Coenzyme Q10 and its therapeutic potencies against COVID-19 and other similar infections: A molecular review

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Abbreviations:

Coenzyme-$Q_{10:}$ CoQ_{10}
RAS: renin-angiotensin system
COVID19: Coronavirus 2019 infection
CoV: Coronavirus, Ang: Angiotensin
Brain Blood Barrier: BBB
BER: base excision repair

Abstract

New lethal Coronavirus infectious disease (COVID19), currently, has been converted to a disastrous pandemic worldwide. There is, now, no definite treatment for the disease and tens thousands of people have been died due it. The disturbance of renin-angiotensin system (RAS), a huge cytokine storm, and oxidative stress are essential causes in molecular pathology of COVID19. Coenzyme-Q_{10} (CoQ_{10}) is an essential cofactor in the electron transport chain of the phosphorylative oxidation system. It is a powerful lipophilic antioxidant, anti-apoptotic, immunomodulatory and anti-inflammatory supplement which has been tested for the management and prevention of a variety of diseases specially diseases with inflammatory pathogenesis. CoQ_{10} as a free radical scavenger and a membrane stabilizer, prevents phospholipid peroxidation, and regenerates vitamin E (α-tocopherol) and vitamin C (ascorbate). CoQ_{10} is also a strong anti-inflammatory agent which can reduce TNF-α, IL-6, CRP, and other inflammatory cytokines. The endogenous insufficiency of CoQ_{10} synthesis causes the up-regulation of oxidation reactions and the down-regulation of multiple genes which are crucial for growth such as RNA polymerase II. The cardio-protective role of CoQ_{10} in improving viral myocarditis and drug induced cardiotoxicity has been determined in different studies. CoQ_{10} could also improve the interference in the RAS system caused by COVID19 infection through exerting anti-Angiotensin II effects and decreasing oxidative stress. CoQ_{10} leads to the raise of cellular metabolism and the patient's response to oxygenation through improving the mitochondrial dysfunction via stabilizing the plasma membrane, sustaining the function of the NA^{+}/K^{+} ATPase, and regulating the oxidative phosphorylation system. CoQ_{10} passes easily through Brain Blood Barrier (BBB) and as a neuroprotective agent can reduce oxidative stress and modulate the immunologic reactions, which could decrease systemic inflammation, prevent BBB damage and neuronal apoptosis in COVID19 patients. Accordingly, CoQ_{10} supplementation could prevent the COVID19-induced morbidities and has a potential protective role against the deleterious consequences of the disease. (Figure1)

KeyWords: Coenzyme Q10, therapeutic, COVID-19, molecular, infection, coronavirus

Introduction

After reporting the first case of Coronavirus 2019 (COVID19) on 31 December 2019 in China,(1) the virus is rapidly spreading worldwide. World Health Organization (WHO) officially declared COVID19 as pandemic on 11 March 2020 and tens of thousands of people have so far died from the disease (2) SARS-CoV-2, the cause of COVID19, and the previously known viruses SARS-CoV and MERS-CoV are known to cause threatening epidemics with severe clinical features mostly involving the respiratory system (3). The Coronaviridae family consists of enveloped viruses containing large positive-sense single-stranded RNA genomes (2) which is restricted within a protein capsid and their envelope is covered with glycoprotein spikes in the shape of crowns (4). The spikes contain receptor binding domains and facilitate the attachment and replication of the virus (5). Angiotensin converting enzyme 2 (ACE2) is known as the mutual receptor for SARS-CoV-2 and its similar ancestor SARS-CoV(6). ACE2 is considerably expressed in the lung epithelium (6), and its possible role in the pathogenesis of COVID19 has been suggested in different studies (7). COVID19 is currently considered the greatest health threat internationally and there is yet no definitive treatment or vaccine for the virus (6). Therefore, current management policy has been mainly focused on the preventive and supportive approaches (1). As the virus continues to rapidly spread and infect millions of people, the urge to find a definite treatment intensifies, and great research attempts are being conducted to solve this global concern.

