Natural Resources for Human Health

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Review

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Received 05 September 2023
Revised 12 October 2023
Accepted 19 October 2023
Available online 22 November 2023

Edited by Vivek Chavda

KEYWORDS:
Coenzyme Q
Ubiquinol
Antioxidant
Cardiovascular Disease

Natr Resour Human Health 2023; 3 (4): 491-505
https://doi.org/10.53365/nrfhh/174300
eISSN: 2583-1194

Coenzyme q10 in cardiovascular disease: an insight for a potential therapeutic benefit

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ABSTRACT: The human body synthesizes the provitamin coenzyme Q10 (CoQ10), which plays a crucial role in the electron transport chain by ensuring a consistent and sufficient energy supply. CoQ10 exhibits multiple cellular roles, including its involvement in mitochondrial function, numerous cellular compartments, and plasma lipoproteins. Furthermore, CoQ10 plays a crucial role as an important antioxidant. The chemical composition of CoQ10 exhibits a strong correlation with vitamin K. It consists of a benzoquinone ring serving as the head group, accompanied by a tail made of ten isoprene units. A lack of CoQ10 has been identified as a fundamental factor contributing to numerous age-related and chronic illness problems. The efficacy of CoQ10 in various medical conditions has been proved by empirical evidence. Numerous research trials are now investigating the therapeutic and nutritional potential of CoQ10. CoQ10 continues to be predominantly utilized in the realm of cardiac research and reproductive treatments. However, there has been a notable surge of interest in exploring novel applications, notably in the context of topical administration.

1. INTRODUCTION

CoQ10 is a natural substance produced by the human body, which acts as a provitamin and serves a crucial role as a cofactor for mitochondrial enzymes, a pivotal component of the oxidative phosphorylation process. CoQ10 is present in the mitochondrial inner cell membrane of each cell of the human body and is also found in other animals, the plant kingdom, and in microbes (Kohlmeier, 2003). CoQ10 contributes to two major functions in the living body. First, as a crucial cellular coenzyme serves in the electron transport chain for ATP synthesis, which is the energy source for vital cellular works (Ernster & Dallner, 1995). The second role is as an antioxidant by suppressing the harmful impacts of free radicals on important biomolecules in the living body (Bliznakov, 1998; Weber et al., 1994). Moreover, other functions have also been described, such as cell signaling, membrane stabilization, and gene expression (Crane, 2002). The chemical name CoQ10 comes from its structure, consisting of a side chain composed of 10 isoprene units and a benzoquinone ring.

An average individual consumes around 5 mg of CoQ10 every day. (Mattila & Kumpulainen, 2001), however, 30 mg is appraised as an ample intake daily requirement for a healthy human. The daily requirement of CoQ10 is difficult to obtain frequently from dietary sources alone and the remaining fraction of CoQ10 is biosynthesized at the cellular level more specifically in hepatic cells (Bomer et al., 2022). However, the peak level is seen at the age of 20 years and then natural production of CoQ10 reduces with aging, also decline levels can be detected in pathological circumstances like muscle diseases and cardiac disorders (Marincola, 1997). Normal serum level of CoQ10 varies from 1.65 to 0.5 mg/mL and scarcity in the body results in poor health conditions and a variety of diseases including cardiac disorders, asthma, parkinsonism, infections, periodontal disease, hypertension, and some cancers (Bank et al., 2011). The beneficial effects of CoQ10 have been extensively shown in various medical conditions. Numerous research trials are currently being conducted to examine the potential of CoQ10 as a pharmaceutical candidate or as a dietary supplement.As the contribution of CoQ10 in the ATP synthesis, CoQ10 is a crucial component for the healthy operation of heart muscles. Further various reported studies demonstrated the beneficial role of supplementation with CoQ10, which is a strong antioxidant and may boost cellular bioenergetics (Chavda et al., 2022). Taking into account the aforementioned factors,

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our aim was to conduct a comprehensive review that examines the chemical profile, biochemical functioning, contemporary investigations, and clinical data of CoQ10 in relation to cardiovascular disease.

2. CHEMICAL CONSTITUENT

CoQ10 is the generic name of 2,3-dimethoxy-5- methyl-6-decaprenyl-1,4-benzoquinone that naturally exists in the trans configuration. The molecular composition of Coenzyme Q10 (CoQ10) exhibits similarities to that of vitamin K however is not in the category of vitamins as it is biosynthesized de novo in the living body (Bhagavan & Chopra, 2006). Chemically CoQ10 consists of a two-component structure, a benzoquinone nucleus or head, and a side chain of lipophilic isoprenoid tail (Figure 1). Various species display varying lengths of side chains. There is a method or approach. CoQ10 molecules are categorized according to the length of their side chains. In the case of humans, CoQ10 is composed of a side chain comprising 10 isoprenoid units. The stable conformation of CoQ10 exhibits exclusively monounsaturated trans configurations of its isoprenoid side chain. (Boicelli et al., 1981). A preliminary hypothesis was proposed. The isoprenoid chain in question may potentially exhibit an elongated and linear shape within the mitochondrial membrane (Jagow et al., 1980). Nevertheless, certain pieces of evidence have indicated the presence of a folded conformation in CoQ10, which exhibits notable stability (Jagow et al., 1980; Lenaz et al., 1999).

The polar quinone group of CoQ10 behaves as a functional group that is capable of reversible, two-step metabolic reactions of oxidation and reduction, which generate three types of redox states of CoQ10 (Figure 2). Ubiquinone is oxidized form and chemically it is 2, 3-dimethoxymethyl-6-decaprenyl-1, 4-benzoquinone. Ubiquinol is in reduced form and chemically it is 2, 3-dimethoxy-methyl-6-decaprenyl-1, 4-benzohydroquinone, and semiquinone (radical form) (Anna et al., 2015; Raizner, 2019).

