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Coenzyme Q_{10}: Clinical Update and Bioavailability

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Abstract

Coenzyme Q_{10} (CoQ_{10}) supplementation has been reported to be beneficial in treating a variety of health conditions and diseases, with more than 200 clinical trials investigating its use as a drug or dietary supplement. Numerous reviews of the safety and clinical potential of CoQ_{10} have been published. Successful treatment and efficacy is dependent on the bioavailability of CoQ_{10}, which is well known to be poor because of its lipophilic nature and large molecular weight. A number of recent clinical trials on CoQ_{10} have investigated new formulations of CoQ_{10} for improvements in absorption and bioavailability. This review provides an update of clinical efficacy trials using CoQ_{10} and describes recent advances in formulation technology to improve the bioavailability of CoQ_{10}. The authors also discuss a new method to improve the standards of reporting the bioavailability results of such advanced CoQ_{10} formulations to help clinicians and consumers make informed decisions.

Keywords

coenzyme Q_{10}, cardiovascular diseases, neurodegenerative disorders, reproductive health, CoQ_{10}, periodontal disease, bioavailability

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Coenzyme Q_{10} (also known as CoQ_{10}, ubiquinone, ubidecarenone) is a lipid-soluble vitamin-like compound present in the inner membrane of the mitochondria of every cell of the body. The structure of CoQ_{10} consists of a benzoquinone ring and a lipophilic isoprenoid side chain. The length of the side chain varies among different organisms. In humans, the side chain is composed of 10 trans-isoprenoid units (Figure 1). CoQ_{10} plays 2 major roles in the body. In the mitochondria, CoQ_{10} is a vital coenzyme in the electron transport chain for the synthesis of ATP, the major source of cellular energy. CoQ_{10} is found at its highest levels in cells with high energy requirements such as heart, brain, liver, and kidney cells. The second function of CoQ_{10} is as an antioxidant, particularly in preventing lipid peroxidation.

CoQ_{10} is endogenously synthesized by a multistep process consisting of synthesis of the benzoquinone ring from tyrosine or phenylalanine, synthesis of the isoprenoid side chain via the mevalonate pathway, and condensation of the two to form CoQ_{10} (Figure 2). The mevalonate pathway also leads to the synthesis of cholesterol among other end products. The formation of mevalonate from 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) by HMG-CoA reductase is the rate-limiting step in the mevalonate pathway. The biosynthetic pathway involves multiple enzymes, cofactors, vitamins, and trace minerals. The complexity of the pathway suggests that any defects in the enzymes, cofactors, or dietary nutrient deficiencies can impair the biosynthesis of CoQ_{10}. Cellular production of CoQ_{10} drops during aging.[1] Whereas CoQ_{10} occurs in some food, the dietary sources with the highest levels of CoQ_{10}, such as organ meats, are still at insufficient levels to make up for the lowered production associated with aging. The normal blood level of CoQ_{10} ranges from 0.5 to 1.65 μg/mL.

CoQ_{10} deficiencies have been seen in patients with a variety of diseases and health conditions such as heart disease,[2] hypertension,[3] Parkinson's disease,[4] some cancers,[5] periodontal disease,[6,7] asthma,[8] and human immunodeficiency virus (HIV) infection.[9] Individuals taking cholesterol-lowering statin drugs also have reduced levels of CoQ_{10} since these drugs block the synthesis of CoQ_{10}.[10] CoQ_{10} deficiency can also be due to mutations in genes directly or indirectly involved in CoQ_{10} biosynthesis. Such primary deficiency states are rare but result in severe disorders for which CoQ_{10} supplementation is beneficial.[11] Other conditions in which CoQ_{10} deficiency has been reported, such as inherited or acquired mitochondrial

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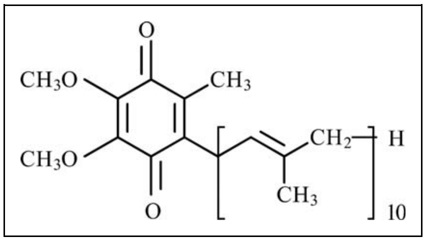

Figure 1. Structure of CoQ_{10}.

