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Coenzyme Q۱۰; Importance, Effective Sources and Improving its Bioavailability

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ABSTRACT

Coenzyme Q۱۰ (CoQ۱۰), a lipid-soluble endogenous pro-vitamin found naturally in the mitochondria, is present in many organisms. It has crucial roles in many biochemical pathways and important health functions. It has an essential role as a vital intermediate of the electron transport system in mitochondria. CoQ۱۰, as an electron and proton carrier for energy coupling leads to adenosine triphosphate (ATP) formation. CoQ۱۰ also acts as a potent antioxidant and scavenger of reactive oxygen species and is involved in multiple aspects of cellular metabolism. Furthermore, in medicine, the pharmacological use of CoQ۱۰ has received increasing attention following the reports of its benefits in treating cardiovascular and degenerative neurologic diseases. CoQ۱۰ is a hydrophobic compound with a molecular weight of ۸۶۳ Da. The long isoprenoid side chain is responsible for its water insolubility. Because of its hydrophobicity, its bioavailability is low and application of CoQ۱۰ in aqueous foods and drugs is limited. Various approaches such as emulsion and nanoemulsion formulations have been developed to improve its water solubility. CoQ۱۰ is found in plants such as soya bean, peanut, palm oil and litchi pericarp and in animals such as pelagic fish, beef and pork hearts. Various analytical methods have been published for the extraction and analysis of CoQ۱۰ from different matrices. The most common methods for extracting CoQ۱۰ from different samples are liquid–liquid or ultrasound extraction. CoQ۱۰ also can be produced by chemical synthesis and microbial fermentation. Microbial production offers an environmentally benign option based on the enzymatic catalysis at

the cellular level for CoQ۱۰ assembly. Moreover, this approach is attractive to the industry because the process is easy to control at a relatively low production cost. This review provides an overview of CoQ۱۰ importance, health benefits and its effective sources. Improving of CoQ۱۰ bioavailability are also discussed and future growth prospects and recommendations are also given for areas of future research.

KEYWORDS: CoQ۱۰, adenosine triphosphate (ATP), mitochondrial enzymes, bioavailability, microbial fermentation

INTRODUCTION

Coenzyme Q۱۰ (۲،۳ dimethoxy, ۵-methyl, ۶-decaprenyl benzoquinone, CoQ۱۰), a lipid-soluble endogenous pro-vitamin found naturally in the mitochondria, is present in many organisms (Xue, ۲۰۱۲). Coenzyme Q۱۰ (CoQ۱۰), also known as ubiquinone or ubiquinone-۱۰, and its active form is ubiquinol, occurs widely in animals, plants, and the cells of microorganisms (Yuan etal., ۲۰۱۲). It plays a crucial role in the transfer of electrons between respiratory complexes of the electron transport chain, located within the inner mitochondrial membrane (Cluis etal. ۲۰۱۲). Coenzymes are cofactors upon which the comparatively large and complex enzymes absolutely depend for their function. CoQ۱۰ is the coenzyme for at least three mitochondrial enzymes (complexes I, II and III) as well as enzymes in other parts of the cell. Mitochondrial enzymes of the oxidative phosphorylation pathway are essential for the production of the high-energy phosphate, adenosine triphosphate (ATP), upon which all cellular functions depend. Mitochondria, specialized compartments present in every cell of the body (except red blood cells), produce ۹۰٪ of the energy needed to support growth and sustain life [Marin, ۲۰۱۵]. Recently CoQ۱۰ has received great attention for its application as therapeutic agent as well as in related fields such as a potential antioxidant (Tokdar etal., ۲۰۱۴). Despite of many advantages of CoQ۱۰, because of its hydrophobicity, application of CoQ۱۰ in aqueous foods and drugs is limited and its bioavailability is low. Various approaches such as emulsion and nanoemulsion formulations have been developed to improve its water solubility.[]

CoQ۱۰ is naturally produced in the body, but its levels decrease as we age and may be low in people with cancer, genetic disorders, diabetes, heart problems, and Parkinson's disease. Symptoms of CoQ۱۰ deficiency include heart failure, high blood pressure, and chest pain. CoQ۱۰, can be produced by chemical synthesis, extraction from biological tissues (plants and animal). CoQ۱۰ is naturally present in small amounts in a wide variety of foods, but is particularly high in organ meats such as heart, liver and kidney, as well as beef, soy oil, sardines, mackerel, and peanuts (Langsjoen, ۱۹۹۴). CoQ۱۰ can also be produced by microbial fermentation including bacteria, molds, yeasts, etc. Microbial biosynthesis offers several advantages over chemical synthesis and extraction including specificity towards the all-trans biologically active isomer of CoQ۱۰, and the reduced production of environmentally hazardous waste based on the enzymatic catalysis at the cellular level for CoQ۱۰ assembly, (Cluis, ۲۰۱۲).