Coenzyme Q_{10} (CoQ_{10}) is a naturally lipid soluble electron transporter found in the mitochondrial membrane. It is an essential cofactor in the electron transport chain of the phosphorylative oxidation system. This coenzyme molecule could undergo oxidation/reduction reactions(8), and act as a powerful lipophilic antioxidant, anti-apoptotic, immunomodulatory and anti-inflammatory supplement which has been tested for the management and prevention of a variety of diseases specially diseases with inflammatory pathogenesis(9). The role of CoQ_{10} supplementation in heart failure and neurodegenerative diseases has been well established (10,11). Other clinical applications of CoQ_{10} have been tested in several clinical trials in patients with inflammatory diseases such as rheumatoid arthritis, fatty liver and diabetes(12). CoQ_{10} supplementation has presented ameliorative effects on serum inflammatory markers(13). Moreover, studies on critically ill and intensive care unit (ICU) patients have revealed a severe depletion of CoQ_{10} levels. It means that CoQ_{10} supplementation solely or in combination with other micronutrients like carnitine and selenium could have a considerable positive effect on disease progression and treatment outcomes(14). Recent

studies on CoQ_{10} revealed the immunomodulatory effects of this coenzyme(15–17), especially in the context of a viral disease. In fact, the systemic inflammation and hypercytokinemia caused by acute viral infections may become suppressed by immunomodulatory and anti-apoptotic properties of CoQ_{10}(18–20).

Molecular basis of SARS-CoV-2 infection and consequent clinical characteristics of the disease

The binding of SARS-CoV-2 spike to transmembrane ACE2 is not only the first step in pathogenesis of COVID19 but also is the most fundamental. In fact, the RNA entrance, replication and consequent cell damage is not the main pathologic concern of COVID19 (21). As mentioned, the viral spike protein has a strong affinity to ACE2 and this is the key point of protein interaction and further deleterious clinical and pathological properties of COVID19 (22). ACE2 is a transmembrane enzyme producing angiotensin $_{(1\text{-}7)}$ and a heptamer opposing the action of angiotensin II (AngII), which is correlated with the pathogenesis of several diseases like cardiovascular, renal and fibrotic diseases. Further studies about AngII revealed that besides its vasoconstrictor effect, the immunologic, inflammatory, fibrogenic and leukocyte migratory effects are also considerable aspects of this molecular axis. AngII signaling pathway is transmitted through two G-protein-coupled receptors called AT_1 and AT_2. The most concerns is about ACE/AngII/AT_1 route through which a variety of AngII adverse effects including: oxidative stress production specially through NADPH oxidase enzyme upregulation, inflammatory response by the activation of NF-κB translation factor and consequent TNF-α and IL-6 production, activating the leukocyte migratory pathway through increasing both the endothelial adhesion molecules like VCAMs and cell adhesion molecules on leukocytes, contributing to endothelial dysfunction, and increasing the risk of arrhythmia and fibrosis through activating the proliferating pathways of fibroblasts and smooth muscle cells (23). Given the fact that these effects are all opposed by angiotensin $_{(1\text{-}7)}$(24), the pathophysiology of SARS-CoV-2 becomes easy to understand. The viral spike protein interaction suppresses the inhibitory effect of ACE2(21) on the AngII system and consequently over-activates AT_1 resulting in a propagated systemic inflammation and hypercytokinemia state, in addition to immense oxidative stress in affected organs(25). Current studies show that the secondary hemophagocytic lymphohistiocytosis (sHLH) as an hyperinflammatory status which leads to hypercytokinaemia is a common reason for death after a multiorgan failure in patients infected by COVID19(26). These events are characterized by a cytokine storm due to the fulminant increased cytokines includes: interleukin (IL)-2, IL-7, granulocyte colony stimulating factor (GCSF), interferon-γ, inducible protein 10 (IP-10), monocyte

