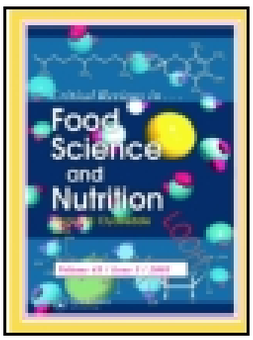

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Coenzyme Q_{10}: from bench to Clinic in Aging Diseases, a translational review.

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ABSTRACT

Coenzyme Q_{10} (CoQ_{10}) is a ubiquitous molecule present in all eukaryotic organisms whose principal role in the cell is related to its participation in the electron transport chain in the inner mitochondrial membrane. CoQ_{10} plays a major role in the control of cell redox status,

and both the amount and functionality of this molecule have been related to the regulation of reactive oxygen species generation. Numerous reports can be found discussing the implications of CoQ_{10} supplementation in human studies and clinical trials related to aging. However, few reviews have made an updating through the translational point of view to integrate both basic and clinical aspects. The aim of this paper is to review our current knowledge from CoQ_{10} implications at biochemical and physiological level, in order to unravel the molecular mechanisms involved in its application in clinical practice. Although the importance of CoQ_{10} has been mainly attributed to its role as an agent for energy transduction in mitochondria, new functions for CoQ_{10} have been described in the recent past years, including anti-inflammatory effects, gene expression regulation and lipid bilayer membranes stabilization, which explain its involvement in aging and age-related diseases such as cardiovascular diseases, renal failure and neurodegenerative diseases.

Keywords: Coenzyme Q_{10} supplementation, Antioxidant, Age-related diseases, Oxidative stress, Coenzyme Q_{10} functions, Mediterranean Diet.

ABBREVIATION LIST

8-OHdG 8-hydroxydeoxyguanosine

Acyl-CoA Acyl-Coenzyme A

AD Alzheimer's disease

ADCK3 aarF domain containing kinase 3

AGER1 AGE receptor 1

AGEs Advanced glycation end products

AMPK Adenosine monophosphate-activated protein kinase

AP-1 Activator protein-1

ATP Adenosine triphosphate

BiP/Grp78 Binding immunoglobulin protein/78 kDa glucose regulated-protein

cAMP Cyclic adenosine monophosphate

CKD Chronic kidney disease

CoQ_{10} Coenzyme Q_{10}

CREB cAMP response element-binding

CRP C reactive protein

CRT Calreticulin

CVD Cardiovascular diseases

DHODH Dihydroorotate dehydrogenase

ED Endothelium dysfunction

ecSOD Extracellular superoxide dismutase

EF Ejection fraction

eNOS Endothelial Nitric oxide synthase

EPCs Endothelial progenitor cells

ER Endoplasmic reticulum

ESRD End-stage renal disease

ETF/ETF:QO Electron transfer flavoproteine/electron transfer flavoproteine:ubiquinone oxidorreductase

FAD Flavin adenine dinucleotide

FMD Flow-mediated dilation

Glox1 Glyoxal oxidase 1

GPx Glutathione peroxidase

GSH Reduced glutathione

GSSG Oxidized glutathione

HD Huntington's disease

HepG2 Human hepatocellular carcinoma cell

HF Heart failure

HL-60 Human promyelocytic leukemia cell

HMG-CoA Hydroxyl-methylglutaryl-coenzyme A

hnRNP Heterogeneous nuclear ribonucleoprotein

HO-1 Heme oxygenase 1

HuR Human antigen R

HUVEC Human umbilical vein endothelial cell

IDH2 Isocitrate dehydrogenase 2

IKK-β Inhibitor of nuclear factor kappa-B kinase subunit beta

IL-1 Interleukin-1

IL-1-β Interleukin-1-beta

IL-6 Interleukin-6

JNK-1 c-Jun N-terminal kinase 1

LDL Low density lipoproteína

LKB1 Liver kinase B1

LVEF Left ventricular ejection fraction

MCAD Medium-chain fatty acyl-CoA

mtDNA Mitochondrial DNA

NADH/NADPH Nicotinamide adenine dinucleotide reduced/Nicotinamide adenine dinucleotide phosphate reduced

NF-κB Nuclear factor kappa B

NMD Nitroglycerin-mediated dilation

NO Nitric oxide

NOS Nitric oxide synthase

Nrf2 Nuclear factor (erythroid-derived 2)-like 2

nSMase Neutral Mg^{2+} -dependent sphingomyelinase

NT-proBNP N-terminal prohormone of brain natriuretic peptide

NYHA New York Heart Association

PD Parkinson's disease

PDE4 Phosphodiesterase 4

PeD Peritoneal dialysis

PGC-1α Peroxisome proliferator-activated receptor gamma coactivator 1 alpha

PPARα Peroxisome proliferator-activated receptor alpha

ROS Reactive oxygen species

sCML Serum N-Carboxymethyllysine

SFA-diet Satarated fatty acid-rich diet

SIRT Sirtuin

sMG Serum methylglyoxal

SOD Superoxide dismutase

sXBP-1 Spliced isoform of X-box binding protein 1

TFAM Mitochondrial transcription factor A

TNF-α Tumor necrosis factor alpha

1. Introduction

Festenstein *et al* (1955) isolated and characterized a substance which was named ubiquinone ("ubiquitous quinone") relating to the presence of this substance in all cells, and Crane *et al* (1957) established that this compound functions as an electron carrier in the mitochondrial electron transport chain (Crane *et al.*, 1957; Festenstein *et al.*, 1955). Chemically, CoQ_{10} is 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone, a lipid-soluble and biologically active

quinone comprising a benzoquinone ring with an attached isoprenoid side-chain (a structure resembling in some aspects that of vitamin E) which is endogenously synthesized in the body from tyrosine or phenylalanine (benzoquinone ring) and mevalonic acid (isoprenoid side-chain). The term CoQ_{10} refers to both the quinone chemical group and the 10 isoprenes in the compound's structure. The length of the isoprenyl chain varies among organisms, being CoQ_{10} the major species observed in humans. The all *trans* polyisoprenoid chain ensures an affinity for the hydrophobic interior of cell membranes whereas its functional group is the quinone ring, which carries protons and electrons by its reversible reduction to quinol (Lenaz, 1985). Less well-established functions of CoQ_{10} include an oxidant action in the generation of signals and the control of cellular redox state. There is also evidence for a role in proton gradient formation in endomembranes and at the plasma membrane. In addition, there exists evidence about the participation of CoQ_{10} in the control of membrane structure and phospholipid status (Lenaz *et al.*, 1999; Lopez-Lluch *et al.*, 1999). The main chemical feature of CoQ_{10} which is responsible for its various functions is the existence of three alternate redox states: the fully oxidized *ubiquinone* form, the semioxidized (or semireduced) *semiquinone* (a free radical intermediate) and the fully reduced *ubiquinol* form (Alcazar-Fabra et al., 2016) (Figure 1).

CoQ_{10} is also distributed in all membranes throughout the cell. In mitochondria there are CoQ_{10} binding sites in the enzymes involved in its oxidation/reduction, which is fundamental for its role in cellular bioenergetics as a cofactor in the mitochondrial electron transport chain and indeed for adenosine triphosphate (ATP) production (Acosta *et al.*, 2016; Alcazar-Fabra *et al.*, 2016). The major source of CoQ_{10} relies on endogenous biosynthesis, which takes place in all tissues of the organism, whereas lower amount derives from dietary uptake. However, a deficit of endogenous production has been described to occur in the pathophysiology of different diseases and, most importantly, a decay can be associated with aging, where the

uptake from the diet may become relevant. CoQ_{10} content distribution in different food sources is depicted in Table 1. In the literature, numerous reports can be found discussing the implications of CoQ_{10} supplementation in human studies and clinical trials related to aging. Although basic research has focused mainly on the biochemical function of CoQ_{10} in the organism, few reviews have made an updating through the translational point of view to integrate both basic and clinical aspects. Regarding to that, the aim of this article is to review our current knowledge from CoQ_{10} implications at biochemical and physiological level, in order to unravel the molecular mechanisms involved in its application in clinical practice. We focused on highlighting the recent investigations which not only give to scientific community an overview about CoQ_{10} in aging diseases, but also molecular mechanisms explaining such relation.

2. Molecular Biology of CoQ_{10}

2.1. CoQ_{10} functions

The primary function of this lipid-soluble substance is to participate as an essential intermediate of the electron transport chain located in the mitochondrial inner membrane, where it accepts electrons from several donors as the respiratory complexes I and II to donate the reducing equivalents to the cytochrome complex system (complex III) (Figure 2a). At the same time, CoQ_{10} also transfers protons to the intermembrane space of the mitochondria, contributing to the generation of the electrochemical proton gradient which provides energy to power the ATP synthase (Crane, 2001), thus participating in the production of energy for cell growth and maintenance (Overvad et al., 1999). In the inner mitocondrial membrane, CoQ_{10} also participates as a coenzyme of the dihydroorotate dehydrogenase (DHODH) which catalyzes the fourth step in de novo pyrimidine biosynthesis, involved in the oxidation of dihydroorotate to orotate (Figure 2b) (Munier-Lehmann et al., 2015). In this context, CoQ_{10} also participates in the fatty acids oxidation throughout the electron transfer

