 2–3% of CoQ10 given orally was absorbed. rat trial. CoQ10 is found in variable quantities in all tissues of humans and animals. In a healthy adult, CoQ10's entire body pool is predicted to be between 0.5 and 1.5 grammes. CoQ10 concentrations are generally higher in heart, kidney, liver, and muscles are examples of tissues having high energy demands or metabolic activity. With the exception of the brain and lungs, a large part of CoQ10 in tissues is reduced as hydroquinone or ubiquinol. Increased oxidative stress in these two tissues appears to be the cause. About 95% of CoQ10 in the blood is in the reduced form. 14C-labeled CoQ10 was given intravenously to guinea pigs, 4.8 percent of the radioactivity was retrieved in the bile. The major metabolite was thought to be a Q acid I glucuronide [2,3 dimethoxy-5-methyl-6-(30 -methyl-50 -carboxy-2- pentenyl)-1,4-benzohydroquinone] produced in the liver. Over the course of 48 hours, 8.3% of radioactivity in the urine was recovered, consisting of a mixture of conjugated and unbound metabolites, tentatively recognised as Q acid I and Q acid II [2,3 dimethoxy-5-methyl-6-(30-carboxypropyl)-1,4-benzoquinone] in free and conjugated forms, respectively (Bhagavan & Chopra, 2006).

Table 1. Pharmacokinetic profile of CoQ10

Coenzyme Q10	Species, Dose (mg) & route	Tmax (h)	Cmax (µmol/l)	AUC (µmol h/l)	Reference
Powder	180	6.70	0.14	-	Bhagavan & Chopra, 2006).
Liquid 1	180	6.20	1.16	59.85	Bhagavan & Chopra, 2006).
Liquid 2	180	8.10	1.47	64.01	Bhagavan & Chopra, 2006).
Liquid 3	180	5.80	1.16	44.94	Bhagavan & Chopra, 2006).

Pharmacological properties

The drug atorvastatin (ATV), which is commonly used to treat dyslipidemia, has been shown to protect against 6-hydroxydopamine (6-OHDA)-induced neurotoxicity. Furthermore, by lowering the level of Q10 in the mitochondria, atorvastatin can impair mitochondrial activity. MMP was stabilised by ATV+Q10, and mitochondrial integrity was preserved. Furthermore, a rise in lipids peroxidases (LPO) and nitric oxide (NO), as well as a reduction in super oxide dismutase, indicated a considerable activation of oxidative stress (SOD). The aforesaid effects were dramatically altered after treatment with ATV+Q10, demonstrating antioxidant action. The recent findings suggest that combining Q10 with ATV has a synergistic impact in lowering dopamine toxicity (Prajapati et al. 2017). Coenzyme Q10 (Coenzyme q10) is a constituent of the electron transport system that performs a variety of tasks, including acting as an antioxidant (Crane et al. 1991). Low CoQ10 levels have been linked to inflammatory responses and oxidative stress, which have been linked to atherosclerosis, obesity, NAFLD (Farsi et al. 2016), and metabolic syndrome (MS). Obesity, dyslipidemia, and hyperglycemia are all associated with cardiovascular risk factors in MS. CoQ10 supplementation has been shown to be beneficial in the treatment of overweight, oxidative stress, Metabolic syndrome (Linkner & Humphreys, 2018) and Non-alcoholic fatty liver disease in recent studies (Casagrande et al. 2018). Coenzyme Q10 is found helpful in formation of ATP and shows anti-oxidant effect. It is also used in cure or prophylaxis of cardiovascular disease- hypertension (Lee et al. 2013), cancer (breast, lungs) (Folkers et al. 1997; Folkers, 1996) chronic kidney disease (Barden et al. 2018), periodontal disease, mitochondrial diseases, radiation exposure, obesity, diabetes, Parkinson's disease (Saults et al.2004), AIDS, stomach ulcers, allergies, kidney failure, muscular dystrophy, neurodegenerative disorder (Sanoobar et al. 2015), polycystic ovarian syndrome (Rahmani et al. 2018) inherited ataxia, lower the anticoagulant efficacy of warfarin (CoQ10, LIP, 2022) and ageing (Fan et al. 2018). The anti-inflammatory effects of CoQ10 in cancer are thought to be mediated by the suppression of transcription pathways NFkB (activator protein-1) activation (Mantle et al. 2021) immunostimulatory action-T & B Lymphocytes (Tian et al. 2014) and increased physical performance (Saini, 2011).

