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COMPREHENSIVE REVIEWS IN FOOD SCIENCE AND FOOD SAFETY

Coenzyme Q10 supplementation: Efficacy, safety, and formulation challenges

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Abstract

World population growth and aging are posing unprecedented challenges in sustaining the health of 9.1 billion people that will be occupying the planet by 2050. Although noncommunicable diseases such as cardiovascular and neurodegenerative diseases, cancer, and diabetes are among the top 10 global causes of death, they can be prevented by risk factor reduction, early detection, and adequate treatment. Since a healthy diet along with dietary supplementation could play an important role to reduce morbidity and cut off its associated health care costs, research in the food and nutrition area is required to find solutions to global challenges affecting health.

As a result of the healthy living trend, dietary supplements category is growing fast, leading to an urgent need for dietitians, physicians, and policy makers to broaden the scientific evidence on the efficacy and safety of a wide range of active ingredients. Coenzyme Q10 (CoQ10), as the third most consumed dietary supplement, and as a potential candidate for the treatment of various noncommunicable diseases that are among the global top 10 causes of death, has gained interest over years. Scientific evidence regarding mainly CoQ10 efficacy and safety, as well as formulation challenges, is addressed in this review.

KEYWORDS
bioactive compound, coenzyme Q10, dietary supplements, efficacy, food safety

1 | INTRODUCTION

The world faces unprecedented challenges in sustaining the health of the 9.1 billion people that will be occupying the planet by 2050 (Food and Agriculture Organization of the United Nations [FAO], 2009). Research in the food and nutrition area is required to find solutions to global challenges affecting health and food systems. In fact, food security and nutrition remain priorities for the World Health Organization (WHO, 2015a).

Improvements in health care in the past century have contributed to an increase in the average life expectancy, and a dramatic increase of older people proportion worldwide (FAO, 2018). Population aging is leading to a sharp increase in chronic and non-communicable diseases incidence, which is placing pressure on countries' overall health care spending (WHO, 2015b). While cardiovascular diseases, including heart disease and stroke, have remained the leading causes of death globally in the last 15 years, other noncommunicable diseases such as cancer, diabetes mellitus, Alzheimer disease, and other dementias are also in the top 10 global causes of death list (WHO, 2018a). In fact, not only these leading causes of death are killing more people each year than all

Abbreviations: CoQ10, coenzyme Q10; EFSA, European Food Safety Authority; FAO, Food and Agriculture Organization of the United Nations; FDA, US Food and Drug Administration; IFN, interferons; NOAEL, no observed adverse effect level; ROS, reactive oxygen species; SEDDS, Self-Emulsified Drug Delivery Systems; WHO, World Health Organization.

other causes combined, but are also replacing infectious diseases and malnutrition as the leading cause of disability and premature death (WHO, 2015a). Despite that noncommunicable diseases have reached epidemic proportions, they are preventable and could be significantly reduced by means of risk factors reduction, early detection, and adequate treatment (WHO, 2010). In this spirit, the WHO released "Active ageing: a policy framework" to prevent and delay aging, chronic diseases and premature mortality, as well as their risk factors (WHO, 2002), and has set as a main target the reduction of premature noncommunicable disease mortality by one third by 2030 (WHO, 2018b). Governments are also interested in promoting healthy habits, not only to reduce morbidity and mortality, but also to cut off its associated health care costs.

In line with WHO's health action plan, and thanks to an unprecedented access to information, consumers are increasingly interested in health care (Kearney, 2010). Moreover, health technologies, including wearables and fitness apps, have made people more aware of their state of health, powering the growth of health and wellness market (Arenas-Jal, Suñé-Negre, Pérez-Lozano, & García-Montoya, 2019). With healthy living standing out as one of the most relevant global trends, more people are adopting an active lifestyle, embracing a healthier dietary pattern and recognizing the benefits of food supplements (Euromonitor, 2017). For this reason, a double-digit growth has been predicted for this category in the United States by 2020 (Business Development Bank of Canada, 2016). Consumers are becoming more aware than ever of ingredients in their food and their properties, and while an increasing number of consumers are seeing food as a medicine, dietary supplements stand out as one of the fastest growing healthcare categories (Nielsen, 2016). While this is having positive implications in health, well-being and healthcare-associated costs, the consumer base expansion is leading to an urgent need for dietitians, physicians, and regulators to broaden the scientific evidence on the efficacy and safety of a wide range of active ingredients found in food supplements. Some misinformed consumers perceive food supplements as all natural and healthy products without any contraindications or possible interactions with drugs, which taking into consideration the enormous growth of this healthcare category is posing a risk for a great number of certain consumers (National Center for Complementary and Integrative Health, 2019; National Institutes of Health, 2011). Thus, besides receiving proper dietary recommendations from healthcare providers, consumers should also be informed about the current level of scientific evidence for each indication, as well as the precautions, interactions, and safety dose of the ingredients contained in food supplements. For this reason, competent authorities like the US Food and Drug Administration (FDA, 2017, 2018) and the European Food Safety Authority (EFSA, 2019) continuously carry out safety and efficacy assessments of substances to approve or dismiss them, as well as health claim evaluation. However, further research on physicochemical properties, pharmacokinetics, stability, and efficacy is needed to deepen the knowledge on these ingredients, and also to allow formulators to improve ingredients' properties by means of different techniques. By way of example, appropriate formulations could improve ingredients' stability and bioavailability, leading to greater shelf-life and efficacy (Beg, Javed, & JKohli, 2010; Bule, Singhal, & Kennedy, 2010; Kumar, Rao, Kumar, Mahant, & Nanda, 2016; Zhao & Tang, 2016).

When it comes to coenzyme Q10 (CoQ10), which is not an FDA-approved drug, but yet sold as a food supplement (DrugBank, 2019), it is currently the third most consumed nutritional supplement after fish oil and multivitamins (Kapoor & Kapoor, 2013). In addition, thanks to its strong antioxidant activity, and physiological key role in mitochondrial bioenergetics (Nelson & Cox, 2017), it has also been considered as a potential candidate for the treatment of various diseases were oxidative stress plays a significant role such as cardiovascular diseases, neurodegenerative disorders, cancer, and diabetes, which are among the top 10 global causes of death (Dhanasekaran & Ren, 2005; Villalba, Parrado, Santos-Gonzalez, & Alcain, 2010; WHO, 2018a). For this reason, considering that CoQ10 supplementation has gained interest over years and has an expanding consumer base, a review of the current scientific evidence regarding CoQ10 supplementation is needed. The aim of this review is to provide researchers, dietitians, physicians, formulators, and regulators with a breadth of evidence on CoQ10 efficacy, safety, and formulation challenges. In order to meet these objectives, this review is organized in the following sections: CoQ10 overview sources and deficiency, and supplementation, which includes pharmacokinetics and bioavailability, therapeutic indications, safety and precautions, and formulation.

2 | OVERVIEW OF COQ10

CoQ10, also known as Ubiquinone, is a fat-soluble, vitamin-like benzoquinone compound that is endogenously synthesized from tyrosine in the human body (Nelson & Cox, 2017). As shown in Figure 1, it comprises a quinone group and a side chain of 10 isoprenoid units (PubChem, 2019). Ubiquinol, the fully reduced form of CoQ10 is a good lipophilic antioxidant, capable of free radical neutralization and regeneration of the reduced form of vitamin E (Kagan, Fabisiak, & Quinn, 2000; Ouchi, Nagaoka, & Mukai, 2010). It can also inhibit lipid peroxidation in biological membranes and protect mitochondrial proteins and DNA from oxidative damage. In fact, it is the only lipophilic antioxidant that can be de novo synthesized by cells and that has enzymatic mechanisms to regenerate its reduced form (Brayfield, 2017).

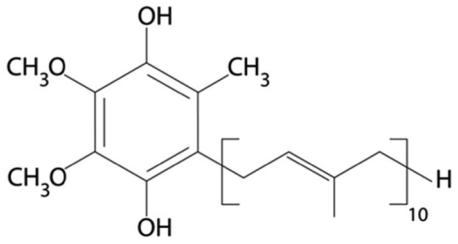

FIGURE 1 CoQ10 chemical structure
Source: PubChem (2019)

Being strongly bound to the inner mitochondrial membrane and participating in the electron transport chain and oxidative phosphorylation, it plays an essential role in the synthesis of cellular energy in the form of ATP (Caballero, Allen, & Prentice, 2013). For this reason, it is found at higher concentrations in tissues with a high metabolic activity, such as heart, kidney, liver, and muscle (Pravst, Žmitek, & Žmitek, 2010).

However, different factors such as genetics, aging, and statins treatment can lower its physiological concentrations (Potgieter, Pretorius, & Pepper, 2013). CoQ10 deficiencies have also been reported for conditions where oxidative stress plays a significant role, such as neurodegenerative disorders, diabetes, cancer, and cardiovascular diseases (Dhanasekaran & Ren, 2005). The lack of CoQ10 can be symptomatic in cells and tissues that are normally rich in mitochondria, such as muscle and nerve tissue, resulting in various types of myopathy and neuropathy. Since some CoQ10-deficient patients showed clinical improvements following supplementation, CoQ10 has been considered as a potential candidate for the treatment of various diseases (Garrido-Maraver et al., 2014). CoQ10 supplementation supports oxidative phosphorylation, cell signaling, and protects certain cell types (Mason, 2018). In addition, thanks to its strong antioxidant activity, it is also gaining popularity in the cosmetic industry (Fuller, Smith, Howerton, & Kern, 2006; Yue et al., 2010).

These findings on the potential health benefits of CoQ10 supplementation have led to an increased consumer demand. In fact, it is currently the third most consumed nutritional supplement after fish oil and multivitamins (Kapoor & Kapoor, 2013). It is highly safe, with a no observed adverse effect level (NOAEL) of 1,200 mg/kg/day (Hidaka, Fujii, Funahashi, Fukutomi, & Hosoe, 2008). In fact, the minor side effects after taking CoQ10 megadoses, such as indigestion, are more associated with the copious amounts of oil used to solvate it (Hathcock & Shao, 2006). Considering CoQ10 physicochemical characteristics, as a strongly hydrophobic compound with a high molecular weight (863 g/mol), it is extremely insoluble in aqueous phase (Brayfield, 2017; O'Neil, 2013), and it is absorbed slowly and incompletely from the small intestine resulting in low oral bioavailability in humans (Miles, 2007). In addition, it is vulnerable to heat, light, and oxygen (Fir, Smidovnik, Milivojevic, Zmitek, & Prosek, 2009). For this reason, research has been focused in overcoming the issues that limit its formulation into food supplements and medicinal products, such as solubility, oral bioavailability (Balakrishnan et al., 2009; Nepal, Han, & Choi, 2010; Terao et al., 2006), and stability (Bule et al., 2010; Zhao & Tang, 2016).

While Figure 2 shows CoQ10 key facts at a glance, an in-depth discussion on CoQ10 sources and deficiency, as well as supplementation, including pharmacokinetics and bioavailability, indications, safety and precautions, and formulation, is provided below.

3 | COQ10 SOURCES AND DEFICIENCY

CoQ10 has a wide distribution in plant and animal tissues that are part of our diet. Though it can be found in vegetables, fruits and cereals (1 to 10 mg/kg range), the richest dietary sources of CoQ10 are meat, fish, nuts, and some oils, which contain 10 to 50 mg/kg. Since CoQ10 is mainly distributed in high energy-demanding tissues, animal hearts and livers represent the richest source of this bioactive molecule, with a content between 30 and 200 mg/kg (Eskin & Snait, 2006; Nabavi & Silva, 2019). Although there is no established nutritional reference value for CoQ10, its daily average intake is around 5.4 mg and 3.8 mg for men and women, respectively (Mattila & Kumpulainen, xvv2001). However, as a nonessential nutrient, endogenous synthesis is believed to be its main source.

While an average healthy adult's body contains 0.5 to 1.5 g of CoQ10, its levels may be compromised by different factors (Bhagavan & Chopra, 2006). Deficiency can occur as a result of physiopathologic conditions such as acquired or genetic alterations in metabolism or biosynthesis (Alcázar-Fabra, Navas, & Brea-Calvo, 2016; Quinzii, DiMauro, & Hirano, 2007), an inadequate intake of CoQ10 or its dietary precursors (Potgieter et al., 2013), aging and oxidative stress that leads to an excessive utilization of the molecule (Nagase, Yamamoto, Matsumoto, Arai, & Hirose, 2018), or due to a combination of these factors. A suboptimal CoQ10 intake led to deficiencies when certain conditions or drugs were present. By way of example, deficiencies have been reported for conditions where oxidative stress plays a significant role, such as Parkinson's and Huntington's disease, type 2 diabetes, and hypertension (Bentinger, Tekle, & Dallner, 2010). Statins can also reduce CoQ10 concentration, since as HMG-CoA reductase inhibitors inhibit the production of mevalonate, which is not only a precursor of cholesterol but also of CoQ10 (Nawarskas, 2005). It has to be noted that CoQ10 endogenous synthesis is a complex process that requires the participation of tyrosine and eight vitamins (Alcázar-Fabra et al., 2016), which results in a high vulnerability of the process.

