International Journal for Pharmaceutical Research Scholars (IJPRS)

V-3, I-4, 2014 ISSN No: 2277 - 7873

REVIEW ARTICLE

Benefits of Co-enzyme Q10 – A Review

Santosh JK Mahto*, Abul Faiz AA Ansari, Priyesh P Singh, Ujjwal R Singh, Vibhavari Chatur

Alard College of Pharmacy, Marunje, Pune – 411057, Maharashtra, India.

Manuscript No: IJPRS/V3/I4/00454, Received On: 24/12/2014, Accepted On: 28/12/2014

ABSTRACT

Coenzyme Q10 is a vitamin-like substance used in the treatment of a variety of disorders primarily related to sub-optimal cellular energy metabolism and oxidative injury. CoQ10 is an antioxidant that is made in the human body. It is an essential cofactor of the electron transport chain as well as a potent free radical scavenger in lipid and mitochondrial membranes. Its levels decrease with age and may be low in people with cancer, certain genetic disorders, diabetes, heart conditions, HIV/AIDS, muscular dystrophies, and Parkinson's disease. Studies supporting the efficacy of CoQ10 appear most promising for neurodegenerative disorders such as Parkinson's disease and certain encephalomyopathies for which CoQ10 has gained orphan drug status. CoQ10 in the body can be increased by taking CoQ10 supplements. There is evidence that idebenone, a man-made compound similar to CoQ10, may help treat Alzheimer's disease. However, evidence is lacking to support the use of itself for this condition. Promising uses of CoQ10 include eye disease; chest pain caused by exercise, asthma, chronic fatigue, and high cholesterol, as well as the treatment of chemotherapy side effects in children. Evidence is conflicting for the use of CoQ10 in heart muscle problems and exercise performance. There is some negative evidence for the use of CoQ10 in the treatment of diabetes, hepatitis C, and Huntington's disease. These results show that oral administration of CoQ10 increases both brain and brain mitochondrial concentrations. CoQ10 appears to be a safe supplement with minimal side effects and low drug interaction potential.

KEYWORDS

CoQ10, Vitamin Q10, Ubiquinone, Ubisemiquinone, Ubiquinol, Antioxidant & Cofactor

INTRODUCTION

CoQ10 was first isolated from beef heart mitochondria by Dr. Frederick Crane of Wisconsin, U.S.A., in 1957.[1] This oil-soluble, vitamin-like substance is present in most eukaryotic cells, primarily in the mitochondria. It is a component of the electron transport chain and participates in aerobic cellular respiration, generating energy in the form of ATP.[2,3] Ninety-five percent of the human body's energy is generated this way.

***Address for Correspondence:**
Santosh Kumar,
Alard College of Pharmacy,
Marunje, Pune-411057, Maharashtra, India.
E-Mail Id: santkr108@gmail.com

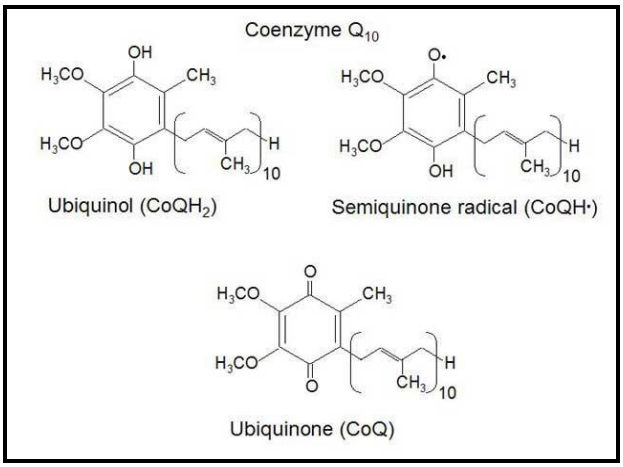

Figure 1: Structure of Coenzyme Q10 and its derivatives

Therefore, those organs with the highest energy requirements- such as the heart, liver and kidney, have the highest CoQ10 concentrations.

There are three redox states of CoQ10:

- Fully oxidized [ubiquinone(CoQ)],
- Semiquinone [ubisemiquinone(CoQH)], and
- Fully reduced [ubiquinol (CoQH2)].

