The Emerging Role of Coenzyme Q-10 in Aging, Neurodegeneration, Cardiovascular Disease, Cancer and Diabetes Mellitus

Muralikrishnan Dhanasekaran[1] and Jun Ren[2,*]

[1]*Scott and White Clinic and the Texas A&M University System Health Science Center, Temple, TX 76504;* [2]*Division of Pharmaceutical Sciences & Center for Cardiovascular Research and Alternative Medicine, University of Wyoming, Laramie, WY 82071, USA*

Abstract: Coenzyme Q (ubiquinone, 2-methyl-5,6-dimethoxy-1,4-benzoquinone), soluble natural fat quinine, is crucial to optimal biological function. The coenzyme Q molecule has amphipathic (biphasic) properties due to the hydrophilic benzoquinone ring and the lipophilic poly isoprenoid side-chain. The nomenclature of coenzyme Q-*n* is based on the amount of isoprenoid units attached to 6-position on the benzoquinone ring. It was demonstrated that coenzyme Q, in addition to its role in electron transport and proton transfer in mitochondrial and bacterial respiration, acts in its reduced form (ubiquinol) as an antioxidant. Coenzyme Q-10 functions as a lipid antioxidant regulating membrane fluidity, recycling radical forms of vitamin C and E, and protecting membrane phospholipids against peroxidation. The antioxidant property, high degree of hydrophobicity and universal occurrence in biological system, suggest an important role for ubiquinone and ubiquinol in cellular defense against oxidative damage. Coenzyme Q-10 is a ubiquitous and endogenous lipid-soluble antioxidant found in all organisms. Neurodegenerative disorders, cancer, cardiovascular diseases and diabetes mellitus and especially aging and Alzheimer's disease exhibit altered levels of ubiquinone or ubiquinol, indicating their likely crucial role in the pathogenesis and cellular mechanisms of these ailments. This review is geared to discuss the biological effect of coenzyme Q with an emphasis on its impact in initiation, progression, treatment and prevention of neurodegenerative, cardiovascular and carcinogenic diseases.

Key Words: aging, antioxidant, cancer, cardiovascular disease, coenzyme Q-10, diabetes, fatigue, neurodegenerative disorders.

INTRODUCTION

Coenzyme Q or ubiquinone is ubiquitous in nature and is widely distributed in plants, animals and microorganisms. Coenzyme Q homologs are classified based on their isoprenoid units (Q-*n*). The number, Q-*n*, refers to the amount of isoprenoid units attached to the 6-position on the benzoquinone ring of the coenzyme Q moiety. Coenzyme Q-10 was first isolated from beef hearts (Crane *et al.*, 1957) and its chemical structure was identified in 1958 (Shunk *et al.*, 1958). The naturally occurring coenzymes, depending on the source, differ from one another in their chemical structures in configuration of the isoprenoid side chain of ubiquinone and plastoquinone (the plant form) (Saitoh *et al.*, 1992), as well as the number of isoprenoid units. Coenzyme Q-*n* is synthesized in the body mainly using 4-hydroxybenzoate and the polyprenyl chains. The primary role of coenzyme Q-10 is to facilitate electron transfer between redox components of electron transport chain in order to create a proton gradient across the inner mitochondrial membrane, thereby facilitating ATP formation (Fernandez-Ayala *et al.*, 2005). Additional biological functions of coenzyme Q-10 encompass maintenance of membrane fluidity, recycling of radical forms of vitamin C and E (Beyer *et al.*, 1985, Villalba *et al.*, 1995, Malchair *et al.*, 2005, Siemieniuk and Skrzydlewska, 2005) and most importantly, antioxidant protection against membrane lipid peroxidation (Al-Thakafy *et al.*, 2005, Bliznakov, 1999, Somayajulu *et al.*, 2005). Coenzyme Q-10 is the only endogenously occurring lipid-soluble antioxidant among all coenzymes ubiquitously synthesized (Ernster and Dallner, 1995, Battino *et al.*, 2003, Molyneux, *et al.*, 2005). Coenzyme Q-10 is the predominant form in humans, while coenzyme Q-9 is predominant in rodents.

The content of coenzyme Q differs drastically in organelles or sub-cellular fractions of cells. However, a significant amount of coenzyme has been found in mitochondria, which functions in concert with other enzymes involved in cellular respiration and ATP generation (Marubayashi *et al.*, 1982). Coenzymes or ubiquinones, which are ubiquitous in nature, are found in certain mammalian species with variations in interspecies concentrations. In mice, the levels of coenzyme Q-9 and coenzyme Q-10 are ~ 3 ng/mg and ~ 10 ng/mg, respectively in the brain. More specifically, there are concentration variations of coenzyme Q-9 and coenzyme Q-10 in brain, heart, liver, kidney, plasma/serum and skin (Naini *et al.*, 2003). In addition, intracellular organelles such as lysosomes, endoplasmic reticulum, nucleus, the Golgi apparatus, cytosol and mitochondria also display different coenzyme concentrations (Ramasarma, 1985). Coenzyme Q-10 is currently obtainable as an over-the-counter dietary supplement in the United States and in several other countries. Coenzyme Q-10 has an enviable therapeutic safety profile for oral usage. Oral administration has been shown to increase coenzyme Q-10 concentration in serum and various organs (Zita *et al.*, 2003). Hence, there is no need for special phar-

*Address correspondence to this author at the Division of Pharmaceutical Sciences, School of Pharmacy, University of Wyoming, Laramie, WY 82701, USA; Tel: +1-307-766-6131; Fax: +1-307-766-2953; E-mail: jren@uwyo.edu

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maceutical delivery system. Use of coenzyme Q-10 is considered as a form of alternative therapy and the modern health care profession has embraced the use of coenzyme Q-10 in various disease conditions including a series of cardiovascular and neurological disorders. Coenzyme Q-10 is quantified using high performance liquid chromatography (HPLC) connected with an ultraviolet detector. Coenzyme Q-10 can be extracted from various samples using hexane and methanol (25% and 75% respectively for the mobile phase in HPLC). Coenzyme Q10 is separated on C-18 Hypersil-ODS silica based column with a length of 125 mm and diameter of 3 mm. The flow rate is 0.3 ml/min and the UV-detection is performed at 275 nm (Albano *et al.*, 2002).

This review will focus on literature dealing with neurodegenerative and cardiovascular etiology associated with alteration of coenzyme Q-10, predominantly those published during the last five years. The goal is to enrich the understanding of the complex interactions among coenzyme Q-10, redox status and bodily function, which should help to better understand the pathogenesis of certain neurodegenerative, cardiovascular and carcinogenic disorders so that optimal therapeutic application of coenzyme Q-10 may be achieved for individuals with the above mentioned health problems.

COENZYME Q-10 IN AGING AND NEURODEGENERATIVE DISORDERS

Aging

As an irreversible physiological process affecting all living organisms, aging is a rather complex physiological phenomenon with several theories being elaborated to help understand its origin. Among such theories, the "evolutionary theory of aging" envisions that human longevity is at the cost of impaired reproductive success (Westendorp and Kirkwood, 1998). An advanced vision of this theory, namely "antagonistic pleiotropy theory of aging" favors genes conferring short-term benefits at the expense of quality of later life (Bowen and Atwood, 2004). The "free radical theory of aging", which favors accumulation of oxidant insult leading to ultimate senescence (Harman, 1956), paved the way to the modern "mitochondrial theory of aging" (Alexeyev *et al.*, 2004), or the newly revised concept of "mitochondrial-lysosomal axis theory of aging" (Brunk and Terman, 2002: Terman, *et al.*, 2004). Age-related increases in oxidative stress could account for aging-induced organ damage. The 'mitochondrial theory of aging', has gained convincing support on the concept of accumulation of somatic mutations of mitochondrial DNA that may lead to loss of mitochondrial function. Alterations of coenzyme Q-10 in relation to mitochondrial function with aging have been carefully studied in both human and rodents. It was speculated that aging-related increases in mitochondrial oxidative stress may be due to the depletion of coenzymes and vitamin E (Vericel *et al.*, 1988, Miles *et al.*, 2004). It was recently accepted that coenzymes in their reduced form, ubiquinol, may act as antioxidants. The antioxidant property of ubiquinol in conjunction with its high degree of lipophilicity and ever present occurrence in biological membranes suggests a likelihood of vital function in the cellular defense against oxidative stress. Ubiquinol acts as an antioxidant, preventing the initiation and propagation of lipid peroxidation in biological membranes and in serum low-density lipoprotein. The antioxidant activity of ubiquinol is independent as compared to the effect of vitamin E. Vitamin E acts as a chain-breaking antioxidant, inhibiting the propagation of lipid peroxidation. In addition, ubiquinol can significantly prolong the effect of vitamin E by recycling the vitamin from the tocopheroxyl radical. Ubiquinol is synthesized de novo only. The amount of coenzyme Q decreases in various tissues with aging (Battino *et al.*, 1995, Beal and Matthews, 1997), which increases the vulnerability towards injury caused by oxidative stress. Several studies have clearly shown an age-related decline of coenzyme Q-10 in both human and rodents (Pignatti *et al.*, 1980, Lonnrot *et al.*, 1995), similar to the decline of vitamin E. Mitochondria obtained from heart, kidney and liver show an age-related decline in the levels of coenzyme Q and _-tocopherol (Kamzalov, Sohal, 2004). Coenzymes are the mandatory components of both the respiratory chain and uncoupling proteins (UCP), both of which are essential to delay the aging process (Villalba *et al.*, 1995). The fact that mitochondrial function, to which coenzyme Q-10 is heavily associated, determines that longevity was substantiated by an RNA interference study of mitochondrial respiration chain. Silencing of the mitochondrial respiratory chain was found to significantly modify the adult life span (Rodriguez-Aguilera *et al.*, 2005). The incorporation of exogenous coenzyme also affects the aging process in nematodes by reducing formation of reactive oxygen species. It was reported that animals supplemented on coenzyme Q may reach a significantly longer mean life span (11.7% higher), a significantly higher maximum life span (24% higher) and increased learning capacity than non-supplemented animals, suggesting that a long-term supplementation with a small dosage of coenzyme Q-10 may represent a good anti-aging therapy (Ishii *et al.*, 2004, Quiles *et al.*, 2004, McDonald *et al.*, 2005). Such a beneficial role of coenzyme Q-10 is speculated to be related to its pivotal effects on levels of flavoproteins and cytochromes in mitochondrial respiratory chain (Battino, 2001, Quiles *et al.*, 2004). In addition, coenzyme Q-10 may protect DNA from oxidative damage, although the precise mechanism still needs full validation (Quiles *et al.*, 2004). Anti-aging therapies based on coenzyme Q-10 are currently being used to alleviate the symptoms of aging. Further study is warranted as to how the aging process may induce a decreased capacity of adequate coenzyme Q-10 levels. It is documented that point mutations in the insulin signaling cascade and/or caloric restriction may effectively slow down the aging process (Tatar *et al.*, 2003). Coenzyme Q-10 has been shown to affect the insulin signaling cascade (McCarty, 2000) and thus insulin signaling-related aging process. On the contrary, no link between coenzyme Q-10 and caloric intake has been documented. Both coenzyme Q-10 and caloric restriction inhibit age-related alterations in gene expression involved in the extracellular matrix, cellular structure and protein turnover. However, unlike caloric restriction, coenzyme Q-10 does not prevent age-related transcriptional alterations associated with energy metabolism (Lee *et al.*, 2004), indicating that coenzyme Q-10 intervention is not as effective as caloric restriction in inhibiting the aging process.