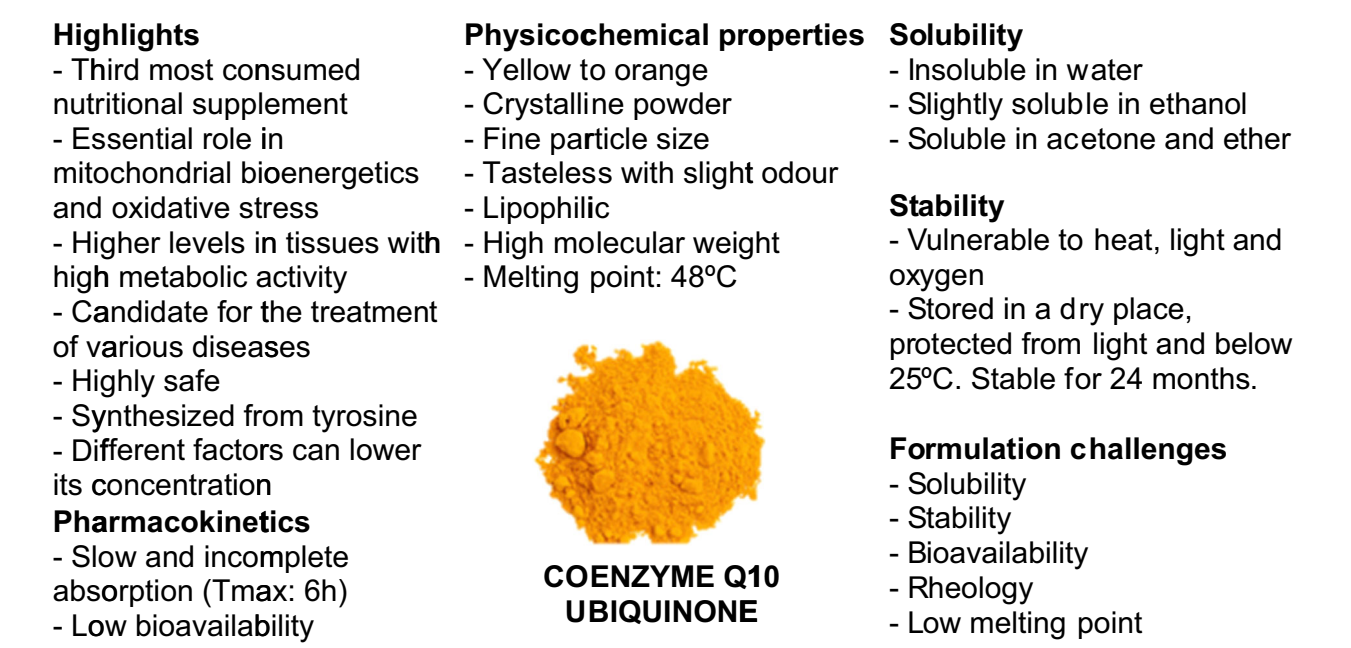

FIGURE 2 CoQ10 key facts at a glance

Several signs, symptoms, and diseases have been associated to a significant depletion of CoQ10 levels. However, whether the deficiency is a cause or consequence of these diseases remains unknown (Niklowitz, Sonnenschein, Janetzky, Andler, & Menke, 2007). Further studies are also needed to clarify the relative importance of CoQ10 intake and endogenous biosynthesis. However, as explained in more detail below, since some CoQ10-deficient patients showed clinical improvements following supplementation (Quinzii et al., 2007), CoQ10 has been considered as a potential candidate for the treatment of statins-induced myopathy, and various cardiovascular, neurodegenerative, neuromuscular, and mitochondrial diseases, as well as other conditions (Garrido-Maraver et al., 2014). For this reason, there is a growing demand for CoQ10 by the pharmaceutical, food supplement, and cosmetic industries. Due to its expanding applications and in order to meet the increased demand for CoQ10, the economical aspect of its industrial production is becoming more important (Shukla & Dubey, 2018). As a consequence, extensive research has been carried out to improve the yield of CoQ10 production.

Regarding CoQ10 industrial sources, since it was first isolated in the 1950s, several production methods have been developed, including chemical synthesis, microbial biosynthesis, and extraction from biological tissues (mainly from plants) (S. Q. E. Lee, Tan, Kawamukai, & Chen, 2017). In general, microbial biosynthesis is the preferred and most widespread method for industrial production of CoQ10, since it offers many advantages over the other methods. Both chemical synthesis and extraction from biological tissues involve the use of organic solvents and chemicals, leading to the production of waste, which nowadays is trying to be avoided due to environmental concerns. In addition, neither of these two techniques exhibit specificity toward the all-trans biologically viable isomer of CoQ10, which adds costs due to the extra purification steps needed (Vaghari, Vaghari, Jafarizadeh-Malmiri, & Berenjian, 2016). For these reasons, and because the process is inexpensive and easy to control, CoQ10 is mainly produced by microbial biosynthesis, including fungi, bacteria, and yeast. Microbial biosynthesis is stereoselective and scalable, it does not require harsh catalytic conditions, and production costs are usually lower (S. Q. E. Lee et al., 2017). However, to overcome the limits of CoQ10 accumulation in cells, different strain improvements have been made using different techniques such as genetic engineering and chemical mutagenesis. Other strategies to overcome limiting steps through the biosynthetic pathway, and to enhance CoQ10 yields include regulation of biosynthetic activators or inhibitors (de Dieu Ndikubwimana & Lee, 2014).

In terms of organism selection, native producers that show higher CoQ10 yields are usually chosen, since in contrast to heterologous hosts, they do not produce unwanted CoQ species with different chain length that results in an additional cost of extracting and separating CoQ10 (Shukla & Dubey, 2018). By way of example, *Rhodobacter sphaeroides* and *Agrobacterium tumefaciens* are native CoQ10 producers. Currently, *R. sphaeroides* is the most productive native host, and remains the best option for industrial scale production of CoQ10. Its production is around 12.96 mg/g dry cell weight of CoQ10. However, despite having higher yields than non-native producers, it does not produce sufficient quantities to meet current market demands, which has led to higher prices

of CoQ10 (S. Q. E. Lee et al., 2017). For this reason, there is still a lot of work to do to develop a cost-effective industrial production system. Different approaches to optimize these techniques and enhance CoQ10 production need to be explored in order to produce sufficient quantities to meet current market demands. Otherwise, the prices of CoQ10 will continue rising along with the demand (Kawamukai, 2009; Parmar, Jaiwal, Dhankher, & Jaiwal, 2015). Nowadays, the price of commercial CoQ10 pure powder is already high, ranging from 700 to 1,000€/kg when purchasing quantities above 15 kg. Otherwise, it is even more expensive. When it comes to its properties, it is a yellow to orange crystalline powder that usually contains at least 99% of pure CoQ10 calculated on the anhydrous basis, and the sum of all impurities is below 1% (Kingdomway Nutrition, 2019). As for additional data regarding molecular weight, physicochemical characteristics, and stability, these have been discussed in more depth under the section CoQ10 Supplementation–Formulation.

4 | COQ10 SUPPLEMENTATION

As a food supplement, CoQ10 is mainly found in mono- or multicomponent softgels, capsules, and tablets. However, while it used to be incorporated as a simple crystalline powder or dispersed in oil, different novel delivery systems have been recently tested to improve its bioavailability. Thus, different formulation approaches, such as self-emulsified drug delivery systems, nanoemulsions, or cyclodextrin complexes, have been used and combined to improve CoQ10 bioavailability when incorporated into different pharmaceutical dosage forms (Barakat, Shegokar, Dittgen, & Müller, 2013; Schulz, Obermüller-Jevic, Hasselwander, Bernhardt, & Biesalski, 2006). The suggested daily dose varies depending on the indication but is usually around 30 to 100 mg for healthy people, reaching up to 60 to 1,200 mg when used in some medical conditions (Pravst et al., 2010). Therapeutic indications, safety, and precautions of CoQ10 supplementation and formulation challenges are explained in more detail below.

4.1 | Pharmacokinetics and bioavailability of the dietary supplement CoQ10

Despite Figure 3 summarizes CoQ10 pharmacokinetics and bioavailability, a more in-depth discussion is provided below.

The chemical structure of CoQ10 consists of a quinone group and a side chain of 10 isoprenoid units. It has a high molecular weight (863.34 g/mol) and is strongly hydrophobic (PubChem, 2019). Therefore, it is extremely insoluble in aqueous phase (Brayfield, 2017; O'Neil, 2013), and is absorbed slowly and incompletely from the small intestine resulting in low oral bioavailability in humans (Miles, 2007). CoQ10 absorption follows a zero-order kinetics and is believed to follow the same pathway as other lipophilic substances. It is a complex process undergone by a combination of passive and active transport mechanisms that takes place in the small intestine (Miles, 2007), being, according to murine models, duodenum, colon, ileum, and jejunum regions from higher to lower permeability to CoQ10 (Palamakula, Soliman, & Khan, 2005). Due to its insolubility in water, limited solubility in lipids, and its relatively high molecular weight, CoQ10 has a poor and slow-rate absorption with a T_{max} value of about 6 hr (Bhagavan & Chopra, 2006). At 24 hr following oral administration, a second plasmatic peak is observed, which could be attributed to enterohepatic recirculation and a redistribution from liver to circulation by lipoproteins (Kalenikova, Gorodetskaya, & Medvedev, 2008). VLDL, LDL, and HDL carry a 16%, 58%, and 26% of serum CoQ10, respectively, and it is believed that CoQ10 is capable to prevent them from oxidation (Tomasetti, Alleva, Solenghi, & Littarru, 1999). In fact, many studies have linked total cholesterol or LDL levels and plasmatic CoQ10 (López-Lluch, del Pozo-Cruz, Sánchez-Cuesta, Cortés-Rodríguez, & Navas, 2019). In general, CoQ10 concentration–time curve fits a three-compartmental pharmacokinetic model based upon the assumption that it is taken up by the liver and then transferred to lipoproteins and redistributed from the liver to systemic blood. This could explain the prolonged elimination phase of CoQ10, with a half-life of about 33 hr (Tomono, Hasegawa, Seki, Motegi, & Morishita, 1986). Regarding metabolism, CoQ10 is metabolized by cytochrome P450 enzymes (Zaki, 2014).

It should be pointed out that since zero-order absorption kinetics suggests an active transport mechanism, limited absorption could occur in certain individuals. Since the efficiency of absorption decreases as the dose increases, doses exceeding absorption capacity unnecessarily increase the treatment cost without having any impact on treatment efficacy (Miles, 2007). When compared to a single dose, divided dosages resulted in increased plasmatic levels of CoQ10. For this reason, high CoQ10 daily doses should be split into several doses (Bhagavan & Chopra, 2007; Liu & Artmann, 2009).

Absorption and bioavailability studies show that, as high-complexity processes, the individual response to CoQ10 supplementation is highly variable, and may be affected by different factors such as age, gender, diet, microbiota, and intestinal absorption capacity of fats among others (Martucci et al., 2019). It has to be noted that while its slow absorption and low bioavailability have been associated with its large molecular weight, high lipophilicity and poor aqueous solubility, as with all water-insoluble compounds, CoQ10 absorption is enhanced by the presence of a lipidic medium, and thus, it is recommended to take it with meals containing fat, or encapsulated within a suitable delivery system (Shuqin Xia, Xu, & Zhang, 2006). While the ingestion of fat

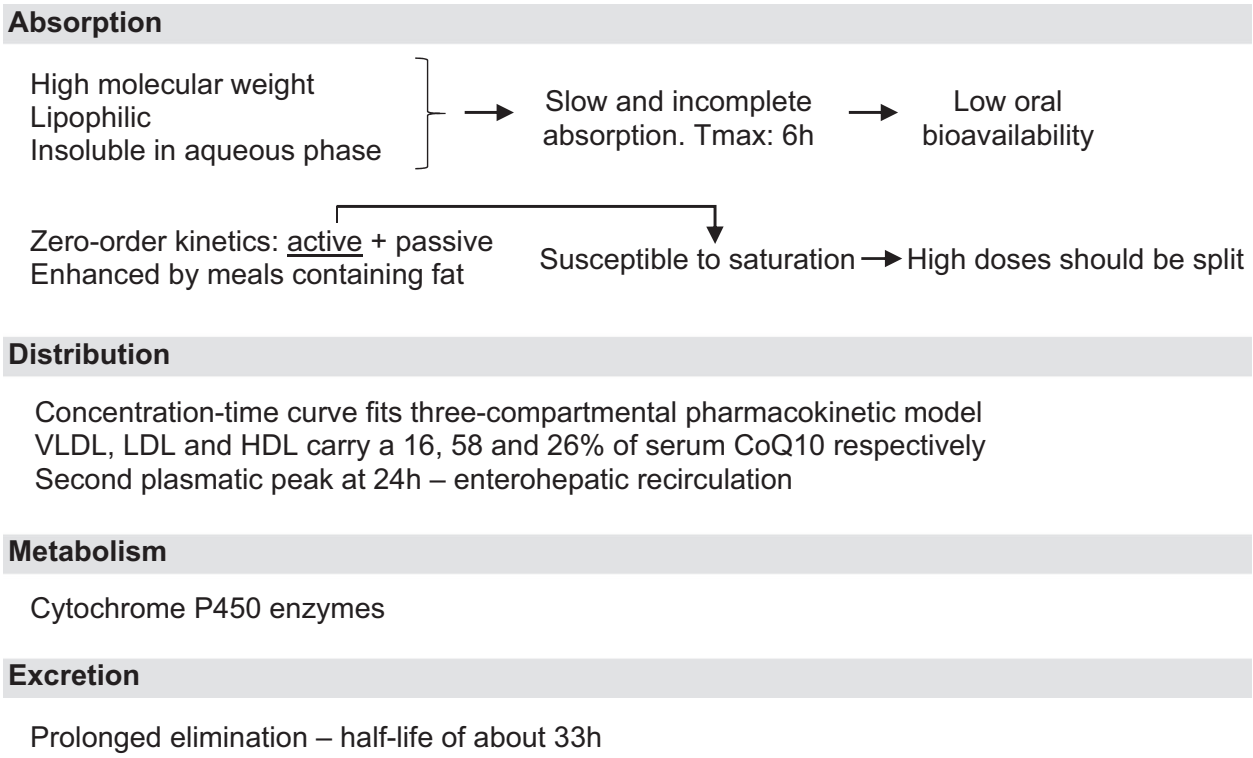

FIGURE 3 CoQ10 pharmacokinetics and bioavailability summary. Note that the individual response might be highly variable depending on several factors such as age, gender, diet, microbiota, and intestinal absorption capacity among others. Information sources are indicated in the main text

stimulates the secretion of bile salts by the liver into the duodenum, which improves the absorption of lipids and lipophilic molecules by means of micelle formation (Vitetta et al., 2018), the intake of vitamin E may interfere with CoQ10 absorption resulting in a lower plasmatic concentration. This is probably caused by a competitive absorption. In contrast, the optimization of formulations can also enhance CoQ10 absorption and bioavailability, which have an influence on efficacy. In fact, besides the aforementioned individual physiologic factors that affect its absorption, some studies have concluded that variations in the excipient composition of a formula may also affect bioavailability (López-Lluch et al., 2019). Therefore, the optimization of formulations is a potential mechanism to enhance the absorption and bioavailability of administered CoQ10. For this reason, it has been discussed in more depth under the corresponding section (CoQ10 Supplementation–Formulation).

Finally, due to its involvement in the cellular energy synthesis, CoQ10 is not uniformly distributed across the body, but concentrated in those tissues with a higher energy requirement (Nelson & Cox, 2017). At a cellular level, because of its liposoluble character, is mainly located in cell membranes, with only a 10% of total CoQ10 located in the cytosol, and around 40 to 50% located in the internal mitochondrial membrane, where it plays its essential role in energy synthesis (Pravst et al., 2010). As for its oxidative state, CoQ10 is mainly found in the reduced form, except in the brain and lungs, where oxidative stress is higher (Åberg, Appelkvist, Dallner, & Ernster, 1992). In fact, 95% of circulating CoQ10 in humans is found in the reduced form, and no significant change in the reduced:oxidized ratio occurs after its ingestion (Bhagavan & Chopra, 2007). This could be due to CoQ10 reduction during the absorption process, as reported in a study with human Caco-2 cells (Bhagavan, Chopra, Craft, Chitchumroonchokchai, & Failla, 2007).