flavoprotein/electron transfer flavoprotein:ubiquinone oxidorreductase (ETF/ETF:QO) system which serves as a short electron transfer pathway to conduct electrons from nine different mitochondrial flavin-adenine dinucleotide (FAD)-containing acyl-coenzyme A (acyl-CoA) dehydrogenases of fatty acid β-oxidation and amino acid catabolism to the CoQ_{10} pool of the main respiratory chain (Figure 2c) (Watmough et al., 2010). Through these processes, mitochondrial CoQ_{10} is in a permanent equilibrium between the reduced (ubiquinol) and the oxidized form (ubiquinone) (Figure 1). Outside the inner mitochondrial membrane, this equilibrium is maintained by, at least, the action of three enzymes located in the plasma membrane and in endomembranes: Nicotinamide adenine dinucleotide reduced/Nicotinamide adenine dinucleotide phosphate reduced (NADH/NADPH) oxidoreductase (DT diaphorase), NADH cytochrome b_5 reductase and NADPH-coenzyme Q reductase (Villalba et al., 2000). In this sense, ubiquinol is regarded as a potent antioxidant that protects cells from free radical-induced oxidative damage and contributes to the stability of the cell membranes avoiding peroxidation of membrane phospholipids. The reduced form of CoQ_{10} has also been reported to protect plasma low density lipoproteins (LDL) from oxidation (Lopez-Lluch et al., 2010). In addition to direct antioxidant radical scavenging, both the fully reduced and the semiquinone intermediate of CoQ_{10} are also capable of recycling and regenerating other antioxidants, such as α-tocopherol and ascorbate, which are thus maintained in a reduced state (Navas et al., 2007) (Figure 2d and 2e). Yamamoto *et al* demonstrated the existence of a redox cycle involving ascorbate, α-tocopherol and CoQ_{10}, whose concerted action is effective to reduce lipid peroxyl radicals *in vitro*, with CoQ_{10} being needed to recycle α-tocopherol and to produce the effective suppression of lipid oxidation (Yamamoto, 2016). In this way, CoQ_{10} is considered as an important antioxidant, even more powerful than α-tocopherol, because it is the only lipophilic antioxidant synthesized endogenously, regenerated by intracellular reducing mechanisms, and present at relatively high concentrations (Forsmark-Andree et al., 1995). Furthermore, available data have also revealed that CoQ_{10} acts as a co-factor for the function

of uncoupling proteins (Figure 2f), and is also essential for the maintenance of the bioenergetic state of skeletal and heart muscle (Littarru *et al.*, 2007; Potgieter *et al.*, 2013).

Recent studies carried out in animal and cellular models have demonstrated anti-inflammatory effects of CoQ_{10} (Bessler *et al.*, 2010; Tarry-Adkins *et al.*, 2016) (Figure 2g). However, clinical trials performed in order to examine the effect of CoQ_{10} supplementation on reducing inflammatory mediators, such as C reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), have been inconsistent (Abdollahzad *et al* , 2015; Carrasco *et al.*, 2014; Mohseni *et al.*, 2015). In a recently published meta-analysis, Fan *et al* performed a systematic review to provide evidence that CoQ_{10} supplementation has a significant lowering effect on inflammatory markers including CRP, IL-6 and TNF-α (Fan et al., 2017). In another systematic review that has also been published recently, Zhai *et al* provided evidence that CoQ_{10} supplementation may partly improve the process of inflammatory state in patients with metabolic diseases (Zhai et al., 2017). Although the mechanisms implicated in the regulation of inflammation by CoQ_{10} are unclear, it has been proposed that CoQ_{10} could exert anti-inflammatory effects *via* the reduction of nuclear factor-κB (NF-κB) dependent gene expression. NF-κB can be activated by reactive oxygen species (ROS) and then up-regulate pro-inflammatory cytokines expression (such as TNF-α and IL-6). As an antioxidant, CoQ_{10} blockade of free radicals results in the inhibition of NF-κB activation and the subsequent decrease of pro-inflammatory cytokines expression. Other authors have pointed out that, among the different mechanisms by which CoQ_{10} could exert its anti-inflammatory effects beyond its action on NF-kB-dependent pathways, CoQ_{10} could also play a potential role in attenuating miR-146a and interleukin-1 (IL-1) receptor associated kinase modulation (Olivieri et al., 2013), thus reducing the secretion of macrophage inflammatory protein-1 alpha and regulating upon activation normal T-cell expressed and secreted factors (Schmelzer et al., 2007). On the other

hand, it has been described that adiponectin can inhibit stimulated monocytes secreting TNF-α, and thus, it has been proposed that a rise in adiponectin levels elicited by CoQ_{10} can indirectly bring about a plunge in inflammatory factors (Farsi et al., 2016).

The various confirmed and suggested functions of CoQ_{10} have motivated further and more detailed studies of both the biological and physical roles of this quinone in cell membranes. Due to the presence of CoQ_{10} in the phospholipid bilayer of the membranes, it is thought that the isoprenoid chain may help to stabilize the lipid bilayer (Lenaz et al., 1999) (Figure 2h). The change of position of this molecule during the oxidation/reduction process may modify structural or enzymatic properties in the membrane, which might be involved in the regulation of phospholipases in the membrane by redox state (Lopez-Lluch et al., 1999). Hernandez *et al,* reported the involvement of CoQ_{10} in membrane stabilization, and it was speculated that this function would be of importance in the cholesterol-poor mitochondrial membranes. However, the influence of the redox state of CoQ_{10} must be further investigated, since the positioning of CoQ_{10} ubiquinone in the membrane has been proposed to depend on its oxidation state, so the specific redox status and those factors involved in the change of configuration might affect the stability of lipid membranes (Agmo Hernandez et al., 2015).

Less well studied biological aspects of CoQ_{10} include its potentially important role in cell growth and certain forms of apoptosis (Figure 2i). Regarding the anti-apoptotic properties of CoQ_{10}, Tsai *et al* demonstrated a decrease in cellular apoptosis and ROS levels, an improvement of endothelial progenitor cells (EPCs) function and an increase in nitric oxide (NO) production by administration of CoQ_{10} in a cell culture assay. Furthermore, AMP-activated protein kinase (AMPK), endothelial NO synthase (eNOS) and Heme oxygenase 1 (HO-1) pathways were mechanistically implicated in this anti-apoptotic effect (Tsai et al., 2016). In

this sense, CoQ_{10} has been described to be involved in NAD(P)H-oxidoreductase-dependent reactions such as in NO synthesis in Golgi and plasma membranes (Navas et al., 2007). In addition, it has been indicated that CoQ_{10} attenuates cellular apoptosis in corneal fibroblasts by inhibition of mitochondrial depolarization (Chen et al., 2013) and prevents human umbilical vein endothelial cell (HUVEC) apoptosis through suppression of mitochondria dependent caspase 3 protein. Indeed, it has been demonstrated that the reduced form of CoQ_{10} is an efficient inhibitor of the neutral Mg^{2+}-dependent sphingomyelinase (nSMase) preventing ceramide accumulation and caspase-3 activation, providing a mechanism for the regulation of cell growth and death by the plasma membrane redox system (Martin *et al.*, 2003, Navas *et al.*, 2002).

2.2. Biosynthesis and intracellular transport of CoQ_{10}.

Intracellular biosynthesis is the major source of CoQ_{10} in tissues, which depends on a pathway involving at least 11 genes (*COQ* genes) which show a high degree of conservation among species. Several of these gene products are believed to be structured into a multi-subunit enzyme complex (Bentinger et al., 2010). The synthesis of the isoprenoid chain takes place through the mevalonate pathway (Figure 3). This pathway comprises a sequence of cellular reactions leading to the production of farnesyl pyrophosphate, the common substrate for the synthesis of cholesterol, dolichol, dolichyl phosphate, CoQ_{10}, and for protein prenylation (a post-translational modification necessary for the targeting and function of many proteins) (Villalba et al., 2010). *De novo* cellular synthesis of CoQ_{10} starts with the synthesis of the benzoquinone ring and the isoprenoid side chain precursors, namely 4-hydroxybenzoate and acetyl-CoA, respectively. The synthesis of the isoprenoid side chain ends with decaprenyl pyrophosphate. Then, both molecules are condensed by the enzyme polyprenil-4-hydroxybenzoate transferase (encoded by the *COQ2* gene). It is known that, at least, six

enzymes (encoded by *COQ3-8*) are implicated in the subsequent C-methylation, decarboxylation, hydroxylation and O-methylation reactions in the ring to yield the final product CoQ_{10} (Quinzii *et al.*, 2007; Turunen *et al.*, 2004).

CoQ_{10} biosynthesis pathway is highly regulated at different levels. It is transcriptionally regulated by transcription factors peroxisome proliferator-activated receptor alpha (PPARα) and NF-κB (Brea-Calvo *et al.*, 2009; Turunen *et al.*, 2000), which control the expression of *COQ7* gene under stress conditions, and at translational level by stabilization of *COQ7* mRNA operated by human antigen R (HuR) and heterogeneous nuclear ribonucleoprotein (hnRNP) C1/C2 bound proteins (Cascajo et al., 2015). Regarding its post-transcriptional regulation, it has been recently described an association between mutations in the human orthologue of *COQ8*, *ADCK3* with the development of primary CoQ_{10} deficiency and cerebellar ataxia (Gerards et al., 2010), termed Autosomal Recessive Cerebellar Ataxia Type 2. Cell lines from these patients display a reduced level and capacity to synthesize CoQ_{10} (Gerards et al., 2010). Since *ADCK3* belongs to a family of atypical kinases, it has been speculated that *ADCK3* plays a regulatory rather than a catalytic role in CoQ_{10} biosynthesis, suggesting a pathway of phosphorylation/dephosphorylation implicated on its regulation (Cullen *et al.*, 2016; Xie *et al.*, 2011).