Alzheimer's Disease

Alzheimer's disease is the foremost age-related neurodegenerative disorder prevalent in the United States and rest of

the world. The prevalence of developing Alzheimer's disease has significantly increased recently and is expected to double every 5 years, due to the lengthened overall life span. Deposition of the β-amyloid peptide into plaques in the brain parenchyma and cerebral blood vessel walls is one of the distinguishing neuropathological features of Alzheimer's disease. β-Amyloid peptide production and deposition have been hypothesized to begin the cascade of events that result in the neurodegenerative changes responsible for the memory loss and behavioral changes associated with Alzheimer's disease (Näslund *et al.*, 2000). Reduction in β-amyloid deposition and/or destabilization of preformed β-amyloid peptide in the brain is now considered the most effective therapeutic approach for the treatment of Alzheimer's disease. Coenzyme Q-10 has shown to inhibit the *in vitro* formation of the β-amyloid peptide (Ono *et al.*, 2005). Oxidative stress and mitochondrial dysfunctions are implicated in the pathophysiology of the disease. Coenzyme Q-10 has been found to be significantly increased in most regions of the brain in patients with Alzheimer's disease (Edlund *et al.*, 1992, 1994, de Bustos *et al.*, 2000). A reduction in serum ubiquinone deficiency related mitochondrial dysfunction could contribute to the etiology and pathology of Alzheimer's disease (Kurup and Kurup, 2003). Decreased mRNA expression of NADH dehydrogenase-4 and NADH dehydrogenase-15 was found in the hippocampus and inferior parietal lobe of the brains of patients with Alzheimer's disease. This decrease of NADH dehydrogenase-4 gene expression may cause the inhibition of ubiquinone oxidoreductase activity (Aksenov *et al.*, 1999). Several reports suggest that the coenzyme Q-10 deficiency may be related to increased risk of Alzheimer's disease or vascular dementia. Combinations of antioxidants (vitamins E, vitamin C and ubiquinone) may serve as an effective therapy for Alzheimer's disease (Grundman *et al.*, 2002, Beal, 2004, Bragin *et al.*, 2005).

Amyotrophic Lateral Sclerosis

In the United States, amyotrophic lateral sclerosis is called as *Lou Gehrig's disease*, after the Yankees baseball player who died of it in 1941. In Britain and rest of the world, amyotrophic lateral sclerosis is called *motor neuron disease*, in reference to the cells that are lost in this disorder. This is a disease involving nervous system controlling voluntary muscle movement. Amyotrophic lateral sclerosis is a progressive neurodegenerative disorder for which no cure or effective treatment presently exists. Various types of drugs have been tested; most of which are based on different hypotheses of mechanisms for neuronal death, including oxidative damage, loss of trophic factors, glutamate-mediated excitotoxicity, and chronic inflammation. The discovery that a small percentage of amyotrophic lateral sclerosis cases are familial and involve mutation in a superoxide dismutase gene led to the development of transgenic mouse models widely used for drug testing. Mutations in vascular endothelial growth factor gene and oxidative stress also appear to be involved in the etiology of this disease. Patients suffering from amyotrophic lateral sclerosis have a significantly increased amount of oxidized coenzyme Q-10 in the plasma, suggesting systemic oxidative stress in the pathogenesis of this disease (Sohmiya *et al.*, 2005). An ample amount of evidence shows that bioenergetic dysfunction plays either a primary or secondary role in the etiology of cell death in neurodegeneration. Drugs that ameliorate bioenergetic defects are useful in therapy. Creatine and coenzyme Q-10, which increase muscle and brain phosphocreatine concentrations, may inhibit the activation of the mitochondrial permeability transition and protect against neuronal degeneration (Strong and Pattee, 2000, Tarnopolsky and Beal, 2001). Similarly, in animal models of amyotrophic lateral sclerosis, coenzyme Q-10 significantly decreased striatal lesions produced by systemic administration of 3-nitropropionic acid and significantly increased the life span in a transgenic mouse model of familial amyotrophic lateral sclerosis. These studies provide further evidence that coenzyme Q-10 can exert neuroprotective effects in amyotrophic lateral sclerosis and might be useful in the treatment of neurodegenerative diseases (Matthews *et al.*, 1998).

Fatigue

It is one of the most widespread but not clearly understood symptom in humans. Fatigue is the seventh most common symptom in primary health care (Kroenke *et al.*, 1988). Fatigue is defined physiologically as the inability to maintain the expected power output. It is most often chronic and at times severe in intensity. Fatigue is very often identified as central or peripheral in nature. Chronic fatigue in elderly people causes functional dependence, which may lead to interruption of treatment, decline in quality of life and expensive home care (Tralongo *et al.*, 2003). There is evidence that mitochondrial dysfunction and oxidative stress are directly related to fatigue in humans (Schulte-Mattler *et al.*, 2003; Finsterer, 2004). Mitochondrial injuries are considered the main link between cellular stress signals activated during acute and chronic injury leading to the death of cells. Mitochondrial dysfunction can lead to the initiation of cell death processes that are believed to contribute to cell death in aging and neurodegenerative disorders. Similarly, mitochondrial mutations cause excessive metabolic muscle fatigue (Schulte-Mattler *et al.*, 2003). Complex-I is a crucial member of the mitochondrial respiratory chain that is necessary for the synthesis of ATP. Defects in mitochondrial complex I activity are also found in fatigue (Tsao and Mendell, 2002). Nicotinamide adenine dinucleotide, another cofactor similar to coenzyme Q-10 is known to resist fatigue and to have beneficial effects in the treatment of fatigue (Forsyth *et al.*, 1999; Logan *et al.*, 2003; Lands *et al.*, 1999, Santaella *et al.*, 2004). The administration of coenzyme Q-10 to heart transplant candidates led to a significant improvement in functional status, clinical symptoms, and quality of life (Berman *et al.*, 2004). Thus, enhancement of mitochondrial functions with coenzyme Q-10 may be an important mechanism by which fatigue can be reduced (Werbach, 2000).

Friedreich's Ataxia

Friedreich's ataxia is caused by a pronounced lack of frataxin, a mitochondrial protein. Several reports suggest that continuous oxidative damage resulting from hampered superoxide dismutase signaling participates in the mitochondrial deficiency and ultimately the neuronal and cardiac cell death. Mitochondrial abnormalities are linked to neurodegenerative diseases through a variety of different pathways, including free-radical generation, impaired calcium buffering

and the mitochondrial permeability transition. This results in apoptotic and necrotic cell death. Current studies have shown increased mitochondrial iron content, which appears to be linked to increased free-radical generation in Friedreich's ataxia (Beal *et al.*, 1999b). Hence, the current therapeutic trials for Friedreich's ataxia rely on antioxidative treatment with coenzyme Q-10 or its short-chain variant idebenone (Beal *et al.*, 1999a, Cooper and Schapira, 2003, Schols *et al.*, 2004, Hart *et al.*, 2005, Seznec *et al.*, 2005, Quinizi *et al.*, 2005, Aure *et al.*, 2004). Lack of frataxin homologs in yeast and mice also leads to increased sensitivity to oxidative stress, depletion of proteins with iron-sulfur clusters such as respiratory chain complexes I-III and aconitase, and to iron accumulation in mitochondria. Alternative strategies aiming at an enhancement of frataxin by stem cell transplantation, gene transfer or frataxin supplementation are also currently under research. Additionally, more efficient biomarkers are needed to monitor treatment effects. Interestingly, idebenone, a coenzyme Q-10 analog profoundly reduced cardiac mass in patients with Friedrich's ataxia (Tarnopolsky and Beal, 2001).

Huntington's Disease

Huntington's disease is a progressive, prototypical, and genetic neurodegenerative disease characterized by selective loss of neurons in the basal ganglia. Bioenergetic defects, oxidative stress and excitotoxicity play an important role in the pathogenesis of Huntington's disease. Huntington's disease patients have a significant reduction in NADH:ubiquinone oxidoreductase (complex I) activity without any changes in the other electron transport chain activities. Huntington's disease may be caused by a mutation in one of the nuclear coded subunits of NADH: ubiquinone oxidoreductase (Parker *et al.*, 1990). Coenzyme Q-10 enhances mitochondrial complex I activity and may therefore provide a therapeutic benefit in Huntington's disease (Parker *et al.*, 1990, Feigin *et al.*, 1996, Huntington Study group, 2001, Beal and Shults, 2003, Andrich *et al.*, 2004, Steele *et al.*, 2004, Walker and Raymond, 2004). The tolerability of coenzyme Q-10 (600 to 1,200 mg per day) suggests it to be a good candidate for evaluation in long-term clinical trials designed to slow down the progression of Huntington's disease. Oral administration of coenzyme Q-10 significantly reduces concentrations of lactate assessed by using magnetic resonance spectroscopy in the occipital cortex, cortex and striatum of Huntington's disease patients, which are typically increased in Huntington's disease patients as compared to non-diseased patients. This may be due to the increased coenzyme Q.10 concentrations in brain mitochondria leading to neuroprotective effects in animal models of Huntington's disease and ALS (Matthews *et al.*, 1998).