4.2 | Therapeutic indications

Despite CoQ10 has been proposed as a potential candidate for the treatment of different diseases, it is not an FDA approved drug. Instead, it is sold as a food supplement, and therefore, is not meant to treat, cure, or prevent any disease (DrugBank, 2019). However, a number of clinical trials have observed that CoQ10 oral administration provided beneficial effects on a range of different disorders that have been associated with low CoQ10 levels and high oxidative stress, such as mitochondrial, cardiovascular, and neurodegenerative diseases (Garrido-Maraver et al., 2014). These beneficial effects are associated with CoQ10 antioxidant activity and physiological key role in mitochondrial bioenergetics. Since CoQ10 is the only lipid-soluble antioxidant synthesized endogenously, and it plays an essential role in ATP synthesis, it is indispensable

for the proper functioning of all tissues and organs, especially those with a high-energy demand (Nelson & Cox, 2017).

In addition, CoQ10 has also been reported to exert beneficial effects on energy-yielding metabolism, maintenance of normal blood pressure and cholesterol concentrations, maintenance of normal cognitive function, protection of DNA, proteins and lipids from oxidative damage, and increase in endurance performance. However, since clinical evidence is still limited, the scientific panel of the EFSA could not establish a cause–effect relationship between the consumption of CoQ10 and these claimed effects. Thus, it does not have any of these food supplement health claims approved (EFSA Panel on Dietetic Products, Nutrition and Allergies, 2010).

Different indications, as well as their level of scientific evidence are discussed in more detail below. However, these have also been summarized in Table 1.

4.2.1 | Cardiovascular diseases

While CoQ10 is mostly recognized for its role in counteracting statin-associated muscular symptoms, which is discussed in more detail below, it may also have a potential benefit for patients with cardiovascular diseases. Oxidative stress and impaired mitochondrial function play a central role in the pathogenesis of cardiovascular diseases (Chistiakov, Shkurat, Melnichenko, Grechko, & Orekhov, 2018). For this reason, considering the essential role of CoQ10 in mitochondrial bioenergetics and its antioxidant properties, it could be a promising therapeutic agent to prevent and slow the progression of cardiovascular disease. Flowers, Hartley, Todkill, Stranges, and Rees (2014) reviewed the previous findings on CoQ10 supplementation for the primary prevention of cardiovascular disease, and found that although CoQ10 is considered possibly effective for the treatment of cardiovascular diseases, further studies with a longer follow-up were needed to conclude whether it has a role in the primary prevention of cardiovascular diseases.

It has to be noted that low endogenous levels of CoQ10 were associated with cardiomyopathy and heart failure, and plasma levels were found to be an independent predictor of mortality and might be implicated in the long-term prognosis of chronic heart failure (Molyneux et al., 2008). Since CoQ10 has an essential role in the production of energy, supplementation may have beneficial effects in patients with heart failure, which is the reduced contractile function of cardiac muscle due an energy depletion status that has been associated with low CoQ10 levels and high oxidative stress (Villalba et al., 2010). In fact, Q-SYMBIO trial concluded that long-term treatment of this patient was safe, improved symptoms, and reduced major adverse cardiovascular events (Mortensen et al., 2014). Despite available evidence suggests that CoQ10 may be useful for the effective management of patients with heart failure (DiNicolantonio, Bhutani, McCarty, & O'Keefe, 2015), and thus, that it has the potential to improve morbidity and mortality in these patients, results of Q-SYMBIO trial should be interpreted with caution since they may not be generalizable to the entire heart failure population (Ayers, Cook, Koenig, Sisson, & Dixon, 2018).

In addition, CoQ10 protective role in cardiovascular diseases may also be attributed to its beneficial effect on cardiovascular risk factors such as hypertension and atherosclerosis (Flowers et al., 2014). The suggested antihypertensive and antiatherosclerotic mechanism of action may be related to its antioxidant properties. While oxidative stress reduces nitric oxide availability resulting in vasoconstriction that leads to an elevated blood pressure, CoQ10 supplementation may result in nitric oxide preservation (Y.-K. Yang et al., 2015). As for atherosclerosis, CoQ10 antioxidant activity may reduce LDL peroxidation and endothelial dysfunction, which is considered to be an early marker for atherosclerosis (Gao et al., 2012; Witting, Pettersson, Letters, & Stocker, 2000). Despite a number of clinical trials have been carried out, further studies with a larger sample size are needed to conclude whether CoQ10 has a role in the prevention of hypertension and atherosclerosis (Ayers et al., 2018).

4.2.2 | Statin-induced myopathy

Statins are essential drugs in the treatment of dyslipidaemia, and thus in the prevention of cardiovascular diseases. Despite statins are generally safe, a variety of myopathies have been reported following treatment (Selva-O'Callaghan et al., 2018). In fact, 10.5% of patients on statin therapy may experience myalgia, which is the most common side effect (Bruckert, Hayem, Dejager, Yau, & Bégaud, 2005). While this is considered a minor adverse effect, it may have a huge repercussion on patient's compliance. In fact, patient surveys suggest that around 30% of statin-prescribed patients discontinue therapy because of muscular pain, stiffness, cramps, weakness, and fatigue (Rosenbaum, Dallongeville, Sabouret, & Bruckert, 2013). Besides these minor side effects, rhabdomyolysis, which is severe and life threatening but extremely rare, may also occur (Mendes, Robles, & Mathur, 2014).

The exact mechanism of statin-induced myopathy has not been determined yet, but among the multiple mechanisms that have been proposed, the inhibition of CoQ10 synthesis stands out as one of the leading theories (Banach et al., 2015).The treatment of hypercholesterolemia with statins results in a reduction of plasma/serum levels of CoQ10 (Banach et al., 2015; Qu et al., 2018). Statins are inhibitors of HMG-CoA reductase, an enzyme that plays an important regulatory role in the production of mevalonate, which is not only a key precursor in the metabolic pathway of cholesterol, but also in the CoQ10 synthesis (Nawarskas, 2005). As a consequence of CoQ10 synthesis inhibition, the mitochondrial respiratory chain could be compromised, impairing

TABLE 1 Therapeutic indications of CoQ10: Pathogenesis, CoQ10 mechanism of action, and level of evidence

Therapeutic indication	Pathogenesis	CoQ10 mechanism of action	Level of evidence	References
Cardiovascular diseases	– Low endogenous CoQ10 levels – Reduced contractile function of cardiac muscle and energy depletion. – Oxidative stress	– Replenishment of CoQ10 levels – Improvement of mitochondrial bioenergetics – As an antioxidant counteracts oxidative stress, which also results in the reduction of risk factors (hypertension and atherosclerosis).	Possibly effective, further studies with a larger sample size and longer follow-up are needed.	Ayers et al. (2018), Flowers et al. (2014), Molyneux et al. (2008), Villalba et al. (2010)
Statin-induced myopathy	– Inhibition of CoQ10 synthesis by statins and reduction of LDL (CoQ10 carriers). – CoQ10 deficiency results in impaired energy production, ultimately inducing myopathy (muscular pain, stiffness, cramps, weakness and fatigue). Rhabdomyolysis and heart muscle function impairment may also occur.	– Replenishment of CoQ10 levels. – Improvement of mitochondrial respiratory chain and energy production.	Possibly effective, larger, and well-designed trials are necessary. Considering that it is safe, it could be considered in high-risk patients that do not tolerate statin therapy and cannot be treated with any other therapeutic agents.	Banach et al. (2015), Littlefield et al. (2014), Marcoff & Thompson (2007), Mendes et al. (2014)
Neurodegenerative diseases	– Low serum levels of CoQ10 – Oxidative stress, increased oxidative damage, and inflammation. – Mitochondrial dysfunction with abnormal energy metabolism. – Cell damage, dysfunction, and death.	– Replenishment of CoQ10 levels. – Antioxidant: reduction of oxidative stress, and of cell dysfunction and death (neuroprotectant). – Mitochondrial function enhancer – Reduction of β-amyloid plaque in transgenic mouse models of Alzheimer disease	Insufficient evidence, further and more robust clinical trials are needed.	Chang et al. (2018), Dhanasekaran & Ren (2005), Mancuso et al. (2009), Somayajulu et al. (2005), X. Yang et al. (2010)
Cancer	– Oxidative stress results in mutagenic and cytotoxic lesions – Low CoQ10 levels associated to higher risk of suffering cancer and with a worse prognosis (especially in breast cancer and melanoma).	– Antioxidant: prevention of lipid peroxidation, and oxidative damage of DNA and proteins. – Possible protective effect in breast cancer and melanoma. – Improved tolerability of anticancer drugs by protection of surrounding normal cells from toxicity. – Reduction of the risk of developing metastases by means of enhancement of IFN action	Insufficient evidence, further studies should be carried out to confirm CoQ10 potential benefits in cancer.	Portakal et al. (2000), Roffe et al. (2004), Rusciani et al. (2006, 2007)
Diabetes	– Hyperglycemia leads to increased production of oxygen free radicals, resulting in tissue damage, insulin resistance, and diabetic complications.	– Antioxidant and free radical scavenger. Prevents tissue damage and the development of diabetic complications such as endothelial dysfunction, which is triggered by oxidative stress.	Insufficient evidence, further studies should be carried out.	Chew and Watts (2004), Giacco and Brownlee (2010), Wei et al. (2009),
CoQ10 deficiencies	– Impaired mitochondrial bioenergetics due to CoQ10 deficiency caused by mutations that affect genes involved in CoQ10 biosynthesis or other causes.	– Restoration of normal CoQ10 levels and mitochondrial bioenergetics, except for when irreversible damage has occurred.	Further evidence is needed regarding optimal treatment of CoQ10 deficiency	Quinzii and Hirano (2011), Potgieter et al. (2013)

(Continues)

TABLE 1 (Continued)

Therapeutic indication	Pathogenesis	CoQ10 mechanism of action	Level of evidence	References
Migraine	– Low CoQ10 concentrations, oxidative stress, and mitochondrial impairment.	– Restoration of normal CoQ10 levels and mitochondrial bioenergetics, which leads to reduction of inflammation, as well as the severity, length, and frequency of migraine attacks	Possibly effective, further research is needed to clarify the role of CoQ10 in the management of migraine.	Dahri et al. (2018), Mason (2018), Rozen et al. (2002), Shoeibi et al. (2017)
Athletic performance	– High-rate aerobic metabolism during physical exercise results in increased production of free radicals.	– Reduction of oxidative stress and muscular damage, resulting in improved exercise capacity.	Insufficient evidence. Further research is needed.	Abdizadeh et al. (2015), Díaz-Castro et al. (2012), Leelarungrayub et al. (2010),
Male infertility	– Oxidative stress leads to increased DNA damage and lipid peroxidation, and is detrimental on sperm function, ultimately resulting in infertility. – Low CoQ10 levels associated to impaired sperm count and motility.	– CoQ10 counterbalances excessive amounts of reactive oxygen species. – It also plays a role in energy production at sperm mitochondria, which leads to pro-motility effects and improved seminal parameters.	Insufficient evidence, further studies are needed to clarify the role of CoQ10 in the management male infertility.	Bisht et al. (2017), Hosen et al. (2015), Majzoub (2018)

energy production and ultimately inducing myopathy (Abd & Jacobson, 2011). In addition, considering that serum CoQ10 is carried by lipoproteins, statins-induced LDL reduction has been proposed as another probable mechanism for CoQ10 blood levels depletion (Marcoff & Thompson, 2007).

Patients on statin therapy who complain about muscular symptoms may need to discontinue the treatment depending on their symptom tolerability, and due to the possible presence of rhabdomyolysis. The administration of CoQ10 has been suggested to prevent and treat statin-induced myopathy. In fact, Langsjoen and Langsjoen (2003) recommended to use supplemental CoQ10 with all HMG-CoA reductase inhibitors, since its increased potency or dose could result in a more severe CoQ10 depletion, leading to an increased likelihood of heart muscle function impairment. Caso, Kelly, McNurlan, and Lawson (2007) and Littlefield, Beckstrand, and Luthy (2014) reported that CoQ10 supplementation (30 to 200 mg/day) may decrease muscular pain associated with statin treatment, offering an alternative to treatment discontinuation. However, despite mechanistic studies and deductive reasoning suggest that CoQ10 dysregulation could be the cause or contribute to statin-associated muscular symptoms (Qu et al., 2018; Zaleski, Taylor, & Thompson, 2018), a meta-analysis of the available randomized controlled trials and a systematic review did not suggest any significant benefit of CoQ10 supplementation in improving statin-induced myopathy (Banach et al., 2015; Marcoff & Thompson, 2007). So, larger and well-designed trials are necessary to address this issue, since there is insufficient evidence to prove the role of CoQ10 deficiency in statin-associated myopathy, and thus to support its routine use. However, taking into consideration that CoQ10 supplementation is safe, it could be considered in those high-risk patients that do not tolerate optimal doses of statin therapy, and who cannot be satisfactorily treated with any other therapeutic agents (Deichmann, Lavie, & Andrews, 2010; Marcoff & Thompson, 2007).

4.2.3 | Neurodegenerative diseases

Oxidative stress, mitochondrial dysfunction with abnormal energy metabolism, increased oxidative damage, and inflammation play a role in different neurodegenerative diseases. As a consequence, there is an interest in exploring antioxidant treatments (Salama et al., 2013; Villalba et al., 2010). CoQ10, as a strong antioxidant and mitochondrial function enhancer, could be a promising neuroprotectant to slow the progression of Alzheimer's, Parkinson's, and Huntington's disease, as well as other neurodegenerative disorders such as amyotrophic lateral sclerosis and Friedrich's ataxia (Dhanasekaran & Ren, 2005; Mancuso, Orsucci, Calsolaro, Choub, & Siciliano, 2009). In fact, CoQ10 had an in vitro neuroprotective role, since it was capable of stabilizing the mitochondrial membrane when neuronal cells were subjected to oxidative stress. This led to reduced cell dysfunction and death, which is a characteristic of the aforementioned neurodegenerative diseases (Somayajulu et al., 2005). In studies with animal models, results confirmed its neuroprotective role (Spindler, Beal, & Henchcliffe, 2009). Indeed, CoQ10 was not only capable of protecting neuronal cells from oxidative damage in a Parkinson's disease model (S. Sharma et al., 2004), but also reduced β-amyloid plaque in

transgenic mouse models of Alzheimer disease (X. Yang, Dai, Li, & Yang, 2010), and led to behavioral and survival improvement in transgenic mouse models of fronto-temporal dementia (Elipenahli et al., 2012). In addition, different neurodegenerative diseases were found to be associated with lower serum levels of CoQ10, which indicated a lower antioxidant capacity, leading to a higher oxidative damage and cell death. Thus, assessing serum CoQ10 levels could useful for predicting the development of different neurodegenerative diseases, such as dementia (Momiyama, 2014).