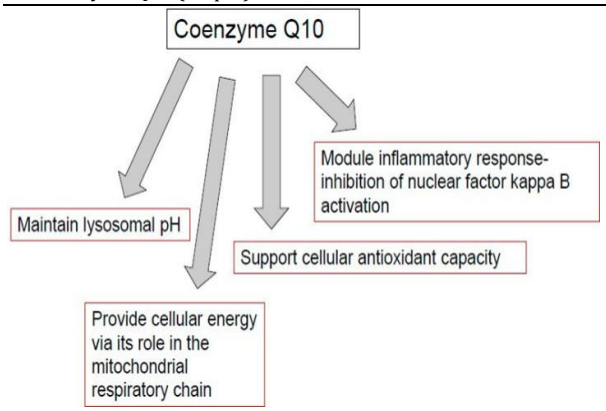


Fig. 1 Physiological roles of CoQ10 in cancer

Structure and SAR of CoQ10

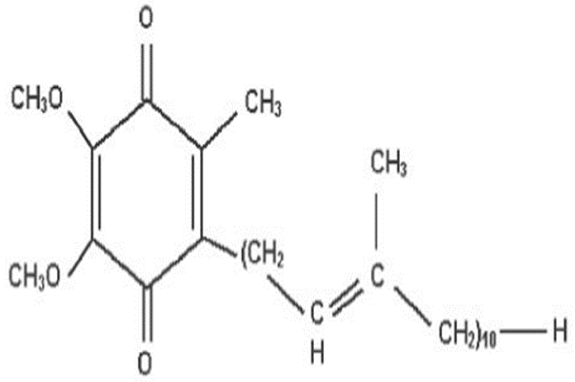


Fig. 2 Structure of Coenzyme Q10 (Chee-Ho, et al. 2010)

IUPAC name: 2-[(2E,6E,10E,14E, 18E,22E, 26E, 30E,34E)-3,7,11,15,19,23,27,31,35,39-Decamethyltetraconta-2,6,10,14,18,22,26,30, 34,38-decaenyl]-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione

In SAR, three analogues were discovered to have much improved effects in mitochondrial oxygen uptake and membrane potential, as well as providing significant cyto-protection in cultured mammalian cells when glutathione had been depleted by diethyl maleate treatment. In addition, the analogues inhibited the electron transport chain less than idebenone. Idebenone, a CoQ10 counterpart that has been tested in a variety of clinical trials, is one of the most well-studied. We previously shown that idebenone analogues with one or both OCH3 groups substituted with CH3 groups could still enable O2 consumption throughout the mitochondrial respiratory chain in a previous work. The structural differences in CoQ10 in this investigation were limited to the alkyl side chain just at 6-position of 1,4-benzoquinone ring (Fash et al. 2013).

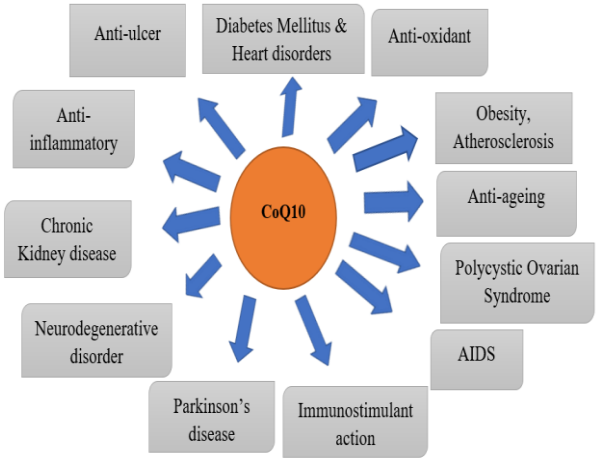
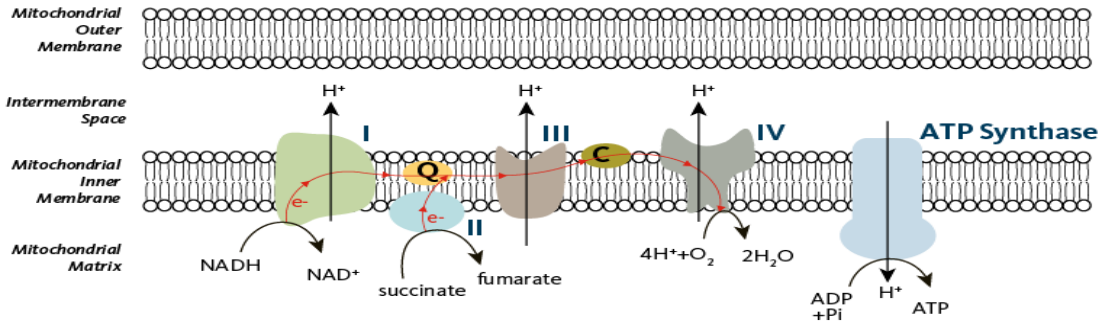