Independently of the location of endogenous CoQ_{10} synthesis or whether CoQ_{10} is incorporated through the diet, this compound is found in all subcellular compartments and, hence, there should exist a mechanism to regulate its amount and efficient distribution from the mitochondria to other membranes. Even the enzymes involved in the last steps of the quinone ring modifications are located in the inner mitochondrial membrane, some other enzymes have been also located in the endoplasmic reticulum (ER)-Golgi system and even in

peroxisomes. Thus, the endomembrane system dynamics appears to be involved in the transport of newly synthesized CoQ_{10} to the plasma membrane (Baba *et al.*, 2004; Belogrudov *et al.*, 2001). Fernandez-Ayala *et al* demonstrated in HL-60 human cells that CoQ_{10} distribution depends on the endomembrane system showing that the brefeldin A-sensitive pathway is essential for both endogenous and exogenous distribution among cell membranes, especially to plasma membrane (Fernandez-Ayala et al., 2005). Indeed, CoQ_{10} transport also occurs in the opposite direction, since exogenous CoQ_{10} must be translocated through the plasma membrane to other organelles and further intracellular transport requires an appropriate mechanism**.**

2.3. Levels and distribution of CoQ_{10} in humans.

In humans, the main form of the coenzyme is CoQ_{10}. This form is produced in all cells and is present in all tissues in varying amounts. The distribution and redox state of CoQ_{10} in different human tissues have been described (Bhagavan et al., 2006). Human CoQ_{10} levels range from 8 µg/g in lung to 114 µg/g in heart. As a general rule, tissues with high-energy requirements or metabolic activity, such as the heart, kidney, liver and muscle, contain relatively high concentrations of CoQ_{10} (Ernster et al., 1995). Small amounts of CoQ_9 (accounting for 2–7% of total CoQ) are also found in all human tissues (Jeya et al., 2010). By employing rapid extraction, partition and direct injection of the extract into HPLC columns, it is possible to estimate the degree of reduction, which most probably resembles that existing *in vivo* (Yamashita et al., 1997). This approach indicates that the proportion of human CoQ_{10} in the reduced state, ubiquinol, is very high in most tissues, with the exception of lung and brain.

Data on the subcellular distribution of CoQ_{10} show high levels (40–50%) localized in the mitochondrial inner membrane, with smaller amounts in the other organelles (Golgi vesicles, ER or lysosomes) and also in the cytosol, reflecting a CoQ_{10} compartmentalization. The high concentration of CoQ_{10} in the mitochondria reflects its important role in the mitochondrial electron transport chain.

Overall concentration of CoQ_{10} in tissues originates from its various sources, which include endogenous synthesis, food intake and oral supplements. CoQ_{10} levels in cells and tissues are highly regulated and depend on dietary conditions, sex, race and age (Sohal et al., 2007). CoQ_{10} amounts also vary greatly in human diseases such as Alzheimer's disease, cardiomyopathies, Niemann-Pick disease, and diabetes (Rodriguez-Aguilera *et al.*, 2017; Sohal *et al.*, 2007). In normal healthy young persons, the total blood content of CoQ_{10} has been ranged between 0.55 mg/L and 1.87 mg/L (mean: 0.99 ± 0.3 mg/L) but it decreases in patients with cardiomyopathies, congestive heart failure and degenerative diseases, during aging, and in age-related diseases (Fotino *et al.*, 2012; Shetty *et al.*, 2012). For instance, it has been described that, due to a decline in the endogenous production of CoQ_{10}, only half of the production persists in the myocardium at the age of 80 years (Kalen et al., 1989).

2.4. Uptake and bioavailability of CoQ_{10}.

CoQ_{10} is found naturally in dietary sources and can be also used as a dietary supplement. It is present in a wide variety of foods from animal and vegetable sources. In animal sources, large amounts are present e.g. in chicken legs, heart, liver and herrings. In vegetable sources, it occurs e.g. in spinach, cauliflower and whole grains – although in a lower concentration compared with meat and fish (Crane, 2001; Weber *et al.*, 1997) (Table 1).

Dietary contribution of CoQ_{10} is estimated to be 3–5 mg/day. However, in tissues with unimpaired synthetic capacity, it appears that CoQ_{10} reaches a saturation level, and its exogenous supplementation in the diet does not results in a significant increase of tissue levels above normal (Bhagavan et al., 2006).

The lipophilic characteristics of CoQ_{10} are important for an understanding of its uptake and distribution following oral ingestion, due to its extremely poor water solubility. Thus, the empirically derived regimen for oral administration of CoQ_{10} takes advantage of its lipophilic solubility and recommends co-administration with lipid-rich foods (Zhou et al., 2014). Exogenous CoQ_{10} is taken up from the intestine into chylomicrons and hence to the circulation – similar to the uptake of α-tocopherol – with a range of between 2 and 4% of the total uptake (Zhang et al., 1995). In the plasma, CoQ_{10} is mainly carried by lipoproteins, mostly in LDL particles where it is predominantly in its reduced form (Bhagavan *et al.*, 2007; Zhang *et al.*, 1995). The circulating concentrations of CoQ_{10} may be useful for assessing its status in the body, and also for monitoring the response to CoQ_{10} supplementation.

Research on exogenous CoQ_{10} absorption and bioavailability has shown that it varies greatly depending on the type of CoQ_{10} preparation studied (Bhagavan *et al.*, 2006; Villalba *et al.*, 2010). During the last decade, CoQ_{10} has been available as e.g. oil-based, softgel or powder-filled capsules and tablets in the context of dietary supplements. Many formulations have been developed to improve CoQ_{10} solubility in the human body.

Given the limited bioavailability of CoQ_{10}, recent studies have been focused on the stimulation of its endogenous biosynthesis. For instance, in experiments carried out with animal models, Bertinger *et al* showed that agonists of PPARα receptor increase CoQ_{10} synthesis and its amount was significantly elevated in all organs in the rat (Bentinger et al., 2008). However, it has to be considered that the two ligands used in these experiments are toxic compounds and thus, unsuitable for human use. *In vitro* studies carried out by Bentinger *et al* with HepG2 cell lines, have demonstrated that several polyisoprenoid epoxides stimulated the biosynthesis of CoQ_{10} while inhibiting cholesterol synthesis (Bentinger *et al.*, 2014; Bentinger *et al.*, 2008). Interestingly, a recent study carried out by Fernandez-del-Rio *et al* showed that Kaempferol, a polyphenol compound, increased levels of CoQ_{10} in kidney cells which is related directly with stimulation of endogenous biosynthesis, where Kaempferol served as biosynthetic ring precursor (Fernandez-Del-Rio et al., 2017). Furthermore, the effect of Kaempferol was observed at doses that can be attainable physiologically both by consumption of flavonoids-containing food and by oral supplementation (Kozlowska et al., 2014).

2.5. Adverse effect of CoQ_{10} supplementation and nutrient interaction.

In general, there exists no important adverse effect for CoQ_{10} supplementation described within bibliography. Hidaka *et al.* reviewed regarding the safety assessment of CoQ_{10}, concluding that exogenous supplementation of the quinone does not influence on the endogenous biosynthesis and there was not any sigh of accumulation in to plasma or tissues after cessation of supplementation. The observed safety level for CoQ_{10} is described at 1200 mg/day/person. Indeed, doses up to 3000 mg/day did not cause serious adverse effects in humans, but several moderate adverse effects were reported, including nausea and other gastrointestinal effects (Villalba *et al.*, 2010). However, those effects could not be related to active ingredient since there was no dose-response relationship. Regarding long-term intake of

CoQ_{10} at very high doses in rats (2.6 mg/g) has been reported to have exacerbated cognitive and sensory impairments in old mice, whereas lower amounts had no discernable negative impact on these functions (Sumien *et al.*, 2009). Furthermore, a recent publication reported the tolerability doses of CoQ_{10} supplementation in dialysis patients in a dose escalation study finding that oral administration to be safe and well-tolerated at doses under 1800 mg/day (Yeung *et al.*, 2015). On the basis of the available studies published, it seems that no adverse effect are described for CoQ_{10} supplementation in healthy subjects (Sharma *et al.*, 2016). Interestingly in HF-patients, the largest evaluation of adverse events comes from a 3-month study comprising 2664 patients with HF from 173 Italian centres with a dose range from 50 to 150 mg/day of CoQ_{10}. In this study, 36 patients reported side effects being nausea the most common (Baggio *et al.*, 1994).

With regard nutrients interaction of CoQ_{10}, there exists few report investigating this issue. The main interaction with other nutrients comes from the chemical structure of this antioxidant itself because being a lipid compound its intestinal absorption is reinforced when administered with other lipids. Indeed, it is described that is threefold faster when CoQ_{10} is administrated with food intake (Ochiai *et al.*, 2007). CoQ_{10} intestinal absorption follows the same process than lipids and it seems to be very limited (Zhang *et al.*, 1995).

3. Aging

Aging is defined as a normal decline in functionality and survival with advancing age in all species. It can be viewed as a multifactorial process stemming from the interaction of genetic and environmental factors, which include lifestyle. It is characterized by the onset of several age-related diseases such as dementia, osteoporosis, arthritis, diabetes, cardiovascular diseases, neurodegenerative disorders, and cancer which, though not unique to old age, are nonetheless closely related to it (Rescigno et al., 2017). The physiological decline experienced

by organisms over time is a key factor in increasing the risk of developing age-related diseases (Weinert et al., 2003). Understanding the molecular and cellular mechanisms underlying the aging process would provide a good strategy to address the social, economic and health problems derived from the aged world population.

Many theories have been proposed to explain the aging events, although one of the most accepted suggest that aging, as well as the associated degenerative diseases (Su et al., 2010), is produced by the deleterious, irreversible changes and macromolecular damage produced by ROS (Miquel, 1998; Sohal *et al.*, 2002). In this sense, successful aging can be understood as the long term maintenance of the ability to keep ROS production under control and retain anti-oxidant capacity (Maurya et al., 2016).

ROS are produced from molecular oxygen as a result of normal cellular metabolism and they have beneficial effects at low concentrations. However, under conditions of ROS overproduction, these reactive molecules produce adverse modifications to cell components, such as lipids, proteins, and DNA, inhibiting their normal functions (Valko et al., 2006). Organisms have developed a series of defence mechanisms against ROS: enzymatic antioxidant defences include superoxide dismutase (SOD), catalase or glutathione peroxidase (GPx), among others, while non-enzymatic antioxidants include ascorbic acid, tocopherol, glutathione, CoQ_{10}, and others. Oxidative stress is defined as the imbalance between ROS and antioxidant defence in favour of ROS, thus causing potential damage. Oxidative stress is a condition associated with chronic-degenerative diseases, such as cancer, metabolic and cardiovascular diseases, as well as in the aging process.