CoQ10 occurs in two isomeric forms, namely the "trans" and the "cis" forms. The natural CoQ10 is in the trans form whereas the synthetic CoQ10 contains a mixture of both trans and cis isomers.[4]

Appearance	Orange crystals (at room temperature)
Empirical formula	$C_{59}H_{90}O_4$
Molecular weight	863.358
Melting point	490 C
Solubility	Insoluble in water Limited solubility in oils and fats Soluble in non-polar solvents

Mechanism of Action

Coenzyme Q-10 is a fat-soluble, vitamin-like compound that is naturally found in most tissue of the human body. It is essential for life and health of every living cell. The highest concentrations are found in the heart, liver, kidney, and pancreas. The lowest concentrations are found in the lungs. The human body produces coenzyme Q10. Humans can replenish coenzyme Q10 from dietary sources, including meats and seafood. Everything living or once living contains coenzyme Q10. Within the cell, coenzyme Q-10 is mostly present in the mitochondria (40-50%). It is the electron acceptor for the mitochondrial electron transport chain. It is also a cofactor used in processes of aerobic respiration, aerobic metabolism, oxidative metabolism, and cell respiration. Coenzyme Q10 primary function are as an antioxidant, membrane stabilizer and production of adenosine triphosphate (ATP) in the oxidative respiration process. As an antioxidant and its role in ATP, coenzyme Q10 offers many therapeutic benefits. Also, coenzyme Q10 has been shown to help preserve myocardial sodium-potassium ATPase activity and stabilize myocardial calcium dependent ion channels.[4]

Pharmacology

The plasma peak can be observed 2–6 hours after oral administration, depending mainly on the design of the study. In some studies, a second plasma peak was also observed at about 24 hours after administration, probably due to both entero-hepatic recycling and redistribution from the liver to circulation.[5] Tomono et al. used deuterium-labelled crystalline CoQ10 to investigate pharmacokinetics in human and determined an elimination half-time of 33 hours.[6]

What does CoQ10 do in our body?

The primary function of CoQ10 in our body is in cellular energy production. It is a critical component of mitochondria that are present in practically every cell in our body. Mitochondria may in fact be considered as fuel cells where biological energy called ATP (adenosine triphosphate) is produced. CoQ10 is also a potent antioxidant and it helps protect the tissues and the cellular components in the body from free radical damage. In addition, CoQ10 has other important functions in the body.[7,8]

How does CoQ10 work in our body?

CoQ10 is a crucial component of the electron transport chain (respiratory chain) in the mitochondria where energy derived by a process called oxidative phosphorylation from the products of fatty acid, protein and carbohydrate metabolism is converted into biological energy called adenosine triphosphate (ATP) that drives cellular machinery and all biosynthetic processes.

CoQ10 functions as an essential cofactor for the activities of the enzyme systems called complexes I, II and III in the electron transport chain. It shuttles electrons from complex I

(nicotinamide adenine dinucleotide dehydrogenase) and Complex II (succinate dehydrogenase) to complex III (ubiquinone-cytochrome C reductase) by virtue of its redox (reduction-oxidation) properties. It is during this process of electron transfer along the electron transport chain that vital biological energy as ATP is generated. Thus, CoQ10 plays a critical role in cellular bioenergetics.

CoQ10 is also an important fat-soluble antioxidant and as such, it helps protect vital structures from free radical damage from both endogenous and exogenous sources. CoQ10 has other important functions too in the body. It helps maintain membrane stability and has a role in cell signalling.[9]

Supplementation Benefits

Free Radicals

Chemically, free radicals can be defined as a molecule with an unpaired electron. In the process of trying to balance itself by gaining or losing an electron, the free radical causes oxidative damage on a cellular level. CoQ10 has the unique property of being able to accept or donate an electron without itself becoming a free radical. By doing this CoQ10 can help neutralize free radicals and the oxidative damage they cause. This is significant since numerous disease states are thought to be due to excessive oxidative stress of free radicals, including hydroxyl radical, peroxynitrite, superoxide anion and hydrogen peroxide. In addition, CoQ10 may inhibit certain enzymes involved in the formation of these free radicals.[10]

Cardiovascular Disorders

CoQ10 has been reviewed in the scientific literature, and found to be used in oral form to treat various cardiovascular disorders.[11]

A. Angina

In a review of the scientific literature, CoQ10 was shown to be used orally to treat various cardiovascular disorders including angina.[12] In one study, patients with acute myocardial infarction experienced a significant reduction in angina, arrhythmias (abnormal heartbeat), and poor heart function when supplemented with 120 mg of CoQ10 daily.[13]