CoQ10 can able to work as a transmembrane electron carrier from these reversible biochemical reactions (Nowicka & Kruk, 2010). Ubiquinol serves as a potent lipophilic antioxidant that neutralizes free radicals and additionally contributes to the regeneration of the antioxidant vitamin E in the living system (Kagan et al., 2000). The transitional radical semiquinone has an essential role in the antioxidant operation. The portion of ubiquinol form varies from 30%-90% and has been impacted by the metabolic status of cells (Yamamoto & Yamashita, 1997). Due to possessing a hydrophilic head, ubiquinol has the capacity to dwell in close proximity to the surface of the membrane. The oxidation/reduction processes of CoQ10 have an influence on the structural characteristics within the membrane.

Figure 3 provides a mechanistic overview of CoQ10 in the improvement of heart diseases (Rabanal-Ruiz et al., 2021). Upon the supplementation of CoQ10, elevated level of CoQ10 in plasma increase cellular respiration and decreases oxidative stress, ultimately improving the clinical outcome of major surgeries and lowering cardiovascular mortality. Additionally, dietary CoQ10 controls a variety of risk factors by possessing an anti-atherogenic impact that minimizes blood vessel stiffness and hypertension and inhibits the aggregation of oxidized LDL (oxLDL) in arteries (Rabanal-Ruiz et al., 2021).

3. THERAPEUTIC APPLICATIONS OF COQ10

CoQ10 shows a wide variety of therapeutic applications in cardiovascular, neuroprotective disease as well and mitochondrial disorders. The therapeutic potential ofCoQ10 in cardiovascular problems has been well acknowledged. This fundamental chemical serves a pivotal role in the generation of cellular energy and additionally functions as a strong antioxidant. CoQ10 supplementation has demonstrated potential in various aspects of cardiovascular health. The augmentation of energy production within the myocardium has the potential to boost the efficacy of cardiac performance. Moreover, the antioxidant capabilities of CoQ10 contribute to its ability to mitigate oxidative stress, hence diminishing inflammation and lowering the susceptibility to atherosclerosis. Several studies have indicated that CoQ10 may provide potential benefits in reducing blood pressure and enhancing endothelial function, a critical aspect in the maintenance of optimal vascular health (Zozina et al., 2018).

Moreover, the potential of CoQ10 as a supplementary treatment in heart failure has been investigated, with the aim of enhancing symptomatology and enhancing overall quality of life. Further investigation is required to establish conclusive recommendations for the utilization of CoQ10. However, it is evident that CoQ10 exhibits promise as a valuable therapeutic agent in the management of diverse cardiovascular disorders. This compound offers a comprehensive approach to cardiovascular well-being by bolstering energy metabolism and fortifying antioxidant defense mechanisms. The detailed applications have been described below:

3.1. Cardiovascular disease

CoQ10 mentions its role in supporting heart function and addressing conditions like congestive heart failure, hypertension, and angina. However, it could provide more specific details on the mechanisms involved and the results of clinical studies supporting these claims. Oxidative stress is identified as a pivotal contributor to the emergence of cardiovascular ailments, encompassing conditions like heart failure and hypertension. In the context of heart failure, a critical aspect is the impairment of contractile function, primarily stemming from a depletion of energy within the mitochondria. This depletion is well linked with lower CoQ10 levels that are naturally produced within the body. Notably, individuals afflicted with cardiomyopathy often exhibit insufficient levels of CoQ10 within the myocardium, and the extent of this deficiency appears to parallel the severity of the disease (Folkers et al., 1985). Table 1 presents data on the CoQ10 plasma concentrations derived from various cardiological research studies that incorporated CoQ10 supplementation as part of their investigations.

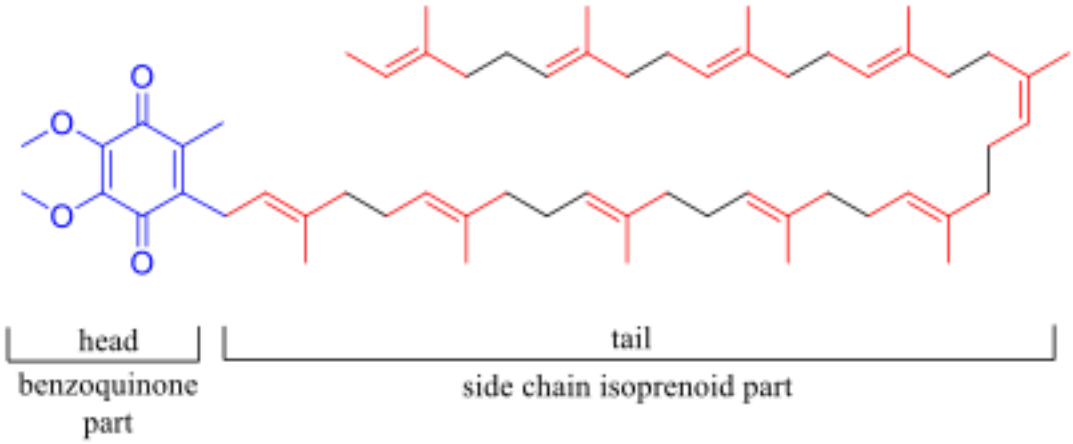

Figure 1. Chemical structure of natural Coenzyme Q10 with "head and tail".

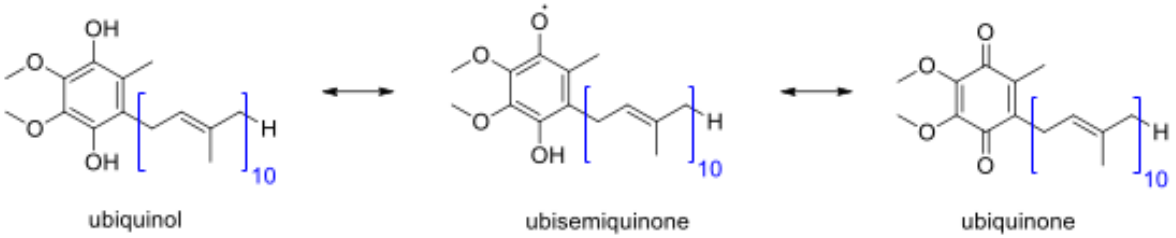

Figure 2. Three types of redox states of Coenzyme Q10.