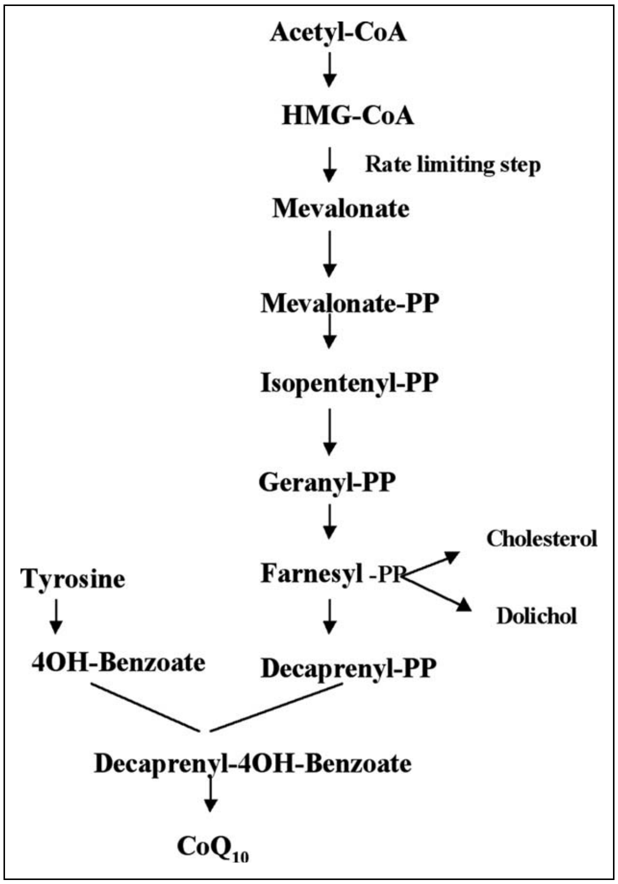

Figure 2. Metabolic pathway for the biosynthesis of CoQ_{10}. Abbreviations: PP, pyrophosphate; CoA, coenzyme A.

myopathies and neuromuscular conditions, also benefit from supplementation. CoQ_{10} supplementation can have a favorable effect on diseases or conditions such as migraines, diabetes mellitus, certain neurological disorders, and renal failure, all of which are not directly linked to CoQ_{10} deficiency. Table 1 presents an overview of the clinical applications of CoQ_{10}.

CoQ_{10} is a highly lipophilic molecule and practically insoluble in water. The absorption and transport of CoQ_{10} appears to be similar to other lipophilic compounds such as vitamin E. Exogenous CoQ_{10} is absorbed in the small intestine and enters the circulation via the lymphatic system. Before absorption, CoQ_{10} is converted to the reduced form ubiquinol by the enterocytes. Nearly 95% of plasma CoQ_{10} is present as ubiquinol in healthy individuals. The proportion of ubiquinol is not altered by oral ingestion of either CoQ_{10} (ubiquinone) or ubiquinol.[12]

Table 1. An Overview of Clinical Applications of CoQ_{10}

Primary CoQ_{10} deficiencies
Mitochondrial myopathies
Neurodegenerative disorders
Parkinson's disease
Amyotrophic lateral sclerosis
Huntington's disease
Progressive supranuclear palsy
Cardiovascular diseases
Chronic heart failure
Arteriosclerosis
Cardiomyopathy (dilated and hypertrophic)
Hypertension
Valvular heart disease
Arrhythmias
Ischemic heart disease
Statin therapy
Periodontal disease
Cancer
Reproductive health
Sperm count and motility
Pre-eclampsia
Diabetes
Asthma
Renal failure
Skin protection
Migraine
HIV/AIDS

Clinical Efficacy of Supplementation

CoQ_{10} has been implicated as a potential therapy for a large number of health conditions and diseases, especially those that result from reduced mitochondrial function. Clinical applications for CoQ_{10} have been the topic of a number of recent published reviews. Since the amount of published CoQ_{10} clinical trials is growing rapidly, we present a summary of recent reviews as well as update them with new clinical findings not covered in the reviews.

Neurodegenerative Disorders

CoQ_{10} treatment of neurodegenerative diseases was the topic of a comprehensive review of clinical trials by Galpern and Cudkowicz.[13] The authors state that CoQ_{10} can slow the progression of numerous neurodegenerative diseases, especially those in which their etiology involves impaired mitochondrial function and oxidative stress. Whereas definitive efficacy trials have not been completed, pilot studies, dosage findings, and safety studies have been completed evaluating CoQ_{10} in amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, and progressive supranuclear palsy. CoQ_{10} appears to be safe and well tolerated, allowing further investigation of clinical efficacy. As of this writing, many clinical trials are ongoing or in the recruitment stage. Another review also concluded that there are extensive preclinical studies supporting CoQ_{10} supplementation as a neuroprotective therapy and that phase III clinical trials are needed. CoQ_{10} has been shown to be safe at up to levels of 3000 mg/d in amyotrophic lateral sclerosis patients with the most common side effect being mild gastrointestinal discomfort occurring in less than 1% of subjects. Currently, no absolute contraindications to the use of CoQ_{10} exist. The authors also state that the therapeutic range of CoQ_{10} in neurodegenerative diseases could be much higher than the doses that have been studied, especially since the central nervous system bioavailability of oral CoQ_{10} is unknown.[14]