Parkinson's Disease

Parkinson's disease is the second most prevalent age-related neurodegenerative disease in the United States today. The recent focus on Parkinson's disease research is the development of neuroprotective therapies to retard the progression of the disease. Parkinson's disease occurs due to the degeneration of dopaminergic neurons in the striatum. Recent studies have shown reduced complex I activity of the electron transport chain in the brain and platelets of patients with Parkinson's disease. The reduced complex I activity may be due to environmental or genetic factors. These factors play a crucial role in the neurodegeneration of Parkinson's disease by generating reactive oxygen species and increasing the risk of neuronal susceptibility to mitochondrial toxins. (Dabbeni-sala *et al.*, 2001, Ebadi *et al.*, 1996, Swerdlow *et al.*, 2001, Moon *et al.*, 2005). The mitochondrial electron transport enzyme, complex I, is encoded by both mitochondrial DNA and nuclear DNA (Somayajulu *et al.*, 2005). There are substantial evidences to show that mitochondria are a major source of free radicals within the cell. Several agents are available that can modulate cellular energy metabolism and may exert antioxidant effects. These effects appear to be produced both at the iron-sulfur clusters of complex I as well as the ubiquinone site. Therapeutic drugs that have shown to be beneficial in animal models of Parkinson's disease include creatine, coenzyme Q-10, *Ginkgo biloba*, nicotinamide, and acetyl-L-carnitine. Coenzyme Q-10 is also effective in animal models and has shown promising effects both in clinical trials of patients with Parkinson's disease, as well as in clinical trials in Huntington's disease and Friedreich's ataxia (Beal, 2003a, Sharma *et al.*, 2004). The level of coenzyme Q-10 is found to be significantly lower in mitochondria from parkinsonian patients than in mitochondria from age and sex-matched control subjects (Shults *et al.*, 1997, 1998, 2002). Platelet coenzyme Q-10 was non-significantly decreased by levodopa treatment but selegiline treatment partially restored coenzyme Q-10 redox ratios (Gotz *et al.*, 2000, Jimenez-Jimenez, *et al.*, 2000). MPTP (1-methy-4-phenyl-1,2,36-tetrahydro pyridine) is a specific dopaminergic toxin that induces neurotoxicity in the nigrostriatal tract of humans and rodents. MPTP causes enhanced hydroperoxides/coenzyme Q-10 molar ratios due to the depletion of coenzyme Q-10 and the concomitant increase in hydroperoxides (Battino *et al.*, 1996). Coenzyme Q-10 has shown to protect against MPTP-induced toxicity in mice (Matthews *et al.*, 1998). Coenzyme Q-10 also protects against striatal lesions produced by both malonate and 3-nitropropionic acid. Coenzyme Q-10 has shown to extend the duration of survival in a transgenic mouse model of amyotrophic lateral sclerosis (Beal, 1999a). Coenzyme Q-10 has shown to possess significant therapeutic effects in the treatment of Parkinson's disease (Strijks *et al.*, 1997, Ogawa *et al.*, 2002, Koller and Cersosimo, 2004). In another study, oral administration of coenzyme Q-10 caused a substantial increase in the plasma coenzyme Q-10 level. Coenzyme Q-10 was well tolerated orally and no adverse effect was seen (Ulm, 2004). A trend towards an increase in complex I activity in the subjects treated with coenzyme Q-10 was observed (Shults *et al.*, 1998). This data suggests that coenzyme Q-10 may play a role in cellular dysfunction found in Parkinson's disease and may be a potential protective agent for parkinsonian patients (Shults *et al.*, 1999). There is also evidence for increased numbers of activated microglia in both Parkinson's disease postmortem tissues as well as in animal models of Parkinson's disease. Impaired mitochondrial function and activated microglia may both contribute to oxidative damage in Parkinson's disease. A number of therapies targeting inflammation and mitochondrial dysfunction are efficacious in the MPTP model of Parkinson's disease. Of these, coenzyme Q-10 appears to be particularly promising based on the results of a recent phase II clinical trial in

which it significantly slowed the progression of Parkinson's disease (Beal., 2003b). Coenzyme Q-10 provides a significant symptomatic benefit on Parkinson's disease symptoms and a significantly better improvement of FMT (fluorescence-mediated tomographic technique) performance compared with placebo (Muller *et al.*, 2003). Thus, coenzyme Q-10 is a safe and well tolerated drug for the therapeutic treatment of Parkinson's disease and a significant rise in its levels were seen in parkinsonian patients (Sohmiya *et al.*, 2004). Table 1 summarizes the significant role of enzyme Q-10 in aging and neurodegenerative diseases.

COENZYME Q-10 AND CARDIOVASCULAR DISEASES

Cardiomyopathy

Cardiomyopathy is a heart muscle disease, which occurs due to the impaired contractility and dilation of the ventricles. Cardiomyopathy includes the contractile cardiomyocytes and the autonomic innervation of the heart. Cardiomyopathy augments the risk for abrupt cardiac mortality. The mitochondrial respiratory chain in cardiomyocytes directly controls the cardiac metabolism. In humans, coenzyme Q-10 is significantly deficient in myocardial tissue (Littarru *et al.*, 1972, Folkers *et al.*, 1985, Nawarskas, 2005). It is well accepted that this disease is caused by a decrease in cellular bioenergetic activity that is secondary to myocarditis and oxidative phosphorylation. A small group of patients has shown familial inheritance of cardiomyopathy resulting in the identification of specific genomic loci and gene defects. However, little evidence is available pointing to a single gene in the initiation and progression of cardiomyopathy. It was demonstrated that environmental factors such as viral or genetic defects can increase the vulnerability of this disease (Poller *et al.*, 2005). Coenzyme Q-10 has shown significant improvement in cardiomyopathy (Langsjoen 1985, 1998, Permanetter *et al.*, 1992, Jones *et al.*, 2004, Conklin, 2005, Lalani *et al.*, 2005, Rosenfeldt *et al.*, 2005).

Hypertension

Hypertension is a condition in which the blood pressure is persistently higher than normal. People with hypertension are at risk for heart attack, stroke or kidney failure. Oxidative and nitrosative stress are observed in hypertension (Rosenfeldt *et al.*, 2003). Elevated oxidative and nitrosative stress within the arterial wall leads to augmented blood pressure and vascular dysfunction. The maintenance of increased blood pressure could be chiefly due to contraction of the arterial wall. Contraction or relaxation of the arterial wall is dependent upon bioenergetics, which also supplies the energy for biosynthesis of angiotensin II, renin, aldosterone, and the energy for sodium and potassium transport. It appears that coenzyme Q-10 is decreased during therapy with beta blockers, gemfibrozil, and adriamycin (Kish *et al.*, 1975). Coenzyme Q-10 deficiency has also been observed in patients with congestive heart failure, angina pectoris, coronary artery disease, cardiomyopathy, hypertension, mitral valve prolapse and following coronary revascularization. The current therapies for hypertension are based on blood pressure reduction associated with the implementation of certain lifestyle modifications. Coenzyme Q-10, fish oil, garlic, vitamin C, and L-arginine are currently being used for the therapeutic treatment of hypertension (Langsjoen *et al.*, 1994, Wilburn *et al.*, 2004). The clinical benefits of coenzyme Q-10 are mainly due to its ability to improve energy production, antioxidant activity, and membrane stabilizing properties. Hypertensive patients treated with coenzyme Q-10 showed significant reductions in systolic and diastolic pressures. However, the treatment did not affect cardiac out-

Table 1. Effects of Coenzyme Q-10 in Aging and Various Neurodegenerative Disorders and the Possible Cellular Mechanisms Involved in its Protective Effect

	Effects of coenzyme Q-10	Possible cellular mechanisms involved
Aging	Increased longevity (Ishii *et al.*, 2004, McDonald *et al.*, 2005) Delayed aging process (Quiles *et al.*, 2004); (Quiles *et al.*, 2004)	Enhanced mitochondrial functions (Battino, 2001) Affect insulin signaling cascade (McCarty, 2000)
Alzheimer's disease	Increased the mitochondrial substrates and cofactors Enhanced antioxidant defense system	Enhancement of ubiquinone oxidoreductase activity Scavenged reactive oxygen species (Beal, 2004)
Amyotrophic lateral sclerosis	Ameliorated bio-energetic defects Protected against neuronal degeneration (Tarnopolsky and Beal, 2001) Extended the duration of survival in animal models (Beal, 1999a)	Increaseed muscle and brain phosphocreatine (Strong and Pattee, 2000) Inhibited activation of mitochondrial permeability transition
Fatigue	Enhances mitochondrial functions Improves quality of life (Berman *et al.*, 2004)	Increased mitochondrial complex-I activity
Friedreich's ataxia	Decreased cardiac mass ((Tarnopolsky and Beal, 2001)	Reduced generation of free radicals
Huntington's disease	Provided therapeutic benefit and neuroprotective effects (Matthews *et al.*, 1998)	Enhanced mitochondrial complex I activity (Parker *et al.*, 1990, Huntington Study group, 2001) Reduced lactate in brain
Parkinson's disease	Provided symptomatic and therapeutic benefit (Beal 2003b, Muller *et al.*, 2003, Sohmiya *et al.*, 2004)	Enhanced mitochondrial complex-I activity Increase in the plasma coenzyme Q-10 level

puts or stroke volumes (Folkers *et al.*, 1981). A clinical benefit from administration of coenzyme Q-10 to patients with essential hypertension could be based upon correcting a deficiency in bioenergetics, and points to possible combination treatments with a form of coenzyme Q-10 and antihypertensive drugs (Yamagami *et al.*, 1975). Its efficacy is associated with a decrease in total peripheral resistance, and appears to reflect a direct impact of coenzyme Q-10 on the vascular wall. A reasonable interpretation of these findings is that coenzyme Q-10 acts as an antagonist of vascular superoxide anion, either by scavenging it or suppressing its synthesis. Moreover, once superoxide is formed, it readily reacts with nitric oxide to produce peroxynitrite, which is toxic to endothelial cells and smooth muscle cells causing vascular dysfunction (Chung *et al.*, 2000, Guzik *et al.*, 2002, Koppenol *et al.*, 1992). Coenzyme Q-10 can quench the toxic properties of peroxynitrite and may inhibit nitrosative damage to proteins and lipids (Schopfer *et al.*, 2000, Hodgson and Watts, 2003). By improving the efficiency of shuttle mechanisms that transfer high-energy electrons from the cytoplasm to the mitochondrial respiratory chain, coenzyme Q-10 may decrease cytoplasmic NADH levels and thereby diminish the reductive power that drives superoxide synthesis in endothelium and vascular smooth muscle (McCarty 1999). Coenzyme Q-10 has been administered to patients having essential hypertension. In these patients, the systolic and diastolic pressures were reduced, the specific activity of coenzyme Q-10 was increased and the deficiency of coenzyme Q-10 activity was negated. These effects of coenzyme Q-10 administration are presumably due to improved bioenergetics through correction of a deficiency of endogenous coenzyme Q-10 (Yamagami *et al.* 1976, Drzewoski *et al.*, 1981, Sarter, 2002, Li *et al.*, 2005).

Ischemic Damages

Ischemia is a condition in which blood flow (and thus oxygen) is restricted to a part of the body. Coenzyme Q-10 is involved in the synthesis of ATP and, hence, is useful in preventing cellular damage during ischemia-reperfusion injury. Coenzyme Q-10 synthesis is known to decrease during ischemia (Sugawara *et al.*, 1990). NADH: ubiquinone oxidoreductase of heart mitochondria is known to induce superoxide radicals (Vinogradov *et al.*, 2005). Administration of α -tocopherol and coenzyme Q-10 has shown to increase the survival rate by nearly 50% of the rats subjected to ischemia and coenzyme inhibitors have shown to induce cardiac toxicity (Combs *et al.*, 1976, Nakamura *et al.*, 1982, 1984, Okamoto *et al.*, 1983). These results indicate that α-tocopherol and coenzyme Q-10 have a protective effect on ischemic damage to the rat kidney, demonstrated by an increase in ATP re-synthesis after re-flow following ischemia and by the maintenance of a lower serum creatinine level (Takenaka *et al.*, 1981, Nakamura *et al.*, 1982, Fujioka *et al.*, 1983). The protective effect of coenzyme Q-10 on the ischemic and reperfused myocardium was also investigated in the isolated rat heart preparation. Rats were treated with coenzyme Q-10 intraperitoneally, and the recovery of cardiac power by coenzyme Q-10 was significantly better than the control. Creatine phosphokinase release during reperfusion was significantly reduced by coenzyme Q-10. Tissue lactate content in ischemia was significantly lower in the coenzyme Q-10 pretreated group. These results suggest that pretreatment with coenzyme Q-10 is effective for reducing ischemic injury caused by aortic cross clamping (Tominaga *et al.*, 1983). Coenzyme Q-10 has shown to protect myocardial and arterial smooth muscle cell function *via* antioxidant mechanisms such as scavenging reactive oxygen species (Whitman *et al.*, 1997). Pretreatment with coenzyme Q-10 results in an improved tolerance to myocardial reperfusion injury due to decreases in the oxidative stress after an ischemic insult, supporting the pivotal role of coenzyme Q-10 in cardiovascular diseases (Table 2).

