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Role of coenzyme Q10 supplemantation to improve endoplasmic reticulum stress

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ABSTRACT

Coenzyme Q10 (CoQ10) is a quinone derivative that is vital in biological systems and is one of the most preferred nutritional supplements today. Its central role in cellular metabolism is widely discussed in the literature, with its effect on mitochondrial functions being particularly critical. CoQ10 acts as a key electron carrier in the mitochondrial electron transport system (ETS), playing a crucial role in the synthesis of ATP, the cell's energy unit, through oxidative phosphorylation. In addition to this metabolic function, CoQ10 is one of the most powerful endogenous antioxidants, defending all cellular membranes against oxidative damage triggered by free radicals. Studies are investigating the complex relationship of this molecule with processes such as inflammation, apoptosis, angiogenesis, gene expression, and cellular signaling pathways. Recently, the protective effects of CoQ10 on endoplasmic reticulum stress (ERS), associated with disruption of cellular homeostasis, have begun to attract attention. Although sufficient data is not yet available in this area, the potential of KoQ10 to modulate ERS mechanisms is a promising area of research. In this review, we aim to elucidate the interaction of KoQ10 with ERS, considering the existing literature.

Keywords: Coenzyme Q10, endoplasmic reticulum stress, oxidative stress, apoptosis, chronic disease

Endoplazmik retikulum stresini iyileştirmede koenzim Q10 takviyesinin rolü

ÖZET

Koenzim Q10 (KoQ10), biyolojik sistemlerde hayati öneme sahip olan ve günümüzde en çok tercih edilen besin takviyelerinin başında gelen bir kinon türevidir. Hücre metabolizmasındaki merkezi rolü literatürde geniş bir yer tutmakla birlikte, özellikle mitokondriyal fonksiyonlar üzerindeki etkisi kritiktir. KoQ10, mitokondriyal elektron taşıma sisteminde (ETS) temel bir elektron taşıyıcısı olarak görev yaparak, hücrenin enerji birimi olan ATP'nin oksidatif fosforilasyon yoluyla sentezlenmesinde anahtar rol üstlenir. Bu metabolik görevinin yanı sıra KoQ10, tüm hücresel membranları serbest radikallerin tetiklediği oksidatif hasara karşı savunan en güçlü endojen antioksidanlardan biridir. Çalışmalar bu molekülün inflamasyon, apoptoz, anjiyogenez, gen ekspresyonu ve hücre sinyal iletim yolları gibi süreçlerle olan karmaşık ilişkisini incelemektedir. Son dönemde ise KoQ10'un, hücresel homeostazın bozulmasıyla ilişkili olan endoplazmik retikulum stresi (ERS) üzerindeki koruyucu etkileri dikkat çekmeye başlamıştır. Bu alanda henüz yeterli veri bulunmamasına rağmen, KoQ10'un ERS mekanizmalarını modüle etme potansiyeli gelecek vaat eden bir araştırma alanıdır. Bu derlemede, KoQ10'un ERS ile olan etkileşimini mevcut literatür ışığında aydınlatmayı amaçladık.

Anahtar kelimeler: Koenzim Q10, endoplazmik retikulum gerilimi, oksidatif stres, apoptoz, kronik hastalık

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INTRODUCTION

Oxidative stress is reported to play a critical role in the pathogenesis of many chronic diseases. Supplementation of CoQ10, an important antioxidant, can contribute to treating these diseases.[1,2] Additionally, recent studies have suggested that CoQ10 supplementation, which works in scavenging reactive oxygen species (ROS) and free radicals, improves general health conditions.[3,4]

The endoplasmic reticulum is an important organelle that stores calcium and directs protein translation. Therefore, it is essential to maintain endoplasmic reticulum homeostasis. Disruptions in endoplasmic reticulum homeostasis cause ERS.[5] ERS causes or promotes various diseases such as atherosclerosis, diabetes, obesity, and cancer.[6-8] Dandekar et al. suggested that there is a relationship between ERS response, oxidative stress, inflammation, and metabolic diseases.[9] However, there are not enough studies on regulating ERS by CoQ10. This review elucidates the potential role and mechanism of action of CoQ10, which is thought to ameliorate oxidative damage, in ERS management.