A review published in early 2010 examining the role of CoQ_{10} in clinical practice in treatment of neurodegenerative disorders reported results from the most recent clinical trials on supplementation for treating such disorders. CoQ_{10} has been shown to be safe and well tolerated in Parkinson's disease patients (up to 1200 mg/d) but did not result in symptomatic effects on midstage Parkinson's disease. CoQ_{10} was also well tolerated in Huntington's disease patients and can slow the decline in total functional capacity over 30 months at dosages of 600 mg/d. A recently completed phase II clinical trial for treating amyotrophic lateral sclerosis reported finding no significant difference between 2700 mg/d CoQ_{10} and placebo. The authors conclude that while CoQ_{10} treatment elicits some efficacy in a number of mitochondrial and neurological disorders, additional studies are still required before CoQ_{10} can be universally accepted for treatment of these disorders.[11] In an update of their previous review of the clinical applications of CoQ_{10}, Littarru and Tiano[15] described positive results of clinical trials where the common biochemical feature is the evidence of oxidative stress, damage, and mitochondrial respiratory chain dysfunction, such as in Friedrich's ataxia, Parkinson's disease, and progressive supranuclear palsy. In a recently completed clinical trial, the Huntington Study Group reported that dosages of 2400 mg/d can provide the best balance between tolerability and blood levels achieved in Huntington's disease patients and healthy individuals.[16]

Cardiovascular Diseases

Several studies have shown that CoQ_{10} can be useful as an adjuvant therapy in patients with various cardiovascular diseases such as chronic heart failure, arteriosclerosis, cardiomyopathy (dilated and hypertrophic), hypertension, valvular heart disease, arrhythmias, and ischemic heart disease.

The cardiovascular effects of CoQ_{10} have been ascribed to its bioenergetic role, its capability of antagonizing oxidation of plasma low-density lipoproteins, its regulation of cell membrane channels, and its effect in ameliorating endothelial damage, specifically by improving endothelial function. Improvement in endothelial function was seen in a double-blind, randomized, controlled study of patients with ischemic heart disease. Treatment with 100 mg of CoQ_{10} 3 times per day showed a significant improvement in extracellular superoxide dismutase activity. Trials have also shown improvement in exercise tolerance and beneficial effects in ischemic heart disease, arrhythmias, and following cardiac surgery. However, most of the trials used a small number of patients with a short duration of treatment; therefore, further research is needed. Clinical studies have also confirmed the protective role of CoQ_{10} in coronary artery bypass surgery. Patients treated preoperatively with CoQ_{10} showed significantly fewer postoperative complications and shorter hospitalization compared with a control group.[2,15]

A number of clinical trials indicate that CoQ_{10} supplementation is beneficial for some patients with hypertension. A review of 3 double-blind, randomized, placebo-controlled parallel or crossover trials evaluating the blood pressure lowering efficacy of CoQ_{10} supplementation concluded that it is uncertain whether or not CoQ_{10} supplementation reduces blood pressure in long-term management of primary hypertension.[17] Wyman et al[18] reviewed 9 clinical trials assessing the efficacy and safety of CoQ_{10} in patients with hypertension and concluded that CoQ_{10} is safe and well tolerated and does appear to lower blood pressure with a typical dosage of 120 to 200 mg given orally in 2 divided doses. Possible mechanisms include antioxidant effect; ability to boost prostacyclin (PGI_2), a potent vasodilator and inhibitor of platelet function; and potential to enhance the sensitivity of arterial smooth muscle to prostacyclin (PGI_2).

Statin Therapy

Statins reduce the synthesis of mevalonate, a key intermediate in the biosynthesis of cholesterol and CoQ_{10}. Whereas very efficient in reducing serum low-density lipoprotein and cholesterol levels, statin therapy carries a risk of myopathy and other adverse effects such as neuropathy and liver damage. Statin myopathy, usually in the form of mild to severe muscle pain or soreness, is the most common adverse effect in patients taking statin drugs. The major theory behind this side effect is that statin therapy reduces CoQ_{10} levels in the muscle mitochondria, leading to muscle injury.[19] In addition, statins are reported to reduce CoQ_{10} levels in serum and lymphocytes. Several studies have shown that supplementation restores the serum CoQ_{10}. However, the effects of supplementation on intramuscular CoQ_{10} levels are not clear. Some articles indicate that statin treatment can result in subclinical cardiomyopathy and is reversed by CoQ_{10} supplementation.[20]