The present study aimed to discuss about importance, benefits of CoQ۱۰ and also its effective sources. Moreover, improving of CoQ۱۰ bioavailability was mentioned and future growth prospects and recommendations were given for areas of future research.

CHEMICAL NATURE AND PROPERTIES OF CoQ۱۰

In the body CoQ۱۰ exists in either an oxidized (ubiquinone) or reduced form (ubiquinol and hydroquinone). Mainly in its reduced form, CoQ۱۰ is also known as a very effective antioxidant (Pravst et al., ۲۰۱۰). The chemical structure of CoQ۱۰, elucidated by Dr. Karl Folkers and his group. Fig. ۱ shows chemical structures of ubiquinone and ubiquinol and properties of them are summarized in table ۱.

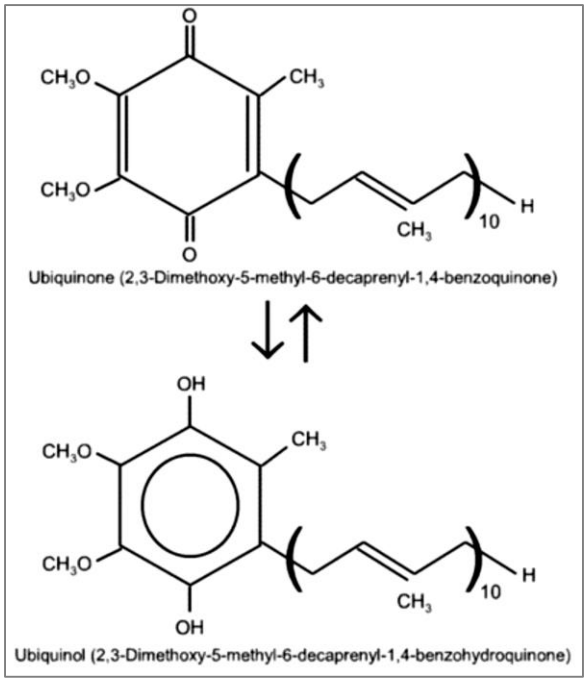

Fig. ۱. Structures of CoQ۱۰; Ubiquinone (۲،۳-dimethoxy-۵-methyl-۶-decaprenyl-۱،۴-benzoquinone) and ubiquinol (۲،۳-dimethoxy-۵-methyl-۶-decaprenyl-۱،۴-benzohydroquinone)

Table ۱. Properties of Ubiquinone (CoQ۱۰) and Ubiquinol (CoQ۱۰ H۲)

	Ubiquinone (CoQ۱۰)	Ubiquinol (CoQ۱۰ H۲)
Appearance	Orange crystals (at room temperature)	White to very pale yellow crystalline powder
Empirical formula	$C_{۵۹}H_{۹۰}O_{۴}$	$C_{۵۹}H_{۹۲}O_{۴}$
Molecular weight	۸۶۳،۳۵۸	۸۶۵،۳۷
Melting point	۴۹۰ °C	۴۹۵□C
Solubility	Insoluble in water Limited solubility in oils and fats Soluble in nonpolar solvents	Practically insoluble in water. Limited solubility in oils and fats. Soluble in nonpolar solvents.