COENZYME Q-10 AND CANCER

Cancer is one of the leading causes of death in the United States, second only to cardiovascular disease. Cancer is diagnosed in over one million people a year. Low blood levels of coenzyme Q-10 have been found in patients with myeloma, and cancers of the breast, lung, prostate, pancreas, colon, kidney, brain and neck (Folkers *et al.*, 1981, 1993). Patients with malignant tumors exhibited characteristic and highly significant changes in the serum patterns of immuno-

Table 2. Effects of Coenzyme Q-10 in Cardiovascular Diseases and the Possible Cellular Mechanisms Involved in its Protective Effect

	Effects of coenzyme Q-10	Possible cellular mechanisms involved
Cardiomyopathy	Improvement in cardiomyopathy (Langsjoen 1985, 1998, Permanetter *et al.*, 1992, Jones *et al.*, 2004, Conklin, 2005, Lalani *et al.*, 2005, Rosenfeldt *et al.*, 2005)	Augmented cellular bioenergetic activity
Hypertension	Reductions in systolic and diastolic pressures (Hodgson and Watts, 2003) Decrease in total peripheral resistance Direct impact on the vascular wall	Improved energy production Membrane stabilizing properties Quenched toxic properties of peroxynitrite Inhibits nitrosative damage Schopfer *et al.*, 2000, Hodgson and Watts, 2003
Ischemic damages	Prevented cellular damage during ischemia-reperfusion injury Increased the survival rate of rats in valid model of ischemia (Combs *et al.*, 1976, Nakamura *et al.*, 1982)	Increase in ATP re-synthesis Maintained a lower serum creatinine level (Takenaka *et al.*, 1981, Nakamura *et al.*, 1982, Fujioka *et al.*, 1983 Decreased lactate content

globulin-G subclasses, which consist of decreased immunoglobulin G1 and increased immunoglobulin G2 (Felsner *et al.*, 2000). Interest in coenzyme Q-10 as a potential treatment for cancer began in 1961, when a deficiency was noted in the blood of cancer patients. There is a plethora of anecdotal evidence where claims have been made for the beneficial effects of coenzyme Q-10 in patients with cancer (Shekelle *et al.*, 2003, Forgionne, 2004, Perumal *et al.*, 2005). Studies have shown that when patients with regressing tumors were treated with coenzyme Q-10, levels of tumor necrosis factors-_ were reduced to below the detection threshold (Hodges *et al.*, 1999). In addition, levels of immunoglobulin-G significantly increased when patients were administered with coenzyme Q-10. However, further in-depth studies are required to confirm the therapeutic role of coenzyme Q-10 in cancer.

COENZYME Q-10 AND DIABETES MELLITUS

Diabetes is a multifactorial disorder that leads to deleterious effects in many organ systems within the body, potentially as a result of enhanced oxidative stress. Accumulating evidences suggest that oxidative stress plays an important role in the pathogenesis of diabetes mellitus (Baynes, 1999, Thorpe, 1999). Although the mechanism behind the enhanced oxidative stress associated with diabetes is not well understood, impaired balance between pro-oxidants such as free radicals, reactive oxygen species and antioxidants such as superoxide dismutase and catalase is speculated to play a role in the cellular damage in diabetes (Rosen *et al.*, 2001, Schroeder *et al.*, 2005). Under normal conditions, mitochondrial respiration generates reactive oxygen species that will be efficiently scavenged by various antioxidant defense mechanisms. However, in diabetes, this scavenging mechanism is believed to be impaired resulting in cellular dysfunction (Chen *et al.*, 2001). A previous study using the streptozotocin-induced rat model of diabetes revealed alteration of coenzyme Q-10 in the liver and kidney (Wold *et al.*, 2003). Insulin-like growth factor 1 (IGF-1) has been considered as an "essential surviving factor" and its level has been shown to be compromised in diabetes. Administration of IGF-1 to the above rat model of diabetes prevented the alteration of coenzyme Q-10. Exogenous coenzyme Q-10 administration has shown to increase myocardial coenzyme Q-10 content and improve myocardial relaxation in streptozotocin-administered diabetic rats (Serizawa *et al.*, 1988). Coenzyme Q-10 administration to diabetic patients was effective in relieving symptoms in the legs, fatigue, and residual urine in the bladder (Suzuki *et al.*, 1995).

One of the key mechanisms coenzyme Q-10 offers to protect against diabetes is through "recoupling" of endothelial NOS. Increased oxidative stress in diabetes may trigger diabetic complications by reducing the bio-availability of nitric oxide (NO). This is believed to be mediated through uncoupling of eNOS due to presence of redox imbalance and oxidation of tetrahydrobiopterin (BH_4) – a key cofactor for eNOS (Esberg and Ren, 2003). In mitochondria, increased redox potential uncouples oxidative phosphorylation leading to inhibition of electron transport and increased electron transfer to oxygen to form superoxide anion and $ONOO^-$. Coenzyme Q10 (CoQ), a potent antioxidant and a critical intermediate of the electron transport chain, may improve mitral valvular and endothelial dysfunction by 'recoupling' eNOS and mitochondrial oxidative phosphorylation (Chew and Watts, 2004, Oda *et al.*, 1985). Coenzyme Q-10 acts by blocking the endothelial dysfunction by activating endothelial nitric oxide synthase and mitochondrial oxidative phosphorylation. Coenzyme Q-10 may also act synergistically with anti-atherogenic agents, such as fibrates and statins, to improve endotheliopathy in diabetes. Arteriopathy is the main complication of diabetes mellitus (type 2) and this is due to endothelial dysfunction. Fenofibrate and coenzyme Q-10 have shown to enhance endothelial function by regulating dyslipidemia and oxidative stress (Playford *et al.*, 2003). Thus, coenzyme Q-10 supplementation has shown to alleviate the symptoms of diabetes mellitus in animals and humans. Coenzyme Q-10 treatments in humans are generally consistent in decreasing blood pressure in hypertensive individuals (Hodgson and Watts, 2003). Similarly, in type 2 diabetic patients with endothelial dysfunction, coenzyme Q-10 and fenofibrate had a synergistic action.

COENZYME Q-10 DEFICIENCY AND THERAPY IN OTHER DISEASES:

There are several other diseases like anemia (Niklowitz *et al.*, 2004, Ohnishi *et al.*, 2004), arthrosclerosis (Chapidze

Table 3. Effects of Coenzyme Q-10 in Cancer, Diabetes and Other Disease and the Possible Cellular Mechanisms Involved in its Protective Effect

	Effects of coenzyme Q-10	Possible cellular mechanisms involved
Anemia	Inhibited dense cell formation (Ohnishi, *et al.*, 2000)	Protected the cell membrane against reactive oxygen species damage
Arthrosclerosis	Prevented further development of atherosclerosis in native coronary arteries (Chapidze *et al.*, 2005)	Decreased oxidative stress and reduces platelet aggregation
Cancer	Decreased tumor necrosis factors-α (Hodges *et al.*, 1999)	Decreased tumor necrosis factors-α (Hodges *et al.*, 1999) Increased immunoglobulin-G
Diabetes	Relieved symptoms in the legs, fatigue, and residual urine in the bladder (Suzuki *et al.*, 1995)	Improved myocardial relaxation (Serizawa *et al.*, 1988) Activated endothelial nitric oxide synthase and mitochondrial oxidative phosphorylation
Stroke	Improved lactic acidosis (Berbel-Garcia *et al.*, 2004)	Enhanced mitochondrial function

et al., 2005, Kuettner *et al.*, 2005, Wang *et al.*, 2004, Yalcin *et al.*, 2004, Singh *et al.*, 2003), asthma (Konno and Yamaguchi *et al.*, 1990,Gazdik *et al.*, 2002a, Gazdik *et al.*, 2002b), visual dysfunctions (Chariot *et al.*, 1999, Huang *et al.*, 2002, Feher *et al.*, 2003, Feher *et al.*, 2005), and stroke (Shinkai *et al.*, 2000. Berbel-Garcia *et al.*, 2004), which are related to coenzyme Q-10 deficiency and hence, currently, coenzyme Q-10 is being used as an alternative therapy or adjuvant for the treatment of these disorders (Table 3).

CONCLUSION

Coenzyme Q-10 is intrinsic to human tissues and is considered as a vitamin, according to the basic science of nutrition. Coenzyme Q-10 plays a significant role in the respiratory process, involved in the mechanism of blood coagulation and controls the membrane fluidity and oxidative stress (Fig 1). Hence deficiency of coenzyme Q-10 may be related to various cardiovascular and neurological diseases. Thus, these deficits are currently overcome by therapeutically treating with coenzyme Q-10 (Fig. 2).

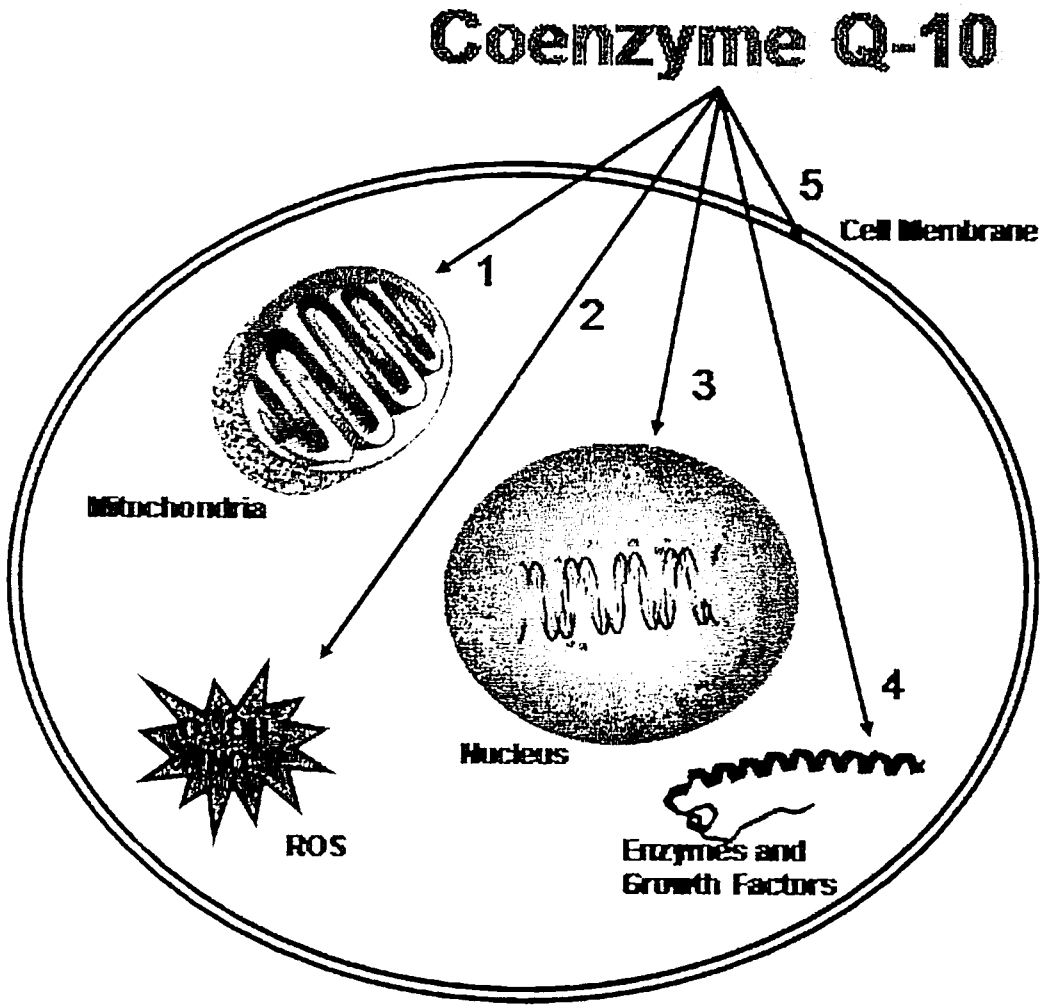

Fig. (1). Various cellular functions of coenzyme Q-10.