Several studies have reported contradictory results on the effects of supplementation on myopathic symptoms. In a recent multinational study involving 1191 patients with ischemic systolic heart failure, McMurray et al[21] reported that treatment with rosuvastatin did not result in muscle symptoms and was not associated with an increased risk of adverse events such as death due heart failure or heart failure hospitalization. The overall consensus is that there is not enough present evidence to support routine use of CoQ_{10} until larger scale studies have been completed. However, there are no known risks to CoQ_{10} supplementation and there is some anecdotal and preliminary trial evidence of its effectiveness.[18,19,22]

Reproductive Health

CoQ_{10} concentrations in human seminal fluid have been shown to be directly correlated to seminal parameters such as sperm count and motility and inversely associated with oxidative stress.[23] Balercia et al[24] studied the effect of CoQ_{10} supplementation in patients with idiopathic asthenozoospermia. Following treatment, levels of CoQ_{10} and its reduced form, ubiquinol, increased significantly in both the seminal plasma and sperm cells and also improved sperm motility. Safarinejad[25] also investigated the efficacy of CoQ_{10} supplementation on semen parameters and sperm function, as well as reproductive hormone profiles, in infertile men. Treatment with 300 mg of CoQ_{10} for 26 weeks produced significant improvements in sperm density and motility, and a positive correlation was found between treatment duration and sperm count and motility. CoQ_{10} therapy also significantly decreased serum follicle-stimulating hormone and luteinizing hormone levels.

Pre-eclampsia (toxemia) is a condition in pregnant women and is marked by high blood pressure, edema, and proteinuria. The pathogenesis of pre-eclampsia is still not fully understood. The condition is associated with oxidative stress, antioxidant imbalance, and impaired production of vasoactive eicosanoids such as thromboxane (vasoconstrictor) and prostacyclin (vasodilator).[26]

Teran et al[27] reported that in pregnant women with pre-eclampsia there is a significant decrease in plasma levels of CoQ_{10} compared with normal pregnant women. In a recent study, Roland et al[26] determined the plasma levels of CoQ_{10}, vitamin E, thromboxane, and prostacyclin in normotensive and pre-eclamptic pregnant women and concluded that CoQ_{10} is a sensitive marker of oxidative stress in pre-eclampsia. CoQ_{10} supplementation was reported to reduce the risk of developing pre-eclampsia in women at risk for the condition.[28]

Cancer

Previous research has pointed out that low plasma levels of CoQ_{10} have been seen in women with breast cancer, in melanoma patients, and in cervical cancer patients. CoQ_{10} has potential to reverse mitochondrial dysfunction, fatigue, and the adverse effects of chemotherapy for metastatic diseases such as breast cancer.[29-31] A recent pilot study evaluated the survival of patients with end-stage cancers (breast, brain, lungs, kidneys, pancreas, esophagus, stomach, colon, prostate, ovaries, and skin) who received supplements of CoQ_{10} and other antioxidants (vitamin C, selenium, folic acid, and β-carotene). Seventy-six percent of these patients survived longer than the median predicted survival. Treatment was well tolerated and there were few adverse effects.[32]

Some case studies have reported tumor regression in breast cancer patients.[5] However, in a cohort study that examined the association of plasma CoQ_{10} levels with postmenopausal breast cancer risk, Chai et al[33] observed that higher plasma CoQ_{10} levels in postmenopausal women could be positively associated with increased breast cancer risk. The authors noted that the association was significant especially in women who were diagnosed 1 year after the baseline CoQ_{10} evaluation, which suggests that inclusion of women with latent breast cancer could have somewhat attenuated the association. The study also found that plasma CoQ_{10} levels were higher among breast cancer cases who were currently on hormone replacement therapy compared with those who were not on hormone replacement therapy. The influence of hormone replacement therapy on the relation between CoQ_{10} and breast cancer requires further investigation. It is also not known whether increased plasma CoQ_{10} represents a marker of adverse physiologic conditions. The authors concluded that a prospective larger sample size and longer follow-up are needed to determine the potential role of CoQ_{10} in the etiology of breast cancer.