chemo-attractant protein 1 (MCP1), macrophage inflammatory protein 1-α (MIP-1α), and tumor necrosis factor-α (TNF-α) (27). In another recent work, it was demonstrated that the CD4+ and CD8+ T cells counts in the patients with severe form of COVID19 had been reduced in negative correlation with increased IL-6, IL-10 and TNF-α, suggesting the apoptotic effect of these factors on T cells (28). It was also demonstrated that the apoptotic pathway triggered by IL-10, IL-6 and TNF-α passes through mitochondrial stress which is pursued by the activated caspase-9 and caspase-3 (29). The two mentioned phenomena, systemic inflammation and oxidative stress, are the main causes of almost all clinical events in COVID19. Pneumonia in COVID19 is not only due to the pulmonary epithelium infection but also the increased vascular permeability, leukocyte migration and vascular hyper-inflammation play an undeniable role in the pathophysiology of the disease(30). The pathophysiology of cardiovascular effects of COVID19 is not completely understood, but most researchers consider cytokine storm and myocardial inflammation as the key contributors to the events(31,32). In very recent and novel studies, the neuro-infective properties of SARS-CoV-2 have been discussed(33–35). Steardo et al(33) postulated that like SARS, MERS and other members of coronaviridae, SARS-CoV-2 could infect the CNS and PNS causing neurologic impairment. The suggested mechanism of neuro-infection in COVID19 is hematogenous and retrograde neuronal rout invasion to CNS. Furthermore, the systemic inflammatory state could cause the neuronal damage as made in many neuro-degenerative diseases. The first study about neurological involvement in COVID19 patients ran in Wuhan, China, reported the neurological impairment and complications including: impaired consciousness, hyposmia, hypogeusia, dizziness, headache, and cerebrovascular accidents in severely ill patients, concluding that CNS and PNS involvement are signs of poor prognosis of the disease(34). Li et al (35) discussed the association of respiratory failure with neuro-invasiveness of SARS-CoV-2 and demonstrated that viral invasion to the medullary cardiorespiratory centers through the root of mechanoreceptors and chemoreceptors in lower respiratory tract could cause respiratory failure in severely ill patients. (Figure1)

Biochemical and Pharmacological characteristics of Coenzyme Q_{10}

In 1957 Frederick Crane et al (36) reported the first time a Quinone was found in oxidized and reduce forms. Coenzyme Q_{10} or CoQ_{10} (2, 3dimethoxy-5methyl-6-decaprenyl benzoquinone) is a lipophilic vitamin-like compound which is also known as ubiquinone (oxidized) or ubiquinol (reduced) (14). The chemical structure (Fig.1) consists of a benzoquinone ring connected to a long side chain containing 10 isoprene units (44). CoQ_{10} is endogenously synthesized from mevalonic