CoQ10

CoQ10 is a fat-soluble, vitamin-like quinone, generally known as ubiquinone, CoQ, and vitamin Q10. CoQ10 was first isolated in bovine mitochondria in 1957 and was found in the highest concentrations in organs with high energy metabolism, such as the heart, brain, liver, and kidney.[10,11] The primary source of CoQ10 consists of its endogenous biosynthesis and can be produced in all cellular organisms. A tiny proportion of CoQ10 can also be obtained from dietary sources.[12]

CoQ10 is a ubiquitous substance vital for various activities associated with energy metabolism. It is critical for the appropriate transfer of electrons within the mitochondrial oxidative respiration system, whose primary function is the production of ATP. CoQ10 is a cofactor for mitochondrial enzyme complexes that produce adenosine triphosphate in oxidative phosphorylation.[13,14] CoQ10 carries electrons from Complex I and Complex II to Complex III with redox capabilities (Figure 1).[15,16]

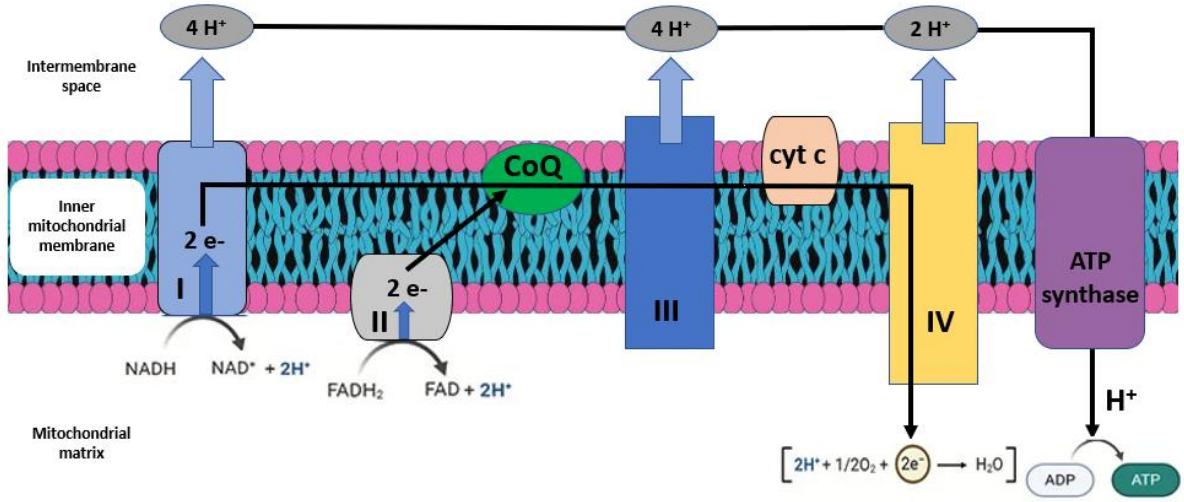


Figure 1. Role of CoQ10 in the mitochondrial electron transport system. ADP, adenosine diphosphate; CoQ10, coenzyme Q10; NADH, nicotinamide adenine dinucleotide; FAD, flavin adenine dinucleotide; $FADH_2$, reduced flavin adenine dinucleotide.

Coenzyme Q10 and Its Antioxidant Role

CoQ10 is a powerful antioxidant and plays a crucial role in protecting cells from oxidative stress damage.[10] CoQ10 has a strong antioxidant capacity, acting on the mitochondrial membrane, other cell membranes, plasma, and cytoplasm. The antioxidant abilities of CoQ10 in the electron transport system in mitochondria increase the activity of electron transport, prevent uncontrolled electron loss, and reduce and neutralize compounds by acting directly on free radicals or oxidants. CoQ10 also helps recycle other antioxidants like vitamin C or vitamin E. The antioxidant capacity of CoQ10 is due to its ability to exchange electrons as it transforms between its redox forms (Figure 2).[12]

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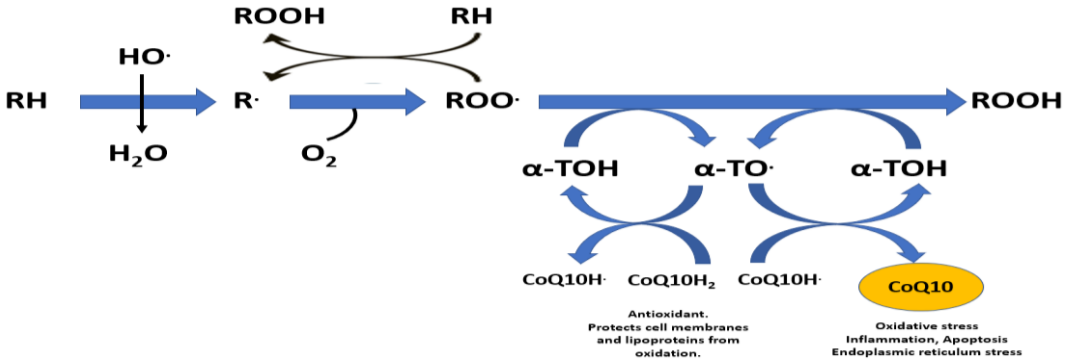


Figure 2. Antioxidant activity of CoQ10.