IMPORTANCE OF COQ۱۰

For several years, the study of CoQ۱۰ in foodstuffs and animal tissue has attracted special attention owing to its crucial roles in many biochemical pathways and important health functions (Rodriguez, ۲۰۰۶). CoQ۱۰ is the coenzyme for at least three mitochondrial enzymes (complexes I, II and III). CoQ۱۰ as shown in Fig. ۲ is a core component of cellular energy production and respiration, shuttling electrons down the electron transport chain to produce the key energy-rich molecule ATP. Due to its involvement in ATP synthesis, CoQ۱۰ affects the function of every cell in the body, making it important for the health of all tissues and organs. CoQ۱۰ has been shown to have quite powerful antioxidant potential. Therefore, it can effectively defend against reactive oxygen species and free radical damage, protects the body from damage caused by harmful molecules (Ruiz, ۲۰۰۷) through protecting membranes and proteins from oxidation by scavenging free radicals and by regenerating pools of tocopherols (Cluis, ۲۰۱۲). There is evidence that CoQ۱۰ is involved in the transcriptional regulation of genes, some of which play roles in inflammatory responses and in cholesterol metabolism (Schmelzer et al, ۲۰۰۷).

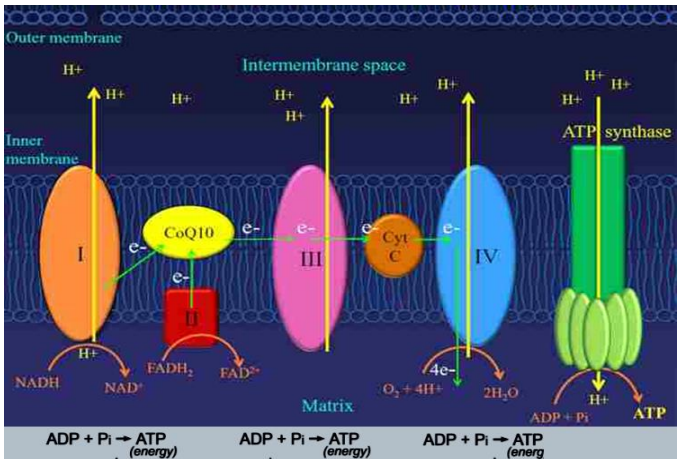

Fig. ۲. Central role of CoQ۱۰ in electron transport chain

Health benefits and clinical conditions of CoQ۱۰

CoQ۱۰ is naturally produced in the body, but its levels decrease as we age and may be low in people with cancer, genetic disorders, diabetes, heart problems, and Parkinson's disease. Symptoms of CoQ۱۰ deficiency include heart failure, high blood pressure, and chest pain. On the other hand, the concentration of CoQ۱۰ in the body decreases year by year, indicating that it has a close relationship with aging (Fig. ۲.). For these reasons, some people rely on CoQ۱۰ supplements. The daily intake of CoQ۱۰ is suggested as ۱۲ mg kg^{-1} (Rujiralai, ۲۰۱۴).

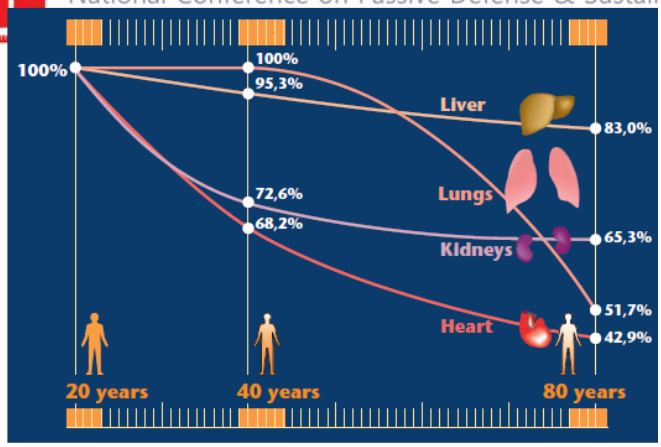

Fig. ۳. CoQ۱۰ decline with age (Littarru and Lambrechts, ۲۰۱۱)

Nowadays, in medicine, the pharmacological use of CoQ۱۰ has received increasing attention following the reports of its benefits in treating cardiovascular and degenerative neurologic diseases (Weant and Smith, ۲۰۰۵). Recently, some natural health products and commercial nutraceutical supplements containing CoQ۱۰ have gained increasing popularity in health management [Buettner et al., ۲۰۰۷].

There is a large body of data on the beneficial effects of CoQ۱۰ supplementation in various disease states. CoQ۱۰ supplements have been demonstrated to have positive effects on patients suffering from certain cardio-vascular conditions (such as conjunctive heart failure, congestive heart failure, angina pectoris, arrhythmias, mitral valve prolapse, hypertension, atherosclerosis and cardiotoxicity) and neurodegenerative diseases (such as Huntington, parkinson, alzheimer) (Hodgson et al., ۲۰۰۲; Yang et al., ۲۰۱۰).