1. Coenzyme enhances the mitochondrial functions and increases ATP production;

2. Scavenges reactive oxygen species and renders protection to the cells;

3. Protects against DNA damage and has anti-apoptotic effects;

4. Enhances the antioxidant enzyme activities and modulates the activities of growth factors;

5. Inhibits the peroxidation of lipids and protects the cell membrane.

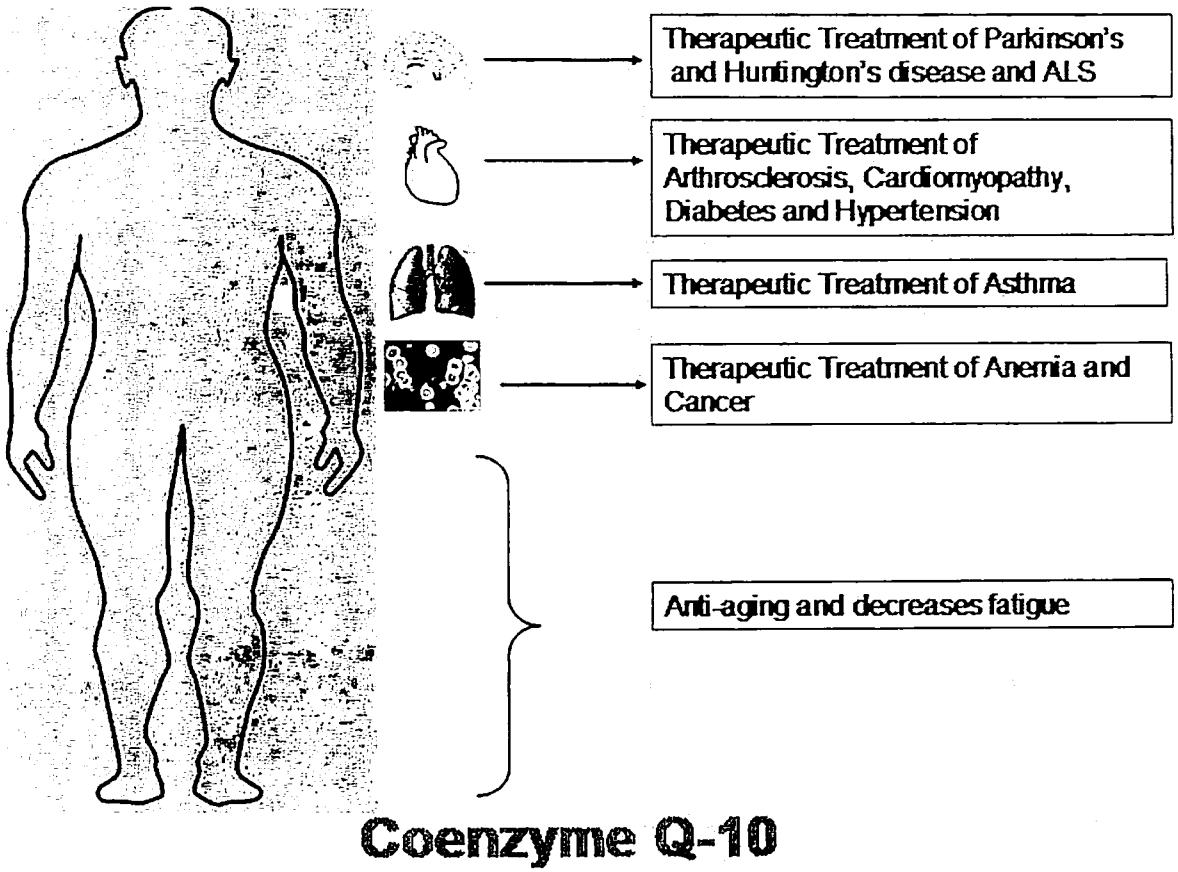

Fig. (2). Effect of coenzyme Q-10 in the various organs.

REFERENCES

Aksenov, MY, Tucker, HM, Nair, P, Aksenova, MV, Butterfield, DA., Estus, S, Markesbery, WR. (1999) The expression of several mitochondrial and nuclear genes encoding the subunits of electron transport chain enzyme complexes, cytochrome c oxidase, and NADH dehydrogenase, in different brain regions in Alzheimer's disease. *Neurochem Res* 24: 767-774.

Albano, CB, Muralikrishnan, D, Ebadi, M. (2002) Distribution and quantification of various coenzyme Q homologs in cell lines and in brains of rodents and chicken. *Neurochem Res* 27: 359-368.

Alexeyev, MF, Ledoux, SP, Wilson, GL. (2004) Mitochondrial DNA and aging. *Clin Sci (Lond.)* 107: 355-364.

Al-Thakafy, HS, Khoja, SM, Al-Marzouki, ZM, Zailaie, MZ, Al-Marzouki, KM. (2004) Alterations of erythrocyte free radical defense system, heart tissue lipid peroxidation, and lipid concentration in streptozotocin-induced diabetic rats under coenzyme Q10 supplementation. *Saudi Med J* 25: 1824-1830.

Andrich, J, Saft, C, Gerlach, M, Schneider, B, Arz, A, Kuhn, W, Muller, T. (2004) Coenzyme Q10 serum levels in Huntington's disease. *J Neural Transm Suppl* 68: 111-116.

Aure, K, Benoist, JF, Ogier de Baulny, H, Romero, NB, Rigal, O, Lombes, A. (2004) Progression despite replacement of a myopathic form of coenzyme Q10 defect. *Neurology* 63: 727-729.

Battino, M, Giunta, S, Galeazzi, L, Galeazzi, R, Mosca, F, Santolini, C, Principi, F, Ferretti, G, Bacchetti, T, Bencivenga, R, Piani, M, Riganello, G, Littarru, GP. (2003) Coenzyme Q10, antioxidant status and ApoE isoforms. *Biofactors* 18: 299-305.

Battino, M, Gorini, A, Villa, RF, Genova, ML, Bovina, C, Sassi, S, Littarru, GP, Lenaz, G. (1995) Coenzyme Q content in synaptic and non-synaptic mitochondria from different brain regions in the ageing rat. *Mechanisms of ageing and Development* 78: 173-187.

Battino, M, Littarru, GP, Gorini, A, Villa, RF. (1996) Coenzyme Q, peroxidation and cytochrome oxidase features after parkinson's-like disease by MPTP toxicity in intra-synaptic and non-synaptic mitochondria from Macaca fascicularis cerebral cortex and hippocampus: action of dihydroergocriptine. *Neurochem Res* 21: 1505-1514.

Battino, M. (2001) Natural distribution and occurrence of coenzyme Q homologs in mammals. In: Ebadi, M., Marwah, J. and Chopra, R., Editors, *Mitochondrial Ubiquinone (Coenzyme Q_{10}): Biochemical, Functional, Medical and Therapeutic Aspects in Human Health and Diseases*, Prominent Press, Irvine, pp. 152–182.

Baynes, JW, Thorpe, SR. (1999) Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. *Diabetes* 48: 1-9.

Beal, MF, Matthews, RT. (1997) Coenzyme Q10 in the central nervous system and its potential usefulness in the treatment of neurodegenerative diseases. *Mol Aspects Med* 18: S169-179.

Beal, MF. (1999) Coenzyme Q10 administration and its potential for treatment of neurodegenerative diseases. *Biofactors* 9: 261-266.

Beal, MF. (1999) Mitochondria, NO and neurodegeneration. *Biochem Soc Symp* 66: 43-54.

Beal, MF, Shults, CW. (2003) Effects of coenzyme Q10 in Huntington's disease and early Parkinson's disease. *Biofactors* 18: 153-161.

Beal, MF. (2003) Bioenergetic approaches for neuroprotection in Parkinson's disease. *Ann Neurol* 53: 39-47.

Beal, MF. (2003) Mitochondria, oxidative damage, and inflammation in Parkinson's disease. *Ann N Y Acad Sci* 991: 120-131.

Beal, MF. (2004) Mitochondrial dysfunction and oxidative damage in Alzheimer's and Parkinson's diseases and coenzyme Q10 as a potential treatment. *J Bioenerg Biomembr* 36: 381-386.

Berbel-Garcia, A, Barbera-Farre, JR, Etessam, JP, Salio, AM, Cabello, A, Gutierrez-Rivas, E, Campos, Y. (2004) Coenzyme Q 10 improves lactic acidosis, strokelike episodes, and epilepsy in a patient with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes). *Clin Neuropharmacol* 27:187-191.

Berman, M, Erman, A, Ben-Gal, T, Dvir, D, Georghiou, GP, Stamler, A, Vered, Y, Vidne, BA, Aravot, D. (2004) Coenzyme Q10 in patients with end-stage heart failure awaiting cardiac transplantation: a randomized, placebo-controlled study. *Clin Cardiol* 27: 295-299.

Beyer, RE, Burnett, BA., Cartwright, K, Edington, D, Falzon, M, Keitman, K. Kuhn, T, Ramp, B, Rhee, S, Rosenwasser, M. (1985) Tissue coenzyme Q and protein concentrations over the life span of the laboratory rat. *Mech Ageing Dev* 32: 267-281.

Bliznakov, EG. (1999) Aging, mitochondria, and coenzyme Q-10: the neglected relationship. *Biochimie* 81: 1131-1121.

Bowen, RL, Atwood, CS. (2004) Living and dying for sex. A theory of aging based on the modulation of cell cycle signaling by reproductive hormones. *Gerontology* 50: 265-290.

Bragin, V, Chemodanova, M, Dzhafarova, N, Bragin, I, Czerniawski, JL, Aliev, G. (2005) Integrated treatment approach improves cognitive function in demented and clinically depressed patients. *Am J Alzheimers Dis Other Demen* 20: 21-26.

Brunk, UT, Terman, A. (2002) The mitochondrial-lysosomal axis theory of aging: accumulation of damaged mitochondria as a result of imperfect autophagocytosis. *Eur J Biochem* 269: 1996-2002.

Chapidze, G, Kapanadze, S, Dolidze, N, Bachutashvili, Z, Latsabidze, N. (2005) Prevention of coronary atherosclerosis by the use of combination therapy with antioxidant coenzyme Q10 and statins. *Georgian Med News* 1: 20-25.

Chariot, P, Brugieres, P, Eliezer-Vanerot, MC, Geny, C, Binaghi, M, Cesaro, P. (1999) Choreic movements and MRI abnormalities in the subthalamic nuclei reversible after administration of coenzyme Q10 and multiple vitamins in a patient with bilateral optic neuropathy. *Mov Disord* 14: 855-859.