Despite findings in cell and animal models have demonstrated a relationship between CoQ10 and neuroprotection, there is insufficient evidence to support its routine use in humans. Chang, Cheng, Chiang, and Chen (2018) reviewed the current findings on lipophilic antioxidants and their implication in neurodegenerative diseases, and concluded that since no clinical trials demonstrated that a specific antioxidant intervention prevented disease progression or decreased risk, it is necessary that further and more robust clinical trials are carried out in order to develop new or improved therapeutic strategies for neurodegenerative diseases.

4.2.4 | Cancer

CoQ10 is an important antioxidant capable of preventing lipid peroxidation and oxidative damage of DNA and proteins (Brayfield, 2017). Since oxidative DNA damage, including mutagenic and cytotoxic lesions, is implicated in the initiation phase of cancer (Valko, Izakovic, Mazur, Rhodes, & Telser, 2004), CoQ10 could reduce the susceptibility of cells to cancer development. In addition, low levels of CoQ10 were observed in breast tumour tissues, when compared to the corresponding noncancerous tissues. For this reason, its exogenous administration may help increase the protective effect of endogenous CoQ10 in breast tissue, especially in high-risk patients (Portakal et al., 2000). CoQ10 levels were also significantly lower in melanoma patients and in those who developed metastasis, than in control subjects, and the disease-free interval was shorter in patients with lower levels of CoQ10. Moreover, there was a significant correlation between CoQ10 levels and the thickness of the primary tumour, with the highest CoQ10 levels being observed in patients with thinner tumors (Rusciani et al., 2006).

In contrast, concerning the cell response to chemotherapeutic agents, tumor cells tend to present higher antioxidant activities, that is the Warburg effect, which confers an increased protection to oxidative stress, and therefore resistance to pro-oxidant chemotherapeutic treatments (Sosa et al., 2013). In addition, Brea-Calvo, Rodríguez-Hernández, Fernández-Ayala, Navas, and Sánchez-Alcázar (2006) reported that chemotherapy induced an increase in CoQ10 levels in cancer cell lines, which is believed to be part of a cellular defence mechanism against chemotherapy treatment. Therefore, by means of the same mechanism, the administration of CoQ10 could be translated into increased CoQ10 levels (Bhagavan & Chopra, 2007) that may also protect the surrounding normal cells from toxicity and contribute to its survival, leading to an improved tolerability of anticancer drugs (Portakal et al., 2000). For instance, cardiotoxicity associated to anthracyclines treatment, which is a commonly used chemotherapeutic agent, may be preventable by its concurrent administration with CoQ10 (Conklin, 2005). Roffe, Schmidt, and Ernst (2004) reviewed the evidence available for oral supplementation with CoQ10 to reduce the toxicity and improve the tolerability of cancer treatments and concluded that CoQ10 may provide improved tolerability as well as protection against toxicity. However, due to weaknesses in the design and a poor overall methodologic quality of the trials reviewed, these results should be interpreted with caution.

CoQ10 could also be useful to reduce the risk of developing metastases. While immunomodulators such as interferons (IFN) are used in patients with melanoma to prevent the development of residual micrometastases after surgery, the immune response initiated by IFN seems to require large amounts of ATP. Thus, CoQ10 could be useful to enhance IFN action. In fact, Rusciani et al. (2007) reported that the risk of developing metastases was about 10 times lower in patients treated with IFN+CoQ10, compared with the IFN group. In addition, Premkumar, Yuvaraj, Vijayasarathy, Gangadaran, and Sachdanandam (2007) reported a reduction of serum tumor marker levels, and thus a reduced risk of cancer recurrence and metastases when breast cancer patients received a supplement of CoQ10, riboflavin, and niacin, along with tamoxifen.

Overall, observational studies showed that lower CoQ10 plasmatic concentrations were associated with a higher risk of suffering cancer, and with a worse prognosis. In contrast, those patients receiving CoQ10 treatment may have an increased life expectancy, probably due to antioxidant protection against heart and hepatic toxicity caused by free radicals generated by chemotherapy (Mason, 2018). Thus, while CoQ10 may be effective as a chemopreventive and antimetastatic agent, and in improving the tolerability to cancer treatments, further studies should be carried out to confirm CoQ10 potential benefits in cancer, since scientific evidence is insufficient at the moment.

4.2.5 | Diabetes

Diabetes is characterized by hyperglycaemia, which has been reported to cause an increased production of oxygen free radicals leading to oxidative stress, and that may play an important role in the pathogenesis of diabetes and diabetic complications (Wei et al., 2009). Indeed, high levels of free radicals and antioxidant defence depletion can lead to cellular damage, increased lipid peroxidation, and development of insulin resistance, which may result in

diabetic complications (Maritim, Sanders, & Watkins, 2003). Since CoQ10 is a potent antioxidant and free radical scavenger, it may be regarded as an indicator for oxidative stress and has been proposed as a complementary therapeutic approach for diabetes. A higher blood concentration of CoQ10 was reported not only in rats with induced diabetes (Kucharská, Braunová, Ulicná, Zlatos, & Gvozdjáková, 2000), but also in children with type 1 diabetes when compared to healthy individuals (Menke, Niklowitz, Wiesel, & Andler, 2008). However, lower CoQ10 levels were observed in heart and liver mitochondria of rats with induced diabetes. Taking all these into consideration, CoQ10 may be regarded as a body self-protection mechanism during a state of oxidative stress.

In addition, several studies were carried out to evaluate the possible protective role of CoQ10 supplementation in diabetic complications. These are caused by prolonged exposure to high glucose levels, which leads to mitochondrial superoxide overproduction that is the major mediator of tissue damage (Giacco & Brownlee, 2010). Cardiovascular disease is the major complication of type 2 diabetes and its inception is related to endothelial dysfunction. While oxidative stress may be central to the development of endothelial dysfunction, several reports suggest that CoQ10 supplementation may improve abnormal endothelial function by activating endothelial nitric oxide synthase and mitochondrial oxidative phosphorylation (Chew & Watts, 2004). By way of example, Watts et al. (2002) reported that CoQ10 supplementation improved endothelial function of the brachial artery in patients with type 2 diabetes. In addition, CoQ10 may also act synergistically with anti-atherogenic agents to improve endothelial dysfunction. Indeed, Playford, Watts, Croft, and Burke (2003) reported that the combination of fenofibrate and CoQ10 improved endothelial function in dyslipidaemic type 2 diabetic patients, probably by the regulation of dyslipidaemia and oxidative stress, which increased the bioactivity and/or response to endothelium relaxing factors, including nitric oxide.

To sum up, while CoQ10 may be effective as a complementary therapeutic agent for the treatment of diabetes, further studies should be carried out to confirm CoQ10 potential benefits in diabetes, since scientific evidence is insufficient at the moment.

4.2.6 | Treatment of CoQ10 deficiencies

CoQ10 deficiency, which can be classified as primary when mutations affect genes involved in its biosynthesis, or secondary if related to other causes, is involved in cardiomyopathies and degenerative muscular and neuronal diseases. The major phenotypes provoked by primary CoQ10 deficiencies are encephalomyopathy, severe infantile multisystemic disease, cerebellar ataxia, isolated myopathy, and nephrotic syndrome (Quinzii & Hirano, 2011). The symptoms of these patients ameliorated after receiving long-term and high-dose CoQ10 oral treatment. However, probably due to an irreversible brain damage before treatment and because the poor penetration of CoQ10 across the blood–brain barrier, there was only a partial clinical improvement in cerebral symptoms (Quinzii et al., 2007). Further evidence is needed regarding optimal treatment of CoQ10 deficiency. When it comes to secondary deficiencies, these may occur as a result of mutations in genes not directly involved in CoQ10 biosynthesis, dietary insufficiency, and the use of certain pharmacotherapeutic agents such as statins (Potgieter et al., 2013). The latter has already been reviewed in detail in the corresponding section.

4.2.7 | Migraine

Some studies have suggested that migraine may be the result of mitochondrial impairment, and therefore, since CoQ10 has been shown to improve mitochondrial oxidative phosphorylation in humans, it could be used as a successful migraine preventive to reduce the severity, length, and frequency of headaches (Rozen et al., 2002). In addition, there is an evidence of oxidative stress in migraine pathophysiology, which could explain the depletion of antioxidant levels in migraine patients when compared to controls (Tripathi, Kalita, & Misra, 2018). In fact, migraine patients have lower CoQ10 concentrations (Mason, 2018). Moreover, migraine has also been linked to higher levels of inflammation, and since CoQ10 supplementation was able to decrease certain endogenous inflammatory mediators such as tumor necrosis factor (TNF-α), it showed a significant prophylactic effect on migraine attacks (Dahri, Tarighat-Esfanjani, Asghari-Jafarabadi, & Hashemilar, 2018).

Considering previous studies, a randomized controlled trial confirmed the results of a previous open label study, suggesting that CoQ10 effect began after 1 month of supplementation and it was maximal after 3 months. However, while the open label study reported that CoQ10-treated patients had a reduction in the number of days with migraine headache greater than 50% after 5 to 12 weeks of treatment (Rozen et al., 2002), the average reduction in attack frequency was lower in the placebo-controlled trial, that is, around 33% (Sandor et al., 2005). In addition, recent studies have considered CoQ10 treatment safe and possibly effective for the treatment of migraine. Besides possibly reducing the frequency, length, and severity of headaches (Shoeibi et al., 2017), its use along with other migraine prophylactic agents is well tolerated and efficacious over time (Dahri, Hashemilar, Asghari-Jafarabadi, & Tarighat-Esfanjani, 2017).

Finally, as for recent meta-analysis investigating the effects of CoQ10 supplementation in migraine, Parohan, Sarraf, Javanbakht, Ranji-Burachaloo, and Djalali (2019) concluded

that the greatest impact was on the frequency of attacks. In contrast, Zeng, Li, Lu, Huang, and Di (2019) reported that CoQ10 was able to reduce migraine duration but not the severity and frequency of attacks. Therefore, despite further research is needed to clarify the role of CoQ10 in the management of this health condition, its supplementation in migraine patients is promising and possibly effective.

4.2.8 | Athletic performance

CoQ10 not only has an essential role in energy production, but it is also an efficient free radical scavenger. Due to its high rate of aerobic metabolism, muscle is a potent source of free radicals, whose production can be increased during physical exercise. Given the importance of oxidative stress, inflammation, and muscular damage associated with high-intensity exercise, it would be interesting to assess the possible effect of oral supplementation with antioxidants. In a systematic review, Rosenfeldt, Hilton, Pepe, and Krum (2003) reported that the available studies showed contradictory results.

When it comes to more recent studies, while Lee-larungrayub, Sawattikanon, Klaphajone, Pothongsunan, and Bloomer (2010) reported that CoQ10 supplementation was capable of reducing oxidative stress and improving athletic performance in young swimmers, Östman, Sjödin, Michaëlsson, and Byberg (2012) could not demonstrate that such effects existed. However, this could be explained by differences in dose that was of 300 mg and 90 mg, respectively. Díaz-Castro et al. (2012) reported that CoQ10 was capable of reducing exercise-induced oxidative stress and proinflammatory signaling, and thus to reduce muscular damage, which may result in improved exercise capacity. In addition, CoQ10 may also be beneficial for the prevention of downhill running-induced skeletal muscular damage (Abdizadeh, Jafari, & Armanfar, 2015). Thus, while CoQ10 may be effective to reduce exercise-induced oxidative stress, further studies are needed to clarify its role in performance enhancement since available studies have shown contradictory results.

4.2.9 | Male infertility

Male infertility is a multifactorial disorder involving a wide range of factors including genetic, epigenetic, environmental, and lifestyle-related factors. However, while in most cases the exact cause remains unknown, at a molecular level the contribution of oxidative stress is remarkable (Bisht, Faiq, Tolahunase, & Dada, 2017). Reactive oxygen species (ROS) are produced by sperm cells in small quantities and they play an important role in cell signaling and homeostasis. However, higher ROS levels could have detrimental effects on sperm function, leading to increased DNA damage and lipid peroxidation of the sperm membrane, ultimately resulting in infertility (Hosen, Islam, Begum, Kabir, & Howlader, 2015; Wright, Milne, & Leeson, 2014). CoQ10, as an antioxidant, could help to counterbalance excessive amounts of ROS (A. Mancini, De Marinis, Littarru, & Balercia, 2005). In fact, enzymatic and nonenzymatic antioxidants are naturally occurring in sperm cells and seminal plasma, and among them, CoQ10. It is present at particularly high concentrations in sperm mitochondria, where it plays a role in energy production. For this reason, it is believed to be a pro-motility and antioxidant molecule capable of inhibiting superoxide formation (Majzoub, 2018). Indeed, CoQ10 can be quantified in seminal fluid, where there is a correlation between its concentration and peroxides depletion, as well as sperm count and motility increase (A. Mancini & Balercia, 2011). In addition, lower CoQ10 concentrations in seminal have been correlated with impaired sperm parameters. For this reason, it was interesting to study whether exogenous administration of CoQ10 could improve semen quality and pregnancy rates.

Regarding CoQ10 supplementation, A. Mancini et al. (1994) and Nadjarzadeh et al. (2014) reported that CoQ10 levels increased in seminal plasma following supplementation, which attenuated oxidative stress and improved semen parameters. Results of a systematic review showed that despite CoQ10 improved seminal parameters such as sperm concentration and motility, it was not capable of increasing live birth or pregnancy rates (Lafuente et al., 2013). In contrast, an open-label prospective study found that CoQ10 supplementation improved semen quality with beneficial effects on pregnancy rate (Safarinejad, 2012). Thus, while a beneficial influence was observed in reversing ROS-induced sperm dysfunction and in improving pregnancy rates in some studies, additional studies are needed to determine the optimal dose and antioxidant combination that can be used for the management of male infertility.

4.3 | Safety and precautions

CoQ10 has been widely used as a food supplement and medicinal product for more than 30 years. However, due to an increased scientific evidence supporting the role of oxidative stress and energy impairment in the pathogenesis of different diseases, and the emerging evidence supporting CoQ10 supplementation as an antioxidant and an essential cofactor in mitochondrial synthesis of energy, its use has recently grown with the corresponding increase in daily dosage (Clarke, Black, Stussman, & Nahin, 2015; Hathcock & Shao, 2006). For this reason, safety concerns have received increasing attention. Despite Figure 4 summarizes CoQ10 supplementation safety and precautions, a more in-depth discussion is provided below.