Some oxidative modifications (mainly those related to DNA) are not completely repaired and thus accumulate, leading to cell death, organism malfunction, and the "aging phenotype." Nowadays, a version of this theory, related with mitochondria as a major source as well as target of ROS, is one of the most popular theories of aging (Barja, 2007; Miquel *et al.*, 1980). This theory explores mitochondrial dysfunction as a source for free radical accumulation, leading to an increase of ROS production and a misbalance in Ca^{2+} homeostasis. These changes increase sensitivity of mitochondrial DNA (mtDNA) to oxidative damage resulting in the accumulation of mutated mtDNA which led to the concept of the "vicious cycle": an initial ROS-induced impairment of mitochondria produces an increased oxidant production that, in turn, leads to further mitochondrial damage (Gilmer et al.). This increased mitochondrial dysfunction yields inefficient flow of electrons through the electron transport chain leading to elevated ROS production (Ma et al., 2014). Superoxide produced in mitochondria is generated by electrons leaking form the electron transfer system at the inner membrane. These electrons are then captured by molecular oxygen to yield superoxide (Wallace, 1997). The normal function in mitochondrial electron transport is depending on CoQ_{10} levels, where it has been observed that the electron leaking occurs between the complex I and II to complex III (Turrens, 2003). CoQ_{10} levels decline with aging, connecting the postulated increase in ROS production with advanced age.

According to this concept, the development of strategies to delay and improve the aging process, focused on extending the maximum lifespan and / or retard the age-associated biological changes, including age-related diseases, is of major importance (Lee, 2004). Nutritional and pharmacological interventions have been previously shown to extend lifespan in diverse model organisms, including *Saccharomyces cerevisiae*, *Drosophila melanogaster*, mice and rats, as well as monkeys. Some antioxidants, as well as interventions related to

dietary fat have proved to be useful as dietary antiaging therapies (Duntas, 2011; Lopez-Dominguez *et al.*, 2012).

3.1. CoQ_{10} deficiency in advanced aged

As stated above, CoQ_{10} is synthesized by all cells in healthy individuals (Schultz, 1999). CoQ_{10} levels are increased in the first 20 years of life; however, the organism begins to lose its ability to synthesise CoQ_{10} along aging and its concentration may become deficient (Blatt *et al.*, 2011; Gutierrez-Mariscal *et al.*, 2012; Ochoa *et al.*, 2007). In addition to a decrease in its biosynthesis, additional factors or conditions may affect the levels or functions of CoQ_{10}, including an increase in its degradation (Nakamura et al., 1999) or changes in membrane lipids which prevent the movement of this quinone, as occurs in different age-related diseases (Kagan VE, 1996). Factors that have been reported regarding this loss of CoQ_{10} function are related to the occurrence of genetic mutations, aging, cancer and the use of statin-type drugs which can cause a decrease of CoQ_{10} in serum and tissues. However, changes in CoQ_{10} levels with aging are tissue- and organ-dependent. The precise membranes in all cells which suffer the loss of CoQ_{10} are not well known, and this deficiency can be observed in mitochondria of some cells but not in others. For example, old rats have increased levels of CoQ_{10} in mitochondria from the brain (Battino et al., 1997) but lower levels in mitochondria from skeletal muscle (Lass et al., 1999), so it would be important to determine whether these tissue-dependent changes are related to a loss of function or antioxidant capability.

In young and healthy individuals CoQ_{10} supplementation does not increase tissue levels above normal (except in liver and spleen) but, in older animals with decreased CoQ_{10} levels supplemental CoQ_{10} can restore normal levels (Beal, 1999; Rosenfeldt *et al.*, 1999). Low levels

of CoQ_{10} have been related to the higher oxidative stress produced during aging and in the course of different related diseases. However, in the advanced aged the amount of CoQ_{10} in the diet is not sufficient to increase significantly plasma CoQ_{10}. In fact, a supplementation with about 100 mg/day of CoQ_{10} would be necessary to get a significant increase of this quinone in serum (Crane, 2001). Based on that, oral CoQ_{10} supplementation appears as a viable antioxidant strategy in many neurodegenerative disorders, diabetes, cancer, muscular and cardiovascular diseases, such as chronic heart failure and hypertension, where oxidative stress is implicated (Bhagavan *et al.*, 2006; Gonzalez-Guardia *et al.*, 2015; Gutierrez-Mariscal *et al.*, 2012; Gutierrez-Mariscal *et al.*, 2014; Villalba *et al.*, 2010; Yubero-Serrano *et al.*, 2013).

3.2. CoQ_{10} and aging

Since CoQ_{10} deficiency has been described in the advanced aged, intake of exogenous CoQ_{10} could help prevent the occurrence and progression of age-related alterations. In the last years, several authors have describe a molecular mechanism by which CoQ_{10} could exert its anti-aging effects in age-related diseases through the activation of AMPK and sirtuin (SIRT) family of protein deacetylases (specifically SIRT1 and SIRT3) (Tian *et al.*, 2014; Xu *et al.*, 2017) (Figure 3). In this context, Xu *et al* have shown that CoQ_{10} increased cyclic adenosine monophosphate (cAMP) and enhanced the activity of SIRT1 and PGC-1α, thereby improving mitochondrial function and inhibiting oxidative stress in animal models (Xu et al., 2017). Furthermore, Tian *et al* have recently observed a decelerated age-related accumulation of oxidative damage in mice with accelerated senescence by dietary supplementation with CoQ_{10}. In this observation, they found that CoQ_{10} induces the activation of SIRT1, SIRT3 and peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), modulating the mitochondrial function and oxidative stress damage in the liver and inner ear by enhancing the activity of mitochondrial antioxidant defense systems (Tian et al., 2014). The activation of SIRT3 by CoQ_{10} triggers the

deacetylation of SOD in the mitochondria, increasing its specific activity and its ROS-scavenging capacity. In addition, other studies have shown that CoQ_{10} content in adipose tissue gradually decreased with the development of obesity in both mice and humans, and that CoQ_{10} synthesis-related enzymes were upregulated as a compensatory measure. CoQ_{10} also inhibits adipocyte differentiation and cholesterol synthesis, but the molecular mechanism throughout the involvement of PPARα by PGC-1α remains unclear (Bour et al., 2011).

Among the aging-related diseases, it has been demonstrated that osteoporosis can be prevented by CoQ_{10} in a rat model of osteoporosis induced by spinal-cord injury (Zhang et al., 2015). Additionally, *in vitro* studies have demonstrated that CoQ_{10} reduced osteoclast formation from bone-marrow-derived monocytes and RAW264.7 mouse cells (Moon et al., 2013). Furthermore, a recent study in postmenopausal women suggested that CoQ_{10} may prevent bone-mass loss associated to aging (Casado-Díaz et al., 2017).

4. Therapeutic uses of CoQ_{10} in age-related diseases

The therapeutic use of CoQ_{10} is based upon its fundamental role in mitochondrial function, cellular bioenergetics as well as its antioxidant capacity. Also, at the inner mitochondrial membrane it is a cofactor of uncoupling proteins and is involved in modulation of the mitochondrial transition pore. Furthermore, CoQ_{10} affects the expression of genes involved in human cell signalling, metabolism and transport, and some of CoQ_{10} effects may be due to this property. Animal data show that, when used in large doses, CoQ_{10} can be taken up by all

tissues including the heart and brain mitochondria. This fact has implications for therapeutic applications in human diseases which are developed with oxidative stress, and evidence exists for its beneficial effects in cardiovascular, neurodegenerative and age-related diseases (Bhagavan *et al.*, 2006; Gonzalez-Guardia *et al.*, 2015; Gutierrez-Mariscal *et al.*, 2012; Gutierrez-Mariscal *et al.*, 2014; Villalba *et al.*, 2010; Yubero-Serrano *et al.*, 2013).

4.1. Study of CoQ_{10} supplementation in elderly population

In the past few years, our group has been performing an interventional cross-over study where we sought to investigate in elderly subjects the effect of CoQ_{10} supplementation to a healthy diet as a Mediterranean diet on molecular mechanisms related to oxidative stress as well as inflammation, in order to evaluate its influence in aging and age-related diseases (Gonzalez-Guardia *et al.*, 2015; Gutierrez-Mariscal *et al.*, 2012; Gutierrez-Mariscal *et al.*, 2014; Lopez-Moreno *et al.*, 2016; Yubero-Serrano *et al.*, 2011; Yubero-Serrano *et al.*, 2013; Yubero-Serrano *et al.*, 2012). During an intervention period of 4 weeks, the participants took a dose of 200 mg/day of CoQ_{10} and a single dose of 400 mg during the postprandial study. The effect of CoQ_{10} supplementation was estimated from comparison with the consumption of Mediterranean diet + placebo or a saturated fatty acids-rich diet (SFA-diet) in a random cross-over by latin squares study. Within this context, we demonstrated that the supplementation with CoQ_{10} resulted in a postprandial decrease in soluble oxidative biomarkers such as oxidized-LDL and lipoperoxides, with consequent decreases in the activity of antioxidant enzymes such as SOD, catalase and GPx, compared to the consumption of the SFA-diet (Yubero-Serrano et al., 2011). We also observed an increase in capillary flow and NO production, which could be an indirect effect of lower production of superoxide anion due to the augmented efficiency in the electron transport chain due to the elevation in CoQ_{10} content (Yubero-Serrano et al., 2011). Since CoQ_{10} has been described as gene expression regulator, we

also explored its influence at this level and found a postprandial decrease in expression of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and GPx1 (Yubero-Serrano et al., 2013). In this sense, we also observed an increase in the cytoplasmic Nrf2 and Keap-1 protein levels compared to the other diets, where the presence of ROS enhanced the translocation of Nrf2 to the nucleus and activated the antioxidant defense (Yubero-Serrano et al., 2013). Given the decreased oxidative stress observed after the supplementation of CoQ_{10} to a Mediterranean diet, we wondered whether this supplementation could also protect DNA from oxidative damage. In this sense, we demonstrated, for the first time in a human dietary intervention study, the influence of CoQ_{10} supplementation on p53 activation in response to oxidative DNA damage (Gutierrez-Mariscal et al., 2012). We observed lower levels of 8-hydroxydeoxyguanosine (8-OHdG) (a DNA damage biomarker) in the group that consumed the Mediterranean diet supplemented with CoQ_{10} compared to the other diets, likely as a consequence of lower levels of oxidative stress. Indeed, we also showed the involvement of Mdm2 and poly- and mono-ubiquitination post-translational modifications in the activation of p53 (Gutierrez-Mariscal et al., 2012). Furthermore, this activation triggered the DNA repair machinery after the consumption of SFA-diet compared to the CoQ_{10} supplementation (Gutierrez-Mariscal et al., 2014).