Of course everyone knows that exercise is good to prevent cardiovascular disease. But in one study, patients with ischemic heart disease/effort angina were found to experience a faster loss of CoQ10 during exercise.[14] Does this mean that you shouldn't exercise if you have angina? No, it just means you should supplement with CoQ10. In another study, 150 mg of CoQ10 given to angina patients not only increased their blood levels of CoQ10, but also increased their ability to exercise longer. These results lead the researchers to conclude, "This study suggests that Co-enzyme Q10 is a safe and promising treatment for angina pectoris."[15] (Note: If you have acute angina, you should only exercise in accordance to a program approved by your physician.)

B. Congestive Heart Failure

A few researchers have said that in many cases, a lack of CoQ10 is the cause of congestive heart failure. Whether or not this is ultimately proven to be true, research certainly supports the use of this supplement by patients with CHF. A meta-analysis of eight controlled clinical trials of CoQ10 treatment of CHF revealed a significant improvement in several important cardiac parameters.[16] Other research on CHF patients using CoQ10 has shown similar benefits, including the improvement of quality of life, as well as survival.[17,18]

C. High Blood Pressure

Research indicates that CoQ10 affects blood vessels in a way that should cause a decrease in blood pressure.10 In fact, this has been substantiated in a number of studies where CoQ10 significantly lowered blood pressure in people with hypertension.[19,20,21,22] All of these studies used at least 50 mg of CoQ10 taken twice daily. You should expect about 10 weeks of supplementation to pass before look for results.

Breast Cancer

Biochemical, biomedical and clinical research on CoQ10 and its relationship to treating cancer has evolved internationally over 35 years. Some

interesting research published in a scientific journal in 1995 discussed three specific breast cancer patients who underwent a conventional protocol of therapy which included 390 mg of CoQ10.

In one 44-yearold patient, the numerous liver metastases "disappeared," and no signs of metastases were found elsewhere. Another 49 year-old patient revealed no signs of tumor in the pleural cavity after six months, and her condition was excellent. A 75-year-old patient with carcinoma in one breast showed no cancer in the tumor bed or metastases after lumpectomy and 390 mg of CoQ10 daily.[23]

Of course it's great to quote a few isolated cases where breast cancer patients responded well to CoQ10 therapy, but have there been positive results when CoQ10 was given to larger groups of patients? As a matter of fact, yes. Thirty-two typical patients with breast cancer, aged 32-81 ears and classified 'high risk' because of tumor spread to lymph nodes, where studied for 18 months following the administration of a special dietary supplement program.

The supplement program included a combination of antioxidants including vitamin C, Vitamin E, beta-carotene, selenium, essential fatty acids, and 90 mg of CoQ10 daily. The results of the study were: 1) none of the patients died during the study period (the expected number was four); 2) none of the patients showed signs of further distant metastases; 3) quality of life was improved (no weight loss, reduced use of pain killers); 4) six patients showed apparent partial remission.[24]

Interestingly, in a subsequent follow-up study, one of the aforementioned six patients who showed partial remission had her dose increased to 390 mg daily. In one month, the tumor was no longer palpable, and in another month, mammography confirmed the absence of tumor. Another patient who had non-radical surgery still had residual tumor in the tumor bed. She was treated with 300 mg of CoQ10, and in 3 months was in excellent clinical condition and there was not residual tumor tissue.[25]

Diabetes

Research has shown that some diabetic patients who use diet to control their blood sugar may have a deficiency of CoQ10, which may be further exacerbated by certain commonly used anti-diabetic drugs. Such a deficiency of CoQ10 in the pancreas could impair aspects of energy metabolism, and the biosynthesis of insulin.[26] Other research has also demonstrated that CoQ10 levels are lower in diabetic patients, which can cause diabetic cardio-myopathy. That same research, however, also showed that the diabetic cardio-myopathy can also be reversed by CoQ10 supplementation.[27] And speaking of a cardiac condition, research has also demonstrated that CoQ10 exhibits an effective anti-arrhythmic (i.e., prevents abnormal heart beat) in patients with diabetes.[28]