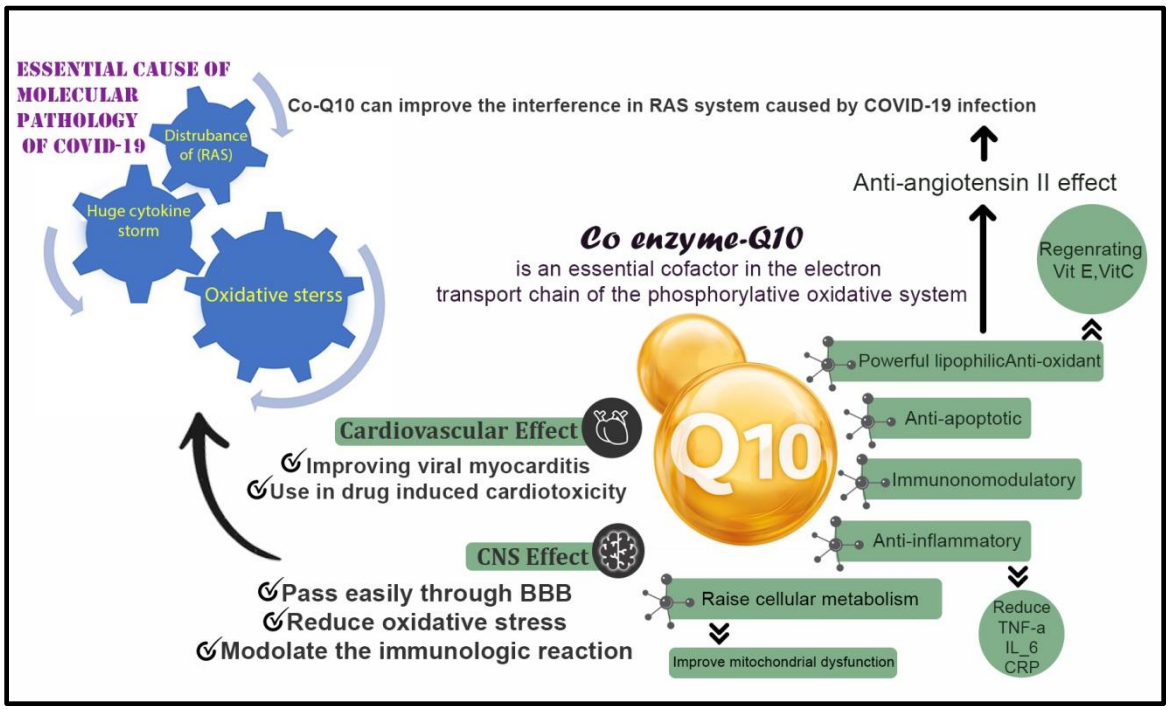

Figure1. The potential protective effects of Co-enzyme-Q10 against COVID-19:

CoQ10 is an essential co-factor in electron transport chain of the phosphorylation oxidative system. Because of its lipophilic anti-oxidant power, it has potential ability for regenerating the VitE and VitC. Moreover, the anti-angiotensin 2 effect of CoQ10 improve the RAS activity which is upregulated in COVID-19. The anti-apoptotic, immunomodatory, and anti-inflammatory effects of CoQ-10 have been also confirmed through reducing TNF-a, IL-6, and CRP. The cardiovascular protective effects of CoQ-10 have been also determined, such as improving viral myocarditis and using in drug induced cardiotoxicity. Moreover, CoQ10 has some protective effects in CNS. It can pass easily through BBB, Reduce oxidative stress, and modulate the immunologic reaction.

acid and phenylalanine (41). Coenzyme Q_{10} is a well-defined physiological component of the mitochondrial respiratory chain which supports the generation of energy in the form of ATP by converting the energy in carbohydrates and fatty acids into the energy-rich adenosine triphosphate(48). It also reduces oxidative and nitrosative stress by decreasing the superoxide radicals and interfering with the production of peroxynitrite. CoQ_{10} exists in two forms in the body: reduced form also known as ubiquinol is used by the body as an endogenous antioxidant, and oxidized or ubiquinone form is an electron carrier during mitochondrial respiration(14). Due to several features including solubility in lipid and its role in the inhibition of lipid peroxidation, CoQ_{10} is a very effective antioxidant agent against the radicals produced in the biological membranes(51). Since the quinol form of the coenzyme Q is present in cell membranes more than the other form, it

can be a very efficient antioxidant. Some enzymes such as NADH cytochrome b5 reductase, NADPH coenzyme Q reductase and NADH/NADPH oxidoreductase are effective enzymes which can keep the coenzyme Q reduced in plasma and endomembranes (55).

Recent studies show that CoQ_{10} has numerous other roles including: gene expression modifying, protection of membranes and lipoproteins from protein oxidation and lipid peroxidation, and cell signaling. Therefore, these vital roles led us to its clinical application, especially in energy-demanding tissues involved by the disease, such as heart and liver(37,38).

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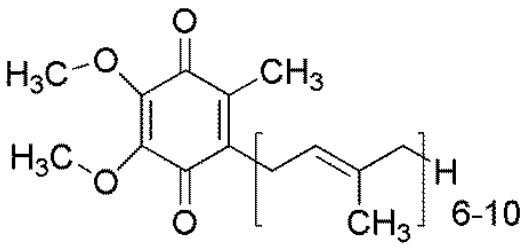