The reduced CoQ10 ($CoQ10H_2$) protects cell membranes and lipoproteins from oxidation. Cell membranes contain significant amounts of $CoQ10H_2$ and enzymes that can reduce oxidized CoQ10 back to $CoQ10H_2$. This suggests that $CoQ10H_2$ is an important cellular antioxidant.[16,17] $CoQ10H_2$ inhibits lipid peroxidation when LDL is exposed to oxidizing conditions. Therefore, when oxidized LDL accumulates, $CoQ10H_2$ is the first antioxidant consumed. CoQ10 can protect cell proteins and mitochondrial DNA from oxidative damage.[16,18,19] $CoQ10H_2$ also limited the consumption of α-tocopherol (Figure 2).[20]

CoQ10 is also linked to improving the function of superoxide dismutase (SOD), which is an endogenous enzymatic antioxidant that converts superoxide ions to hydrogen peroxide (H_2O_2) in cells. Endothelial nitric oxide (NO), an essential factor in vascular homeostasis, reduces platelet aggregation and inflammation. ROS produced through oxidative stress in many chronic diseases can increase NO^- production by forming peroxynitrite, a potent oxidative agent that can exacerbate oxidative stress. CoQ10, as an antioxidant, can increase SOD activity by protecting NO^- from forming prooxidant agents to preserve endothelial activity.[15]

Other Roles of CoQ10

CoQ10 downregulates the expression of important enzymes involved in lipid synthesis. CoQ10 can inhibit abnormal accumulation of hepatic lipids by acting as an AMPK activator. Therefore, it is also known as an anti-adipogenic molecule. In addition, since CoQ10 modulates the response to inflammation through NF-κB-dependent gene expression, its deficiency may lead to increased levels of NF-κB.[21]

The anti-inflammatory function of CoQ10 has been described in more detail in some studies. CoQ10 decreases the production of proinflammatory cytokines by inhibiting NF-kB gene expression.[22] CoQ10 may mediate inflammation by affecting circulating proinflammatory markers such as CRP, IL-1, IL-8, and TNF-α. In addition, it has also been noted that the levels of these markers decreased significantly after CoQ10 supplementation (100-300 mg/day for 3 months) in various diseases such as chronic kidney disease, cardiovascular disease, and polycystic ovary syndrome.[23]

CoQ10 acts directly on the endothelium, causing vasodilation and lowering blood pressure. A clinical study involving 684 people has shown that CoQ10 supplementation considerably decreased systolic blood pressure. This effect of CoQ10 is associated with its ability to improve NO bioavailability and induce vasodilation. CoQ10 also adjusts the effect of angiotensin on sodium retention and decreases aldosterone levels.[21,24]

CoQ10 Deficiency and Diseases

CoQ10 is essential for normal cellular respiration, and any reduction in its bioavailability negatively affects cell function. These changes in function, which lead to an increase in lipid peroxidation, oxidative damage, and inflammation, can lead to possible cancer initiation. Many studies also show that patients with lung, pancreas, and breast cancer have lower plasma CoQ10 levels than healthy controls.[15]

CoQ10 deficiency can cause mitochondrial electron transport system defects, impairment of cellular ATP production, and pyrimidine synthesis. Because of high energy demands, coQ10 deficiency can affect any body part, especially the brain, muscles, and kidneys. The severity of CoenzymeQ10 deficiency symptoms may vary depending on age; while severe symptoms can occur in infancy, mild symptoms may not be seen even when the person is older.[25]

CoQ10 deficiency may impair the body's defense systems against oxidative stress caused by hyperglycemia in diabetes. Studies show that patients with diabetes have significantly lower plasma CoQ10 levels than normal healthy individuals. Exogenous supplementation of CoQ10 is suggested to potentially attenuate oxidative stress-induced mitochondrial dysfunction, thus improving glycemic control in diabetes mellitus.[26-29] Furthermore, recent clinical studies link insulin resistance to decreased CoQ10 in the body and suggest that exogenous CoQ10 supplementation may restore insulin sensitivity.[30]