Hidaka et al. (2008) reviewed published reports concerning CoQ10 safety and concluded that it has low toxicity, no genotoxic potential, and does not induce serious adverse effects in humans. In addition, it does not influence endogenous synthesis, nor does it accumulate into plasma or

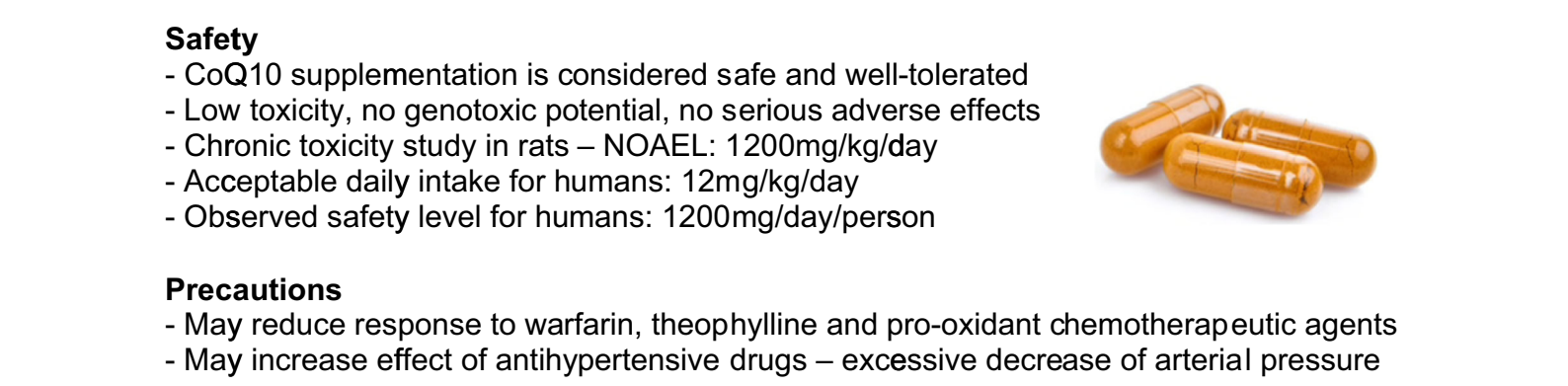

FIGURE 4 CoQ10 supplementation safety and precautions summary

tissues after cessation of supplementation. When it comes to the acceptable daily intake, it is set at 12 mg/kg/day for humans, based on a chronic toxicity study in rats, where the NOAEL was 1,200 mg/kg/day. Moreover, clinical data indicate that the observed safety level for CoQ10 in humans is 1,200 mg/day/person, which is a much higher dose than usual. In line with these findings, in a double-blind, randomized, placebo-controlled trial, no serious adverse events were observed when CoQ10 was taken for 4 weeks at 300, 600, and 900 mg/day by healthy adults. Despite some subjects reported adverse events when CoQ10 was administered, these were also observed with placebo and exhibited no dose dependency, and therefore were regarded as nonrelated to CoQ10 administration. The most commonly reported events included gastrointestinal effects, such as abdominal pain and soft feces, and common cold symptoms, which could be attributed to seasonal factors, since the study was performed in winter. The first may be attributed to the copious amounts of oil used to solvate CoQ10 (Ikematsu, Nakamura, Harashima, Fujii, & Fukutomi, 2006). In addition, a meta-analysis that evaluated CoQ10 effects in Parkinson's disease found that treatment with 1,200 mg/day, and even 2,400 mg/day, was safe and well tolerated. In fact, there was no significant difference of adverse events between CoQ10 and placebo (Zhu et al., 2017). It has to be noted that plasma levels reached a plateau at 2,400 mg/day and did not increase further at 3,000 mg/day (Shults, Flint Beal, Song, & Fontaine, 2004). Finally, Pre2CARE Investigators (2010) reported that high CoQ10 dosages (up to 3,600 mg/day) appeared to be generally safe and well tolerated in subjects with Huntington's disease and in healthy controls. While no serious adverse events were attributed to CoQ10, the most common adverse events were gastrointestinal symptoms. A CoQ10 dose higher than 2,400 mg/day led to higher blood levels, which may result in an increased probability of experiencing gastrointestinal symptoms. For this reason, 2,400 mg/day may provide the best balance between safety/tolerability and blood level of CoQ10.

Overall, data from preclinical and clinical studies indicate that CoQ10 supplementation is highly safe and well tolerated at doses much higher than usual over long periods of time and with limited side effects. Despite doses up to 3,000 mg/day did not cause serious adverse effects in humans, gastrointestinal symptoms may appear when dose is increased beyond 1,200 mg/day/person (Villalba et al., 2010). It has to be noted that safety in children, pregnancy, and lactancy has not been established.

When considering drug interactions, since CoQ10 has some structural similarity to vitamin K, it may increase the metabolism of warfarin through selective interaction with cytochrome P450 enzymes (A. Sharma, Fonarow, Butler, Ezekowitz, & Felker, 2016). As a consequence, CoQ10 may reduce the response to warfarin, causing difficulties in achieving adequate anticoagulation in patients taking CoQ10 and warfarin. This is particularly relevant in heart failure patients, as many of them have concomitant atrial fibrillation requiring lifelong anticoagulation (Ayers et al., 2018). However, there is some preliminary clinical research suggesting that CoQ10 might not significantly decrease the effects of warfarin in patients with a stable international normalized ratio (Nutescu, Shapiro, Ibrahim, & West, 2006). Theophylline may also be affected by CoQ10 supplementation, since it is also metabolized by cytochrome P450 enzymes. In fact, animal studies found altered theophylline pharmacokinetic parameters with CoQ10 coadministration (Baskaran et al., 2008). In addition, as a potent antioxidant, it may confer an increased protection to oxidative stress and therefore, it may reduce the efficacy of certain pro-oxidant chemotherapeutic treatments (Yasueda, Urushima, & Ito, 2016). Finally, since CoQ10 may have an antihypertensive effect, it may lead to an excessive decrease of arterial pressure when is taken together with antihypertensive drugs. Therefore monitoring is advised (Bonakdar & Guarneri, 2005).

To sum up, CoQ10 is safe and well-tolerated with few drug interactions and minor side effects. However, it is important to continue providing safety information and data on CoQ10 to

ensure its appropriate use as a dietary supplement. The FDA recommends that people with certain health conditions and under treatment should consult with a health care professional before using any dietary supplement, including CoQ10.

4.4 | Formulation

CoQ10 is a fine yellow to orange crystalline powder that decomposes and darkens when exposed to light. It is tasteless with a slight odor, practically water insoluble, slightly soluble in ethanol, and soluble in acetone and ether, and with a melting point around 48 °C (Dietary Supplements Compendium, 2019; Ubidecarenone, 2019). Due to its high molecular weight (863.34 g/mol) and strong hydrophobicity (PubChem, 2019), it has a low oral bioavailability in humans (Miles, 2007). In addition, CoQ10 is unstable and vulnerable to heat, light, and oxygen, which also limits its applications in medicine and functional food formulations (Fir et al., 2009). Its stability when stored in the original container, protected from light, in a dry place at low temperature (below 25 °C) is around 24 months.

Concerning its formulation in food supplements, high dose and stable CoQ10 formulations are difficult to achieve due to its physicochemical properties (Li & Chen, 2017). As a fine powder with poor rheology and low melting point, CoQ10 is difficult to be dosed accurately and pressed into tablets, especially when temperature rises beyond its melting point, leading to stickiness and adherence to machinery surfaces (Abdel-Hamid & Betz, 2012; Nakamura, Otsuka, Yoshino, Sakamoto, & Yuasa, 2016). In addition, since CoQ10 is affected by light, heat, and oxidation, it should be stored in a cool and dark place, preferably in an airtight container (Ubidecarenone, 2019). For this reason and taking into consideration that CoQ10 has gained increasing interest over the years, research has been focused in overcoming the issues that limit its formulation into food supplements and medicinal products. Thus, research efforts have been made to improve its solubility, oral bioavailability, and stability (Beg et al., 2010; Kumar et al., 2016).

As a food supplement, CoQ10 suggested daily dose varies depending on the indication, but is usually around 30 to 100 mg for healthy people, reaching up to 60 to 1,200 mg when used in certain medical conditions (Pravst et al., 2010). Since the efficiency of absorption decreases as the dose increases, and reaching certain CoQ10 plasma concentrations is necessary to promote uptake by peripheral tissues and to achieve clinical effects, formulations allowing a higher bioavailability should be developed, improved, and prioritized (Bhagavan & Chopra, 2007). CoQ10 is mainly found in mono- or multicomponent softgels, capsules, and tablets. However, while it is used to be incorporated as a simple crystalline powder, it was found that the amount and characteristics of co-ingested lipids may benefit CoQ10 absorption and bioavailability, and therefore it is usually dissolved in a lipid phase (Shuqin Xia et al., 2006). Carrier oil selection is extremely important, since it may result in different bioavailability. Solubilized formulas have shown higher absorption and bioavailability, and thus plasmatic levels were significantly higher when compared to nonsolubilized CoQ10 powder (Bhagavan & Chopra, 2007; Miles, 2007). For this reason, different formulation approaches including novel delivery systems such as self-emulsified drug delivery systems (SEDDS), nanoemulsions, or cyclodextrin complexes have been tested to improve CoQ10 bioavailability when it is incorporated into softgels, capsules, and tablets (Barakat et al., 2013; Schulz et al., 2006). By way of example, different formulation approaches will be briefly reviewed below.

As for cyclodextrin inclusion, it is widely used in the pharmaceutical and food supplement industry since it provides improved stability against heat, oxidation, and UV. In addition, cyclodextrins can form inclusion complexes with lipophilic substances such as CoQ10, leading to improved stability, water solubility, and bioavailability (Terao et al., 2006). SEDDS, which are composed of an oil, surfactant, and cosurfactant, as well as the vehiculized active ingredient, are also used to enhance solubility and bioavailability of poorly water-soluble substances like CoQ10 (Balakrishnan et al., 2009). In addition, certain formulations may take advantage of CoQ10's low melting point to form an amorphous solid dispersion, which is also effective at enhancing solubility, stability, and dissolution, and may also improve flowability (Nepal et al., 2010). Besides, spray-drying microencapsulation with previous emulsification has also been successfully used to improve water dispersion, stability, and bioaccessibility of CoQ10 (Bule et al., 2010; Zhao & Tang, 2016). Finally, despite further research is needed regarding oral supplementation with CoQ10-containing liposomes in humans, improved bioavailability was reported in oral (Shao, Yang, & Han, 2015) and topical application of liposomal CoQ10 in rats (W.-C. Lee & Tsai, 2010).

5 | CONCLUSION

CoQ10 not only plays an essential role in the synthesis of cellular energy in the form of ATP but it is also a strong lipophilic antioxidant. Despite being endogenously synthesized in the human body and found in plant and animal tissues that are part of our diet, different factors can lower its physiological concentrations. While CoQ10 deficiencies have been reported in certain diseases and conditions where oxidative stress plays a significant role, whether the deficiency is a cause or consequence remains unknown. However, since a number of clinical trials have observed that its oral administration provided beneficial effects on different disorders that have been associated with low CoQ10 levels and high

oxidative stress, it has been suggested as a promising therapeutic agent to prevent and slow the progression of these diseases that include cardiovascular diseases, statins-induced myopathy, neurodegenerative diseases, cancer, diabetes, CoQ10 deficiencies, migraine, athletic performance, and male infertility.

These findings on the potential health benefits of CoQ10 supplementation have led to an increased consumer demand. In addition, in the context of population aging and the healthy living trend, consumers are becoming more aware than ever of ingredients in their food and their properties, and an increasing number of consumers are seeing food as a medicine. For this reason, dietary supplements stand out as one of the fastest growing healthcare categories. Consumer base expansion has led to an urgent need for researchers, dietitians, physicians, and regulators to broaden the scientific evidence on the efficacy and safety of a wide range of active ingredients found in food supplements, including CoQ10. This review intended to provide them with a breadth of evidence on CoQ10 efficacy, safety, and formulation challenges. However, further studies must be carried out in order to clarify the role of CoQ10 and the optimal therapeutic regimen in the management of different health conditions. Additional investigation on physicochemical properties, pharmacokinetics, stability, and efficacy is also needed to deepen the knowledge on CoQ10, and to allow formulators improve CoQ10 properties by means of different techniques. This is especially relevant since solubility, but especially stability and bioavailability concerns, hinders its use in food supplements and medicinal products. For this reason, further research is needed to overcome these issues. Finally, although there is insufficient evidence to conclude its efficacy on different therapeutic indications, it is worth highlighting that CoQ10 supplementation is safe and well tolerated at doses much higher than usual, with few drug interactions and minor side effects. However, people with certain health conditions and under treatment should consult with a health care professional before using CoQ10.

AUTHOR CONTRIBUTIONS

Conception, literature research, and writing were performed by M. Arenas-Jal. Field experience and critical review of the manuscript were performed by J.M. Suñé-Negre and E. García-Montoya.

CONFLICT OF INTEREST

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REFERENCES

Abd, T. T., & Jacobson, T. A. (2011). Statin-induced myopathy: A review and update. *Expert Opinion on Drug Safety*, *10*(3), 373–387. https://doi.org/10.1517/14740338.2011.540568

Abdel-Hamid, S., & Betz, G. (2012). A novel tool for the prediction of tablet sticking during high speed compaction. *Pharmaceutical Development and Technology*, *17*(6), 747–754. https://doi.org/10.3109/10837450.2011.580761

Åberg, F., Appelkvist, E.-L., Dallner, G., & Ernster, L. (1992). Distribution and redox state of ubiquinones in rat and human tissues. *Archives of Biochemistry and Biophysics*, *295*(2), 230–234. https://doi.org/10.1016/0003-9861(92)90511-T

Abdizadeh, L., Jafari, A. & Armanfar, M. (2015). Effects of short-term coenzyme Q10 supplementation on markers of oxidative stress and inflammation after downhill running in male mountaineers. *Science & Sports*, *30*, 328–334. https://doi.org/10.1017/S0007114517003774

Alcázar-Fabra, M., Navas, P., & Brea-Calvo, G. (2016). Coenzyme Q biosynthesis and its role in the respiratory chain structure. *Biochimica et Biophysica Acta (BBA) - Bioenergetics*, *1857*(8), 1073–1078. https://doi.org/10.1016/J.BBABIO.2016.03.010

Arenas-Jal, M., Suñé-Negre, J. M., Pérez-Lozano, P., & García-Montoya, E. (2019). Trends in the food and sports nutrition industry: A review. *Critical Reviews in Food Science and Nutrition*, 1–17. https://doi.org/10.1080/10408398.2019.1643287

Ayers, J., Cook, J., Koenig, R. A., Sisson, E. M., & Dixon, D. L. (2018). Recent developments in the role of coenzyme Q10 for coronary heart disease: A systematic review. *Current Atherosclerosis Reports*, *20*(6), 29. https://doi.org/10.1007/s11883-018-0730-1

Balakrishnan, P., Lee, B.-J., Oh, D. H., Kim, J. O., Lee, Y.-I., Kim, D.-D., … Choi, H.-G. (2009). Enhanced oral bioavailability of coenzyme Q10 by self-emulsifying drug delivery systems. *International Journal of Pharmaceutics*, *374*(1–2), 66–72. https://doi.org/10.1016/J.IJPHARM.2009.03.008

Banach, M., Serban, C., Sahebkar, A., Ursoniu, S., Rysz, J., Muntner, P., … Mikhailidis, D. P. (2015). Effects of coenzyme Q10 on statin-induced myopathy: A meta-analysis of randomized controlled trials. *Mayo Clinic Proceedings*, *90*(1), 24–34. https://doi.org/10.1016/j.mayocp.2014.08.021

Banach, M., Serban, C., Ursoniu, S., Rysz, J., Muntner, P., Toth, P. P., … Sahebkar, A. (2015). Statin therapy and plasma coenzyme Q10 concentrations—A systematic review and meta-analysis of placebo-controlled trials. *Pharmacological Research*, *99*, 329–336. https://doi.org/10.1016/J.PHRS.2015.07.008

Barakat, A., Shegokar, R., Dittgen, M., & Müller, R. H. (2013). Coenzyme Q10 oral bioavailability: Effect of formulation type. *Journal of Pharmaceutical Investigation*, *43*(6), 431–451. https://doi.org/10.1007/s40005-013-0101-4

Baskaran, R., Shanmugam, S., Nagayya-Sriraman, S., Kim, J. H., Jeong, T. C., Yong, C. S., … Yoo, B. K. (2008). The effect of coenzyme Q10 on the pharmacokinetic parameters of theophylline.