Chen, H, Carlson, EC, Pellet, L, Moritz, JT, Epstein, PN. (2001) Overexpression of metallothionein in pancreatic beta-cells reduces streptozotocin-induced DNA damage and diabetes. *Diabetes* 50:2040-2046.

Chew, GT, Watts GF. (2004) Coenzyme Q10 and diabetic endotheliopathy: oxidative stress and the 'recoupling hypothesis'. *QJM* 97: 537-548.

Chung, HY, Yokozawa, T, Kim, MS, Lee, KH., Kim, KW, Yang, R, Choi, JH. (2000) The mechanism of nitric oxide and/or superoxide cytotoxicity in endothelial cells. *Exper Toxicol Path* 52: 227–233.

Combs, AB, Kishi, T, Porter, TH, Folkers, K. (1976) Models for clinical disease. I. Biochemical cardiotoxicity of a coenzyme Q10-inhibitor in rat. *Res Commun Chem Pathol Pharmacol* 13: 333-339.

Conklin, KA. (2005) Coenzyme q10 for prevention of anthracycline-induced cardiotoxicity. *Integr Cancer Ther* 4: 110-130.

Cooper, JM, Schapira, AH. (2003) Friedreich's Ataxia: disease mechanisms, antioxidant and Coenzyme Q10 therapy. *Biofactors* 18: 163-171.

Crane, FL, Hatefi, Y, Lester, RL, Widner, C. (1957) Isolation of a quinone from beef heart mitochondria. *Biochim Biophys Acta* 25: 220-221.

Dabbeni-Sala, F, Di Santo, S, Franceschini, D, Skaper, SD, Giusti, P. (2001) Melatonin protects against 6-OHDA-induced neurotoxicity in rats: a role for mitochondrial complex I activity. *FASEB J* 15: 164-170.

de Bustos, F, Molina, JA, Jimenez-Jimenez, FJ., Garcia-Redondo, A, Gomez-Escalonilla, C, Porta-Etessam, J, Berbel, A, Zurdo, M, Barcenilla, B, Parrilla, G, Enriquez-de-Salamanca, R, Arenas, J. (2000) Serum levels of coenzyme Q10 in patients with Alzheimer's disease. *J Neural Transm* 107: 233-239.

Drzewoski, J, Folkers, K, Richardson, PC, Shizukuishi, S, Baker, LE. (1981) Usefulness of coenzyme Q10 in the treatment of hypertension. *Pol Tyg Lek* 36: 997-1001.

Ebadi, M, Srinivasan, SK, Baxi, MD. (1996) Oxidative stress and antioxidant therapy in Parkinson's disease. *Prog Neurobiol* 48: 1-19.

Edlund, C, Soderberg, M, Kristensson, K, Dallner, G. (1992) Ubiquinone, dolichol, and cholesterol metabolism in aging and Alzheimer's disease. *Biochem Cell Biol* 70: 422-428.

Edlund, C, Soderberg, M, Kristensson, K. (1994) Isoprenoids in aging and neurodegeneration. *Neurochem Int* 25: 35-38.

Ernster, L, Dallner, G. (1995) Biochemical, physiological and medical aspects of ubiquinone function. *Biochim Biophys Acta* 1271: 195-204.

Esberg, LB, Ren, J. (2003) Role of nitric oxide, tetrahydrobiopterin and peroxynitrite in glucose toxicity-associated contractile dysfunction in ventricular myocytes. *Diabetologia* 46:1419-27.

Feher, J, Papale, A, Mannino, G, Gualdi, L, Balacco Gabrieli, C. (2003) Mitotropic compounds for the treatment of age-related macular degeneration. The metabolic approach and a pilot study. *Ophthalmologica* 217: 351-357.

Feher, J, Kovacs, B, Kovacs, I, Schveoller, M, Papale, A, Balacco Gabrieli, C. (2005) Improvement of visual functions and fundus alterations in early age-related macular degeneration treated with a combination of acetyl-L-carnitine, n-3 fatty acids, and coenzyme Q10. *Ophthalmologica* 219: 154-66.

Feigin, A, Kieburtz, K, Como, P, Hickey, C, Claude, K, Abwender, D, Zimmerman, C, Steinberg, K, Shoulson, I. (1996) Assessment of coenzyme Q10 tolerability in Huntington's disease. *Mov Disord* 11: 321-323.

Felsner, P, Steinschifter, W, Fischer, M, Eferl, R, Kenner, L, Zatloukal, K, Lahousen, M, Liebmann, PM, Schauenstein, E, Schauenstein, K. (2000) The tumor-associated shift in immunoglobulin G1/G2 is expressed at the messenger RNA level of peripheral blood B lymphocytes in patients with gynecologic malignancies. *Cancer* 88: 461-467.

Fernandez-Ayala, DJ, Lopez-Lluch, G, Garcia-Valdes, M, Arroyo, A, Navas, P. (2005) Specificity of coenzyme Q10 for a balanced function of respiratory chain and endogenous ubiquinone biosynthesis in human cells. *Biochem Biophys Acta* 1706: 174-183.

Finsterer, J. (2004) Mitochondriopathies. *Eur J Neurol* 11:163-186.

Folkers, K, Drzewoski, J, Richardson, PC, Ellis, J, Shizukuishi, S, Baker, L. (1981) Bioenergetics in clinical medicine. XVI. Reduction of hypertension in patients by therapy with coenzyme Q10. *Res Commun Chem Pathol Pharmacol* 31: 129-140.

Folkers, K, Morita, M, McRee, J. Jr. (1993) The activities of coenzyme Q10 and vitamin B6 for immune responses. *Biochem Biophys Res Commun* 193: 88-92.

Folkers, K, Vadhanavikit, S, Mortensen, SA. (1985) Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with coenzyme Q10. *Proc Natl Acad Sci USA* 82: 901–904.

Forgionne, GA. (2005) Bovine cartilage, coenzyme Q10, and wheat grass therapy for primary peritoneal cancer. *J Altern Complement Med* 11:161-165.

Forsyth, LM, Preuss, HG, MacDowell, AL., Chiazze, L, Birkmayer, GD, Bellanti, JA. (1999) Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. *Ann Allergy Asthma Immunol* 82: 185-191.

Fujioka, T, Sakamoto, Y, Mimura, G. (1983) Clinical study of cardiac arrhythmias using a 24-hour continuous electrocardiographic recorder (5th report)--antiarrhythmic action of coenzyme Q10 in diabetics. *Tohoku J Exp Med* 141: 453-463.

Gazdik, F, Gvozdjakova, A, Horvathova, M, Weissova, S, Kucharska, J, Pijak, MR, Gazdikova, K. (2002) Levels of coenzyme Q10 in asthmatics. *Bratisl Lek Listy* 103: 353-356.

Gazdik, F, Gvozdjakova, A, Nadvornikova, R, Repicka, L, Jahnova, E, Kucharska, J, Pijak, MR, Gazdikova, K. (2002) Decreased levels of coenzyme Q(10) in patients with bronchial asthma. *Allergy* 57: 811-814.

Gotz, ME, Gerstner, A, Harth, R, Dirr, A, Janetzky, B, Kuhn, W, Riederer, P, Gerlach, M. (2000) Altered redox state of platelet coenzyme Q10 in Parkinson's disease. *J Neural Transm* 107: 41-48.

Grundman, M, Grundman, M, Delaney, P. (2002) Antioxidant strategies for Alzheimer's disease. *Proc Nutr Soc* 61: 191-202.

Guzik, TJ, West, NE., Pillai, R, Taggart, DP, Channon, KM. (2002) Nitric oxide modulates superoxide release and peroxynitrite formation in human blood vessels. *Hypertension* 39: 1088–1094.

Harman, D. (1956) Aging: a theory based on free radical and radiation chemistry. *J Gerontol* 11: 298-300.

Hart, PE., Lodi, R, Rajagopalan, B, Bradley, JL, Crilley, JG, Turner, C, Blamire, AM, Manners, D, Styles, P, Schapira, AH, Cooper, JM. (2005) Antioxidant treatment of patients with Friedreich ataxia: four-year follow-up. *Arch Neurol* 62: 621-626.

Hodges, S, Hertz, N, Lockwood, K, Lister, R. (1999) CoQ10: could it have a role in cancer management? *Biofactors* 9: 365-370.

Hodgson, JM, Watts, GF. (2003) Can coenzyme Q10 improve vascular function and blood pressure? Potential for effective therapeutic reduction in vascular oxidative stress. *Biofactors* 18: 129-136.

Huang, CC, Kuo, HC, Chu, CC, Kao, LY. (2002) Rapid visual recovery after coenzyme q10 treatment of leber hereditary optic neuropathy. *J Neuroophthalmol* 22 :66.

Huntington Study group. (2001) A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. *Neurology* 57: 397-404.

Ishii, N, Senoo-Matsuda, N, Miyake, K, Yasuda, K, Ishii, T, Hartman, PS, Furukawa, S. (2004) Coenzyme Q10 can prolong C. elegans lifespan by lowering oxidative stress. *Mech Ageing Dev* 125: 41-46.

Jimenez-Jimenez, FJ, Molina, JA, de Bustos, F, Garcia-Redondo, A, Gomez-Escalonilla, C, Martinez-Salio, A, Berbel, A, Camacho, A, Zurdo, M, Barcenilla, B, Enriquez de Salamanca, R, Arenas, J. (2000) Serum levels of coenzyme Q10 in patients with Parkinson's disease. *J Neural Transm* 107: 177-181.

Jones, K, Hughes, K, Mischley, L, McKenna, DJ. (2004) Coenzyme Q-10 and cardiovascular health. *Alt Ther Health Med* 10:22-30.

Kamzalov, S, Sohal, RS. (2004) Effect of age and caloric restriction on coenzyme Q and alpha-tocopherol levels in the rat. *Exp Gerontol* 39: 1199-205.

Kishi, H, Kishi, T, Folkers, K. (1975) Bioenergetics in clinical medicine. III. Inhibition of coenzyme Q10-enzymes by clinically used antihypertensive drugs. *Res Commun Chem Pathol Pharmacol* 12: 533-540.

Koller, WC, Cersosimo, MG. (2004) Neuroprotection in Parkinson's disease: an elusive goal. *Curr Neurol Neurosci Rep* 4: 277-283.

Konno, K, Yamaguchi, M. (1990) Therapeutic management of chronic respiratory failure. *Nippon Naika Gakkai Zasshi* 79: 762-770.

Koppenol, WH, Moreno, JJ, Pryor, WA, Ischiropoulos, H, Beckman, JS. (1992) Peroxynitrite, a cloaked oxidant formed by nitric oxide and superoxide. *Chem Res Toxicol* 5: 834–842.

Kroenke, K, Wood, DR, Mangelsdorff, AD, Meier, NJ, Powell, JB. (1988) Chronic fatigue in primary care. Prevalence, patient characteristics, and outcome. *JAMA* 260:929-934.

Kuettner, A, Pieper, A, Koch, J, Enzmann, F, Schroeder, S. (2005) Influence of coenzyme Q(10) and cerivastatin on the flow-mediated vasodilation of the brachial artery: results of the ENDOTACT study. *Int J Cardiol* 98: 413-419.