Figure2: The structure of COenzyme Q_{10}

CoQ_{10} is expressed in all tissues. The body is not normally dependent on exogenous sources of CoQ_{10}, but its biosynthesis is decreased with age and also many critical conditions in which the serum and tissue levels of this coenzyme are reduced by oxidative stress. In such conditions, exogenous CoQ_{10} is required to maintain the normal blood and tissue levels (56). CoQ_{10} is absorbed as a lipophilic substance and its uptake increases with high fat food. The main absorption is in the small intestine without any specific receptors. In circulation, CoQ_{10} is reduced to ubiquinol and then taken up rapidly by the liver where CoQ_{10} is incorporated mostly into VLDL/LDL particles. CoQ_{10} supplements have poor bioavailability in oral administration due to their insolubility in water and high molecular weight (42). CoQ_{10} metabolism has not been well studied in humans, but studies in animal models suggest that CoQ_{10} is metabolized in all tissues. The main route of the elimination of CoQ_{10} is through bile and stool excretion. A small fraction of the metabolites is phosphorylated in the cells, transported to the kidneys through blood, and excreted in the urine (51).

Coenzyme Q_{10} and medical molecular biology

The primary physiological effect of CoQ_{10} is described as a part of the cellular ATP synthesis system. CoQ_{10} is a fundamental part of the oxidative phosphorylation of mitochondria. Five protein-lipid complexes situated in the inner mitochondrial membrane, which use molecular oxygen as the final electron acceptor, are engaged in oxidative phosphorylation. Complexes I–IV are responsible for the transportation of electrons to molecular oxygen. CoQ_{10} is an electron carrier in this process. Finally, this process creates an electrochemical proton-motive force and the final complex (complex V) uses this force to form ATP(60,61). Further studies revealed other molecular properties of CoQ_{10} as a powerful antioxidant, gene regulator, anti-inflammatory, and immune modulating agent which are discussed as following.

Coenzyme Q_{10}: a powerful antioxidant and anti-inflammatory agent

An antioxidant is defined as a substance that inhibits or retards oxidation. CoQ_{10} is a lipid-soluble antioxidant which acts as a free radical scavenger and a membrane stabilizer, prevents phospholipid peroxidation, and regenerates vitamin E (α-tocopherol) and vitamin C (ascorbate)(58). Kagan et al. (59) postulated that the vitamin E regenerative property of this coenzyme is a more effective pathway to reduce oxidative stress than the free radical scavenging characteristics of CoQ_{10}. The preventive effect of CoQ_{10} against lipid peroxidation also plays a role as an anti-atherosclerotic property through diminishing the oxidation of low density lipoproteins(LDL)(60). CoQ_{10} also has an upregulating effect on some enzymatic antioxidants like superoxide dismutase(SOD) and glutathione peroxidase(61). The ubiquinone (oxidized form of CoQ_{10}) is reduced to ubiquinol through the enzymatic actions of NADH-cytochromeb5 reductase and NAD(P)H: quinone oxidoreductase 1(62). Researches on human body revealed that the production of CoQ_{10} is reduced with aging. Inflammation is both the cause and the consequence of oxidative stress. CoQ_{10} as an immunomodulatory and an antioxidant could rationally act as a strong anti-inflammatory agent. Moreover, in clinic, Various meta-analysis on RCTs strongly suggest that CoQ_{10} significantly reduces TNF-α, IL-6 and CRP(18,68). In another study CoQ_{10} treatment proves to have a role in reducing the mir146-a expression which is a regulation factor of inflammatory pathways. Additionally, CoQ_{10} can reduce the further release of IL-6 (65).(Figure3)