Archives of Pharmacal Research, *31*(7), 938–944. https://doi.org/10.1007/s12272-001-1250-1

Beg, S., Javed, S., & JKohli, K. (2010). Bioavailability enhancement of coenzyme Q10: An extensive review of patents. *Recent Patents on Drug Delivery & Formulation*, *4*(3), 245–257. https://doi.org/10.2174/187221110793237565

Bentinger, M., Tekle, M., & Dallner, G. (2010). Coenzyme Q—Biosynthesis and functions. *Biochemical and Biophysical Research Communications*, *396*(1), 74–79. https://doi.org/10.1016/J.BBRC.2010.02.147

Bhagavan, H. N., & Chopra, R. K. (2006). Coenzyme Q10: Absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radical Research*, *40*(5), 445–453. https://doi.org/10.1080/10715760600617843

Bhagavan, H. N., & Chopra, R. K. (2007). Plasma coenzyme Q10 response to oral ingestion of coenzyme Q10 formulations. *Mitochondrion*, *7*, S78–S88. https://doi.org/10.1016/J.MITO.2007.03.003

Bhagavan, H. N., Chopra, R. K., Craft, N. E., Chitchumroonchokchai, C., & Failla, M. L. (2007). Assessment of coenzyme Q10 absorption using an in vitro digestion-Caco-2 cell model. *International Journal of Pharmaceutics*, *333*(1–2), 112–117. https://doi.org/10.1016/J.IJPHARM.2006.10.007

Bisht, S., Faiq, M., Tolahunase, M. & Dada, R. (2017). Oxidative stress and male infertility. *Nature Reviews Urology*, *14*, 470–485. https://doi.org/10.1038/nrurol.2017.69

Bonakdar, R. A., & Guarneri, E. (2005). Coenzyme Q10. *American Family Physician*, *72*(6), 1065–1070.

Brayfield, A. (Ed.). (2017). Ubidecarenone. In *Martindale: The complete drug reference* (39th ed.). London: Pharmaceutical Press. Retrieved from https://www.medicinescomplete.com

Brea-Calvo, G., Rodríguez-Hernández, Á., Fernández-Ayala, D. J. M., Navas, P., & Sánchez-Alcázar, J. A. (2006). Chemotherapy induces an increase in coenzyme Q10 levels in cancer cell lines. *Free Radical Biology and Medicine*, *40*(8), 1293–1302. https://doi.org/10.1016/J.FREERADBIOMED.2005.11.014

Bruckert, E., Hayem, G., Dejager, S., Yau, C., & Bégaud, B. (2005). Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—The PRIMO study. *Cardiovascular Drugs and Therapy*, *19*(6), 403–414. https://doi.org/10.1007/s10557-005-5686-z

Bule, M. V., Singhal, R. S., & Kennedy, J. F. (2010). Microencapsulation of ubiquinone-10 in carbohydrate matrices for improved stability. *Carbohydrate Polymers*, *82*(4), 1290–1296. https://doi.org/10.1016/j.carbpol.2010.07.012

Business Development Bank of Canada. (2016). Five game-changing consumer trends. Retrieved from https://www.bdc.ca/EN/Documents/analysis_research/Consumer_Trends_Report_EN.pdf

Caballero, B., Allen, L., & Prentice, A. (2013). *Encyclopedia of human nutrition* (3rd ed.). Academic Press.

Caso, G., Kelly, P., McNurlan, M. A., & Lawson, W. E. (2007). Effect of coenzyme Q10 on myopathic symptoms in patients treated with statins. *The American Journal of Cardiology*, *99*(10), 1409–1412. https://doi.org/10.1016/J.AMJCARD.2006.12.063

Chang, K.-H., Cheng, M.-L., Chiang, M.-C., & Chen, C.-M. (2018). Lipophilic antioxidants in neurodegenerative diseases. *Clinica Chimica Acta*, *485*, 79–87. https://doi.org/10.1016/J.CCA.2018.06.031

Chew, G. T., & Watts, G. F. (2004). Coenzyme Q10 and diabetic endotheliopathy: Oxidative stress and the "recoupling hypothesis." *QJM*, *97*(8), 537–548. https://doi.org/10.1093/qjmed/hch089

Chistiakov, D. A., Shkurat, T. P., Melnichenko, A. A., Grechko, A. V., & Orekhov, A. N. (2018). The role of mitochondrial dysfunction in cardiovascular disease: A brief review. *Annals of Medicine*, *50*(2), 121–127. https://doi.org/10.1080/07853890.2017.1417631

Clarke, T. C., Black, L. I., Stussman, B. J., & Nahin, R. L. (2015). Trends in the use of complementary health approaches among adults: United States, 2002–2012. Retrieved from https://www.cdc.gov/nchs/data/nhsr/nhsr079.pdf

Conklin, K. A. (2005). Coenzyme Q10 for prevention of anthracycline-induced cardiotoxicity. *Integrative Cancer Therapies*, *4*(2), 110–130. https://doi.org/10.1177/1534735405276191

Dahri, M., Hashemilar, M., Asghari-Jafarabadi, M., & Tarighat-Esfanjani, A. (2017). Efficacy of coenzyme Q10 for the prevention of migraine in women: A randomized, double-blind, placebo-controlled study. *European Journal of Integrative Medicine*, *16*, 8–14. https://doi.org/10.1016/J.EUJIM.2017.10.003

Dahri, M., Tarighat-Esfanjani, A., Asghari-Jafarabadi, M., & Hashemilar, M. (2018). Oral coenzyme Q10 supplementation in patients with migraine: Effects on clinical features and inflammatory markers. *Nutritional Neuroscience*, 1–9. https://doi.org/10.1080/1028415X.2017.1421039

de Dieu Ndikubwimana, J., & Lee, B. H. (2014). Enhanced production techniques, properties and uses of coenzyme Q10. *Biotechnology Letters*, *36*(10), 1917–1926. https://doi.org/10.1007/s10529-014-1587-1

Deichmann, R., Lavie, C., & Andrews, S. (2010). Coenzyme Q10 and statin-induced mitochondrial dysfunction. *The Ochsner Journal*, *10*(1), 16–21.

Dhanasekaran, M., & Ren, J. (2005). The emerging role of coenzyme Q-10 in aging, neurodegeneration, cardiovascular disease, cancer and diabetes mellitus. *Current Neurovascular Research*, *2*(5), 447–459.

Díaz-Castro, J., Guisado, R., Kajarabille, N., García, C., Guisado, I. M., de Teresa, C., & Ochoa, J. J. (2012). Coenzyme Q10 supplementation ameliorates inflammatory signaling and oxidative stress associated with strenuous exercise. *European Journal of Nutrition*, *51*(7), 791–799. https://doi.org/10.1007/s00394-011-0257-5

Dietary Supplements Compendium. (2019). Ubidecarenone. Retrieved from https://www.usp.org/products/dietary-supplements-compendium

DiNicolantonio, J. J., Bhutani, J., McCarty, M. F., & O'Keefe, J. H. (2015). Coenzyme Q10 for the treatment of heart failure: A review of the literature. *Open Heart*, *2*(1), e000326. https://doi.org/10.1136/openhrt-2015-000326

DrugBank. (2019). Ubidecarenone. Retrieved from https://www.drugbank.ca/drugs/DB09270

EFSA Panel on Dietetic Products; Nutrition and Allergies. (2010). Scientific opinion on the substantiation of health claims related to coenzyme Q10 and contribution to normal energy-yielding metabolism, maintenance of normal blood pressure, protection of DNA, proteins and lipids from oxidative damage, contribution to no. *EFSA Journal*, *8*(10), 1793. https://doi.org/10.2903/j.efsa.2010.1793

Elipenahli, C., Stack, C., Jainuddin, S., Gerges, M., Yang, L., Starkov, A., … Dumont, M. (2012). Behavioral improvement after chronic administration of coenzyme Q10 in P301S transgenic mice. *Journal of Alzheimer's Disease*, *28*(1), 173–182. https://doi.org/10.3233/JAD-2011-111190

Eskin, N. A. M., & Snait, T. (2006). *Dictionary of nutraceuticals and functional foods*. Boca Raton, FL: CRC Press.

Euromonitor. (2017). Consumer lifestyles in 2017: Global survey results. Retrieved from https://go.euromonitor.com/white-paper-survey-2017-lifestyles.html

European Food Safety Authority. (2019). Food supplements. Retrieved from https://www.efsa.europa.eu/en/topics/topic/food-supplements

Fir, M. M., Smidovnik, A., Milivojevic, L., Zmitek, J., & Prosek, M. (2009). Studies of CoQ10 and cyclodextrin complexes: Solubility, thermo- and photo-stability. *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, *64*(3–4), 225–232. https://doi.org/10.1007/s10847-009-9555-4

Flowers, N., Hartley, L., Todkill, D., Stranges, S., & Rees, K. (2014). Co-enzyme Q10 supplementation for the primary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD010405.pub2

Food and Agriculture Organization of the United Nations. (2009). How to feed the world in 2050. Retrieved from http://www.fao.org/fileadmin/templates/wsfs/docs/expert_paper/How_to_Feed_the_World_in_2050.pdf

Food and Agriculture Organization of the United Nations. (2018). *Global health observatory data*. Geneva, Switzerland: World Health Organization. Retrieved from https://www.who.int/gho/mortality_burden_disease/life_tables/en/

Fuller, B., Smith, D., Howerton, A., & Kern, D. (2006). Anti-inflammatory effects of CoQ10 and colorless carotenoids. *Journal of Cosmetic Dermatology*, *5*(1), 30–38. https://doi.org/10.1111/j.1473-2165.2006.00220.x

Gao, L., Mao, Q., Cao, J., Wang, Y., Zhou, X., & Fan, L. (2012). Effects of coenzyme Q10 on vascular endothelial function in humans: A meta-analysis of randomized controlled trials. *Atherosclerosis*, *221*(2), 311–316. https://doi.org/10.1016/j.atherosclerosis.2011.10.027

Garrido-Maraver, J., Cordero, M. D., Oropesa-Ávila, M., Fernández Vega, A., de la Mata, M., Delgado Pavón, A., … Sánchez-Alcázar, J. A. (2014). Coenzyme Q10 therapy. *Molecular Syndromology*, *5*(3–4), 187–197. https://doi.org/10.1159/000360101

Giacco, F., & Brownlee, M. (2010). Oxidative stress and diabetic complications. *Circulation Research*, *107*(9), 1058–1070. https://doi.org/10.1161/CIRCRESAHA.110.223545

Hathcock, J. N., & Shao, A. (2006). Risk assessment for coenzyme Q10 (Ubiquinone). *Regulatory Toxicology and Pharmacology*, *45*(3), 282–288. https://doi.org/10.1016/J.YRTPH.2006.05.006

Hidaka, T., Fujii, K., Funahashi, I., Fukutomi, N., & Hosoe, K. (2008). Safety assessment of coenzyme Q10 (CoQ10). *BioFactors*, *32*(1–4), 199–208. https://doi.org/10.1002/biof.5520320124

Hosen, M. B., Islam, M. R., Begum, F., Kabir, Y. & Howlader, M. Z. H. (2015). Oxidative stress induced sperm DNA damage, a possible reason for male infertility. *Iranian Journal of Reproductive Medicine*, *13*, 525. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/26568756

Hosen, M. B., Islam, M. R., Begum, F., Kabir, Y. & Howlader, M. Z. H. (2015). Oxidative stress induced sperm DNA damage, a possible reason for male infertility. *Iranian Journal of Reproductive Medicine*, *13*, 525. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4637119/

Ikematsu, H., Nakamura, K., Harashima, S., Fujii, K., & Fukutomi, N. (2006). Safety assessment of coenzyme Q10 (Kaneka Q10) in healthy subjects: A double-blind, randomized, placebo-controlled trial. *Regulatory Toxicology and Pharmacology*, *44*(3), 212–218. https://doi.org/10.1016/J.YRTPH.2005.12.002

Kagan, V. E., Fabisiak, J. P., & Quinn, P. J. (2000). Coenzyme Q and vitamin E need each other as antioxidants. *Protoplasma*, *214*(1–2), 11–18. https://doi.org/10.1007/BF02524257

Kalenikova, E. I., Gorodetskaya, E. A., & Medvedev, O. S. (2008). Pharmacokinetics of coenzyme Q10. *Bulletin of Experimental Biology and Medicine*, *146*(3), 313–316. https://doi.org/10.1007/s10517-008-0270-8

Kapoor, P., & Kapoor, A. K. (2013). Coenzyme Q10-A novel molecule. *JIACM*, *14*, 37–45. Retrieved from http://medind.nic.in/jac/t13/i1/jact13i1p37.pdf

Kawamukai, M. (2009). Biosynthesis and bioproduction of coenzyme Q_{10} by yeasts and other organisms. *Biotechnology and Applied Biochemistry*, *53*(4), 217–226. https://doi.org/10.1042/BA20090035

Kearney, J. (2010). Food consumption trends and drivers. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *365*(1554), 2793–2807. https://doi.org/10.1098/rstb.2010.0149

Kingdomway Nutrition. (2019). Coenzyme Q10. Retrieved from http://kdw-usa.com/products/173.htm

Kucharská, J., Braunová, Z., Ulicná, O., Zlatos, L., & Gvozdjáková, A. (2000). Deficit of coenzyme Q in heart and liver mitochondria of rats with streptozotocin-induced diabetes. *Physiological Research*, *49*(4), 411–418.