Periodontal Disease

The positive effects of oral supplementation with CoQ_{10} for treating periodontal disease and gingivitis have been known for more than 30 years.[5] CoQ_{10} therapy has been reported to significantly increase the T4/T8 lymphocyte ratios and IgG levels, reduce the level of subgingival microorganisms, and improve the oxygen utilization in the gingiva. Several open and double-blind trials demonstrated that CoQ_{10} therapy resulted in reduced disease, improved immune system, and restored periods of natural prevention of disease. CoQ_{10} is therefore recommended for both prophylactic and therapeutic treatment of periodontal disease.[34] Topical application of CoQ_{10} on gum tissues has also been shown to improve periodontitis and gingivitis in a clinical study. Topical application as a sole treatment reduced pocket depth, attachment loss, bleeding, and inflammation.[35] More recently, a toothpaste containing CoQ_{10} has been clinically proven to reduce mild to moderate gingivitis.[36]

Efficacy in Other Conditions

CoQ_{10} supplementation has shown favorable results in a number of other clinical conditions, some of which are likely related to its antioxidant properties rather than its ability to improve cellular bioenergetics. While these conditions have few clinical trials completed and additional studies are recommended, recent reviews make note of the therapeutic potential of CoQ_{10}. Littarru and Tiano[15] report several prospective uses for CoQ_{10} including improving physical performance, reducing migraine frequency, and rejuvenating wrinkled skin. Based on a small number of trials, a monograph published in *Alternative Medicine Review* also reviewed clinical trials with CoQ_{10} as a potential therapy for HIV/AIDS, diabetes, pregnancy, asthma, thyroid disorders, and renal failure.[5]

Current Clinical Trials

According to the website clinicaltrials.gov, there are 25 phase I, II, or III clinical trials currently recruiting to investigate the safety, tolerability, and/or effects of CoQ_{10} on patients with Huntington's disease, Parkinson's disease, progressive supranuclear palsy, geriatric bipolar depression, statin myopathy, muscular dystrophy, Charcot-Marie-Tooth disease, migraines, developmental disabilities, primary progressive multiple sclerosis, cardiovascular disease, hypertension, mitochondrial disease, and sleep apnea. In addition, recruitment is in progress for studies using CoQ_{10} as adjuvant treatment for neovascular age-related macular degeneration and diabetic macular edema, for infertility, and as concurrent therapy for breast cancer patients to reduce the adverse effects of doxorubicin treatment.

Bioavailability and Formulation Technology of CoQ_{10}

It is well established that the bioavailability of crystalline CoQ_{10} in humans is low and variable because of its poor solubility and high molecular weight. Therefore, improved bioavailability is a major factor for ensuring successful CoQ_{10} treatment for the various conditions that have shown promising results. In fact, the amount of scientific literature dedicated to clinical investigations of the bioavailability of various formulations is almost as vast as clinical studies examining its efficacy. Clinical trials have studied a number of variables associated with oral CoQ_{10} supplementation, including whether it is taken with or without food and the type of formulation technology used to improve the poor systemic absorption of crystalline CoQ_{10}. Formulation technology is the most commonly used science in improving bioavailability and its level of complexity varies from simple to multifaceted.

A very basic improvement to powdered CoQ_{10} formulations is to disperse, suspend, or emulsify the CoQ_{10} in oil suitable for soft gels, as CoQ_{10} absorption is known to improve in the presence of fat.[12] Oil-dispersed products have been shown to have improved bioavailability over crystalline CoQ_{10}.[37] Slightly more advanced technology also developed for soft gels includes various solubilized formulations in emulsifiers such as soy lecithin, polysorbates, and medium-chain triglycerides. Many of these formulations rely on some form of micronization or micellarization and are often coupled with absorbance enhancers. Even more sophisticated formulation technology is the complexation of CoQ_{10} with cyclodextrins to form a water-soluble powder, which is often used in the pharmaceutical industry. Other advanced formulations include colloidal-based delivery systems and nano-beadlets. Numerous brands of CoQ_{10} using these advanced formulations have been clinically tested against crystalline CoQ_{10}, oil dispersions, and against each other. The results of these human trials suggest that this vast assortment of delivery systems for CoQ_{10} exhibit significant relative differences in bioavailability. As a result, a major selling point of commercially available CoQ_{10} formulations is an improved bioavailability claim to help distinguish one brand from another. Unfortunately, comparing the data across studies and helping consumers understand these bioavailability claims is often difficult because of the ambiguous definition of bioavailability in the dietary supplement industry when compared with the pharmaceutical industry. The remainder of this review examines results of controlled clinical trials comparing various formulations of CoQ_{10} in healthy adults and a method of redefining bioavailability for CoQ_{10} and (and other dietary supplements) to help consumers decipher "improved bioavailability" claims. Table 2 summarizes the representative clinical trials described in the following section.