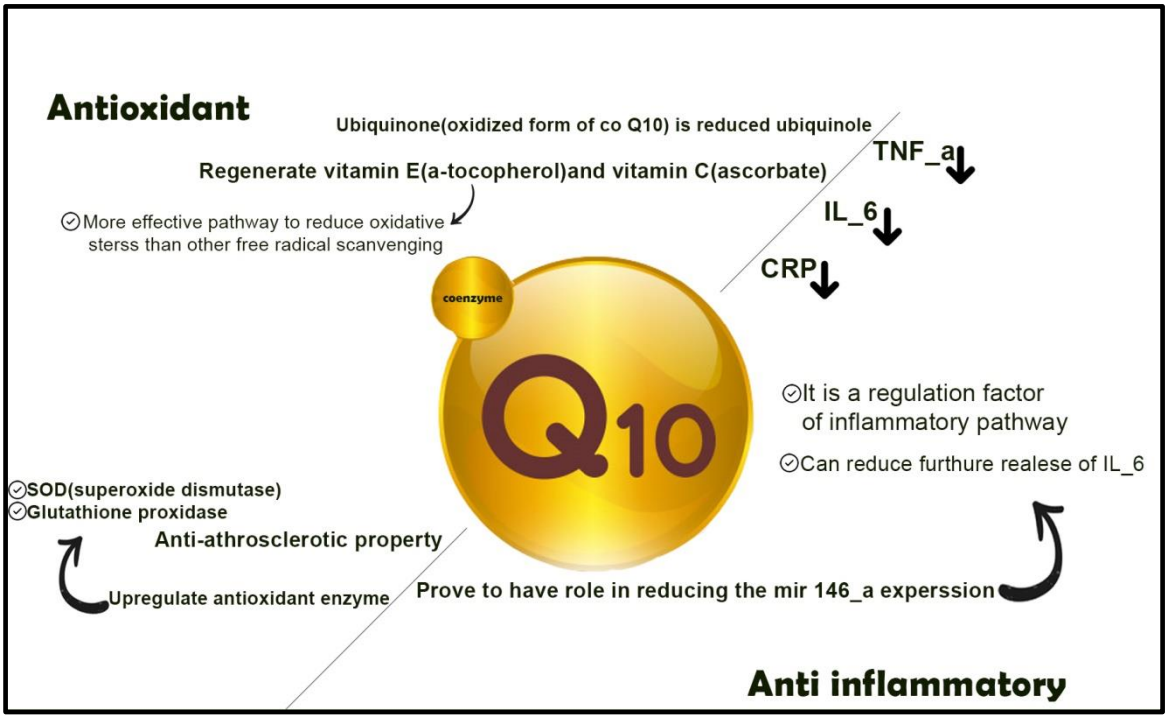

Figure3. The anti-oxidant and anti-inflammatory effects of Co-Q10:

CoQ10 can reduce oxidative stress, through free radial scavenging methods, the best effective pathway which is performed by vitamin E (a- tocopherol) ; and the regeneration of this vitamin beside vitamin C (ascorbate) is also one of the CoQ-10 functions. Addition to decreasing the TNF-a, IL-6, and CRP, CoQ-10 can play the role in preventing the lipid peroxidation. Meanwhile CoQ-10 can up-regulate the anti-oxidant enzymes like SOD (superoxide dismutase), and Glutathione proxidase. Moreover, it has proven that CoQ-10 can reduce the expression of mir-146, resulting in decreasing the release of IL-6 and could be a regulation factor for inflammatory pathway.

Coenzyme Q_{10}: a gene expression regulator

Coenzyme Q_{10} (CoQ_{10}) has been identified as a modulator of several biological processes like cell signaling and has a vital role in the mitochondrial respiratory chain and antioxidant activity (71). Moreover, many *in vitro* and *in vivo* studies have demonstrated that CoQ_{10}, in addition to its well-known functions, affects the expression of several human genes involved in metabolism, cell signaling, nutrient transport, cell death and cell differentiation(73). Its diverse functions reflect its therapeutic potential as a dietary supplement for a number of diseases such as mitochondrial myopathies, migraine and cardiovascular diseases(70). On the other hand, the conversion of Q_{10} into its reduced form is accompanied by the generation of reactive oxygen species (ROS) which may also have an additional impact on gene expression (71). A study conducted by Schmelzer et al. presented that the reduced form of CoQ_{10} (Q10H2) has a stronger effect on gene expression than the oxidized

form CoQ_{10}, primarily due to differences in bioavailability (71). The endogenous insufficiency of CoQ_{10} synthesis causes the up-regulation of oxidation reactions and the down-regulation of multiple genes which are crucial for growth such as RNA polymerase II. Exogenous CoQ_{10}supplies partially restore the expression of these genes; however, the expression level of another subset of genes which are involved in some biological functions such as metabolism and cell signaling is not affected by exogenous CoQ_{10}supplementation and depends solely on endogenous synthesis of CoQ_{10} (72).