A newly discovered form of diabetes is referred to as maternally inherited diabetes mellitus and deafness (MIDD). The characteristic clinical features of MIDD are progressive worsening of insulin secretion and, as the name would suggest, neuro-sensory deafness and maternal inheritance. After three years of treatment with CoQ10 therapy on MIDD patients, however, prevented progressive hearing loss and improved blood sugar metabolites after exercise. Furthermore, there were no side effects during therapy.[29]

Periodontal Disease

Did you know that in Japan, over half the dentists recommend supplements of CoQ10, for periodontal and gum disease? There is are very good reasons for this. First of all, research has shown that patients with periodontal disease have a deficiency of 20-63% of CoQ10 activity in their gums.[30] Secondly, treatment with CoQ10 in periodontal patients resulted in significant improvement in their condition.[31] The reason that CoQ10 works may have to do with an ability to inhibit bacterial growth due to improved oxygen metabolism at the cellular level (bacteria often do not survive in the presence of oxygen).

Lifespan

One study demonstrated that low dosages of CoQ10 reduce oxidation and DNA double-strand

breaks, and a combination of a diet rich in polyunsaturated fatty acids and CoQ10 supplementation leads to a longer lifespan in rats. Coles and Harris demonstrated an extension in the lifespan of rats when they were given CoQ10 supplementation. But multiple studies have since found no increase in lifespan or decrease in aging in mice and rats supplemented with CoQ10.Another study demonstrated that CoQ10 extends the lifespan of C. elegance (nematode).[32]

Anti-Aging

A 2013 study that characterizes an aspect of aging due to a nucleic communication breakdown with mitochondria inherently postulates a novel approach for CoQ10 as an anti-aging factor, being that it facilitates mitochondria in energy production, thereby reversing the aging effect resulting from nutrient-deprived mitochondria, likened to the findings of non-functioning mitochondria as described in the study.[33,34]

Boosting Energy Levels

CoQ10 can also boost energy levels, increase stamina, and reduce fatigue. Dr. Langsjoen described 16 patients ranging from 80 to 88 years old who took an average of 220 mg of CoQ10 daily (range of 60 to 480 mg daily).

The patients were in generally good health for their age except for fatigue and laboured breathing when doing physical work. After three months, all of the patients stated that they felt better and had less fatigue after physical exertion. The benefits lasted for as long as the patients took CoQ10 supplements—for several years—and the patients' heart function improved as well.

Recent studies have confirmed that CoQ10 supplements boost energy levels and enhance stamina. In one study, Japanese researchers reported that people were able to cycle faster and achieved quicker recovery times after just one week of taking 300 mg of CoQ10 daily.

Another study, conducted at Baylor University in Waco, Texas, also found that both trained and untrained men and women had greater endurance after taking 200 mg of CoQ10 for two weeks.[35, 36.]

Chronic Fatigue Syndrome

Just recently, a team of European doctors reported that low levels of CoQ10 were common in 58 people with chronic fatigue syndrome (CFS). All of the CFS patients had abnormally low CoQ10 levels, and almost half of them had CoQ10 levels below the lowest level found in healthy patients. More evidence: CFS patients risk dying of heart failure 25 years earlier than people in the general population, another link that points to low CoQ10 levels.[36]

Neurological Diseases

Brain cells also require large amounts of energy, and CoQ10 can benefit some neurological disorders. A study conducted at 10 U.S. hospitals discovered that CoQ10 supplements reduced the symptoms and slowed the progression of Parkinson's disease. Eighty patients were given 300, 600 or 1,200 mg of CoQ10 or placebos daily for sixteen weeks. All of the patients taking CoQ10 had less severe symptoms than those in the placebo group. The highest dose of CoQ10 provided the greatest benefits. Inherited ataxias, another type of neurological disease, affect coordination and arm and leg function. Researchers reported that taking 300 to 3,000 mg of CoQ10 daily helped patients with hereditary ataxias, improving their strength and coordination, and reducing the frequency of seizures. A separate study of 77 patients with Friedreich ataxia found that a combination of 400 mg of CoQ10 and 2,100 IU of natural vitamin E led to a significant reduction in symptoms.[37,38]

Migraines and Tinnitus

Peter S. Sandor, M.D., of University Hospital, Zurich, Switzerland, treated 42 patients with a history of migraines, giving them either CoQ10 (100 mg, three times daily) or placebos. After three months, half the patients taking CoQ10 had fewer and shorter headaches and less headache-related nausea. Hardly anyone in the placebo group improved. Other studies have found similar benefits. Meanwhile, other research has found that CoQ10 (100 mg, three times daily) may help people with chronic ringing or buzzing in the ears.[39]

Parkinson Disease

A study in 2002 was carried out by the Parkinson's Study Group, a group of Parkinson's experts working in the USA and Canada. It involved 80 participants in ten centres around the SA. Participants had been diagnosed with Parkinson's within five years of beginning the trial and had received no drug treatment for their symptoms up to that point.