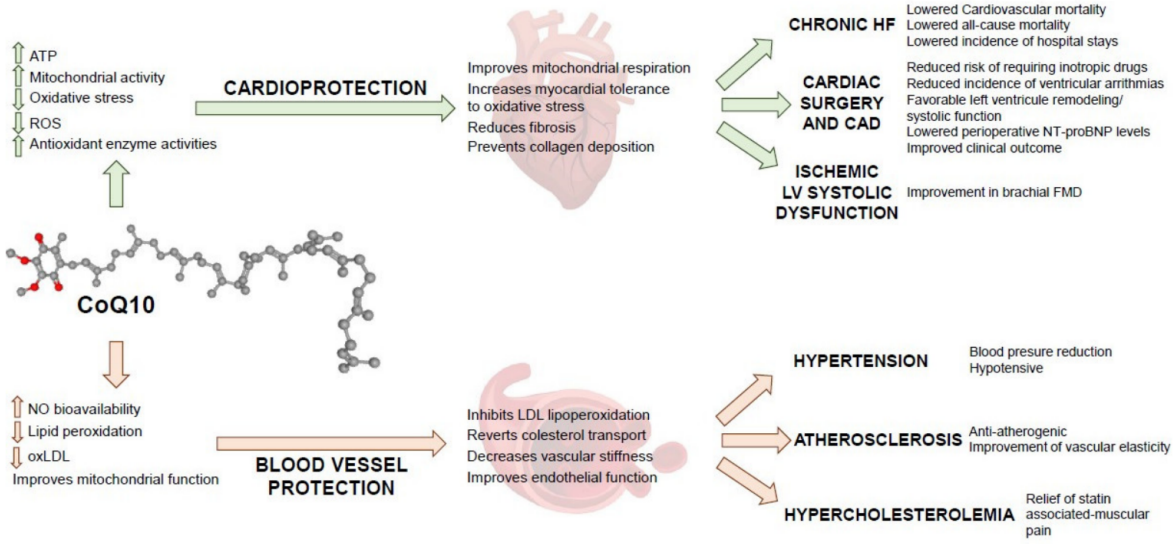

Figure 3. Schematicmechanism demonstrating the beneficial effect of CoQ10 in cardiovascular disease. CAD: coronary artery disease; ATP: adenosine triphosphate; LDL: low-density lipoprotein; NO: nitric oxide; NT-proBNP: N-terminal prohormone BNP; ROS: reactive oxygen species; FMD: flow-mediated dilation; (Adopted under CC BY from (Rabanal-Ruiz et al., 2021))

Table 1
Plasma level of CoQ10 supplementation in different cardiac conditions.

Diseases	Dose(mg/day)	Plasma CoQ10 levels before treatment (mg/ml)	Plasma CoQ10 levels after treatment (mg/ml)	Reference
Hypertrophic cardiomyopathy	240	-	1.5 - 4.7	(Langsjoen & Langsjoen, 2008)
Coronary artery bypass graft surgery	300	0.38 ± 0.083	2.61 ± 0.47	(Hadj et al., 2006)
Coronary artery disease	300	0.63 + 0.03	2.79 + 0.34	(Tiano et al., 2007)
Type 2 diabetes (blood pressure)	200	0.95	2.93 ± 0.26	(Hodgson et al., 2002)

One of the first apparent symptoms of myocardial insufficiency is diastolic dysfunction, which plays a substantial role, accounting for approximately 30% to 50%, of instances of heart failure. This impairment further resulted in to enlargement of the left ventricle. In recent studies, researchers have established a noteworthy correlation between plasma CoQ10 concentration and mortality risk in individuals with chronic heart failure. Notably, a deficiency in CoQ10 has emerged as an independent factor that adversely impacts the long-term diagnosis of severe cardiac failure (Molyneux et al., 2008). Lei et al. conducted a comprehensive review of clinical trial meta-analyses focused on the role of CoQ10 in heart failure (Lei & Liu, 2017). Their results indicate that CoQ10 therapy improved cardiac index, stroke volume, and cardiac output. Their findings indicated that treatment with CoQ10 led to improvements in cardiac output, cardiac index, and stroke volume. As a result, they recommend daily CoQ10 supplementation in the range of 150 to 300 mg for patients experiencing symptomatic heart failure. Furthermore, they suggest monitoring CoQ10 blood levels alongside clinical responses (Villalba et al., 2010). A current study has highlighted that severe heart failure patients experience increased absorption of CoQ10 in its reduced form, rather than the oxidized form. Importantly, improvement in left ventricular function and clinical improvements are both tightly correlated with rising plasma CoQ10 levels (Langsjoen & Langsjoen, 2008) (Table 1). Hadj et al. investigated several stress factors prior to cardiac surgery, incorporating a regimen of 300 mg daily CoQ10 dosing combined with additional antioxidants. This treatment-receiving group exhibited noteworthy enhancements in quality-of-life questionnaire scores when compared to their preoperative baseline (Hadj et al., 2006). Additionally, CoQ10 has shown promise in addressing hypertension and enhancing endothelial function in patients treated with statins or fibrates for type 2 diabetes. The administration of 200 mg/day of CoQ10 led to enhanced endothelial function and better long-term glycemic control among individuals with type 2 diabetes. Consequently, this resulted in lowered blood pressure levels. However, studies also showed that these improvements were not associated with a minimization of oxidative stress (Hodgson et al., 2002; Playford et al., 2003; Watts et al., 2002).