Coenzyme Q_{10}: an immune-modulating agent

In one in-vitro study, the peripheral blood mononuclear cells (PBMC) were exposed to CoQ_{10} for 24h and the secretion of some cytokines was examined including: IL-1β, IL-1RA, IL-6, IL-10, IL-2, INF-γ, TNF-α and IL-2. As a result, only TNF-α and IL-2 secretion was significantly decreased. Notably the outcome of this experiment presented that the treatment with an average concentration of 1.25μM CoQ_{10} had the best effect, and the higher levels (up to 10μM) did not exert a significant difference (73). The different behavior of CoQ_{10} in lower and higher dosages is suggestive of a biphasic role for CoQ_{10}. Moreover, in another study by Gullapodi, CoQ_{10} presented an apoptotic protective effect on CD4+ and CD8+ which had been induced with an oxidative stressor. The selected T cells after treatment with CoQ_{10} (under 10μM concentration) for 24h showed a strong resistance to an oxidative stress-induced mitochondrial apoptotic pathway. It represented that CoQ_{10} could inhibit the activation of both caspase-9 and caspase-3 in apoptotic cascades. Moreover, it can reduce the production of reactive oxygen species (ROS) and prevent the oxidative stress-induced mitochondrial membrane depolarization in CD4+ and CD8+ T cells (74). Another critical step in apoptotic process that is also suppressed by CoQ_{10} is cytochrome C release from mitochondria according to some experimental studies (75). Furthermore, some studies demonstrated a lowered TNF-α secretion and a significant declined secretion of MIP-1α, MCP1 with CoQ_{10} treatment on THP-1 cell line, the events which are very important in the COVID19-induced hyper-inflammatory state. Since the monocytes are able to convert oxidized CoQ_{10} into its reduced form, this reduction can be justified. NF-κB is a transcription factor for many genes involved in immune responses including which encode MIP-1α, MCP1, and TNF-α. It is believed that down-modulation of these factors is due to NF-κB inhibition. It has not been clearly confirmed that how CoQ_{10} effects on NF-κB, but there are some evidences for NF-κB inhibition by antioxidant compounds (81,82). (Figure4)