The researchers were concerned that they should not attribute a symptomatic benefit to CoQ10 when it might in fact be coming from another drug or treatment. Participants were randomly selected to receive a placebo (an inactive pill given to compare the effects of those receiving treatment with those who are not), or doses of 300, 600 or 1200mg of CoQ10 daily. They remained in the trial for a maximum of 16 months, or until such time as they required drug treatment.

The study was designed to measure the progression of Parkinson's. This was done by measuring movement difficulty or disability. Participants were measured according to a commonly used scale known as the Unified Parkinson's Disease Rating Scale (UPDRS), prior to and at regular intervals during the study.

This scale measures motor abilities, mental function, mood and independence in activities of daily living, such as dressing, feeding or washing. A higher score on the UPDRS means a greater amount of difficulty in performing tasks, and can be assumed to imply an accelerated progression of the condition. In the study, differences in scores between the four groups of participants began to emerge clearly after eight months.

Those people who were receiving doses of 300mg or 600mg had scores that were equivalent to or lower than those who were receiving a placebo. However, the scores for people receiving doses of 1200mg were significantly lower than the placebo group, implying a significantly slower rate of progression. This pattern of disability reduction continued until the end of the study. Benefits were seen for people receiving large doses of CoQ10 primarily in mental function, mood and activities of daily living, while the beneficial effect on motor function was not significant. The researchers estimated a 44% reduction in disability among these people, compared with the placebo group.

They argue that CoQ10 could not be merely having a beneficial effect on the symptoms of Parkinson's, as this would have been seen in the initial checkups given to participants after the first month. If any side effects were reported, these were mostly mild and none of the participants required a reduction in their dose. Occasional mild stomach upsets occurred, but these were usually alleviated by taking CoQ10 with meals. The number of people reporting side effects was not significantly different in any of the groups, including the placebo group.[40,41,42]

Adverse Effects

Documented adverse effects include nausea, upper abdominal pain, rashes, dizziness, sensitivity to light, irritability, fatigue, headache, heartburn. In doses over 100mg, if taken in the evening, Coenzyme Q10 may cause mild insomnia as it may raise energy levels six to eight hours after being taken.[43,44,45]

Drug Interactions

Antidepressants, Tricyclic/Phenothiazines

Might inhibit enzymes in the heart that are dependent on coenzymes Q10. This may contribute to the cardiac toxicity.[46]

Antihypertensive Drugs

Certain anti-hypertensives drugs (hydralazine, clonidine, and hydrochlorothiazide) can inhibit enzymes depend on coenzyme Q10, but only shown in animals studies.[46]

Beta-Blocker

Some beta-blocker, particularly propranolol inhibit coenzyme Q10 dependent enzymes in the myocardium. Preliminary evidence suggests that this inhibition contribute to the negative inotropic effects of beta-blockers. Advice patients only to use coenzyme Q10 supplements with the advice of their physician.[46]

Chemotherapeutic Agents

Inhibition of coenzyme Q10 dependent enzymes contribute to the cardio-toxic effects associated with doxorubicin.[46]

Hypoglycemic Agents

Evidence has shown that some hypoglycemia agents can inhibit enzymes that are dependent on coenzymes Q10. [46]

Insulin

Advice patients there is chance that coenzyme Q10 might affect blood glucose levels.[46]

Warfarin

Coenzyme is chemically similar to menaquinone and may have vitamin K-like pro-coagulant effects. Therefore, it is advised to closely monitor patients taking both warfarin and coenzyme Q10.[46]

Drug-Disease Interactions

Biliary Obstruction, Hepatic Insufficiency

Coenzyme Q10 plasma levels can increase in patients with biliary obstruction or hepatic insufficiency.[46]

Hypotension, Hypertension

Coenzyme Q10 has been associated with lowering blood pressure. It can have synergistic effects with other antihypertensive medications.[46]

Smokers

Tobacco smoke can deplete body stores of coenzyme Q10.[46]

Other Safety Issues

For most adults, coenzyme Q10 is tolerated well and safe.