Kurup, RK, Kurup, PA. (2003) Hypothalamic digoxin, hemispheric chemical dominance, and Alzheimer's disease. *Int J Neurosci* 113: 361-381.

Lalani, SR, Vladutiu, GD, Plunkett, K, Lotze, TE., Adesina, AM, Scaglia, F. (2005) Isolated mitochondrial myopathy associated with muscle coenzyme Q10 deficiency. *Arch Neurol* 62: 317-320.

Lands, LC, Grey, VL, Smountas, AA. (1999) Effect of supplementation with a cysteine donor on muscular performance. *J Appl Physiol* 87:1381-1385

Langsjoen, PH, Langsjoen, AM. (1998) Coenzyme Q10 in cardiovascular disease with emphasis on heart failure and myocardial ischaemia. *Asia Pac Heart J* 7: 160–168.

Langsjoen, P, Langsjoen, P, Willis, R, Folkers, K. (1994) Treatment of essential hypertension with coenzyme Q10. *Mol Aspects Med* 15: S265-272.

Langsjoen, PH, Vadhanavikit, S, Folkers, K. (1985) Response of patients in classes III and IV of cardiomyopathy to therapy in a blind and crossover trial with coenzyme Q10. *Proc Natl Acad Sci USA* 82: 4240–4244.

Lee, CK, Pugh, TD, Klopp, RG, Edwards, J, Allison, DB, Weindruch, R, Prolla, TA. (2004) The impact of alpha-lipoic acid, coenzyme Q10 and caloric restriction on life span and gene expression patterns in mice. *Free Radic Biol Med* 36: 1043-1057.

Li, FC, Tseng, HP, Chang, AY. (2005) Neuroprotective Role of Coenzyme Q10 against Dysfunction of Mitochondrial Respiratory Chain at Rostral Ventrolateral Medulla during Fatal Mevinphos Intoxication in the Rat. *Ann N Y Acad Sci* 1042: 195-202.

Littarru, GP, Ho L, Folkers K. (1972) Deficiency of coenzyme Q10 in human heart disease. *Int J Vitam Nutr Res* 42: 413–434.

Logan, AC, Venket Rao, A, Irani, D. (2003) Chronic fatigue syndrome: lactic acid bacteria may be of therapeutic value. *Med Hypotheses* 60: 915-923.

Lonnrot, K, Metsa-Ketela, T, Alho, H. (1995) The role of coenzyme Q-10 in aging: a follow-up study on life-long oral supplementation Q-10 in rats. *Gerontology* 41: 109-120.

Malchair, P, Van Overmeire, L, Boland, A, Salmon, E, Pierard, L, Seutin, V. (2005) Coenzyme Q10: biochemistry, pathophysiology of its deficiency and potential benefit of an increased intake. *Rev Med Liege* 60: 45-51.

Marubayashi, S, Dohi, K, Ezaki, H, Hayashi, K, Kawasaki, T. (1982) Preservation of ischemic rat liver mitochondrial functions and liver viability with CoQ10. *Surgery* 91: 631-637.

Matthews, RT, Yang, L, Browne, S, Baik, M, Beal, MF. (1998) Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. *Proc Natl Acad Sci USA* 95: 8892-8897.

McCarty, MF. (1999) Coenzyme Q versus hypertension: does CoQ decrease endothelial superoxide generation? *Med. Hypotheses* 53: 300-304.

McCarty, MF. (2000) Toward a wholly nutritional therapy for type 2 diabetes. *Med Hypotheses* 54: 483-7.

McDonald, SR, Sohal, R.S, Forster, M.J. (2005) Concurrent administration of coenzyme Q10 and alpha-tocopherol improves learning in aged mice. *Free Radic Biol Med* 38: 729-36.

Miles, MV, Horn, PS, Tang, PH., Morrison, JA, Miles, L, DeGrauw, T, Pesce, AJ. (2004) Age-related changes in plasma coenzyme Q10 concentrations and redox state in apparently healthy children and adults. *Clin Chim Acta* 347: 139-144.

Molyneux, SL, Florkowski, CM, Lever, M, George, PM. (2005) Biological variation of coenzyme Q10. *Clin Chem* 51: 455-457.

Moon, Y, Lee, KH, Park, JH, Geum, D, Kim, K. (2005) Mitochondrial membrane depolarization and the selective death of dopaminergic neurons by rotenone: protective effect of coenzyme Q10. *J Neurochem* 93: 1199-1208.

Muller, T, Buttner, T, Gholipour, AF, Kuhn, W. (2003) Coenzyme Q10 supplementation provides mild symptomatic benefit in patients with Parkinson's disease. *Neurosci Lett* 341: 201-204.

Naini, A, Lewis, VJ, Hirano, M, DiMauro, S. (2003) Primary coenzyme Q10 deficiency and the brain. *Biofactors* 18: 145-152.

Nakamura, Y, Takahashi, M, Hayashi, J, Mori, H, Ogawa, S, Tanabe, Y, Hara, K. (1982) Protection of ischaemic myocardium with coenzyme Q10. *Cardiovasc Res* 16: 132-137.

Nakamura, Y, Konishi, T, Kawai, C. (1984) Exogenous coenzyme Q attenuates the tension prolongation phenomenon. *Jpn Circ J* 48: 37-42.

Näslund, J, Haroutunian, V, Mohs, R, Davis, KL, Davies, P, Greengard, P, Buxbaum, JD. (2000) Correlation between elevated levels of amyloid ß-peptide in the brain and cognitive decline. *JAMA* 283:1571-1577.

Nawarskas, JJ. (2005) HMG-CoA reductase inhibitors and coenzyme Q10, *Cardiol Rev* 13:76-79.

Niklowitz, P, Menke, T, Wiesel, T, Mayatepek, E, Zschocke, J, Okun, JG, Andler, W. (2002) Coenzyme Q10 in plasma and erythrocytes: comparison of antioxidant levels in healthy probands after oral supplementation and in patients suffering from sickle cell anemia. *Clin Chim Acta* 326: 155-161.

Oda, T. (1985) Effect of coenzyme Q10 on stress-induced cardiac dysfunction in paediatric patients with mitral valve prolapse: a study by stress echocardiography. *Drugs Exp Clin Res* 11: 557-576.

Ogawa, O, Zhu, X, Perry, G, Smith, MA. (2002) Mitochondrial abnormalities and oxidative imbalance in neurodegenerative disease. *Sci Aging Knowledge Environ* 2002: 16.

Ohnishi, ST, Ohnishi, T, Ogunmola, GB. (2000) Sickle cell anemia: a potential nutritional approach for a molecular disease. *Nutrition* 16: 330-338.

Okamoto, F, Karino, K, Ohori, K, Abe, T, Komatsu, S. (1983) Effect of coenzyme Q10 on hypertrophied ischemic myocardium during aortic cross clamping for 2 hr, from the aspect of energy metabolism. *Adv Myocardiol* 4: 559-566.

Ono, K, Hasegawa, K, Naiki, H, Yamada, M. (2005) Preformed beta-amyloid fibrils are destabilized by coenzyme Q10 *in vitro*. *Biochem Biophys Res Commun* 330: 111-116.

Parker, WD, Boyson, SJ, Luder, AS, Parks, JK. (1990) Evidence for a defect in NADH: ubiquinone oxidoreductase (complex I) in Huntington's disease. *Neurology* 40: 1231-1234.

Permanetter, B, Rossy, W, Klein, G, Weingartner, F, Seidl KF, Blomer, H. (1992) Ubiquinone (coenzyme Q10) in the long-term treatment of idiopathic dilated cardiomyopathy. *Eur Heart J* 13: 1528–1533.

Perumal, SS., Shanthi, P, Sachdanandam, P. (2005) Augmented efficacy of tamoxifen in rat breast tumorigenesis when gavaged along with riboflavin, niacin, and CoQ10: effects on lipid peroxidation and antioxidants in mitochondria. *Chem Biol Interact* 152: 49-58.

Pignatti, C, Cocchi, M, Weiss, H. (1980) Coenzyme Q10 levels in rat heart of different age. *Biochem Exp Biol* 16: 39-42.

Playford, DA, Watts, GF, Croft, KD, Burke, V. (2003) Combined effect of coenzyme Q10 and fenofibrate on forearm microcirculatory function in type 2 diabetes. *Atherosclerosis* 168: 169-179.

Poller, W, Kuhl, U, Tschoepe, C, Pauschinger, M, Fechner, H, Schultheiss, HP. (2005) Genome-environment interactions in the molecular pathogenesis of dilated cardiomyopathy. *J Mol Med* Jun 2; [E pub ahead of print]

Quiles, JL, Ochoa, JJ, Huertas, JR, Mataix, J. (2004) Coenzyme Q supplementation protects from age-related DNA double-strand breaks and increases lifespan in rats fed on a PUFA-rich diet. *Exp Gerontol* 39: 189-194.

Quinzii, CM, Kattah, AG, Naini, A, Akman, HO, Mootha, VK, DiMauro, S, Hirano, M. (2005) Coenzyme Q deficiency and cerebellar ataxia associated with an aprataxin mutation. *Neurology* 64: 539-541.

Ramasarma,T. (1985) Natural occurrence and distribution of coenzyme Q. *Coenzyme Q.* John Wiley & Sons Ltd., New York, pp67-81.

Rodriguez-Aguilera, JC, Gavilan, A, Asencio, C, Navas, P. (2005) The role of ubiquinone in Caenorhabditis elegans longevity. *Ageing Res Rev* 4: 41-53.

Rosenfeldt, F, Hilton, D, Pepe, S, Krum, H. (2003) Systematic review of effect of coenzyme Q10 in physical exercise, hypertension and heart failure. *Biofactors* 18: 91-100.

Rosenfeldt, F, Marasco, S, Lyon, W, Wowk, M, Sheeran, F, Bailey, M, Esmore, D, Davis, B, Pick, A, Rabinov, M, Smith, J, Nagley, P, Pepe S. (2005) Coenzyme Q10 therapy before cardiac surgery improves mitochondrial function and *in vitro* contractility of myocardial tissue. *J Thorac Cardiovasc Surg* 129: 25-32

Rosen, P, Nawroth, PP, King, G, Moller, W, Tritschler, HJ, Packer, L. (2001) The role of oxidative stress in the onset and progression of diabetes and its complications: a summary of a Congress Series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society. *Diabetes Metab Res Rev* 17: 189-212.

Saitoh, I, Miyoshi, H, Shimizu, R, Iwamura, H. (1992) Comparison of structure of quinone redox site in the mitochondrial cytochrome-bc1 complex and photosystem II (QB site). *Eur J Biochem* 209: 73-79.

Santaella, ML, Font, I, Disdier, OM. (2004) Comparison of oral nicotinamide adenine dinucleotide (NADH) versus conventional therapy for chronic fatigue syndrome. *P R Health Sci J* 23: 89-93.

Sarter, B. (2002) Coenzyme Q10 and cardiovascular disease: a review. *J Cardiovasc Nurs* 16: 9-20.

Schols, L, Meyer, CH, Schmid, G, Wilhelms, I, Przuntek, H. (2004) Therapeutic strategies in Friedreich's ataxia. *J Neural Transm* 68:135-45.

Schopfer, F, Riobo, N, Carreras, MC., Alvarez, B, Radi, R, Boveris, A, Cadenas, E, Poderoso, JJ. (2000) Oxidation of ubiquinol by peroxynitrite: implications for protection of mitochondria against nitrosative damage. *Biochem J* 349: 1–42.