Kumar, S., Rao, R., Kumar, A., Mahant, S., & Nanda, S. (2016). Novel carriers for coenzyme Q10 delivery. *Current Drug Delivery*, *13*(8), 1184–1204.

Langsjoen, P. H., & Langsjoen, A. M. (2003). The clinical use of HMG CoA-reductase inhibitors and the associated depletion of coenzyme Q10. A review of animal and human publications. *BioFactors*, *18*(1–4), 101–111. https://doi.org/10.1002/biof.5520180212

Lee, S. Q. E., Tan, T. S., Kawamukai, M., & Chen, E. S. (2017). Cellular factories for coenzyme Q10 production. *Microbial Cell Factories*, *16*(1), 39. https://doi.org/10.1186/s12934-017-0646-4

Lee, W.-C., & Tsai, T.-H. (2010). Preparation and characterization of liposomal coenzyme Q10 for in vivo topical application. *International Journal of Pharmaceutics*, *395*(1–2), 78–83. https://doi.org/10.1016/J.IJPHARM.2010.05.006

Leelarungrayub, D., Sawattikanon, N., Klaphajone, J., Pothongsunan, P., & Bloomer, R. J. (2010). Coenzyme Q10 supplementation decreases oxidative stress and improves physical performance in young swimmers: A pilot study. *The Open Sports Medicine Journal* (Vol. *4*). https://doi.org/10.2174/1874387001004010001

Lafuente, R., González-Comadrán, M., Solà, I., López, G., Brassesco, M., Carreras, R., & Checa, M. A. (2013). Coenzyme Q10 and male infertility: A meta-analysis. *Journal of Assisted Reproduction and Genetics*, *30*, 1147–1156. https://doi.org/10.1007/s10815-013-0047-5

Li, H., & Chen, F. (2017). Preparation and quality evaluation of coenzyme Q10 long-circulating liposomes. *Saudi Journal of Biological Sciences*, *24*(4), 797–802. https://doi.org/10.1016/j.sjbs.2015.10.025

Littlefield, N., Beckstrand, R. L., & Luthy, K. E. (2014). Statins' effect on plasma levels of coenzyme Q10 and improvement in myopathy with supplementation. *Journal of the American Association of Nurse Practitioners*, *26*(2), 85–90. https://doi.org/10.1002/2327-6924.12046

Liu, Z.-X., & Artmann, C. (2009). Relative bioavailability comparison of different coenzyme Q10 formulations with a novel delivery system. *Alternative Therapies in Health and Medicine*, *15*(2), 42–46.

López-Lluch, G., del Pozo-Cruz, J., Sánchez-Cuesta, A., Cortés-Rodríguez, A. B., & Navas, P. (2019). Bioavailability of coenzyme Q10 supplements depends on carrier lipids and solubilization. *Nutrition*, *57*, 133–140. https://doi.org/10.1016/J.NUT.2018.05.020

Mancuso, M., Orsucci, D., Calsolaro, V., Choub, A., & Siciliano, G. (2009). Coenzyme Q10 and neurological diseases. *Pharmaceuticals (Basel, Switzerland)*, *2*(3), 134–149. https://doi.org/10.3390/ph203134

Mancini, A., De Marinis, L., Littarru, G. P. & Balercia, G. (2005). An update of Coenzyme Q10 implications in male infertility: Biochemical and therapeutic aspects. *BioFactors*, *25*, 165–174. https://doi.org/10.1002/biof.5520250119

Mancini, A. & Balercia, G. (2011). Coenzyme Q10 in male infertility: Physiopathology and therapy. *BioFactors*, *37*, 374–380. https://doi.org/10.1002/biof.164

Mancini, A., Conte, B., De Marinis, L., Hallgass, M. E., Pozza, D., Oradei, A. & Littarru, G. P. (1994). Coenzyme Q10 levels in human seminal fluid: Diagnostic and clinical implications. *Molecular Aspects of Medicine*, *15*, s249–s255. https://doi.org/10.1016/0098-2997(94)90035-3

Majzoub, A. (2018). Systematic review of antioxidant types and doses in male infertility: Benefits on semen parameters, advanced sperm function, assisted reproduction and live-birth rate. *Arab Journal of Urology*, *16*, 113–124. https://doi.org/10.1016/j.aju.2017.11.013

Marcoff, L., & Thompson, P. D. (2007). The role of coenzyme Q10 in statin-associated myopathy: A systematic review. *Journal of the American College of Cardiology*, *49*(23), 2231–2237. https://doi.org/10.1016/J.JACC.2007.02.049

Maritim, A. C., Sanders, R. A., & Watkins, J. B. (2003). Diabetes, oxidative stress, and antioxidants: A review. *Journal of Biochemical and Molecular Toxicology*, *17*(1), 24–38. https://doi.org/10.1002/jbt.10058

Martucci, A., Reurean-Pintilei, D., Manole, A., Martucci, A., Reurean-Pintilei, D., & Manole, A. (2019). Bioavailability and sustained plasma concentrations of CoQ10 in healthy volunteers by a novel oral timed-release preparation. *Nutrients*, *11*(3), 527. https://doi.org/10.3390/nu11030527

Mason, P. (Ed.). (2018). Coenzyme Q10. *Dietary supplements*. London: Pharmaceutical Press. Retrieved from www.medicinescomplete.com

Mattila, P., & Kumpulainen, J. (2001). Coenzymes Q9and Q10: Contents in foods and dietary intake. *Journal of Food Composition and Analysis*, *14*(4), 409–417. https://doi.org/10.1006/JFCA.2000.0983

Mendes, P., Robles, P. G., & Mathur, S. (2014). Statin-induced rhabdomyolysis: A comprehensive review of case reports. *Physiotherapy Canada*, *66*(2), 124–132. https://doi.org/10.3138/ptc.2012-65

Menke, T., Niklowitz, P., Wiesel, T., & Andler, W. (2008). Antioxidant level and redox status of coenzyme Q_{10} in the plasma and blood cells of children with diabetes mellitus type 1. *Pediatric Diabetes*, *9*(6), 540–545. https://doi.org/10.1111/j.1399-5448.2008.00389.x

Miles, M. V. (2007). The uptake and distribution of coenzyme Q(10). *Mitochondrion*, *7*, S72–S77. https://doi.org/10.1016/J.MITO.2007.02.012

Molyneux, S. L., Florkowski, C. M., George, P. M., Pilbrow, A. P., Frampton, C. M., Lever, M., & Richards, A. M. (2008). Coenzyme Q10: An independent predictor of mortality in chronic heart failure. *Journal of the American College of Cardiology*, *52*(18), 1435–1441. https://doi.org/10.1016/J.JACC.2008.07.044

Momiyama, Y. (2014). Serum coenzyme Q10 levels as a predictor of dementia in a Japanese general population. *Atherosclerosis*, *237*(2), 433–434. https://doi.org/10.1016/J.ATHEROSCLEROSIS.2014.08.056

Mortensen, S. A., Rosenfeldt, F., Kumar, A., Dolliner, P., Filipiak, K. J., Pella, D., … Investigators, Q.-S. S. (2014). The effect of coenzyme Q 10 on morbidity and mortality in chronic heart failure. *JACC: Heart Failure*, *2*(6), 641–649. https://doi.org/10.1016/j.jchf.2014.06.008

Nabavi, S. M., & Silva, A. S. (2019). Nonvitamin and nonmineral nutritional supplements. Cambridge, MA: Academic Press.

Nadjarzadeh, A., Shidfar, F., Amirjannati, N., Vafa, M. R., Motevalian, S. A., Gohari, M. R., Nazeri Kakhki, S. A., Akhondi, M. M. … Sadeghi, M. R. (2014). Effect of Coenzyme Q10 supplementation on antioxidant enzymes activity and oxidative stress of seminal plasma: a double-blind randomised clinical trial. *Andrologia*, *46*, 177–183. https://doi.org/10.1111/and.12062

Nagase, M., Yamamoto, Y., Matsumoto, N., Arai, Y., & Hirose, N. (2018). Increased oxidative stress and coenzyme Q10 deficiency in centenarians. *Journal of Clinical Biochemistry and Nutrition*, *63*(2), 129–136. https://doi.org/10.3164/jcbn.17-124

Nakamura, S., Otsuka, N., Yoshino, Y., Sakamoto, T., & Yuasa, H. (2016). Predicting the occurrence of sticking during tablet production by shear testing of a pharmaceutical powder. *Chemical & Pharmaceutical Bulletin*, *64*(5), 512–516. https://doi.org/10.1248/cpb.c15-00992

National Center for Complementary and Integrative Health. (2019). Using dietary supplements wisely. Retrieved from https://nccih.nih.gov/health/supplements/wiseuse.htm

National Institutes of Health. (2011). Dietary supplements: What you need to know. Retrieved from https://ods.od.nih.gov/HealthInformation/DS_WhatYouNeedToKnow.aspx

Nawarskas, J. J. (2005). HMG-CoA reductase inhibitors and coenzyme Q10. *Cardiology in Review*, *13*(2), 76–79. https://doi.org/10.1097/01.crd.0000154790.42283.a1

Nelson, D. L., & Cox, M. M. (2017). *Lehninger principles of biochemistry* (7th ed.). New York, NY: Macmillan Learning.

Nepal, P. R., Han, H.-K., & Choi, H.-K. (2010). Enhancement of solubility and dissolution of Coenzyme Q10 using solid dispersion formulation. *International Journal of Pharmaceutics*, *383*(1–2), 147–153. https://doi.org/10.1016/j.ijpharm.2009.09.031

Nielsen. (2016). What's in our food and on our mind: Ingredients and dining-out trends around the world. Retrieved from https://www.nielsen.com/wp-content/uploads/sites/3/2019/04/global-ingredient-and-out-of-home-dining-trends-aug-2016.pdf

Niklowitz, P., Sonnenschein, A., Janetzky, B., Andler, W., & Menke, T. (2007). Enrichment of coenzyme Q10 in plasma and blood cells: Defense against oxidative damage. *International Journal of Biological Sciences*, *3*, 257–262. https://doi.org/10.7150/ijbs.3.257

Nutescu, E. A., Shapiro, N. L., Ibrahim, S., & West, P. (2006). Warfarin and its interactions with foods, herbs and other dietary supplements. *Expert Opinion on Drug Safety*, *5*(3), 433–451. https://doi.org/10.1517/14740338.5.3.433

Östman, B., Sjödin, A., Michaëlsson, K. & Byberg, L. (2012). Coenzyme Q10 supplementation and exercise-induced oxidative stress in humans. *Nutrition*, *28*, 403–417. https://doi.org/10.1016/j.nut.2011.07.010

O'Neil, M. J. (2013). *The merck index* (15th ed.). Cambridge: Royal Society of Chemistry. Retrieved from https://pubs.rsc.org/en/content/ebook/978-1-84973-670-1

Ouchi, A., Nagaoka, S., & Mukai, K. (2010). Tunneling effect in regeneration reaction of vitamin E by ubiquinol. *The Journal*

of Physical Chemistry B, *114*(19), 6601–6607. https://doi.org/10.1021/jp910856m

Palamakula, A., Soliman, M., & Khan, M. M. A. (2005). Regional permeability of coenzyme Q10 in isolated rat gastrointestinal tracts. *Die Pharmazie*, *60*(3), 212–214. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15801676

Parmar, S. S., Jaiwal, A., Dhankher, O. P., & Jaiwal, P. K. (2015). Coenzyme Q10 production in plants: Current status and future prospects. *Critical Reviews in Biotechnology*, *35*(2), 152–164. https://doi.org/10.3109/07388551.2013.823594

Parohan, M., Sarraf, P., Javanbakht, M. H., Ranji-Burachaloo, S., & Djalali, M. (2019). Effect of coenzyme Q10 supplementation on clinical features of migraine: A systematic review and dose–response meta-analysis of randomized controlled trials. *Nutritional Neuroscience*, 1–8. https://doi.org/10.1080/1028415X.2019.1572940

Playford, D. A., Watts, G. F., Croft, K. D., & Burke, V. (2003). Combined effect of coenzyme Q10 and fenofibrate on forearm microcirculatory function in type 2 diabetes. *Atherosclerosis*, *168*(1), 169–179. https://doi.org/10.1016/S0021-9150(02)00417-3

Portakal, O., Özkaya, Öz., Erden inal, M., Bozan, B., Koşan, M., & Sayek, I. (2000). Coenzyme Q10 concentrations and antioxidant status in tissues of breast cancer patients. *Clinical Biochemistry*, *33*(4), 279–284. https://doi.org/10.1016/S0009-9120(00)00067-9

Potgieter, M., Pretorius, E., & Pepper, M. S. (2013). Primary and secondary coenzyme Q10 deficiency: The role of therapeutic supplementation. *Nutrition Reviews*, *71*(3), 180–188. https://doi.org/10.1111/nure.12011

Pravst, I., Žmitek, K., & Žmitek, J. (2010). Coenzyme Q10 contents in foods and fortification strategies. *Critical Reviews in Food Science and Nutrition*, *50*(4), 269–280. https://doi.org/10.1080/10408390902773037

Pre2CARE Investigators. (2010). Safety and tolerability of high-dosage coenzyme Q10 in huntington's disease and healthy subjects. *Movement Disorders*, *25*(12), 1924–1928. https://doi.org/10.1002/mds.22408

Premkumar, V. G., Yuvaraj, S., Vijayasarathy, K., Gangadaran, S. G. D., & Sachdanandam, P. (2007). Effect of coenzyme Q10, riboflavin and niacin on serum CEA and CA 15-3 levels in breast cancer patients undergoing tamoxifen therapy. *Biological & Pharmaceutical Bulletin*, *30*(2), 367–370.