Due to the recent connection established between supplementation with CoQ_{10} and inflammation (described above), we also explored the influence of CoQ_{10} on this context in our dietary intervention study. Supplementation of CoQ_{10} provoked a postprandial decrease in gene expression of p65, inhibitor of nuclear factor kappa-B kinase subunit beta (IKK-β) and IL-1-β consistent with less activation of NFκB, the key regulator of inflammation (Yubero-Serrano et al., 2012). Indeed, CoQ_{10} produced less expression of c-Jun N-terminal kinase 1 (JNK-1) and genes related to ER stress such as spliced isoform of X-box binding protein 1 (sXBP-1),

calreticulin (CRT) and binding immunoglobulin protein/78 kDa glucose regulated-protein (BiP/Grp78) (Yubero-Serrano et al., 2012).

According with these findings, we used a metabolomic approach in order to study those modifications in metabolic biomarkers elicited by the supplementation with CoQ_{10}. We found that CoQ_{10} increased the levels of excreted hippurate in the urine and decreased the levels of phenylacetylglycine (Gonzalez-Guardia et al., 2015). Hippurate is an indicator of antioxidant molecules synthesis by gut microbiota, DNA repair enhancement and NF-kB inhibition. On the other hand, phenylacetylglycine was inversely associated with CoQ_{10} and highly positive correlated to urinary levels of isoprostanes that could be linked to an increase of oxidative stress-related process.

It has been reported the contribution of advanced glycation end products (AGEs) in the origin and progression of age-associated diseases by increasing oxidative stress and inflammation (Cai *et al.*, 2007; Uribarri *et al.*, 2007). Based on that, we investigated the effect of CoQ_{10} supplementation in metabolism of AGEs in our population. AGEs constitute a heterogeneous group of compounds derived from the nonenzymatic glycation of proteins, lipids and nuclear acids *via* a complex sequence of reactions referred as the Maillard reaction (O'Brien et al., 1989). In this sense, we demonstrated for the first time that CoQ_{10} supplementation resulted in a greater decrease in endogenous AGEs levels, serum methylglyoxal and N-carboxymethyllysine (sMG and sCML, respectively) during postprandial state, which is likely a consequence of an increase in gene expression related to AGEs degradation, AGE receptor 1 (AGER1) and Glyoxal oxidase 1 (Glox1) (Lopez-Moreno et al., 2016).

Taking together, the results derived from our study demonstrated the multiple benefits of CoQ_{10} supplementation to a healthy diet as Mediterranean Diet in elderly people, as a dietary strategy to ameliorate the oxidative stress and inflammatory processes underlying aging and age-related diseases.

4.2. CoQ_{10} and cardiovascular disease

Cardiovascular disease (CVD) is one of the major causes of death and disability worldwide. It is estimated that 17 million deaths per year are caused by CVD (Flowers et al., 2014). The burden of CVD will increase with an aging population and increasing levels of obesity and sedentary lifestyles. The prevention of CVD by modifying lifestyle factors is one of the priorities of public health systems. Diet plays an important role in the aetiology of CVD, since a number of dietary factors such as a low consumption of fruit and vegetables, a high intake of saturated fat, and a high consumption of salt have been found to be related with CVD risk (Eilat-Adar et al., 2013). Oxidative stress plays a central role in the pathogenesis of CVD including congestive heart failure, hypertension and ischemic heart disease. Specifically, congestive heart failure, due to an energy depletion status in the mitochondria, has been strongly correlated with significantly low blood and tissue levels of CoQ_{10}. Since antioxidant defences in LDLs tend to decrease with aging, CoQ_{10} supplementation would be a good therapy to reduce LDL oxidation and decrease the high risk of cardiovascular disease in aging or after oxidative injury (Yubero-Serrano et al., 2011). Generally, heart muscle cells have high levels of CoQ_{10} due to the high energy requirements of this cell type. However, in biopsy samples from human heart, a significant decrease of the CoQ_{10} content in cardiomyopathy was found and this deficiency was correlated with the severity of disease (Folkers *et al.*, 1985; Nobuyoshi, 1984). In healthy conditions, myocardium mitochondria possess the highest CoQ_{10} levels as compared with other tissues, and a growing evidence supports the notion that CoQ_{10} deficiency has a role in the

development and progression of congestive heart failure (HF) (Florkowski et al., 2015). As stated above, only half of CoQ_{10} production persists in the myocardium at the age of 80 years because of the decline in its endogenous production, (Kalen et al., 1989). Of note, the grade of this deficiency has been correlated with the severity of the diseases according to New York Heart Association (NYHA) classification (Onur et al., 2015). In this context, the supplementation with CoQ_{10} in the elderly gains relevancy on the CVD risk. The mechanisms behind the CoQ_{10} supplementation effects are related to its power as antioxidant, reducing oxidative stress, leading to ATP synthesis and a as stabilizer of calcium-dependent channels (DiNicolantonio et al., 2015). An overview of the main evidences related to CoQ_{10} supplementation studies, referred in the text, is shown in Table 2. A meta-analysis focused on the effects of CoQ_{10} supplementation on clinical outcomes of congestive HF, such as left ventricular ejection fraction (LVEF), has been published recently showing an improvement in the ejection fraction (EF) in those subjects who received CoQ_{10} supplementation compared with the control group receiving placebo (Fotino et al., 2013). Subsequently, Q-SYMBIO study, a prospective, randomized, double-blind, placebo-controlled, multicenter trial of CoQ_{10} as adjunctive treatment of chronic HF, demonstrated that the treatment with this quinone in addition to standard therapy for patients with moderate to severe heart failure is safe, well tolerated, and associated with a reduction in general symptoms (Mortensen et al., 2014).

CVD in elderly population is normally associated with other complications such as diabetes and hypercholesterolemia. In this sense, it is well known that not only age could affect the lowering levels of CoQ_{10}, but also certain drugs can cause its depletion, in particular hydroxyl-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, as statins prescribed to reduce cholesterol levels by blocking the mevalonate metabolic pathway (Folkers et al., 1990). Mevalonate is a shared precursor in cholesterol and CoQ_{10} synthesis **(**Figure 2**)** (Schaars et al.,

2008); therefore, when statins lower cholesterol levels they may simultaneously affect CoQ_{10} levels. Moreover, statin use is associated with muscle-related symptoms or myopathies and CoQ_{10} supplementation may decrease muscle pain associated with statin treatment (Caso et al., 2007).

Several studies concerning the treatment of heart disease (congestive heart failure, cardiomyopathy, and/or valvular heart disease) conclude that a CoQ_{10} supplement between 50-300 mg/day appears to be the optimal dose, although CoQ_{10} is still safe and well tolerated at doses up to 1200 mg/day (Gao et al., 2011). Alehagen *et al* reported that dietary supplementation with selenium and CoQ_{10} (at a dose of 200 mg/day) during four years led to reduced cardiovascular mortality, less age-dependent increase in the biomarker N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (a cardiac peptide biomarker) (Alehagen et al., 2013), less oxidative stress (Alehagen et al., 2015), and less inflammatory activity (Alehagen et al., 2015) in an intervention study which compromised 443 elderly patients (between 70 to 80 years old). Basically, from a mechanistic point of view, the effects observed in the improvement in the biomarkers parameters for cardiovascular risk are commonly related to two important roles in which CoQ_{10} is involved: on the one hand the accuracy of the electron transport chain avoiding the increment in oxidative species and thus lowering lipid peroxidation (Littarru et al., 2007) and on the other hand, the improvement on the energy production in form of ATP biosynthesis to enhance myocardial contractility (Folkers et al., 1985), with no adverse effects or drug interactions (Kaikkonen et al., 2002).

A recent publication by Alehagen *et al* correlates CoQ_{10} supplementation with changes in expression of microRNAs which can provide novel mechanisms for the cardioprotective effects of this supplementation (Alehagen et al., 2017). An increase in expression of microRNA-29b-3p

was reported, presumably reflecting the protective role of the extracellular matrix genes around the myocardium. In this sense, Kriegel *et al* had previously shown data regarding the microRNA-29 family repressive effects on 16 *in vivo* confirmed extracellular matrix genes (Kriegel et al., 2012). The microRNAs belonging to this family have been found downregulated in the myocardium immediately after an infarction in mice model, but the expression of the extracellular matrix genes increases during the healing process of the infarcted area. Various studies have shown a relationship between these extracellular matrix genes and expression of this microRNA-29 family (van Rooij et al., 2008). However, the findings described in the study of Alehagen *et* al derive from a trial where selenium was co-supplemented with CoQ_{10}, so the observed effects cannot be attributed solely to CoQ_{10}. Furthermore, the functions of both antioxidant supplements are interrelated, since the selenoenzyme thioredoxin reductase 1 is involved in the reduction of oxidized CoQ_{10} (ubiquinone) to its active form ubiquinol (Nordman *et al.*, 2003; Xia *et al.*, 2003), and the synthesis of the selenocysteine-containing proteins requires a functional mevalonate pathway, of which CoQ_{10} is also a product (Moosmann et al., 2004) More research is indeed needed in this area to unveil those mechanisms relating the levels of CoQ_{10} and the expression of these microRNAs.