It has been proved that CoQ۱۰ helps treat muscular dystrophy, amyotrophic lateral sclerosis, neuromuscular, mitochondrial cytopathies, ataxias, diabetes, cancer, chronic obstructive pulmonary disease, asthma, migraine, immune disorders, HIV/AIDS, chronic fatigue syndrome, male infertility and periodontal disease. It is also said to boost energy and speed recovery from exercise. Some people take it to help reduce the effects certain medicines can have on the heart, muscles, and other organs. Furthermore, early research has suggested that CoQ۱۰ supplementation may benefit patients suffering from male infertility, neurodegenerative disease and diabetes-associated nephropathy (Yang etal., ۲۰۱۰; Mancini and Balercia ۲۰۱۱)

CoQ۱۰ is a hydrophobic compound with a molecular weight of ۸۶۳ Da. The long isoprenoid side chain which is responsible for its water insolubility (<۴ ng/mL) generates yellow color. Because of its hydrophobicity, application of CoQ۱۰ in aqueous foods and drugs is limited and its bioavailability after intake is low (Kim etal., ۲۰۱۲). In addition to insolubility in water, the solubility of CoQ۱۰ in lipids is also limited and CoQ۱۰ is thus very poorly absorbed (Pravst et al., ۲۰۱۰). The literature is flooded with the various reports regarding the modification of physiochemical properties to improve its oral bioavailability. There have been various approaches to improve water solubility of CoQ۱۰. Among those, emulsion formulations of CoQ۱۰ using additives have been largely studied. Latest technical developments reveal that encapsulation of CoQ۱۰ in nanoemulsions results in a significantly enhanced bioavailability ((Kim etal., ۲۰۱۲). In addition, multiple nanoemulsions prepared according to a patented process even allow the administration of several incompatible substances at the same time. In the formation of nanoemulsions and nanoparticles mechanical processing, such as ultrasound, high pressure, homogenisation and microfluidization are common techniques (Cheuk etal.,, ۲۰۱۵). Schematic models of various novel forms of CoQ۱۰ is presented in fig.۳.

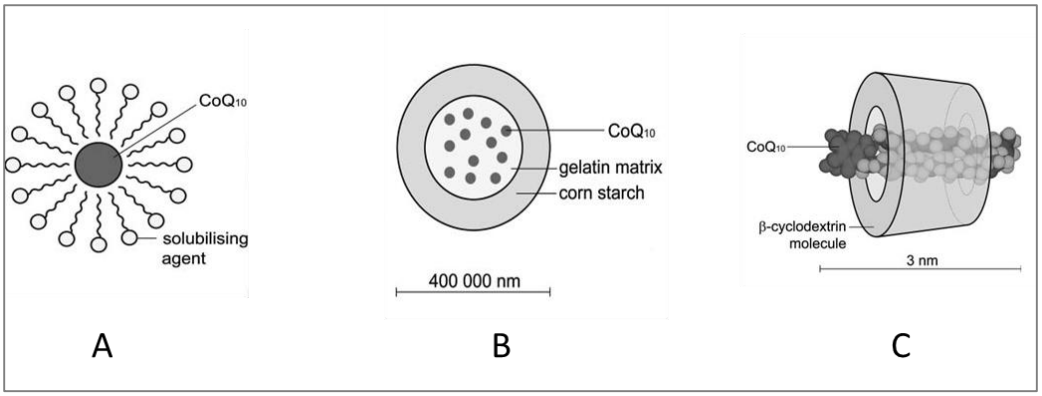

Fig.۴. Schematic models of various novel forms of CoQ۱۰: (A) nanomicelles, (B) CoQ۱۰ beadlets finely dispersed in a water-soluble fish gelatine matrix and coated with starch-based granules (C) CDQ۱۰ - inclusion complex of CoQ۱۰ in *β*-cyclodextrin (Pravst et al., ۲۰۱۰)

The increased water-solubility of otherwise insoluble compounds not only allows the fortification of aqueous based products but also contributes to their improved absorption, which is a common pharmaceutical strategy (Pravst et al., ۲۰۱۰)

CoQ۱۰ EFFECTIVE SOURCES

CoQ۱۰ can be produced by chemical synthesis, extraction from biological tissues (plants and animal) and microbial fermentation (Laplante et al., ۲۰۰۹). CoQ۱۰ compounds are widely distributed in nature, from microorganisms to plants and animals.