PubChem. (2019). NADH. Retrieved from https://pubchem.ncbi.nlm.nih.gov/compound/1_4-Dihydronicotinamide-adenine-dinucleotide#section=2D-Structure

Qu, H., Meng, Y., Chai, H., Liang, F., Zhang, J., Gao, Z., & Shi, D. (2018). The effect of statin treatment on circulating coenzyme Q10 concentrations: An updated meta-analysis of randomized controlled trials. *European Journal of Medical Research*, *23*. https://doi.org/10.1186/S40001-018-0353-6

Quinzii, C. M., DiMauro, S., & Hirano, M. (2007). Human coenzyme Q10 deficiency. *Neurochemical Research*, *32*(4–5), 723–727. https://doi.org/10.1007/s11064-006-9190-z

Quinzii, C. M., & Hirano, M. (2011). Primary and secondary CoQ10 deficiencies in humans. *BioFactors*, *37*(5), 361–365. https://doi.org/10.1002/biof.155

Roffe, L., Schmidt, K., & Ernst, E. (2004). Efficacy of coenzyme Q10 for improved tolerability of cancer treatments: A systematic review. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *22*(21), 4418–4424. https://doi.org/10.1200/JCO.2004.02.034

Rosenbaum, D., Dallongeville, J., Sabouret, P., & Bruckert, E. (2013). Discontinuation of statin therapy due to muscular side effects: A survey in real life. *Nutrition, Metabolism and Cardiovascular Diseases*, *23*(9), 871–875. https://doi.org/10.1016/j.numecd.2012.04.012

Rosenfeldt, F., Hilton, D., Pepe, S. & Krum, H. (2003). Systematic review of effect of coenzyme Q 10 in physical exercise, hypertension and heart failure. *BioFactors*, *18*, 91–100. https://doi.org/10.1002/biof.5520180211

Rozen, T., Oshinsky, M., Gebeline, C., Bradley, K., Young, W., Shechter, A., & Silberstein, S. (2002). Open label trial of coenzyme Q10 as a migraine preventive. *Cephalalgia*, *22*(2), 137–141. https://doi.org/10.1046/j.1468-2982.2002.00335.x

Rusciani, L., Proietti, I., Paradisi, A., Rusciani, A., Guerriero, G., Mammone, A., … Lippa, S. (2007). Recombinant interferon alpha-2b and coenzyme Q10 as a postsurgical adjuvant therapy for melanoma: A 3-year trial with recombinant interferon-alpha and 5-year follow-up. *Melanoma Research*, *17*(3), 177–183. https://doi.org/10.1097/CMR.0b013e32818867a0

Rusciani, L., Proietti, I., Rusciani, A., Paradisi, A., Sbordoni, G., Alfano, C., … Lippa, S. (2006). Low plasma coenzyme Q10 levels as an independent prognostic factor for melanoma progression. *Journal of the American Academy of Dermatology*, *54*(2), 234–241. https://doi.org/10.1016/J.JAAD.2005.08.031

Safarinejad, M. R. (2012). The effect of coenzyme Q10 supplementation on partner pregnancy rate in infertile men with idiopathic oligoasthenoteratozoospermia: An open-label prospective study. *International Urology and Nephrology*, *44*(3), 689–700. https://doi.org/10.1007/s11255-011-0081-0

Salama, M., Yuan, T.-F., Machado, S., Murillo-Rodriguez, E., Vega, J., Menendez-Gonzalez, M., … Arias-Carrion, O. (2013). Co-Enzyme Q10 to treat neurological disorders: Basic mechanisms, clinical outcomes, and future research direction. *CNS & Neurological Disorders-Drug Targets*, *12*(5), 641–664. https://doi.org/10.2174/18715273113129990071

Sandor, P. S., Di Clemente, L., Coppola, G., Saenger, U., Fumal, A., Magis, D., … Schoenen, J. (2005). Efficacy of coenzyme Q10 in migraine prophylaxis: A randomized controlled trial. *Neurology*, *64*(4), 713–715. https://doi.org/10.1212/01.WNL.0000151975.03598.ED

Schulz, C., Obermüller-Jevic, U. C., Hasselwander, O., Bernhardt, J., & Biesalski, H. K. (2006). Comparison of the relative bioavailability of different coenzyme Q_{10} formulations with a novel solubilizate (Solu^{TM} Q10). *International Journal of Food Sciences and Nutrition*, *57*(7–8), 546–555. https://doi.org/10.1080/09637480601058320

Selva-O'Callaghan, A., Alvarado-Cardenas, M., Pinal-Fernández, I., Trallero-Araguás, E., Milisenda, J. C., Martínez, M. Á., … Grau-Junyent, J. M. (2018). Statin-induced myalgia and myositis: An update on pathogenesis and clinical recommendations. *Expert Review of Clinical Immunology*, *14*(3), 215–224. https://doi.org/10.1080/1744666X.2018.1440206

Shao, Y., Yang, L., & Han, H.-K. (2015). TPGS-chitosome as an effective oral delivery system for improving the bioavailability of Coenzyme Q10. *European Journal of Pharmaceutics and Biopharmaceutics*, *89*, 339–346. https://doi.org/10.1016/J.EJPB.2014.12.026

Sharma, A., Fonarow, G. C., Butler, J., Ezekowitz, J. A., & Felker, G. M. (2016). Coenzyme Q10 and heart failure. *Circulation: Heart Failure*, *9*(4), e002639. https://doi.org/10.1161/CIRCHEARTFAILURE.115.002639

Sharma, S., Kheradpezhou, M., Shavali, S., Refaey, H. E., Eken, J., Hagen, C., & Ebadi, M. (2004). Neuroprotective actions of coenzyme Q10 in parkinson's disease. *Methods in Enzymology*, *382*, 488–509. https://doi.org/10.1016/S0076-6879(04)82027-5

Shoeibi, A., Olfati, N., Soltani Sabi, M., Salehi, M., Mali, S., & Akbari Oryani, M. (2017). Effectiveness of coenzyme Q10 in prophylactic treatment of migraine headache: An open-label, add-on, controlled trial. *Acta Neurologica Belgica*, *117*(1), 103–109. https://doi.org/10.1007/s13760-016-0697-z

Shukla, S., & Dubey, K. K. (2018). CoQ10 a super-vitamin: Review on application and biosynthesis. *3 Biotech*, *8*(5), 249. https://doi.org/10.1007/s13205-018-1271-6

Shults, C. W., Flint Beal, M., Song, D., & Fontaine, D. (2004). Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease. *Experimental Neurology*, *188*(2), 491–494. https://doi.org/10.1016/J.EXPNEUROL.2004.05.003

Shuqin Xia, Xu, S., & Zhang, X. (2006). Optimization in the preparation of coenzyme Q10 nanoliposomes. *Journal of Agricultural and Food Chemistry*, *54*, 6358–6366. https://doi.org/10.1021/JF060405O

Somayajulu, M., McCarthy, S., Hung, M., Sikorska, M., Borowy-Borowski, H., & Pandey, S. (2005). Role of mitochondria in neuronal cell death induced by oxidative stress; neuroprotection by coenzyme Q10. *Neurobiology of Disease*, *18*(3), 618–627. https://doi.org/10.1016/J.NBD.2004.10.021

Sosa, V., Moliné, T., Somoza, R., Paciucci, R., Kondoh, H., & LLeonart, M. E. (2013). Oxidative stress and cancer: An overview. *Ageing Research Reviews*, *12*(1), 376–390. https://doi.org/10.1016/J.ARR.2012.10.004

Spindler, M., Beal, M. F., & Henchcliffe, C. (2009). Coenzyme Q10 effects in neurodegenerative disease. *Neuropsychiatric Disease and Treatment*, *5*, 597–610. https://doi.org/10.2147/ndt.s5212

Terao, K., Nakata, D., Fukumi, H., Schmid, G., Arima, H., Hirayama, F., & Uekama, K. (2006). Enhancement of oral bioavailability of coenzyme Q10 by complexation with γ-cyclodextrin in healthy adults. *Nutrition Research*, *26*(10), 503–508. https://doi.org/10.1016/J.NUTRES.2006.08.004

Tomasetti, M., Alleva, R., Solenghi, M. D., & Littarru, G. P. (1999). Distribution of antioxidants among blood components and lipoproteins: Significance of lipids/CoQ_{10} ratio as a possible marker of increased risk for atherosclerosis. *BioFactors*, *9*(2–4), 231–240. https://doi.org/10.1002/biof.5520090218

Tomono, Y., Hasegawa, J., Seki, T., Motegi, K., & Morishita, N. (1986). Pharmacokinetic study of deuterium-labelled coenzyme Q10 in man. *International Journal of Clinical Pharmacology, Therapy, and Toxicology*, *24*(10), 536–541.

Tripathi, G. M., Kalita, J., & Misra, U. K. (2018). A study of oxidative stress in migraine with special reference to prophylactic therapy. *International Journal of Neuroscience*, *128*(4), 318–324. https://doi.org/10.1080/00207454.2017.1374959

Ubidecarenone. (2019). *European pharmacopoeia online* (9th ed.). Retrieved from http://online.edqm.eu/EN/entry.htm

US Food and Drug Administration. (2017). What you need to know about dietary supplements. Retrieved from https://www.fda.gov/food/buy-store-serve-safe-food/what-you-need-know-about-dietary-supplements

US Food and Drug Administration. (2018). Dietary supplements. Retrieved from https://www.fda.gov/food/dietary-supplements

Vaghari, H., Vaghari, R., Jafarizadeh-Malmiri, H., & Berenjian, A. (2016). Coenzyme Q10 and its effective sources. *American Journal of Biochemistry and Biotechnology*, *12*, 214–219. https://doi.org/10.3844/ajbbsp.2016.214.219

Valko, M., Izakovic, M., Mazur, M., Rhodes, C. J., & Telser, J. (2004). Role of oxygen radicals in DNA damage and cancer incidence. *Molecular and Cellular Biochemistry*, *266*(1/2), 37–56. https://doi.org/10.1023/B:MCBI.0000049134.69131.89

Villalba, J. M., Parrado, C., Santos-Gonzalez, M., & Alcain, F. J. (2010). Therapeutic use of coenzyme Q10 and coenzyme Q10-related compounds and formulations. *Expert Opinion on Investigational Drugs*, *19*(4), 535–554. https://doi.org/10.1517/13543781003727495

Vitetta, L., Leong, A., Zhou, J., Dal Forno, S., Hall, S., & Rutolo, D. (2018). The plasma bioavailability of coenzyme Q10 absorbed from the gut and the oral Mucosa. *Journal of Functional Biomaterials*, *9*(4), 73. https://doi.org/10.3390/jfb9040073

Watts, G. F., Playford, D. A., Croft, K. D., Ward, N. C., Mori, T. A., & Burke, V. (2002). Coenzyme Q10 improves endothelial dysfunction of the brachial artery in Type II diabetes mellitus. *Diabetologia*, *45*(3), 420–426. https://doi.org/10.1007/s00125-001-0760-y

Wei, W., Liu, Q., Tan, Y., Liu, L., Li, X., & Cai, L. (2009). Oxidative stress, diabetes, and diabetic complications. *Hemoglobin*, *33*(5), 370–377. https://doi.org/10.3109/03630260903212175

Witting, P. K., Pettersson, K., Letters, J., & Stocker, R. (2000). Anti-atherogenic effect of coenzyme Q10 in apolipoprotein E gene knockout mice. *Free Radical Biology and Medicine*, *29*(3–4), 295–305. https://doi.org/10.1016/S0891-5849(00)00311-7

World Health Organization. (2002). *Active ageing: A policy framework*. Geneva, Switzerland: World Health Organization. Retrieved from https://www.who.int/ageing/publications/active_ageing/en/

World Health Organization. (2010). *Global status report on noncommunicable diseases*. Geneva, Switzerland: World Health Organization. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/44579/9789240686458_eng.pdf?sequence=1

World Health Organization. (2015a). *Health in 2015*. Geneva, Switzerland: World Health Organization. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/200009/9789241565110_eng.pdf?sequence=

World Health Organization. (2015b). *World report on ageing and health*. Geneva, Switzerland: World Health Organization. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/186463/9789240694811_eng.pdf?sequence=1

World Health Organization. (2018a). *The top 10 causes of death*. Geneva, Switzerland: World Health Organization. Retrieved from https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

World Health Organization. (2018b). *World health statistics*. Geneva, Switzerland: World Health Organization. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/272596/9789241565585-eng.pdf?ua=1

Wright, C., Milne, S. & Leeson, H. (2014). Sperm DNA damage caused by oxidative stress: Modifiable clinical, lifestyle and nutritional factors in male infertility. *Reproductive biomedicine online*, *28*, 684–703. https://doi.org/10.1016/j.rbmo.2014.02.004

Yang, X., Dai, G., Li, G., & Yang, E. S. (2010). Coenzyme Q10 reduces β-amyloid plaque in an APP/PS1 transgenic mouse model of Alzheimer's disease. *Journal of Molecular Neuroscience*, *41*(1), 110–113. https://doi.org/10.1007/s12031-009-9297-1

Yang, Y.-K., Wang, L.-P., Chen, L., Yao, X.-P., Yang, K.-Q., Gao, L.-G., & Zhou, X.-L. (2015). Coenzyme Q10 treatment of cardiovascular disorders of ageing including heart failure, hypertension and endothelial dysfunction. *Clinica Chimica Acta*, *450*, 83–89. https://doi.org/10.1016/J.CCA.2015.08.002

Yasueda, A., Urushima, H., & Ito, T. (2016). Efficacy and interaction of antioxidant supplements as adjuvant therapy in cancer treatment. *Integrative Cancer Therapies*, *15*(1), 17–39. https://doi.org/10.1177/1534735415610427

Yue, Y., Zhou, H., Liu, G., Li, Y., Yan, Z., & Duan, M. (2010). The advantages of a novel CoQ10 delivery system in skin photoprotection. *International Journal of Pharmaceutics*, *392*(1–2), 57–63. https://doi.org/10.1016/J.IJPHARM.2010.03.032

Zaki, N. M. (2014). Strategies for oral delivery and mitochondrial targeting of CoQ10. *Drug Delivery*, 1868–1881. https://doi.org/10.3109/10717544.2014.993747

Zaleski, A. L., Taylor, B. A., & Thompson, P. D. (2018). Coenzyme Q10 as treatment for statin-associated muscle symptoms—A good idea, but…. *Advances in Nutrition*, *9*(4), 519S–523S. https://doi.org/10.1093/advances/nmy010

Zeng, Z., Li, Y., Lu, S., Huang, W., & Di, W. (2019). Efficacy of CoQ10 as supplementation for migraine: A meta-analysis. *Acta Neurologica Scandinavica*, *139*(3), 284–293. https://doi.org/10.1111/ane.13051

Zhao, X.-H., & Tang, C.-H. (2016). Spray-drying microencapsulation of CoQ10 in olive oil for enhanced water dispersion, stability and bioaccessibility: Influence of type of emulsifiers and/or wall materials. *Food Hydrocolloids*, *61*, 20–30. https://doi.org/10.1016/J.FOODHYD.2016.04.045

Zhu, Z.-G., Sun, M.-X., Zhang, W.-L., Wang, W.-W., Jin, Y.-M., & Xie, C.-L. (2017). The efficacy and safety of coenzyme Q10 in Parkinson's disease: A meta-analysis of randomized controlled trials. *Neurological Sciences*, *38*(2), 215–224. https://doi.org/10.1007/s10072-016-2757-9