Fig. 3 Schematic depiction of Pharmacological activity of CoQ10

Intracellular signaling pathway of CoQ10

The activity of p-AMPK and FOXP3 was enhanced after treatment with CoQ10. Anti-inflammatory cytokine expression was found to increase in colitis mice given CoQ10. CoQ10 inhibits p-STAT3 and IL-17, which may help to lessen the intensity of colitis and reduce inflammation (Lee et al. 2017). Coenzyme Q10 is an unique lipid that serves as an electron transporter between complexes I & II of the mitochondrial membrane and complex III in mitochondria. It also functions as a cofactor for other dehydrogenases, as well as a regulator of the permeability transition gap and an antioxidant. CoQ10 is produced in mitochondria by a multiprotein complex containing at least 12 proteins. This complex's specific composition is currently unknown. Deficient ATP generation and excessive ROS creation are involved in the pathophysiology of CoQ(10) insufficiency, although other elements of CoQ(10) function may also be involved. CoQ(10) insufficiency is unusual among mitochondrial illnesses in that it has a therapy (Acosta et al. 2016).

Figure 2. Mitochondrial Electron Transport Chain



Coenzyme Q_{10} is a lipid-soluble component of the mitochondrial inner membrane that is critical to electron transport (in red) in the mitochondrial respiratory chain. Coenzyme Q_{10} carries electrons from complexes I and II to complex III, thus participating in ATP production. *C, cytochrome C; e-, electron; H+, proton; Q, coenzyme* Q_{10}.

Fig. 3 Schematic depiction of intracellular pathway in Mitochondrial Electron Transport Chain remodelling

Table 2. Summary of main in-vivo effects of CoQ10 in animal model

Animal model	Pharmacological effects	Mechanism of action	Reference
Animal organisms (Mouse)	Anti-oxidant	oxidative modifications of proteins, lipids, and DNA	Siemieniuk, & Skrzydlewska, 2005
R6/2 and N171-82Q transgenic mouse models	Neurodegenerative disease (Huntington's disease)	NMDA-mediated excitotoxicity	Ferrante et al. 2010
Male mice (10 mg/kg body weight)	Facilitate Testicular Function and Spermatogenesis	protein expression of enzymes essential for testosterone biosynthesis	Tsao et al. 2021
Mice & in clinical trials	Anti-ageing	Biosynthesis of mitochondrial proteins	Hernández-Camacho et al. 2018
Mice	Prophylactic and Antinociceptive	mechanical allodynia, thermal hyperalgesia	Zhang et al. 2013

CONCLUSION

CoQ10 insufficiency has been linked to a variety of clinical diseases and chronic disorders associated with ageing. In some situations, a lack of CoQ10 and its antioxidative activity might dramatically raise the level of oxidative damage. Therefore, supplementing with CoQ10 appears to increase mitochondrial activity and provide antioxidant property for organs and tissues damaged by a variety of pathophysiological diseases (Hernández-Camacho et al. 2018). Many novel researches are needed to evaluate and confirm its numerous activities and draw a proposed mode of action for different pharmacological potentials.

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CONFLICT OF INTEREST

Authors have declared for none conflict of interest.

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