3.1.1 *Fibrosis*

Fibrosis is a typical adaptive reaction to tissue damage and is crucial to the healing and tissue repair processes (Murtha et al., 2017). The development of fibrosis involves stimulated fibroblasts producing collagen-rich fibrous connective tissue. Despite stem cell transplant may offer an acceptable therapeutic, there are momentarily insufficient therapies for this condition (Fujimoto et al., 1993). CoQ10 plasma levels reported with significantly reduced in minority pulmonary fibrosis patients (Sugizaki et al., 2019). Liu et al. demonstrated treatment with CoQ10 improved the outcomes of lung basal stem cell transplantation in rat models with idiopathic lung fibrosis induced by bleomycin (Liu et al., 2022). Idebenone, a CoQ10 analog was reported with its beneficial effect of lowering lung fibroblast activation induced by bleomycin. Sugizaki et al. the effect of idebenone against pulmonary fibrosis. To evaluate the effect, two cell lines, named LL29 and A549 were used to check the viability of the cell. It was found that on the administration of a lower concentration of idebone, cell death was prominent in LL29 as compared to A549. At the concentration 75-1of 25 μM, the inhibition of cell growth was observed wherein the higher dose leads to cytotoxic action on LL29. When pulmonary fibrosis was induced by bleomycin, idebenone showed significant suppression of the same (Sugizaki et al., 2019). This indicates that idebenone has a huge impact and further research should focus on it for the management of cardiac-related problems.

3.1.2 *Hypertension*

CoQ10 is a naturally occurring biomolecule that possesses antioxidant and anti-inflammatory characteristics. It plays a vital role in cellular energy production and aids in the mitigation of detrimental free radicals within the body. Oxidative stress is a significant determinant in the development of hypertension. The antioxidant capabilities of CoQ10 may potentially assist in alleviating stress and promoting cardiovascular well-being. (Wang & Kang, 2020). Many studies show that CoQ10 improves vascular function and promotes vasodilation and the dilation of blood vessels (Rabanal-Ruiz et al., 2021). FL Rosenfeldt et al. reported that CoQ10 prescribed to patients in a meta-analytical crossover study, can reduce blood pressure to 17 mm Hg and diastolic blood pressure to 10 mm Hg without serious side effects through its response

to blood pressure. The fundamental use of CoQ10 as a complementary therapy alongside traditional antihypertensive medications, might enhance the effect of these medications or help to reduce some of their adverse effects (Rosenfeldt et al., 2007). This becomes essential to consider that while there is some promising research, the evidence supporting CoQ10 as a standalone treatment for hypertension is not yet strong enough for it to be recommended as a primary treatment. More high-quality clinical trials are needed to establish its effectiveness and determine optimal dosage forms.

3.1.3 Ischemic heart disease

Ischemic heart disease, also known as coronary artery disease (CAD), is a condition where the heart muscle receives less blood due to narrowing or blocked coronary arteries. The possible application of CoQ10 in managing coronary artery disease has been well-reported. CoQ10 is an essential component of the cellular energy production process (ATP synthesis) and functions as an antioxidant, protecting cells from oxidative stress. Ischemic heart disease involves damage to heart tissue due to reduced blood flow, which can lead to oxidative stress and energy depletion. Antioxidant abilities and function in cellular energy generation of CoQ10 may be able to lessen some of this harm (Martelli et al., 2020). The possibility remains as CoQ10 can enhance endothelial function, which is crucial for maintaining strong blood vessels. Improved endothelial function can help with vasodilation, reducing the workload on the heart and potentially improving blood flow to the heart muscle. Participants in an investigation study examined the impacts of oral CoQ10 supplementation at a dose of 100 mg on the endothelium-dependent vasodilatation activity of extracellular superoxide dismutase (ecSOD) diagnosed with CAD. 38 CAD patients were enrolled of which 19 patients have received a 300 mg/kg dose of CoQ10 for 30 days. The results showed that the group receiving CoQ10 treatment exhibited significantly greater endothelium-dependent relaxation in contrast with those treated with placebo (Tiano et al., 2007). Lee B.J et al. confirmed cardioprotective effects of CoQ10 matched its plasma levels to malondialdehyde levels and the antioxidant activity of glutathione peroxidase, catalase, and superoxide dismutase (Bor-Jen et al., 2012). Glutathione catalase exhibited and peroxidase a positive association with CoQ10 plasma level, but malondialdehyde level and superoxide dismutase had a negative correlation. In addition, giving CoQ10 (150 mg/day) to CAD patients appears to lower their IL-6 levels. This finding reveals its ability to reduce inflammation The high concentration of CoQ10 has a positive relation with minimising the risk of CAD and hence the trial supports the use of CoQ10 (Lee et al., 2012).

3.1.4 Myocardial infarction

CoQ10 is being examined for a possible application in treating myocardial infarction., sometimes referred to as a heart attack. During an episode, oxidative stress has significantly increased due to damage to heart tissue and the fall in blood flow. CoQ10's antioxidant effects could potentially help mitigate some of this oxidative damage and support cell survival. To produce ATP, the electron transport chain in mitochondria needs CoQ10 (Deichmann et al., 2010). Eleawa et al. utilize CoQ10 as a useful preventative measure against myocardial infarction (MI) and MI-induced cardiac alterations. The clinical trial was performed using a rat model separated into six different groups. It was noticed that the combination of resveratrol (20 mg/kg) with CoQ10 (20 mg/kg) was more effective in reducing infarct areas and hemodynamic parameters They discovered that CoQ10 guards against myocardial infarction reinfarction. Additionally, it normalizes left ventricular hemodynamics after MI while reducing inflammation, infarct size, and oxidative stress (Eleawa et al., 2014). Since ATP serves a function in oxidative phosphorylation and the mitochondrial respiratory chain as an electron carrier, CoQ10 (ubiquinone) is necessary to prevent ATP depletion. (Liehn et al., 2011). Moreover, Huang C.H. and colleagues proposed that, during a follow-up period of 6 months, MI patients who exhibited high plasma levels of CoQ10 after having primary angioplasty lasting a month demonstrated improved left ventricular function. Additionally, Higher plasma concentrations of CoQ10 were linked to low oxidative stress and inflammation. Consequently, other investigations anticipated that systemic CoQ10 content may be used as a biomarker to predict left ventricular systolic function following MI revascularization treatment. It's crucial to emphasize that while there are promising indications, CoQ10 should not replace or delay seeking medical attention during a heart attack. Time is of the essence, and immediate medical care is critical for minimizing damage to the heart muscle and improving outcomes (Huang et al., 2016).