Fundamentals of CoQ_{10} Bioavailability

In 2007, Bhagavan and Chopra published a comprehensive review of controlled clinical trials investigating the plasma CoQ_{10} response to oral ingestion of different formulations.[12] From this review, they were able to conclude some basic tenets of CoQ_{10} bioavailability. Plasma CoQ_{10} concentrations and the net increase over baseline plasma CoQ_{10} values show a gradual increase with increasing dosage. The efficiency of absorption decreases significantly at higher dosages (more than 300 mg). Single doses are inferior to split dosages. In terms of formulation technology, they concluded the response following ingestion of solubilized formulations is much greater than nonsolubilized powders regardless of form (compressed tablets, chewable tablets, powder-filled capsules, and soft gels containing CoQ_{10} suspended in oil). Other factors influencing bioavailability include the subject's gender, age, alcohol consumption, as well as their serum cholesterol and triglyceride levels, suggesting that higher low-density lipoprotein cholesterol or triglyceride concentrations could aid absorption of CoQ_{10}.

CoQ_{10} and Formulation Chemistry: Representative Clinical Trials

The absorptive properties of a novel fast-melting tablet (CoQ_{10}, sorbitol, mannitol, magnesium stearate, citric acid, flavoring, and polyvinyl pyrrolidone) and an effervescent tablet (CoQ_{10}, sucralose, glucose, citric acid, sodium bicarbonate, and riboflavin 5′-phosphate) were compared with a soft gel oil dispersion CoQ_{10} formula and CoQ_{10} powder-filled hard gelatin capsules. The randomized, single-dose, crossover study measured CoQ_{10} plasma levels of a single 60-mg dose of CoQ_{10} over 12 hours. In a separate single-dose study, the absorptive characteristics of a different CoQ_{10} solubilized soft gel were studied in 6 male subjects. Bioavailability, as measured by area under the curve value, showed that the fast-melting and effervescent formulations, while marginally greater, were not significantly different when compared with the soft gel and powder-filled preparations. The time to reach maximum plasma concentration, however, was significantly shorter for the fast-melting and effervescent formulations compared with the soft gel and powder-filled forms, suggesting that the fast-melting and effervescent formulations provided a more rapid delivery of CoQ_{10} to the blood while exhibiting a similar area under the curve value compared with current formulations.[38]

The bioavailability of a commercial grade CoQ_{10} powder and a CoQ_{10} formulation obtained by fermentation of a soy-based, CoQ_{10}-rich media with baker's yeast were compared in a randomized 2-way crossover trial. Subjects received 300 mg per day of CoQ_{10} for 1 week. The ingestion of the

Table 2. CoQ_{10} and Formulation Chemistry: Representative Clinical Trials

Formulations Compared	Conclusion	Reference
Fast melting tablet Effervescent tablet Oil dispersion Crystalline powder	Fast melting and effervescent formulas marginally but not significantly more bioavailable then the oil dispersion or crystalline form.	38
CoQ_{10} from fermented formulation Crystalline powder	CoQ_{10} from fermented formulation was significantly more bioavailable than the crystalline form.	39
Chewable form Solubilized form Four oil dispersions Crystalline powder	Solubilized form was superior to the other forms. Significant between-subjects response to the different formulations was found.	40
Nano CoQ_{10} beadlet Solubilized form Oil dispersion	Nano beadlet slightly more bioavailable although bioequivalent to the solubilized. Both more bioavailable than the oil dispersion.	41
Two solubilized formulations Two oil dispersions Crystalline powder	Bioavailability relative to crystalline form: solubilized 1, 142%; oil dispersion 1, 131%; solubilized 2, 107%; oil dispersion 2, 89%.	42
Chewable wafer Chewable wafer with vitamin E Solubilized formulation Crystalline powder	No significant differences were found among the 4 formulations.	43
CoQ_{10}-β-cyclodextrin liquid form and powder form Oil dispersion	Bioavailability relative to the oil dispersion was 120% for the liquid form and 79% for the powder form of CoQ_{10}-β-cyclodextrin.	44
Colloidal-based formula Two solubilized formulations Oil dispersion	Colloidal-based delivery system more bioavailable than the solubilized or oil dispersed forms.	45
Nano-emulsion formulation Crystalline powder	Nano-emulsion formulation more bioavailable than the crystalline form.	46
CoQ_{10}-β-cyclodextrin powder form Solubilized formulation Crystalline powder	CoQ_{10}-β-cyclodextrin powder more bioavailable than the solubilized or crystalline forms.	47

Abbreviation: CoQ10, coenzyme Q_{10}.

fermented formulation significantly increased maximum plasma CoQ_{10} concentration (124%) and tended to increase CoQ_{10} area under the curve from 0 to 24 hours.[39] The authors conclude that the enhanced bioavailability of the CoQ_{10} might be due to its predominantly reduced, hydrophilic membrane–complex form in the fermented product.