Schulte-Mattler, WJ, Muller, T, Deschauer, M, Gellerich, FN, Iaizzo, PA, Zierz, S. (2003) Increased metabolic muscle fatigue is caused by some but not all mitochondrial mutations. *Arch Neurol* 60: 50-58.

Schroeder, MM, Belloto, RJ, Hudson, RA, McInerney, MF. (2005) Effects of antioxidants coenzyme Q10 and lipoic acid on interleukin-1beta-mediated inhibition of glucose-stimulated insulin release from cultured mouse pancreatic islets. *Immunopharmacol Immunotoxicol* 27: 109-122.

Serizawa, T, Oku, J, Iizuka, M, Ohya, T, Ohtani, Y, Sugiura, S, Murakami, T, Sugimoto, T. (1988) Beneficial effects of coenzyme Q10 on impaired left ventricular performance in streptozotocin diabetic rats. *Jpn Heart J* 29: 233-242.

Seznec, H, Simon, D, Bouton, C, Reutenauer, L, Hertzog, A, Golik, P, Procaccio, V, Patel, M, Drapier, JC, Koenig, M, Puccio, H. (2005) Friedreich ataxia: the oxidative stress paradox. *Hum Mol Genet* 14: 463-474.

Sharma, S, Kheradpezhou, M, Shavali, S, El Refaey, H., Eken, J, Hagen, C, Ebadi, M. (2004) Neuroprotective actions of coenzyme Q10 in Parkinson's disease. *Methods Enzymol* 382: 488-509.

Shinkai, T, Nakashima, M, Ohmori, O, Terao, T, Nakamura, J, Hiramatsu, N, Hashiguchi, H, Tsuji, S. (2000) Coenzyme Q10 improves psychiatric symptoms in adult-onset mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes: a case report. *Aust N Z J Psychiatry* 34: 1034-1035.

Shekelle, P, Hardy, ML, Coulter, I, Udani, J, Spar, M, Oda, K, Jungvig, LK, Tu, W, Suttorp, M.J, Valentine, D, Ramirez, L, Shanman, R, Newberry, SJ. (2003) Effect of the supplemental use of antioxidants vitamin C, vitamin E, and coenzyme Q10 for the prevention and treatment of cancer. *Evid Rep Technol Assess* 75: 1-3.

Shults, CW, Haas, RH, Passov, D, Beal, MF. (1997) Coenzyme Q10 levels correlate with the activities of complexes I and II/III in mitochondria from parkinsonian and nonparkinsonian subjects. *Ann Neurol* 42: 261-264.

Shults, CW, Beal, MF, Fontaine, D, Nakano, K, Haas, RH. (1998) Absorption, tolerability, and effects on mitochondrial activity of oral coenzyme Q10 in parkinsonian patients. *Neurology* 50: 793-795.

Shults, CW, Haas, RH, Beal, MF. (1999) A possible role of coenzyme Q10 in the etiology and treatment of Parkinson's disease. *Biofactors* 9: 267-272.

Shults, CW, Oakes, D, Kieburtz, K, Beal, MF, Haas, R, Plumb, S, Juncos, JL, Nutt, J, Shoulson, I, Carter, J, Kompoliti, K, Perlmutter, JS, Reich, S, Stern, M, Watts, RL, Kurlan, R, Molho, E, Harrison, M, Lew, M, Parkinson Study Group. (2002) Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. *Arch Neurol* 59: 1541-1550.

Shunk, CH, Linn, BO, Wong, EL, Wittrih, PE, Robinson, FM, Folkers, K. (1958) Coenzyme Q. II. synthesis of 6-farnesyl and 6-phytyl-derivatives of 2,3-dimethoxy-5-methylbenzoquinone and related analogs. *J Am Chem Soc* 80: 4753.

Siemieniuk, E, Skrzydlewska, E. (2005) Coenzyme Q10: its biosynthesis and biological significance in animal organisms and in humans. *Postepy Hig Med Dosw* 59: 150-159.

Singh, RB, Neki, NS, Kartikey, K, Pella, D, Kumar, A, Niaz, MA, Thakur, AS. (2003) Effect of coenzyme Q10 on risk of atherosclerosis in patients with recent myocardial infarction. *Mol Cell Biochem* 246: 75-82.

Sohmiya, M, Tanaka, M, Tak, NW, Yanagisawa, M, Tanino, Y, Suzuki, Y, Okamoto, K, Yamamoto, Y. (2004) Redox status of plasma coenzyme Q10 indicates elevated systemic oxidative stress in Parkinson's disease. *J Neurol Sci* 223: 161-166.

Sohmiya, M, Tanaka, M, Suzuk,i Y, Tanino, Y, Okamoto, K, Yamamoto, Y. (2005) An increase of oxidized coenzyme Q-10 occurs in the plasma of sporadic ALS patients. *J Neurol Sci* 228: 49-53.

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. *Neurobiol Dis* 18: 618-627.

Steele, PE, Tang, PH, DeGrauw, AJ, Miles, MV. (2004) Clinical laboratory monitoring of coenzyme Q10 use in neurologic and muscular diseases. *Am J Clin Pathol* 121: S113-120.

Strijks, E, Kremer, HP, Horstink, MW. (1997) Q10 therapy in patients with idiopathic Parkinson's disease. *Mol Aspects Med* 18: 237-240.

Strong, MJ, Pattee, GL. (2000) Creatine and coenzyme Q10 in the treatment of ALS. *Amyotroph Lateral Scler. Other Motor Neuron Disord* 1: 17-20.

Sugawara, H, Yamamoto, T, Shimizu, S, Momose, K. (1990) Inhibition of ubiquinone synthesis in isolated rat heart under an ischemic condition. *Int J Biochem* 22: 477-480.

Suzuki, Y, Kadowaki, H, Atsumi, Y, Hosokawa, K, Katagiri, H., Kadowaki, T, Oka, Y, Uyama, K, Mokubo, A, Asahina, T. (1995) A case of diabetic amyotrophy associated with 3243 mitochondrial tRNA(leu; UUR) mutation and successful therapy with coenzyme Q10. *Endocr J* 42: 141-145.

Swerdlow, RH, Parks, JK, Miller, SW, Tuttle, JB, Trimmer, PA, Sheehan, JP, Bennett, JP. Jr., Davis, RE, Parker, WD. Jr. (2001) Origin and functional consequences of the complex I defect in Parkinson's disease. *J Biol Chem* 276: 47239-47247.

Takenaka, M, Tatsukawa, Y, Dohi, K, Ezaki, H, Matsukawa, K, Kawasaki, T. (1981) Protective effects of alpha-tocopherol and coenzyme Q10 on warm ischemic damages of the rat kidney. *Transplantation* 32: 137-141.

Tarnopolsky, MA, Beal, MF. (2001) Potential for creatine and other therapies targeting cellular energy dysfunction in neurological disorders. *Ann Neurol* 49: 561-574.

Tatar, M, Bartke, A, Antebi A. (2003) The endocrine regulation of aging by insulin-like signals. *Science* 299:1346-1351.

Terman, A, Dalen, H, Eaton, JW, Neuzil, J, Brunk, UT. (2004) Aging of cardiac myocytes in culture: oxidative stress, lipofuscin accumulation, and mitochondrial turnover. *Ann N Y Acad Sci* 1019: 70-77.

Tominaga, R, Kouda, Y, Tanaka, J, Nakano, E, Ando, H, Ueno, Y, Tokunaga, K. (1983) Effects of pretreatment with coenzyme Q10 on myocardial preservation during aortic cross clamping. *J Surg Res* 34: 111-117.

Tralongo, P, Respini, D, Ferrau, F. (2003) Fatigue and aging. *Crit Rev Oncol Hematol* 48: S57-64.

Tsao, CY, Mendell, JR. (2002) Combined partial deficiencies of carnitine palmitoyltransferase II and mitochondrial complex I presenting as increased serum creatine kinase level. *J Child Neurol* 17: 304-306.

Ulm, G. (2004) Differential therapy of advanced Parkinson's disease with special reference to complementary therapeutic approaches. *Schweiz Rundsch Med Prax* 93: 1869-1872.

Vericel, E, Croset, M, Sedivy, P, Courpron, P, Dechavanne, M, Lagarde, M. (1988) Platelets and aging. I--Aggregation, arachidonate metabolism and antioxidant status. *Thromb Res* 49: 331-342.

Villalba, JM, Navarro, F, Córdoba, F, Serrano, A, Arroyo, A, Crane, FL, Navas, P. (1995) Coenzyme Q reductase from liver plasma membrane: purification an role in tran-plasma-membrane electron transport. *Proc Natl Acad Sci USA* 92 4887-4891.

Vinogradov, AD, Grivennikova, VG. (2005) Generation of superoxide-radical by the NADH: ubiquinone oxidoreductase of heart mitochondria. *Biochemistry* 70: 120-127.

Walker, FO, Raymond, LA. (2004) Targeting energy metabolism in Huntington's disease. *Lancet* 364: 312-313.

Wang, XL, Rainwater, DL, Mahaney, MC, Stocker, R. (2004) Cosupplementation with vitamin E and coenzyme Q10 reduces circulating markers of inflammation in baboons. *Am J Clin Nutr* 80: 649-655.

Werbach, MR. (2000) Nutritional strategies for treating chronic fatigue syndrome. *Altern Med Rev* 5: 93-108.

Westendorp, RG, Kirkwood, TB. (1998) Human longevity at the cost of reproductive success. *Nature* 396: 743-746.

Whitman, GJ, Niibori, K, Yokoyama, H, Crestanello, JA, Lingle, DM, Momeni, R. (1997) The mechanisms of coenzyme Q10 as therapy for myocardial ischemia reperfusion injury. *Mol Aspects Med* 18: S195-203.

Wilburn, AJ, King, DS, Glisson, J, Rockhold, RW, Wofford, MR. (2004) The natural treatment of hypertension. *J Clin Hypertens (Greenwich)* 6: 242-248.

Wold, LE, Muralikrishnan, D, Albano, CB, Norby, FL, Ebadi, M, Ren, J. (2003) Insulin-like growth factor 1 (IGF-1) supplementation prevents diabetes-induced alterations in coenzymes Q9 and Q10. *Acta Diabetol* 40: 85-90.

Yalcin, A, Kilinc, E, Sagcan, A, Kultursay, H. (2004) Coenzyme Q10 concentrations in coronary artery disease. *Clin Biochem* 37: 706-709.

Yamagami, T, Shibata, N, Folkers, K. (1975) Bioenergetics in clinical medicine. Studies on coenzyme Q10 and essential hypertension. *Res Commun Chem Pathol Pharmacol* 11: 273-288.

Yamagami, T, Shibata, N, Folkers, K. (1976) Bioenergetics in clinical medicine. VIII. Adminstration of coenzyme Q10 to patients with essential hypertension. *Res Commun Chem Pathol Pharmacol* 14: 721-727.

Zita, C, Overvad, K, Mortensen, SA, Sindberg, CD, Moesgaard, S, Hunter, DA. (2003) Serum coenzyme Q10 concentrations in healthy men supplemented with 30 mg or 100 mg coenzyme Q10 for two months in a randomised controlled study. *Biofactors* 18: 185-193.