CoQ10 deficiency can lead to serious diseases in many organs. It can cause ataxia in the brain tissue along with many neurological symptoms. It causes nephrotic syndrome and renal dysfunction in renal tissue, ultimately leading to renal failure. In the heart tissue, it causes weakening of the heart muscle, which is characteristic of hypertrophic cardiomyopathy, due to low energy.[25]

ENDOPLASMIC RETICULUM STRESS (ERS)

ERS is a state that occurs in various physiological and pathological events and is caused by the extreme accumulation of unfolded or misfolded proteins in the endoplasmic reticulum.[31] To restore this disturbed balance in the endoplasmic reticulum lumen and eliminate stress with minimum damage, adaptive and protective pathways called unfolded protein response (UPR) become active. UPR occurs through the endoplasmic reticulum transmembrane receptor proteins PERK, ATF6, and IRE1. UPR proteins, which remain inactive when found with the "glucose regulatory protein" (GRP78) under normal conditions, become activated by separating from GRP78 when faced with stress that exceeds the endoplasmic reticulum capacity.[32] Active UPR proteins are responsible for restoring homeostasis regarding the proper production, processing, and folding of proteins. They also decrease the protein load of the endoplasmic reticulum by inhibiting protein synthesis. GRP78 reduces ERS by binding to misfolded proteins and preventing misfolding during translocation in the endoplasmic reticulum.[31]

Under long-term and severe ERS conditions, the UPR cannot restore normal cellular functions.[33] In this case, cell deaths, usually caused by apoptosis, may be triggered.[32] Increased cell death leads to loss of tissue function and can be the reason for various ERS-related diseases.[34]

Recent studies have found that ERS plays a critical role in damaging pancreatic beta cells and developing insulin resistance.[35,36] It is thought that ERS (especially together with oxidative stress and inflammation) accelerates pancreatic beta cell death and causes absolute insulin deficiency, leading to diabetes.[31,37] Several studies have also reported that ERS triggers pancreatic beta cell dysfunction and diabetes by causing an increase in misfolded proinsulin.[38-40]

ERS and Oxidative Stress

Recent studies have shown the interrelationship of ROS and ERS with redox signaling mediators such as ERO-1, PDI, glutathione/glutathione disulfide, NADPH oxidase 4, NADPH-P450 reductase, and calcium. There is increasing evidence that persistent protein misfolding and ERS initiated by ROS cascades have important roles in the pathogenesis of neurological diseases, diabetes, coronary artery disease, ischemia, and liver diseases.[41-43]

Proper folding of proteins and disulfide formation in the endoplasmic reticulum depend on the redox state within the lumen of the endoplasmic reticulum. Studies have shown that this mechanism is disrupted by ROS's effect on the protein folding process in the endoplasmic reticulum lumen.[41,42,44] PDI is an important and well-characterized enzyme of disulfide bond formation in the endoplasmic reticulum. During disulfide bond formation, ERO-1 can be oxidized by molecular oxygen, resulting in the production of H_2O_2 and the formation of oxidized glutathione from glutathione as a byproduct. Both substances disrupt the redox state of the endoplasmic reticulum lumen, leading to ERS after oxidative stress (Figure 3). Studies also show that PERK stimulates the synthesis of transcription factors such as ATF4 and Nrf2, and that these transcription factors increase glutathione production.[41]

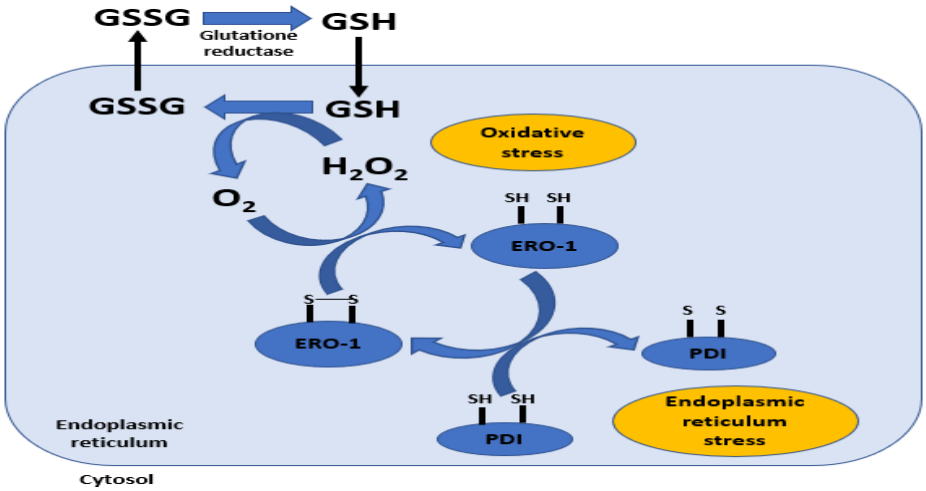


Figure 3. Endoplasmic reticulum stress and oxidative stress. ERO-1, endoplasmic reticulum oxidoreductin-1; PDI, protein disulfide isomerase, GSH, reduced glutathione; GSSG; oxidized glutathione.