3.1.5 Heart Failure

Heart failure happens when the cardiac capacity is impaired and does not pump blood sufficiently to satisfy the needs of the body. CoQ10 has been investigated for its possible usefulness in treating heart failure. The potential of cardiac muscle to produce energy gets weakened in heart failure. CoQ10 supplementation could potentially enhance energy production in heart cells and improve their working, such as increased ejection fraction (the volume of blood that is released with each heartbeat) and improved exercise tolerance. Millions of patients throughout the world receive HF diagnoses each year (Huang et al., 2016). Prior studies demonstrated that plasma levels of CoQ10 may not be a reliable indicator of mortality in individuals with heart failure (Molyneux et al., 2008). Heart failure patients who got CoQ10 treatment also showed decreased levels of inflammatory mediators (Kumar et al., 2009). CoQ10 supplementation enhances endothelial and mitochondrial functioning, which may prolong survival and lessen symptoms in HF patients. Additionally, it is stated that CoQ10 helps shield the myocardium from ischemia (Belardinelli et al., 2006; Soja & Mortensen, 1997). A subsequent research investigation revealed that administering

100mg of CoQ10 three times daily to people with heart failure increased their functional classification for the New York Heart Association (6-minute walk test) at the end of the trial (Schultheiss et al., 2019). According to these findings, a recent meta-analysis of 2149 individuals revealed that heart failure patients who administered CoQ10 saw greater improvements in exercise tolerance and reduced death rates (McKenna et al., 2017).

3.1.6 Arrhythmias

After cardiac surgery, reperfusion arrhythmia has long been researched about myocardial injury. Arrhythmogenic oscillations in membrane potential are assumed to be mediated by reactive oxygen, whereas reperfusion damage is expected to be increased by oxygen-free radicals (Keith et al., 1998). CoQ10 is identified as a lipophilic antioxidant in biological membranes which inhibits lipid peroxidation. Biological membranes are protected from lipid peroxidation by the lipid-soluble antioxidant CoQ10, which also supplies ATP for cell synthesis, the primary source of energy of organisms. This procedure shows how CoQ10 aids in membrane stabilization and prevents crucial metabolite depletion that may be related to reperfusion arrhythmia. Additionally, it is suggested that its impact may be connected to a decrease in malondialdehyde levels, this can minimize the prevalence of atrial fibrillation (AF) (Tanaka et al., 2007). CoQ10 treatment for 12 months at a dosage of 30 mg/d in HF patients reduced the occurrence of cardiac arrest, according to a randomized controlled clinical study done by Tanaka T. et al. (Tanaka et al., 2007). Supplementing with CoQ10 also helped individuals with ventricular premature beats. Additionally, CoQ10 treatment stops QT-interval lengthening in those with acute myocardial infarction (Kumar et al., 2009).

3.1.7 Cardiomyopathy

Cardiomyopathy is a disorder that causes the heart muscle to expand, thicken, or weaken. In cardiomyopathy, the heart muscle ability to generate energy might be compromised. CoQ10 supplementation could potentially enhance energy production in heart cells, which might contribute to improved cardiac function. Cardiomyopathy is also associated with oxidative stress, Which could end in severe cardiac tissue damage. (Şeneş et al., 2008). Based on the study of Kumar A. et al. antioxidant effects of CoQ10 might help mitigate this damage and support overall heart health. The reduction of inflammation, failure of the left ventricle, inflammatory substances, and ventricular thickening by CoQ10 has been demonstrated in studies in rodent models of cardiomyopathy. As a result, an improved fraction of ejection in dilated cardiomyopathy can be seen in patients taking CoQ10 supplements. A daily dosage of 200 mg of CoQ10 also improves NYHA class, quality of life, regurgitation of the mitral valve, the 6-minute walk test, and diastolic dysfunction in those with hypertrophic cardiomyopathy (Kumar et al., 2009).

3.1.8 Viral myocarditis

Inflammation of the heart muscle (myocardium) brought on by viral infections is the hallmark of the disorder known as viral myocarditis. Even though there is continuing study into prospective therapies, such as using CoQ10 (Imazio & Cooper, 2013). In viral myocarditis, the immune response to the viral infection promotes inflammation and oxidative stress, leading to energy depletion in heart cells, which might contribute to myocardial damage. The way the immune system responds to viral infections is modulated by CoQ10 because it possesses immune-modulating properties. By modulating the immune response, CoQ10 might contribute to reducing inflammation in the heart muscle (Frustaci et al., 2003; Nakamura et al., 2013). The positive impacts of CoQ10 have been verified by Shao Liang et al. and trimetazidine when used separately, but it also showed that the two therapies for myocardial infarction, acute ventricular fibrillation, or potentially fatal arrhythmias worked better when used together to treat acute viral myocarditis' biochemical indicators of myocardial damage and cardiac left ventricular ejection fraction (LVEF) (Shao et al., 2016).

3.1.9 Dyslipidaemia

Triglycerides and cholesterol levels that are unusually high in the blood are referred to as dyslipidemia. When treating conditions characterized by excessive cholesterol, medications that inhibit 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase activity are frequently employed (Hong et al., 2006). Additionally, certain antioxidant effectors and vasoactive nitric oxide are inhibited by this class of medications (Asahi et al., 2005). It should be noted that the mevalonate route, which is used in both the manufacture of CoQ10 and cholesterol, is comparable. As a result, by lowering the concentration of farnesyl pyrophosphate, HMG-CoA reductase inhibitors interrupt CoQ10 and cholesterol synthesis (Folkers et al., 1990). Because the endogenous level of CoQ10 declines over time, the depletion of CoQ10 in the elderly is quite essential (Pepe et al., 2007). Statins are HMG-CoA reductase inhibitors and may lower CoQ10 concentrations by as much as forty percent. Heart failure patients should stay away from this effect. Patients who have heart failure should avoid this impact (Pepe et al., 2007).