Apart from oxidative stress, inflammation also underlies the pathogenesis of CVD as an event described to be involved both in the development of the disease and as a risk factor. Given the demonstration of the anti-inflammatory effect of CoQ_{10} in cellular and animal studies (Bessler *et al.*, 2010; Tarry-Adkins *et al.*, 2016), clinical trials have been also set up in order to examine whether CoQ_{10} supplementation could reduce inflammatory mediators in patients. These anti-inflammatory effects of CoQ_{10} have been described to take place through the suppression of TNF-α gene expression in a study focused on adipogenesis induced in ob/ob mice (Carmona et al., 2009) in which CoQ_{10} inhibited the activation of NF-κB and exerted inhibitory effects on IL-6

secretion (Schmelzer et al., 2008). In addition, a possible mechanism to explain the protective effect of CoQ_{10} on inflammatory cytokines can be attributed to its ability to inhibit the activation of the transcription of NADPH oxidase and inducible nitric oxide synthase (NOS) genes (Starace et al., 2005).

Obesity is considered one of the most important conditions in the onset of CVD. In this sense, a recent publication has shown the results from a study of CoQ_{10} supplementation to KKAy mice, a model for obesity and insulin resistance, where the authors demonstrated that a treatment with CoQ_{10} inhibits the development of obesity, as well as visceral fat accumulation, with blood cholesterol and triglyceride content being reduced by CoQ_{10} treatment (Xu et al., 2017). Regarding the molecular mechanisms behind these effects, the authors demonstrated, both by *in vivo* and *in vitro* assays, that CoQ_{10} increased liver PGC-1α gene expression (involved in glucose and lipid metabolism), whose activity is regulated by AMPK and SIRT1. AMPK can inhibit ATP-consuming and promote ATP-forming processes such as β-oxidation of fatty acids (Gerhart-Hines *et al.*, 2011; Park *et al.*, 2012). On the other hand, SIRT1 is widely known for its anti-aging effect. The treatment with CoQ_{10} ameliorated the decrease of SIRT1 protein content and AMPK activity that occurs with age in the mice model described in the study. Indeed, the authors demonstrated that CoQ_{10} also inhibited transcriptional activity of Activator Protein-1 (AP-1) to bind to the phosphodiesterase 4 (PDE4) gene promoter (a specific phosphodiesterase) inhibiting cAMP hydrolysis, thus increasing cAMP content in liver and activating SIRT1 and AMPK.

4.2.1. CoQ_{10} and hypertension

Hypertension is a major risk factor for stroke, myocardial infarction, congestive HF, kidney failure, and peripheral vascular disease, and is also one of the primary modifiable risk factors associated with prevention of these diseases (Ibrahim et al., 2012). Although pharmacological treatment of hypertension has shown efficacy lowering blood pressure and modestly decrease stroke, myocardial infarction, and mortality, hypertension still remains prevalent in the population and additional treatment options are needed (Musini et al., 2009). The primary action of CoQ_{10} in clinical hypertension is on vasodilatation, where directly acts on the endothelium and vascular smooth muscle, with the ability to counteract the vasoconstriction and lower blood pressure, without significant side effects. In fact, the protective effect of CoQ_{10} on hypertension is thought to act in an indirect way through its ability in preventing oxidative stress and nitrative stress as well as inflammation resulting in a recoupling of NOS (Belardinelli et al., 2008). The health effects of CoQ_{10} have been investigated in several controlled intervention studies in human subjects in a range of CoQ_{10} doses from 100 mg to 200 mg/day for prevention against high blood pressure (Gonzalez-Guardia *et al.*, 2015; Young *et al.*, ; Yubero-Serrano *et al.*, 2013). Of note, patients treated with CoQ_{10} exhibited a decrease of a range between 11-17 mmHg in systolic blood pressure and a reduction of 8 mmHg in diastolic blood pressure. These results appear to demonstrate a role for this quinone as a hypotensive agent on its own or in combination with other conventional anti-hypertensive therapies. However, controversy still exists nowadays regarding the real effect of CoQ_{10} in lowering blood pressure. In fact, a recent meta-analysis from Cochrane library concluded that there are not sustainable evidences to support an actual lowering effect for CoQ_{10} in this sense, and pointed out the necessity of more well-controlled clinical trials in order to investigate this putative property of CoQ_{10} (Ho et al., 2016).

4.2.2 CoQ_{10} and endothelial function

Endothelial dysfunction plays a key role in the development, progression, and clinical manifestations of atherosclerosis and CVD. The effect of oral CoQ_{10} supplementation on endothelial function in patients with coronary artery disease, diabetes mellitus or in elderly people has been investigated by several studies (Gao *et al.*, 2011; Tiano *et al.*, 2007; Watts *et al.*, 2002). Endothelial function, measured by flow-mediated dilation (FMD) or nitroglycerin-mediated dilation (NMD), and the extracellular superoxide dismutase activity, improved in most of the subjects treated with CoQ_{10} likely due to its antioxidant and anti-inflammatory activity (Yubero-Serrano et al., 2012), with a decrease in the rate of inactivation of NO to peroxynitrite by superoxide radicals. CoQ_{10} may reduce the levels of these radicals under oxidative stress conditions (Gonzalez-Guardia *et al.*, 2015; Tiano *et al.*, 2007). *In vitro* studies have shown that CoQ_{10} can efficiently prevent high glucose-induced endothelial cell apoptosis and adhesion to monocytes, which are relevant to the pathogenesis of atherosclerosis (Tsuneki et al., 2007). Moreover, *in vitro* studies with endothelial progenitor cells (EPCs) have evidenced that CoQ_{10} could be used as a potential therapeutic agent to counteract high glucose-attenuated EPC angiogenesis functions in diabetic patients through a mechanism involving AMPK, eNOS and HO-1 pathways (Tsai et al., 2016).

4.3. CoQ_{10} and renal failure

Oxidative stress is increased in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients (Himmelfarb et al., 2003). Over 2 million people worldwide currently receive treatment with dialysis or a kidney transplant to stay alive, yet this number may only represent 10% of people who actually need treatment to live (Couser et al., 2011). The balance between ROS and antioxidant systems is turned in favour of ROS in these patients, whose excess mortality may be attributable to an increased risk of CVD as a result of increased oxidative stress (Kuchta et al., 2011). Only a few studies have evaluated the role of CoQ_{10} as a

component of antioxidant system in CKD patients shown in Table 3. Lippa *et al* determined the levels of CoQ_{10} in a group of 48 patients on chronic hemodialysis, in 15 uremic patients, and in a control group of healthy subjects (Lippa et al., 2000). CoQ_{10} levels were significantly lower in CKD patients as compared with a healthy group. In a recent study, where the authors investigated levels and associations of oxidative stress biomarkers and CoQ_{10} in CKD, hemodialysis and peritoneal dialysis (PeD) patients, no differences in CoQ_{10} levels were found between those in CKD and hemodialysis groups. However, other members of the antioxidant system were higher in patients undergoing PeD compared to CKD patients (Gokbel et al., 2011). Regarding the effect of CoQ_{10} supplementation (120 mg/day) in CKD patients, after 28 days of treatment, the number of patients on dialysis was significantly lower compared with the placebo group at the end of the study (Singh, 2000). More recently, Yeung *et al* studied the tolerability and safety of oral CoQ_{10} administration, and its role in reducing oxidative stress in hemodialysis patients. They found oral administration of CoQ_{10} was safe and well-tolerated at doses under 1800 mg/day, and concluded that CoQ_{10} may reduce systemic oxidative stress dose-dependently in this type of patients with an improvement of mitochondrial function and a decreased oxidative stress in patients receiving hemodialysis (Yeung et al., 2015). In a randomized, double-blind, phase IIa, placebo-controlled study, Rodriguez-Carrizalez *et al* have studied the effect of CoQ_{10} treatment in 60 patients with non-diabetic retinopathy, with a daily dose of 400 mg of ubiquinone (Rodriguez-Carrizalez et al., 2016). They found a significant increase in fluidity of the cellular membrane of erythrocytes in the CoQ_{10}-treated group. Normal fluidity in these membranes is relevant in the pathophysiological mechanisms involved in the development and presence of diabetic retinopathy. Indeed, they observed that CoQ_{10} treatment restored the capacity of ATPase to synthesize ATP *vs* its hydrolysis in mitochondria, thus improving energy production.

4.4. CoQ_{10} and neurodegenerative diseases

A common characteristic of the neurodegenerative diseases is a mitochondrial dysfunction with abnormal energy metabolism and an increase in cellular oxidative stress. Since free radicals and neuro-inflammation processes are thought to be involved in the mechanisms and development of neurodegenerative diseases such as Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease (AD), and other neurodegenerative disorders (Koroshetz *et al.*, 1997; Ma *et al.*, 2014; Shults *et al.*, 1997), CoQ_{10}, as an antioxidant molecule with anti-inflammatory properties, has been suggested for testing as a potential neuroprotective therapy (Table 4). Preclinical studies in both *in vitro* and *in vivo* models of PD have demonstrated that CoQ_{10} can protect the nigrostriatal dopaminergic system (Liu et al., 2011). There are evidences that support a role for mitochondrial dysfunction in PD. In this sense, CoQ_{10} levels have been found significantly lower in mitochondria from Parkinsonian patients than in mitochondria from age and sex-matched control subjects (Shults et al., 2002). In a randomised, placebo-controlled and double-blind study, Shults *et al* demonstrated that a dose of 1200 mg CoQ_{10}/day reduced the worsening of PD, with a significant increase in plasma levels of CoQ_{10} and NADH-cytochrome *c* reductase activity. The greatest benefit was seen in everyday activities of the patients, such as dressing, bathing and feeding (Shults et al., 2002). Another placebo-controlled, double-blind trial, conducted by Muller *et al* concluded that CoQ_{10} supplementation provided a significant mild benefit on PD symptoms compared with placebo (Muller et al., 2003).

As well as in PD, strong evidence exists for early oxidative stress in HD, coupled with mitochondrial dysfunction and indeed an impaired energy metabolism (Stack et al., 2008), where a deficiency in CoQ_{10} is considered as part of its physiopathology. CoQ_{10} doses, ranging from 600 to 1200 mg/day tested in 10 HD patients during a six-month open-label trial, produced no significant effect on clinical scores (Delanty et al., 1998). However, treatment with CoQ_{10} resulted in significant decreases in cortical lactate concentrations, which reversed following withdrawal of therapy. This finding supports the predicted metabolic effect of oral CoQ_{10} in cerebral tissue, and is suggestive of an effect upon mitochondrial metabolism (Koroshetz et al., 1997).