However, it can cause some mild side effects including stomach upset, loss of appetite, nausea, and diarrhoea. It also might lower blood pressure, so it is recommended to monitor blood pressure closely of those with low blood pressure.

Dividing the total daily dose into two or three smaller doses a day can help reduce side effects.[46]

CONCLUSION

Coenzyme Q10 exerts beneficial therapeutic effects reducing defects in energy metabolism and oxidative damage play a role in the pathogenesis of neurodegenerative diseases. Coenzyme Q10 supplementation reduces the degenerative symptoms of cardiovascular diseases, neurodegenerative diseases, cancer, diabetes, and metabolic deficiencies. Coenzyme Q10 supplementation has been shown to be a useful adjunct to conventional medical therapy for congestive heart failure. Coenzyme Q10 is required for mitochondrial ATP synthesis and functions as an antioxidant in cell membranes and lipoproteins. Coenzyme Q10 is required for efficient cellular energy metabolism. Coenzyme Q10 is required for maximal antioxidant effects during energy metabolism. Coenzyme Q10 oral dose increases plasma, lipoprotein, blood vessel and tissue levels.

REFERENCES

1. Crane, F. L., Hatefi, Y., Lester, R. I., & Widmer, C. (1957). Isolation of a quinone from beef heart mitochondria. *In: Biochimica et Biophysica Acta*, 25, 220-221.
2. Ernster, L., & Dallner, G. (1995). Biochemical, physiological and medical aspects of ubiquinone function. *Biochimica et Biophysica Acta*, 1271(1), 195–204.
3. Dutton, P. L., Ohnishi, T., Darrouzet, E., Leonard, M. A., Sharp, R. E., Cibney, B. R., Daldal, F., & Moser, C. C. (2000). 4 Co-enzyme Q oxidation reduction reactions in mitochondrial electron transport. In Kagan, VE, Quinn, PJ. Coenzyme Q: *Molecular mechanisms in health and disease*. *Boca Raton*: CRC Press. pp. 65–82.
4. Rauchova, H., Drahota, Z., & Lenaz, G. (1995). Function of coenzyme Q in the cell: Some biochemical and physiological properties. *Physiological Research*, 44, 209-16.
5. Bhagavan, H. N., & Chopra, R. K. (2006). Coenzyme Q10: Absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radical Research*, 40(5), 445–53.