3.1.10 Cardiotoxicity

Cardiotoxicity refers to the damage caused to the heart by certain drugs, chemicals, or medical treatments. Cardiotoxicity often involves oxidative stress, where the balance between harmful reactive oxygen species and antioxidants is disrupted. antioxidant properties of CoQ10 could help restore this balance and reduce oxidative stress-induced damage. CoQ10 has been investigated as a possible additional treatment for several chemotherapy regimens to help mitigate the cardiotoxic effects of chemotherapy drugs. Chemotherapy agents can negatively impact heart function, and CoQ10 might offer some protection against these effects. The anthracycline antibiotic family represents a category of medications employed

in chemotherapy. These drugs are frequently utilized in the medication applicable to various tumor types, including solid tumors such as sarcomas, and carcinomas, and hematological tumors including leukemias and lymphomas. Arguably the most significant and widespread adverse effect of anthracyclines is cardiotoxicity (Conklin, 2005). During the early stages of breast cancer therapy, doxorubicin finds application, and it has demonstrated the potential to enhance overall survival rates. Nonetheless, some individuals may encounter adverse effects, such as cardiomyopathic abnormalities and congestive heart failure. Theoretically, these anomalies might be triggered by a boost in reactive oxygen species (ROS) production. CoQ10 is further well recognized for its ability to safeguard mitochondria against ROS damage and has been considered as an adjuvant therapy to mitigate adverse effects of doxorubicin. However, current evidence suggests that CoQ10 did not influence the cellular damage caused by doxorubicin, indicating the need for further research in this area (Bor-Jen et al., 2012). Subsequently, Mustafa H.N. and colleagues reported that the dosing of doxorubicin, along with L-carnitine, and CoQ10 yielded notable improvements in cardiac performance within five days. This treatment regimen also led to reductions in the levels of Troponin-T, Troponin-I, TNF-α, and IL-1, Furthermore, by lowering the levels of nitric oxide and malondialdehyde, it offered safeguards from oxidative stress. Hence, the combined use of L-carnitine and CoQ10 holds the potential for safeguarding muscle tissues (Mustafa et al., 2017).

3.1.11 Cardia arrest

Cardiac arrest includes the abrupt collapse of heart function, leading to an abrupt cessation of blood circulation, and needs intensive medical emergency. During cardiac arrest, the heart stops pumping blood, and immediate medical intervention is necessary to restore circulation and prevent severe damage to vital organs, including the brain. The standard approach to managing cardiac arrest involves cardiopulmonary resuscitation (CPR) and, if available, defibrillation for the restoration of regular cardiac rhythm. These interventions are critical to providing blood flow to the body and oxygen to the brain while emergency medical services are on their way (Zhen et al., 1994). CoQ10 may be essential during cardiac arrest and avoid reperfusion problems, according to animal studies (Mori & Mohri, 1985; Zhen et al., 1994). After CPR, Damian MS et al. systematically randomized 49 patients to either hypothermia along with supplementation of CoQ10 or hypothermia along with a placebo. In the CoQ10 group, 17 among 25 (68%) people survived three months, compared to nearly thirty percent (7 from 24) given a placebo (P = 0.0413) in the group. Five placebo and nine CoQ10-receiving individuals both had survival rates of 4 or 5 on the Glasgow Outcome Scale. In an ongoing observational examination of post-arrest patients, CoQ10 levels were found to be an independently significant indicator of having poor neurocognitive performance (Cocchi et al., 2012; Damian et al., 2004). These results support earlier research that determined its importance in septic and ischemic shocks (; 2015) (Donnino et al., 2011; Shen et al., 2014). This highlights the need for metabolic recovery, particularly when managing septic shock, though it may also be helpful during other circumstances with substantially changing the flow of blood within the organs and tissues of the body (Leite & Lima, 2016).

3.2. Mitochondrial Disorder:

Mitochondrial dysfunctions are recognized as the root cause of various clinical conditions characterized by diverse multi-systemic manifestations. The primary factor contributing to these disorders is the compromised oxidative phosphorylation process, which results in a reduction in cellular energy production, specifically ATP generation (Thangaraj et al., 2015). Although CoQ10 has demonstrated favorable effects and enjoys widespread utilization in the context of mitochondrial diseases, there is still a notable absence of controlled trials involving substantial patient populations. The supplementation of CoQ10 has yielded encouraging outcomes, particularly in individuals with either primary or secondary CoQ10 deficiencies. Therefore, it is recommended that this approach be considered for all patients exhibiting reduced CoQ10 levels (Quinzii & Hirano, 2010; Tarnopolsky & Raha, 2005). L-arginine is categorized as a semi-essential amino acid, playing essential roles in processes such as growth, urea detoxification, and the synthesis of creatine. In an initial, limited-scale investigation, it was observed that the intravenous administration of L-arginine at a dosage of 500 mg per kilogram per dose along with CoQ10 may minimize the severity of stroke-like symptoms, improvement in microcirculation dynamics, and a decrease in tissue damage caused by ischemia in individuals diagnosed with mitochondrial disorders (Cleren et al., 2008).

4. CLINICAL EVIDENCE IN COQ10 SUPPLEMENTS IN HEART FAILURE:

There are various clinical trial has been done on CoQ10 supplements in patients having congestive heart failure, which is given below in Table 2.

Numerous trials have reported significant improvements in functional status, as assessed by the New York Heart Association (NYHA) classification, following CoQ10 supplementation (Baggio et al., 1994; Hofman-Bang et al., 1995; Langsjoen & Langsjoen, 2008; Morisco et al., 1993; Permanetter et al., 1992; Rengo et al., 1993; Watson et al., 1999) (Table 2).