CoQ10 and ERS

Although the role of CoQ10 in reducing oxidative stress is well known, its relationship with ERS has not been completely elucidated. However, considering the parallel relationship between oxidative stress and ERS, it can be thought that coenzyme Q10 has a decreasing effect on ERS.

Escribano-Lopez et al. showed that hyperglycemia increased ERS markers such as GRP78 and eIF2α, and intracellular calcium. CoQ10 supplementation reversed these effects, suggesting that this molecule ameliorates the mitochondrial disruption, which leads to ERS. These findings show that treatment with CoQ10 modulates ERS. In addition, these findings provide a better understanding of the relationship between CoQ10 and ERS.[45]

Toprak et al. applied CoQ10 supplementation to diabetic rats for 42 days in their study. According to this study, TWEAK, GRP78, ATF6, and PERK protein levels in the brain tissue were significantly lower in the diabetic group treated with CoQ10 than in the diabetic group. Again, in the same study, liver tissue GRP78 and PERK protein levels were significantly lower in the diabetic group treated with CoQ10 than in the diabetic group. These findings suggest that CoQ10 supplementation reduces ERS and may positively affect diabetic brain and liver damage.[46]

The transcription factor XBP-1 is a crucial regulator of the UPR or ERS response, activated by environmental stress factors such as protein overload that require increased endoplasmic reticulum capacity. CRT, BiP/GRP78, calnexin, and other endoplasmic reticulum Ca^{2+} binding chaperons and folding enzymes are important components of protein folding and quality control. Serrano et al. evaluated the effect on ERS by supplementing the volunteers' Mediterranean diet with CoQ10. At 2 and 4 hours after the Mediterranean diet + CoQ10, they found lower postprandial XBP-1 mRNA levels than the control diet. In addition, they found that consumption of a Mediterranean diet + CoQ10 reduced the expression of ERS-related genes (XBP-1, CRT, and BiP/GRP78). This study shows that exogenous CoQ10 supplementation, in synergy with a Mediterranean diet, has an additive effect modulating the inflammatory response and ERS in older adults. Yubero-Serrano et al. reported that CoQ10 supplementation in combination with a Mediterranean diet strongly suppressed the expression of genes encoding proteins involved in the UPR.[47]

Jiang et al. applied CoQ10 treatment via oral gavage to rats with unilateral ureteral obstruction. Western blot analysis showed that CoQ10 supplementation regulated the expression of genes controlling ERS (CHOP, IRE-1, and XBP-1S) and apoptosis (Bcl-2 and Bax).[48]

Recent clinical evidence demonstrates that CoQ10 supplementation may provide therapeutic benefits in neurodegenerative diseases due to its reducing effects on ERS. There is also much evidence demonstrating the beneficial effects of CoQ10 on levels of pro-inflammatory cytokines and ROS, which may both trigger the UPR and be effectors of pathology following activation.[49]

CONCLUSION

CoQ10 is known to play an important role in cellular energy synthesis and is also a potent antioxidant that effectively reduces oxidative stress. Considering the strong relationship between oxidative stress and endoplasmic reticulum stress, coenzyme Q10 may affect endoplasmic reticulum stress. In this article, we investigated whether coenzyme Q10 can be used as an antioxidant in endoplasmic reticulum stress, which plays a role in the pathogenesis of many chronic diseases. In some experimental studies, our research shows that coenzyme Q10 is effective against UPR proteins and reduces ERS. This suggests that coenzyme Q10 may be an important exogenous supplement in treating chronic diseases.

Author Contributions

Study idea/design: MST, ZMCY
Data collection: MST, ZMCY
Data analysis and interpretation: MST, ZMCY
Literature review: MST, ZMCY
Writing of the article: MST, ZMCY
Critical review: MST, ZMCY
Final approval and accountability: MST, ZMCY

***Conflict of Interest**: The authors declare no conflict of interest.*

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