On the other hand, it has been recently reported that CoQ_{10} deficiency occurs in Multiple System Atrophy, a sporadic neurodegenerative disorder clinically characterized by autonomic failure, Parkinsonism and cerebellar ataxia, suggesting that the cerebellum might be selectively vulnerable to a decrease of CoQ_{10} levels (Barca *et al.*, 2016; Kasai *et al.*, 2016; Mitsui *et al.*, 2016).

5. Conclusions

Since described for the first time in 1955, the importance of CoQ_{10} has been mainly attributed to its role as an agent for energy transduction in mitochondria. However, since the final of XX century new findings reported by researchers have shown that CoQ_{10} is indeed an important antioxidant in mitochondria and other membranes of different cell compartments and tissues in the organism, as well as in plasma lipoproteins, with a unique feature for regeneration of its redox capacity. Endogenous CoQ_{10} biosynthesis provides sufficient CoQ_{10} for normal individuals, but evidence for CoQ_{10} deficiency is mainly based on genetic failure, but also on

aging and age-related diseases. The properties of CoQ_{10} make that it can be easily used as a supplement, delaying and mitigating the effects caused by its lack.

The beneficial effect of supplemental CoQ_{10} is reinforced because this antioxidant has an excellent safety record and is well tolerated in high doses for prolonged periods of time with limited side effects. Furthermore, new functions for CoQ_{10} have been described in the recent past years, including anti-inflammatory effects, gene expression regulation and lipid bilayer membranes stabilization, which explain its involvement in aging and age-related diseases. However, more research is needed to examine the appropriate dose, effectiveness, and bioavailability of orally-administered CoQ_{10}, especially in elderly, and even to explore the possibility of designing therapeutic agents that increment its endogenous biosynthesis.

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Table 1. Contents of coenzyme Q_{10} in foods (Data based on Crane et al., 2001; Weber et al., 1997).

Table 2. Coenzyme Q_{10} supplementation studies in human and its relation to cardiovascular disease. CVD: Cardiovascular Disease; NT-proBNP: N-Terminal prohormone of Brain Natriuretic Peptide; CRP: C Reactive Protein; IL-6: Interleukin 6; TNF-α: Tumor Necrosis Factor alpha; FMD: Flow-Mediated Dilation; NMD: Nitroglycerin-Mediated Dilation; ED: Endothelium Dysfunction; ecSOD: Extracellular Superoxide Dismutase; NO: Nitric Oxide.

Food Sources		CoQ_{10} content (μg/g)
Meat	Pork heart	203
	Pork liver	3.1
	Pork ham	20
	Beef heart	41
	Beef liver	19
	Lamb leg	2.9
	Chicken leg	17
Fish	Trout	11
	Sardines	64
	Red Mackerel	43-67
	Tuna canned	0.3
Vegetables	Spinach	2.3
	Pea	0.1
	Cauliflower	0.6
Fruits	Orange	2.2
	Strawberry	0.1
	Apple	0.2
Cereals	Bread (rye)	4.7
	Bread (wheat)	2.1

Authors	Disease	Evidences found	Dosage Recommendation
Fotino, AD et al	Congestive Heart Failure	Improvement in ejection fraction	60 mg to 300 mg/day
Mortensen, SA et al	Heart Failure	Reduction in general symptoms, reducing major adverse cardiovascular events	100 mg 3 times daily
Caso, G et al	Myophathies associated to statins treatment	Decrease muscle pain associated to statin treatment	100 mg/day
Alehagen, U et al	CVD mortality	Reduction in CVD mortality, less NT-proBNP, less oxidative stress, less inflammatory activity	200 mg/day (along with 200 µg/day of Selenium).
Fan, L et al	CVD	Lowering inflammatory biomarkers: CRP, IL-6 and TNF-α	60 mg to 500 mg/day
Gonzalez-Guardia, L et al and Yubero-Serrano, EM et al	Hypertension/Endothelial function	Decrease in systolic blood pressure/Improvement in FMD and NMD	200 mg/day
Young, JM et al	Hypertension	Decrease in systolic blood pressure	100 mg twice a day
Tiano, L et al	Coronary artery disease	Improvement of ED vasodilation and affecting the endothelium-bound ecSOD activity decreasing rate of inactivation of NO to peroxynitrite	300 mg/day

Table 3. Coenzyme Q_{10} supplementation studies in human and its relation to renal disease. CKD: Chronic Kidney Disease.

Authors	Disease	Evidences found	Dosage Recommendation
Singh, RB et al	CKD	Reduction the number of patients on dialysis	60 mg 3 times daily
Yeung, CK et al	CKD	Reduction on the systemic oxidative stress, improving mitochondrial function	up to 1800 mg/day
Rodriguez-Carrizalez, AD et al	Non-diabetic retinopathy	Increase in fluidity of the erythrocyte cellular membrane	400 mg/day

Table 4. Coenzyme Q_{10} supplementation studies in human and its relation to neurodegenerative diseases. PD: Parkinson's Disease.

Authors	Disease	Evidences found	Dosage Recommendation
Shults CW et al	Parkinson's disease	Reduced worsening of PD with benefits in everyday activities of the patients. Increasing in CoQ10 levels and NADH-cytochrome c reductase activity	300, 600 and 1200 mg/day
Müller, T et al	Parkinson's disease	Significant mild benefict on PD symptoms	360 mg/day
Koroshetz WJ et al	Huntington's disease	Significant decrease in cortical lactate concentrations affecting mitochondrial metabolism	360 mg/day

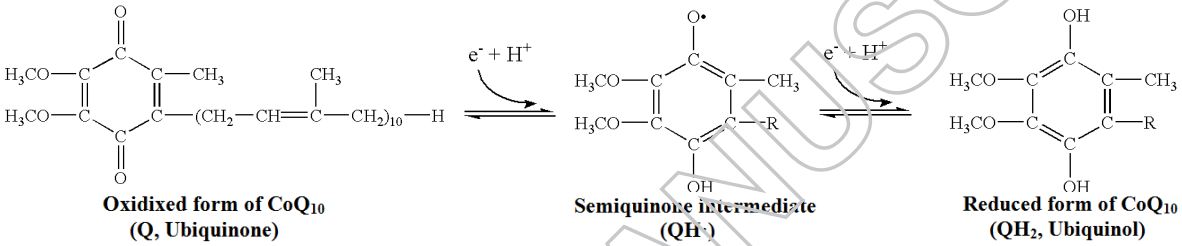

Figure 1. Redox states of Coenzyme Q_{10}.

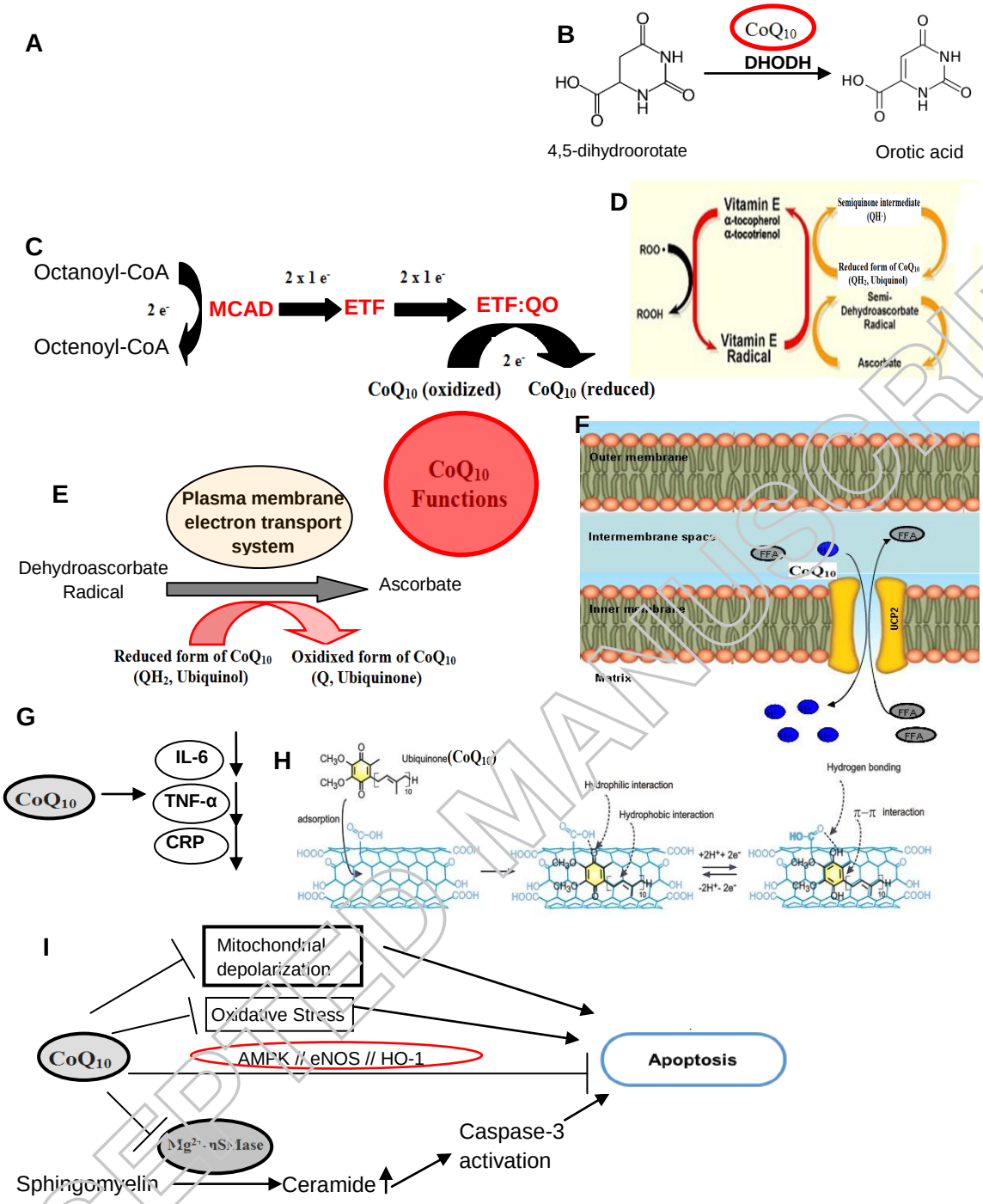

Figure 2. Coenzyme Q_{10} functions. CoQ_{10} as part of electron transport chain in mitochondria (A). CoQ_{10} participation in the novo pyrimidin biosynthesis (B). Electron transport from fatty acids oxidation throughout ETF (C). Antioxidant effect of CoQ_{10} and recycling of others antioxidant such as α-tocopherol and vitamin C (D, E). CoQ_{10} as a cofactor in uncoupling proteins (F). The