Table 2
Clinical trials demonstrating the Potential effect of CoQ10 in various on different cardiac conditions

Disease	Patients enrolled	Trial design	CoQ10 dose and duration	Key points	Reference
Hearth failure	18	Double-crossover and double-blind trial	Three-month therapy of CoQ10 33mg three times per day	• Improvement in stroke volume ejection fraction ($p < 0.0001$)	(Langsjoen & Langsjoen, 2008)
Idiopathic dilated cardiomyopathy	25	A placebo-controlled, double-blind crossover trial	Three-month therapy of CoQ10 30mg four times per day	• LVEF (at rest and during exercise) showed no significant variation • No change on ECG • LVESD and LVEDD remained unchanged • No significant differences in CI (Cardiac Index) and SV (Stroke Volume) • No change in CT ratio, cardiac arrhythmias, exercise tolerance	(Permanetter et al., 1992)
Heart Failure with Reduced Ejection Fraction	641	Double-blind placebo-controlled trial	One year therapy of CoQ10 50 mg twice or thrice a day	• Reduced hospitalization • Decline in pulmonary edema episodes • Decline in cardiac asthma episodes	(Morisco et al., 1993)
NYHA class: III, Heart Failure with Reduced Ejection Fraction,	60	Single-blind placebo randomized trial	Seven months of therapy of CoQ10 100 mg	• The CoQ10 group showed a significant increase in LVEF by 15.79%, while the placebo group decreased by 2% compared to baseline ($p < 0.001$). • Both CoQ10 and placebo groups exhibited a decrease in LVESD (CoQ10: 2%, placebo: 0.16%), with $p < 0.001$. • CoQ10 group displayed an increase in FS by 15.6%, whereas the placebo group decreased by 2.19% ($p < 0.001$).	(Rengo et al., 1993)
NYHA class: II and III , Hearth failure,	2664	Open, non-comparative trial	Three-month therapy of CoQ10 50–150 mg	• Improvements in respiratory rate, heart rate, cardiac pressure, and clinical symptoms • 52 % population of patients reported improvement in at least three symptoms	(Baggio et al., 1994)
Stable Heart Failure with a lower level of Ejection Fraction	79	Double-blind, crossover placebo-controlled trial	Three-month therapy of CoQ10 50 mg thrice a day	• Improvement in ejection fraction • Enhancementn maximal exercise capacity and total score for quality of life (QoL)	(Hofman-Bang et al., 1995)

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Table 2 continued

Heart Failure with Reduced Ejection Fraction (mixed pathogeneses)	30	Double-blind, crossover placebo-controlled trial	Three-month therapy of CoQ10 33 mg thrice a day	• No improvement in ejection fraction, • No change in left ventricular diastolic and systolic volume, and QoL scores	(Watson et al., 1999)
NYHA class: III or IV , Heart Failure with Reduced Ejection Fraction,	55	Randomized, double-blind placebo-controlled trial	Six-month therapy of CoQ10 200 mg	• Maximal oxygen consumption showed no significant difference in the CoQ10 group. • Radionuclide Ventriculography revealed no difference in EF compared to baseline.	(Khatta et al., 2000)
NYHA class: II or III , Heart Failure with Reduced Ejection Fraction (mixed pathogeneses)	39	Randomized, double-blind placebo-controlled trial	Three-month therapy of CoQ10 50 mg 50 mg thrice a day	• Improvement in NYHA score • No improvement in Canadian-specific activity scale score, 6-minute walk test, or Fractional Shortening.	(Keogh et al., 2003)
Heart Failure with Reduced Ejection Fraction	32 patients awaiting heart trans-plantation	Randomized controlled trial	Three-month therapy of CoQ10 60 mg twice a day	• Improvement in NYHA class and the 6-minute walk test • No change in Fractional Shortening.	(Berman et al., 2004)
Idiopathic dilated car-diomyopathy	15	Open-label prospective study	Three month therapy of CoQ10 3.1 ± 0.6 mg/kg	• Significant improvement in NYHA functional class, CT Ratio, QRS duration	(Soongswang et al., 2005)
NYHA class II and III , Heart failure (secondary to ischemic heart disease),	23	Double-blind, placebo-controlled crossover trial	Four-week therapy of CoQ10 100 mg orally four times per day	• Significant improvement in peak VO2 and resting LVEF • Enhanced endothelium-dependent dilation of the brachial artery.	(Belardinelli et al., 2006)
Idiopathic dilated car-diomyopathy	38	Double-blind placebo-controlled trial	Six-month therapy of CoQ10 2 mg/kg	• Cardiac index improved • Improvement in ejection fraction. • FS also showed enhancement following CoQ10 supplementation.	(Kocharian et al., 2009)
50% stenosis of one major coronary artery	51 patients treated with a statin for the last 1 month	Randomized placebo-controlled trial	Twelve-week therapy of CoQ10 300 mg	• Elevated level of CoQ10 in plasma • Antioxidant enzyme activities showed improvement. • Decline level of inflammatory markers	(Lee et al., 2013)

Continued on next page

Table 2 continued

NYHA class: II-IV, Heart Failure with Reduced Ejection Fraction (mixed pathogeneses)	62	Randomized double-blind placebo-controlled trial	Four-month therapy of CoQ10 100 mg two times daily with atorvastatin 10 mg	• Improvement in ejection fraction. • NYHA classification also showed improvement in the CoQ10 group.	(Pourmoghaddas et al., 2014)
NYHA class: I–II, Heart Failure with Reduced Ejection Fraction (mixed pathogeneses)	420	Randomized double-blind placebo-controlled trial	Two-year therapy of CoQ10 100 mg orally thrice a day	• Reduction in risk of death. • Reduced risk of the composite risk outcome • No change in 6 minute walk test	(S.A. Mortensen et al., 2014)
Heart failure	102	Randomized double-blind, placebo-controlled trial	One year therapy of CoQ10 2 mg/kg divided tow or three daily dose	• Significant reduction in inflammatory markers. • Improvement in LVEF • Decrease in Left ventricular end-diastolic pressure	(Zhao et al., 2015)
Dilated Cardiomyopathy	10 children	Open-label trial	24 weeks therapy of Liquid ubiquinol supplementation 10 mg/kg	• Elevation of CoQ10 plasma level • Improvement in ejection fraction. • FS also showed improvement after ubiquinol supplementation.	(Chen et al., 2018)
healthy	443	Prospective randomized double-blind placebo-controlled trial	Four-year therapy of CoQ10 200 mg	• Reduced cardiovascular mortality.	(Alehagen et al., 2018)
Heart failure	420	Randomized double-blind placebo-controlled trial	Two-year therapy of CoQ10 300 mg	• Elevation of CoQ10 plasma level • NT-proBNP levels decreased with CoQ10 supplementation. • Improvement in LVEF	(A.L. Mortensen et al., 2013)
Heart Failure with Reduced Ejection Fraction	30	Single-center, unblinded randomized controlled trial	30-day therapy of CoQ10 100 mg thrice a day	• Reduction in the E/e' ratio. • Improvement was observed in LAVI • LVEF also improved after CoQ10 supplementation.	(Sobirin et al., 2019)