Animal products such as beef, pork and chicken are relatively good sources of CoQ۱۰. As a general rule, tissues with high energy demands contain relatively high amounts of CoQ۱۰. It is particularly high in organ meats such as heart, liver and kidney, CoQ۱۰ is naturally present in small amounts in a wide variety of foods, but it is high in soy oil, palm oil, sardines, mackerel, and peanuts (Langsjoen, ۱۹۹۴). Among foods of plant origin, broccoli and spinach contain significant amounts of CoQ۱۰.

Table ۱- Overview of CoQ۱۰ contents in va rious foods (Pravst et al., ۲۰۱۰)

Food	CoQ_{10} concentration [mg/kg]	Food	CoQ_{10} concentration [mg/kg]
Beef		**Nuts**	
heart	۱۱۳	peanuts	۲۷
liver	۳۹–۵۰	walnuts	۱۹
muscle	۲۶–۴۰	sesame seeds	۱۸–۲۳
Pork		pistachio nuts	۲۰
heart	۱۱,۸–۱۲۸,۲	hazelnuts	۱۷
liver	۲۲,۷–۵۴,۰	almond	۵–۱۴
muscle	۱۳,۸–۴۵,۰	**Vegetables**	
Chicken		parsley	۸–۲۶
heart	۱۱۶,۲–۱۳۲,۲	broccoli	۶–۹
Fish		cauliflower	۲–۷
sardine	۵–۶۴	spinach	up to ۱۰

mackerel		grape	۶–۷
red flesh	۴۳–۶۷	Chinese cabbage	۲–۵
white flesh	۱۱–۱۶	**Fruit**	
salmon	۴–۸	avocado	۱۰
tuna	۵	blackcurrant	۳
Oils		strawberry	۱
soybean	۵۴–۲۸۰	orange	۱–۲
olive	۴–۱۶۰	grapefruit	۱
grapeseed	۶۴–۷۳	apple	۱
sunflower	۴–۱۵		

MICROBIAL SOURCES OF COQ۱۰

CoQ۱۰ can be produced by microbial fermentation including bacteria (e.g. *Agrobacterium*, *Paracoccus*, *Cryptococcusi*, *Rhodobacter*, *Tricosporon*), molds (e.g. *Neurospora*, *Aspergillus*), yeasts (e.g. *Candida*, *Sporidobolus*, *Rhodotorula*), etc. Moreover, presence of CoQ۱۰ in *Artemia* samples as a Crustacean was investigated (Rujiralai, ۲۰۱۴). Microbial production offers an environmentally benign option based on the enzymatic catalysis at the cellular level for CoQ۱۰ assembly. Moreover, this approach is attractive to the industry because the process is easy to control at a relatively low production cost (Tokdar et al., ۲۰۱۴). However, due to the limits of CoQ۱۰ accumulation in cells, strain improvements have been made using genetic engineering (using recombinant nucleic acid technology), chemical mutagenesis, and high hydrostatic pressure treatment (Kim et al., ۲۰۱۵).

CONCLUSION AND FUTURE TRENDS

CoQ۱۰, a lipid-soluble endogenous pro-vitamin found naturally in the mitochondria, is present in many organisms. It has crucial roles in many biochemical pathways and important health functions. Levels of CoQ۱۰ decrease as we age and may be low in people with cancer, genetic disorders, diabetes, heart problems, and Parkinson's disease. For these reasons, some people rely on CoQ۱۰ supplements. CoQ۱۰ is a hydrophobic compound with a long isoprenoid side chain which is responsible for its water insolubility, application of CoQ۱۰ in aqueous foods and drugs is limited and its bioavailability is low. So developing various approaches to improve its water solubility could also be evaluated in the future. Also, it is important to establish a suitable extraction and analysis method for determining the content of CoQ۱۰ in different sources including foods and microorganisms. Moreover, types of reactors that provides high cell concentrations, high productivity, and easy separation of the products for development of CoQ۱۰ production in a better microorganism, could be determined from further research.

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