A study in New Zealand investigated the bioavailability of a single 150-mg dose of 7 popular brands of CoQ_{10} supplements using different delivery systems. The study included 1 chewable tablet formula, 1 solubilized formula, 4 oil dispersion systems, and 1 with CoQ_{10} dry powder. The authors reported significant differences in the bioavailability between the 7 brands, with the solubilized formula containing CoQ_{10} with vitamin E, lecithin, polysorbate 80, sorbitan monooleate, and medium-chain triglycerides being significantly better than the others. There was also a significant correlation between baseline low-density lipoprotein cholesterol concentrations, total cholesterol levels, and baseline triglycerides and the change in CoQ_{10} plasma levels, as has been seen in other trials. To make the bioavailability paradigm even more complex, there was also a significant difference in CoQ_{10} absorption between the 10 participants—some showed efficient absorption from most brands of the supplements whereas others showed inefficient absorption.[40]

A randomized, open-labeled, 3-period crossover trial was conducted to compare the bioavailability of 3 different CoQ_{10} formulations: a 10% CoQ_{10} nano-beadlet available in tablet-grade quality, a solubilized soft gel (vitamin E, lecithin, polysorbate 80, sorbitan monooleate, and medium-chain triglycerides), and an oil-dispersed formulation. To compare bioavailability, baseline and dose-corrected maximum concentrations (C_{max}) and area under the curve were assessed for bioequivalence. The highest C_{max} values were seen after the nano-beadlet formulation, whereas time to C_{max} was nearly identical across all treatments. The area under the curve value was also highest for the nano-beadlet formulation, narrowly followed by the solubilized formula. The tests for bioequivalence showed a bioequivalence between the nano-beadlet formulation and the solubilized formula, and both preparations were found to have better bioavailability properties than the oil-dispersed formula.[41]

Schultz et al[42] compared the relative bioavailability of a daily 60-mg dose of 5 commercially available CoQ_{10} supplements: 2 solubilized soft gel CoQ_{10} formulations, 2 soft gel oil dispersions, and crystalline CoQ_{10}. After 4 hours following the first dose, both solubilized formulations showed equal bioavailability and both were significantly superior to both the crystalline CoQ_{10} and the oil-dispersed products. After a week of supplementation, one solubilized formula seemed to have already reached a plateau level in plasma, whereas a further slight increase was observed for the other preparations in the second week of supplementation. As measured by the area under the value curve for 0 to 14 days, the relative bioavailability of the solubilized CoQ_{10} formulation in medium-chain triglycerides and polysorbate 80 was 142% compared with crystalline CoQ_{10}, followed by oily dispersion CoQ_{10} formulation consisting of 1500 IU vitamin A, soybean oil, gelatin, glycerin, and water (131%); the solubilized formula consisting of 6 IU vitamin E, gelatin, glycerin, water, titanium dioxide, annatto seed extract, polysorbate 80, medium-chain triglycerides, sorbitol, and sorbitan monooleate (107%); and the oily dispersion formulation consisting of 1295 IU vitamin A, 30 IU vitamin E, rice bran oil, yellow beeswax, gelatin, glycerin, water, and annatto extract (89%).

Another randomized, double-blind, crossover trial compared the bioavailability following a single 600-mg dose of 4 different oral CoQ_{10} formulations. The CoQ_{10} formulations used were a plain chewable wafer, a chewable wafer also containing an additional 300 IU of vitamin E, a hard gelatin capsule, and a solubilized soft gel formulation containing 150 IU vitamin E, lecithin, polysorbate, sorbitin monoleate, and medium-chain triglycerides. The study resulted in no significant differences among the 4 oral CoQ_{10} preparations with respect to bioavailability as measured by plasma CoQ_{10} area under the curve value. The authors conclude that contrary to other studies that report a wide variation between formulations, these results suggest that the formulations do not have an important impact on bioavailability.[43]

A randomized 3-period crossover clinical trial was completed to compare a single 60-mg dose of CoQ_{10} from an oil-dispersed soft gel formulation to CoQ_{10}–β-cyclodextrin complex in liquid and powder forms. The study revealed that the plasma CoQ_{10} levels from the 2 β-cyclodextrin complexes were 120% (liquid) and 79% (powder) over the oil-dispersed soft gel formulation. The authors conclude that these results demonstrated that the bioavailability the CoQ_{10}–β-cyclodextrin complex is probably due to the enhanced water solubility.[44]