anti-inflammatory effect of CoQ_{10} supplementation through the decrease of inflammatory markers such as IL-6, TNF-α and CRP (G). Effect of CoQ_{10} on lipid bilayer stabilization (H).Effects of CoQ_{10} in cell cycle control and apoptosis (I). DHODH: Dihydroorotate dehydrogenase; MCAD: Medium-chain fatty acyl-CoA dehydrogenase; ETF: Electron transfer flavoprotein; ETF:QO: Electron transfer flavoprotein:ubiquinon oxidorreductase; IL-6: Interleukin-6; TNF-α: tumor necrosis factor alpha; CRP: C reactive protein; AMPK: AMP-activated protein kinase; eNOS: endothelial NO synthase; HO-1: Heme oxygenase 1; Mg^{2+}-nSMase: neutral Mg^{2+}-dependent sphingomyelinase.

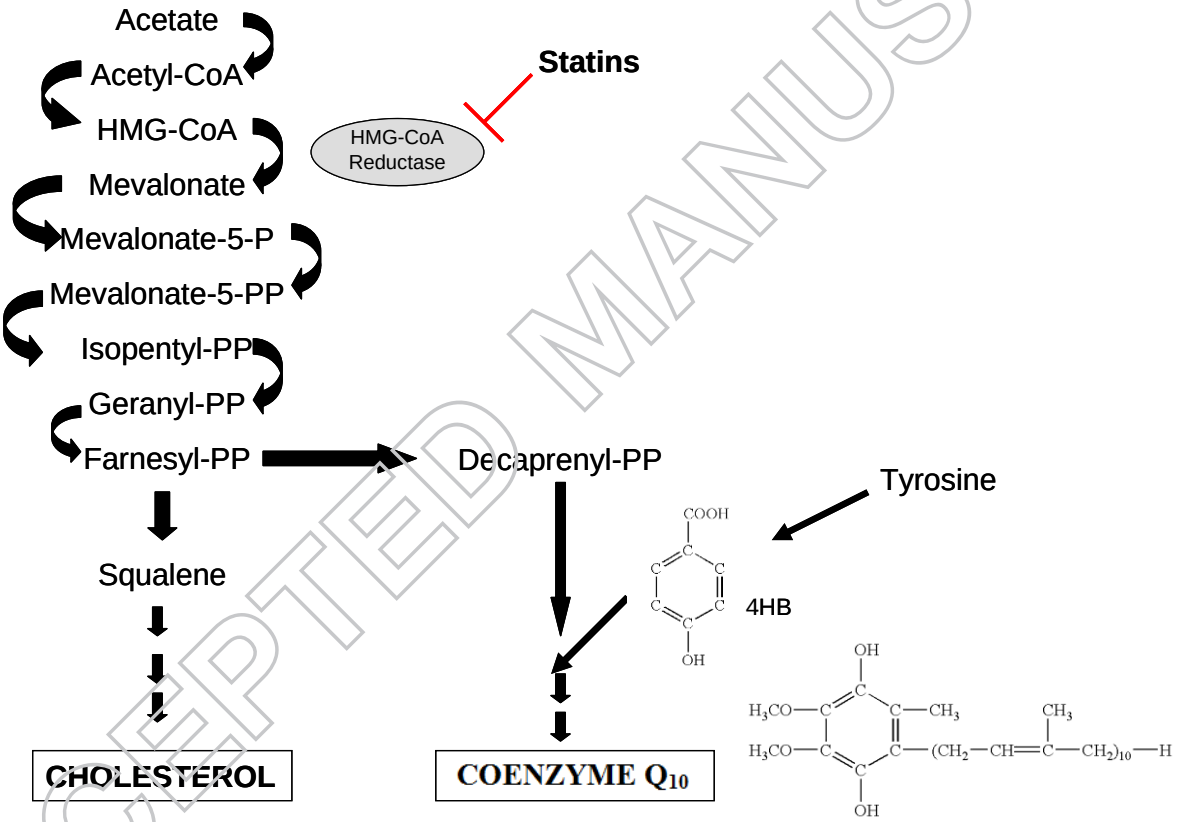

Figure 3. Cholesterol and Coenzyme Q_{10} pathways share mevalonate intermediate and statin interruption. 3-Hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) is transformed into mevalonate by the action of the enzyme HMG-CoA reductase. From here, mevalonate can be used to synthesize both cholesterol and coenzyme Q_{10}. Statins work by inhibiting the action of HMG-CoA reductase, thereby decreasing the amount of mevalonate available to make either cholesterol or Coenzyme Q_{10}.

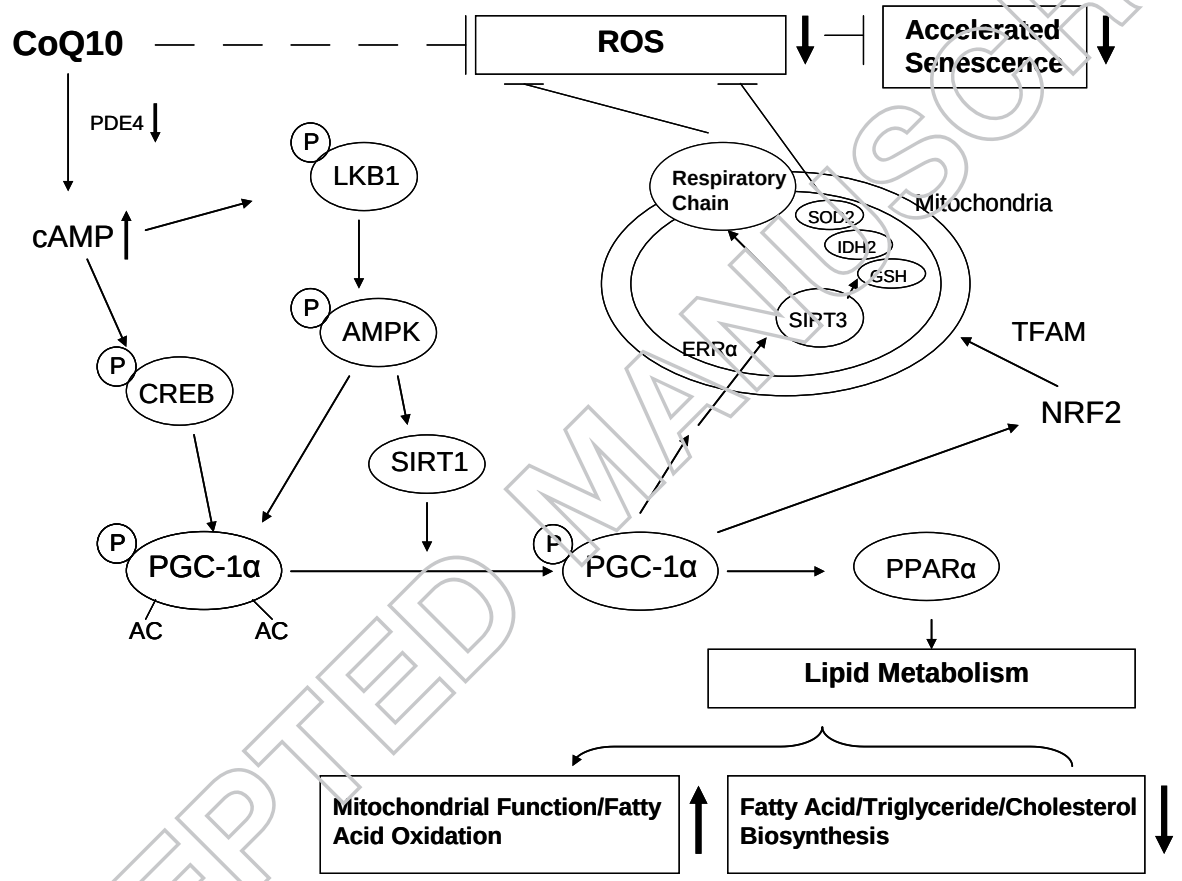

Figure 4. Proposed mechanism by which CoQ_{10} improves metabolic function and exerts its anti-aging effects. In response to CoQ_{10}, increased cAMP levels (throughout the inhibition of phosphodiesterase 4 (PDE4) activity (94)) activate SIRT1 and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) by increasing the levels of phosphorylated cAMP response element-binding (CREB), liver kinase B1 (LKB1) and AMP-activated protein kinase

(AMPK). SIRT1 deacetylates and activates PGC-1α that can then induce Sirt3, which activates superoxide dismutase 2 (SOD2), Isocitrate dehydrogenase 2 (IDH2), and mitochondrial genes though nuclear factor erythroid 2 (NFE2)-related factor 2 (NRF2) and Mitochondrial transcription factor A (TFAM). Activated SOD2, IDH2, and mitochondrial genes produced an increased ratio of GSH:GSSG that decreases reactive oxygen species (ROS) levels and increases the activity of mitochondrial electron transport chain complexes I and IV (95). Indeed, the activation of SIRT1 and PGC-1α enhance the mitochondrial function to promote the decomposition of fatty acids, as well as triglyceride while cholesterol biosynthesis is inhibited (96).