6. Tomono, Y., Hasegawa, J., Seki, T., Motegi, K., & Morishita, N. (1986). Pharmacokinetic study of deuterium-labelled coenzyme Q10 in man. *International Journal of Clinical Pharmacology, Therapy, and Toxicology*, 24 (10), 536–41.
7. Ernster, L., & Dallner, G. (1995). Biochemical, physiological and medical aspects of ubiquinone function. *Biochimica et Biophysica Acta*, 1271, 195-204.
8. Crane, F. L. (2001). Biochemical functions of coenzyme Q10. *Journal of the American College of Nutrition*, 20, 591-598.
9. Nohl, H., Kozlov, A. V., Stanick, K., & Gille, L. (2001). The multiple functions of coenzyme Q. *Bioorganic Chemistry*, 29, 1-13.
10. Pepping, J. (1999). *American Journal of Health-System Pharmacy*, 56, 519-521.
11. Greenberg, S., Frishman, W. H. (1990). *Journal of Clinical Pharmacology*, 30(7), 596-608.
12. Singh, R. B. (1998). *Cardiovascular Drugs and Therapy* 12(4), 347-53.
13. Karlsson, J. (1991). *Annals of Medicine*, 23(3), 339-44.
14. Kamikawa, T. (1985). *American Journal of Cardiology*, 56 (4), 247-51.
15. Soja, A. M., & Mortensen, S. A. (1997). *Ugeskr Laeger*, 159(49), 7302-8.
16. Munkholm, H., Hansen, H. H., Rasmussen. K. (1999). *Biofactors*, 9(2-4), 285-9.
17. Sinatra, S. T. (1997). *Connecticut Medicine*, 61(11), 707-11.
18. Digiesi, V., et al, *Current Therapeutic Research*, (1992) 51:668–72.
19. Folkers, K., et al., (1981). *Research Communications in Chemical Pathology and Pharmacology*, 31, 129–40.
20. Langsjoen, P., et al., (1994). *Molecular Aspects of Medicines*, (Suppl), S265–72.
21. Digiesi, V., et al, (1994). *Molecular Aspects of Medicines*, 15(Suppl), S257–63.
22. Digiesi, V., Cantini, F, & Brodbeck, B. (1990). *Current Therapeutic Research*, 47, 841–45.
23. Lockwood, K., et al, (1995). *Biochemical and Biophysical Research Communications*, 212(1):172-7.
24. Lockwood, K., et al, (1994). *Molecular Aspects of Medicine*, 15, s231-40.
25. Lockwood, K., Moesgaard, S., & Folkers, K. (1994). *Biochemical and Biophysical Research Communications*, 199(3), 1504-8.
26. Kishi, T., et al., (1976). *J Med*, 7(3-4), 307-21.
27. Miyake, Y., et al, (1999). *Arzneimittelforschung*, 49(4), 324-9.
28. Fujioka, T., Sakamoto, Y., Mimura, G. (1983). *Tohoku Journal of Experimental Medicine*, 141, 453-63.
29. Suzuki, S. (1998). *Diabetologia*, 41(5), 584-8.
30. Hansen, I. L., et al, (1976). *Research Communications in Chemical Pathology and Pharmacology*, 14(4), 729-38.
31. Wilkinson, E. G., Arnold, R. M., & Folkers, K. (1976). *Research Communications in Chemical Pathology and Pharmacology*, 14(4), 715-9.
32. Mizuno, K., Tanaka, M., & Nozaki, S. (2008). Antifatigue effects of coenzyme Q10 during physical fatigue. *Nutrition*, 24, 293-299.
33. Cooke, M., Iosia, M., & Buford, T. (2008). Effects of acute and 14-day coenzyme Q10 supplementation on exercise performance in both trained and untrained individuals. *Journal of International Society of Sports Nutrition*, 5, 8.
34. Maes, M., Mihaylova, I., & Kubera, M. (2009). Coenzyme Q10 deficiency in myalgic encephalomyelitis /chronic fatigue syndrome (ME/CFS) is related to fatigue,

autonomic and neurocognitive symptoms and is another risk factor explaining the early mortality in ME/CFS due to cardiovascular disorder. *Neuroendocrinology Letters*, 30, epub ahead of print.

35. *Mayo Clinic Drugs and Supplements: Coenzyme Q10*. Retrieved 13 November 2008.
36. *Results for Orphan Drug Product Designations Search*. Retrieved 12 May 2013.
37. Shults, C. W., Oakes, D., & Kieburtz, K. (2002). Effects of coenzyme Q10 in early Parkinson disease. Evidence of slowing of the functional decline. *Archives of Neurology*, 59, 1541-1550.
38. Musumeci, O., Naini, A., & Slonim, A. E. (2001). Familial cerebellar ataxia with muscle coenzyme Q10 deficiency. *Neurology*, 56, 849-855.
39. Hershey, A. D., Powers, S. W., & Vockell, A. L. B. (2007). Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. *Headache*, 47, 73-80
40. Shults, C. W. (2002). Effects of Coenzyme Q10 in Early Parkinson Disease: Evidence of Slowing of the Functional Decline. *Archives of Neurology*, 59, 1541–1550.
41. Muller, T. (2003). Coenzyme Q10 supplementation provides mild symptomatic benefit in patients with Parkinson's disease' *Neuroscience Letters*, 341, 201–204.
42. Shults, C. W. (2005) 'Therapeutic role of coenzyme Q10 in Parkinson's disease (review)', 107, 120–130.
43. Baggio, E., Gandini, R., Plancher, A. C., Passeri, M., & Carmosino, G. (1994). Italian multicenter study on the safety and efficacy of coenzyme Q10 as adjunctive therapy in heart failure. CoQ10 Drug Surveillance Investigators. *Molecular Aspects of Medicine*. 15, s287-94.
44. 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. *Movement Disorders*. 11 (3), 321-3.
45. Pepping, J. (1999). Coenzyme Q10. *American Journal of Health System-Pharmacy*. 56 (6), 519-21.
46. *Natural Medicines comprehensive database. COENZYMES Q10 monograph*. Available at: http://www.naturaldatabase.com. Accessed January 22, 2003.