The bioavailability of a colloidal-based delivery system for CoQ_{10} was compared with an oil dispersion formula and 2 solubilizates. This double-blind comparative, controlled single-dose (120 mg) trial resulted in significantly higher bioavailability for the colloidal CoQ_{10} compared with the other formulas as measured by area under the curve value for plasma CoQ_{10} levels. Colloidal solubilization is theorized to improve the transport of CoQ_{10} through the aqueous phase of the gastrointestinal-lumen to the absorptive epithelium.[45]

Improved bioavailability of a prepared nano-emulsion of CoQ_{10} in gum arabic compared with crystalline CoQ_{10} was confirmed in rats and humans by Ozaki et al[46] using a commercially available 20% CoQ_{10} formula emulsified with gum arabic. This particular nano-emulsion was shown to have a high modulus of inclusion (98%) and a significantly smaller particle size (536 nm vs 1000 nm) compared with an equivalent, unemulsified gum arabic formulation. The rat study confirmed that the higher modulus of inclusion and smaller particle size of the emulsified gum arabic formulation improved bioavailability as measured by serum CoQ_{10} levels. In humans, a single 120-mg dose of CoQ_{10} as the nano-emulsion formula also showed improved bioavailability compared with the crystalline form.

A comparison of the relative bioavailability of a CoQ_{10}–β-cyclodextrin inclusion complex with a commercially available solubilized CoQ_{10} soft gel formulation and crystalline CoQ_{10} was completed using a single dose of 180 mg of CoQ_{10}. The results indicated that the CoQ_{10}–β-cyclodextrin inclusion complex showed a sustained release and that its bioavailability was significantly better than the crystalline form by a factor of 3.7. Additionally, the intersubject variance (a critical measurement used in the pharmaceutical industry to assess the bioavailability differences from patient to patient in order to ensure proper dosing) in the bioavailability of the solubilized form was significantly greater than the other 2 forms. A second study compared the CoQ_{10}–β-cyclodextrin complex to the solubilized form in a 21-day repeated dosing study using 60 mg of CoQ_{10}. All the subjects showed a minimum of doubling in the plasma CoQ_{10} levels after 21 days supplementation of the CoQ_{10}–β-cyclodextrin complex, a 100% response rate, while the solubilized product showed only 44% response rate.[47]

Bioavailability claims for the various CoQ_{10} products in the market are based on human studies that compare the mean serum concentrations (as area under the curve value) of 2 to 3 treatments. If the differences are statistically significant and "large," then the product claim is that it is "X times more bioavailable." If the differences are modest, then the claim could be simply be "more bioavailable." These studies fail to report or do not consider the high intersubject variance often observed with lipophilic compounds such as CoQ_{10}. As a result, a percentage of the population will not experience the improved bioavailability and health benefits. With so many CoQ_{10} products in the market, it is difficult for consumers and professionals to decide whether a particular brand is likely to be effective.

Kagan et al[48] recently described a method to improve the standards of reporting the bioavailability results. The authors reviewed a series of bioavailability studies of CoQ_{10} in which advanced formulations were compared and claims drawn from statistically significant differences between treatments. In many instances the conclusions and ensuing claims were neither qualified nor modified to account for high levels of intersubject variance. A straightforward algorithm was developed based on the properties of a normal distribution and confidence limits for defining "reliable" absorption results as incorporating 84% of the population and "universal" absorption as those incorporating 98% of the population. These indicators can be readily calculated using reported means and standard deviations and thereby offer an accurate and easily understood way of comparing bioavailability results and claims. The method can also be applied to describe the bioavailability claims of other nutritional supplements.

Summary

CoQ_{10} supplementation has potential therapeutic value for several diseases and health conditions. However, the clinical efficacy in many conditions could be limited by its ability to be absorbed to reach high plasma concentrations required for therapeutic benefit. Advanced formulation technology is being used to improve the bioavailability of CoQ_{10} and at first glance, based on clinical studies on healthy subjects, more sophisticated formulations show great potential. Yet, with additional scrutiny of the reported data, it appears that some studies have high intersubject variance, which means a percentage of the population will not experience the improvement in bioavailability. Improving the standards of reporting the bioavailability of poorly absorbed supplements such as CoQ_{10} is recommended to help clinicians and consumers decide whether or not a product is likely to be effective.

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Author Contribution

All the authors contributed equally to this work.

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