5. COQ10 DOSAGE AND SAFETY:

In clinical trials addressing heart failure (HF), CoQ10 dosages typically fell within the range of 60 to 300 mg per day, administered orally. In a specific study involving 143 HF patients classified as NYHA class III/IV, the administration of a daily dose of CoQ10 100 mg was reported with a 0.85 to 2 mg/L rise in the plasma level of CoQ10 plasma level. This rise in CoQ10 levels correlated with improvements in LVEF with functional improvement, all while reporting none of the adverse effects (Langsjoen et al., 1997). Therefore, the Q-SYMBIO trial adopted the most elevated level of CoQ10 achieved in previous trials, which was 2 mg/L. In this trial, participants received oral CoQ10 at a daily dosage of 300 mg. According to Keogh et al., CoQ10 concentrations of 3.25 ± 1.57 mg/L were achieved in the group, and this resulted in a substantial decrease in the pulmonary capillary pressure, pulmonary artery pressure, and stroke index compared to the placebo group (Keogh et al., 2003). Till now, there has been just a single randomized controlled trial (RCT) accomplished in individuals suffering from ischemic heart disease. In this trial, a CoQ10 dosage of 300 mg/day was administered for three months results of this investigation indicated a noteworthy decline in inflammatory markers., including TNF-α and IL-6 (Lee et al., 2013).

In a study characterized by a limited sample size (n = 7), Patients with advanced HF were the main subject of Langsjoen et al., and patients who had an average LVEF of 22% were classified as NYHA class IV. In this investigation, CoQ10 supplementation at a dosage of 900 mg/day in the ubiquinone form frequently fell short of attaining therapeutic levels in plasma, remaining below 2.5 mcg/mL. However, when these same patients were provided with the reduced form of CoQ10, which is ubiquinol at an average daily dosage of 450 mg, they reached therapeutic plasma levels exceeding 3.5 μg/mL. This shift to ubiquinol supplementation resulted in significant enhancements in EF, with an average increase of up to 39%, and an improvement in NYHA class, which on average transitioned from IV to II (Langsjoen & Langsjoen, 2008). The majority of examined trials had a duration of three months, with the longest CoQ10 supplementation period being two years in the Q-SYMBIO trial (S.A. Mortensen et al., 2014).

6. LIMITATIONS

Various promising health benefits of CoQ10 have improved consumer demand and also secured popularity in the cosmetic field. CoQ10 supplementation was also reported with low toxicity with few adverse effects in humans (Hidaka et al., 2008). However high hydrophobic physicochemical characteristics and high molecular weight of CoQ10 lead to a nearly insoluble nature in the aqueous phase (Williams, 2013). Research on the CoQ10 efficacy in CVD management has produced mixed results. While some studies suggest potential benefits, others fail to demonstrate significant improvements in cardiovascular outcomes. These inconsistencies make it challenging to establish a clear therapeutic role for CoQ10. The high hydrophobic character also slows the absorption from the small intestine which results in lower oral bioavailability formulation as the peak level in the blood occurs 5 to 10 hours (Miles, 2007; Pepping, 1999). Various CoQ10 formulations are in a clinical study with a range of strengths, periods, and dosages of CoQ10 creating confusion in comparing them and concluding the most effective medicament for therapeutic uses. Additionally oxygen, light, and heat can impact the stability of CoQ10 is one of the challenges that need to be overcome with alteration in the composition of supplementation (Fir et al., 2009).

7. CONCLUSION AND FUTURE PROSPECT

Coenzyme Q functions beyond just an intermediary for mitochondria energy transfer and also serves a specific function in each cellular membrane. This extended character is based in part on its antioxidant operation, which has a remarkable ability to replenish redox capacity and its unique position within the membrane structure. Endogenous CoQ10 synthesis delivers sufficient amounts of this quinone in healthy individuals. However, Chronic disorders, age-related diseases, as well as hereditary failure also contribute to CoQ10 insufficiency. One of the popular lipid-lowering drugs is statins which prescribed to patients with cardiovascular disease, suppress the production of endogenous CoQ10. It has been well established that CoQ10 can potentially be hired as a solution to address these inadequacies in this situation. Clinical evidence supports improvements in symptoms in cardiac patients. Improvements in cardiac index, stroke volume, and cardiac output have been reported after a dose of 150 to 300 mg of CoQ10 medical care in cardiac disorders. CoQ10 promises a secure beneficial therapeutic supplement in the management and treatment of cardiovascular disease. To incorporate CoQ10 supplements in the clinical directions for the medical management of patients with heart problems, an extensive effort needs to be undertaken to achieve consensus over the application of CoQ10.

CONFLICT OF INTEREST STATEMENT

No conflict of interest associated with this work.

ACKNOWLEDGMENTS

AZC wants to thanks his student Pankti Balar for her support in lieterature search.

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FUNDING

Obtained No funding support for this work.

AUTHOR CONTRIBUTIONS

AZC - Research concept and design; AZC - Collection and/or assembly of data; RS - Data analysis and interpretation; RS- Writing the article; MV, KP - Critical revision of the article; MV, KP - Final approval of the article.

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