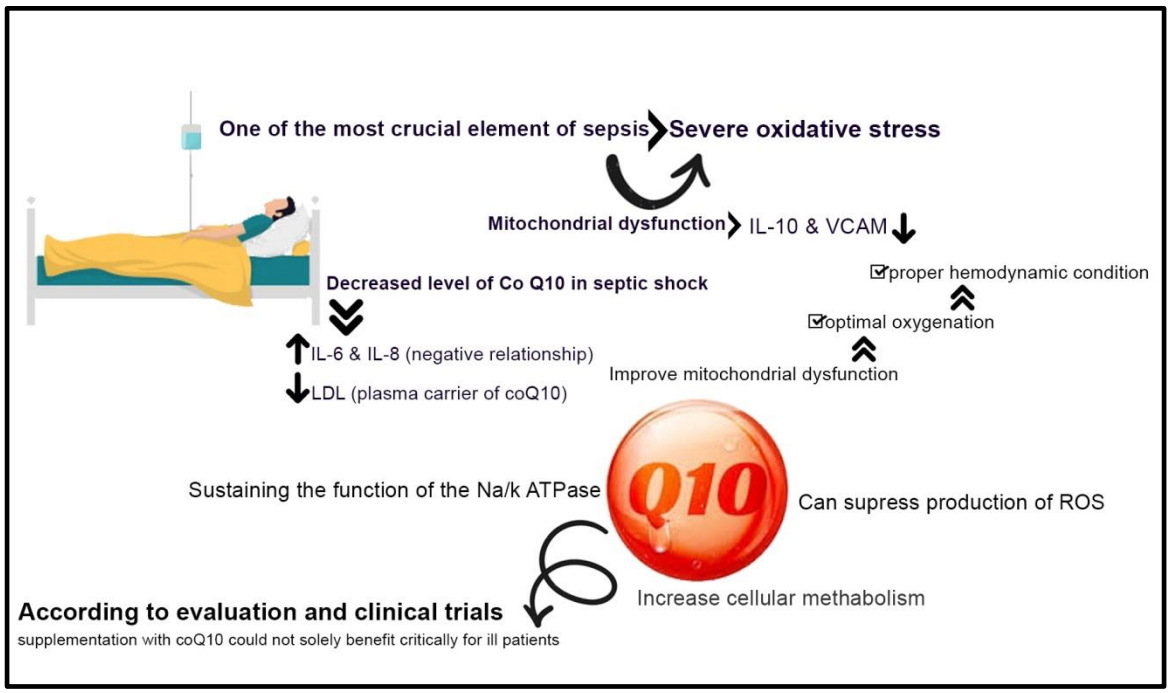

Figure4. The effective role of CoQ10 against severe oxidative stress by improving the mitochondrial dysfunction:

One of the most crucial elements of sepsis infections is severe oxidative stress which is caused by mitochondrial dysfunction leading to decreasing IL-10 and VCAM. During a septic shock, a condition in which the level of CoQ10 is decreased and it accompanies by increasing IL-6 and decreasing LDL(plasma carrier of CoQ10), optimal oxygenation and as a result making proper hemodynamic condition, are supposed to improving the mitochondrial dysfunction. Although CoQ10 has proven benefits in suppressing the production of ROS, raising the cellular metabolism, and sustaining the function of Na/K ATPas, the supplementation with CoQ10 could not solely benefit critically for the ill advanced patients.

ROS: Reactive oxygen species

Coenzyme Q_{10}: an antiviral nutrient

The viral infections, caused by RNA or DNA virus, trigger the production of reactive species (RS) and reactive oxygen species (ROS) including: NO, $O2^{\cdot-}$, $OH^{\bullet}$ and their by-products (such as H2O2), which interfere with normal functions of the infected cells such as gene expression and metabolism(86). As an instance, a higher RS level in the host cell promotes the activating of NF-κB which can lead to increased viral replication(83). There are also some evidences that antioxidant agents can mediate viral pathogenesis through the reinforcement of cell resistance against oxidative stress. Moreover, it has been determined that the antioxidant agents exert an important role in decreasing the replication of RNA viruses such as flaviviruses, alphaviruses, and Japanese encephalitis virus through the various pathways in different stages (87).

Coenzyme Q_{10} and anti-angiotensin II properties

The renin–angiotensin system (RAS) has been shown to play a vital role in physiological and pathophysiological events in cardiovascular system. In this cascade, angiotensin converting enzyme(ACE) converts AngI to AngII, and AngII as the prime component of RAS, disrupts endothelial function by increasing the oxidative stress (90). On the other hand, AngII and its receptor induce the activation of NADPH oxidase whereby the synthesis of reactive oxygen species (ROS) is increased. When the local levels of ROS are increased, a considerable cellular damage and oxidative stress will occur by interaction with cell membranes, DNA and other molecules (90).

Some experimental studies presented that CoQ_{10} is involved in enhancing the expression of the antioxidant enzymes and eliminating the free radicals. Treatment with antioxidant agents may remove the misbalance of RAS caused by oxidative stress (95). Moreover, studies demonstrated the preventive effect of CoQ_{10} against angiotensin induced up-regulation of NADPH oxidase enzyme (93).

Clinical implications of Coenzyme Q_{10} in COVID19

Coenzyme Q_{10} has been the subject of interest in a variety of diseases including cardiovascular, neurodegenerative, kidney and systemic inflammatory diseases(9)**.** The antioxidant, anti-inflammatory, immunomodulatory and gene expression regulator properties of this molecule highlight its application as a considerable choice for nutrient therapy in the aforementioned diseases (58). Some of these conditions such as cardiovascular diseases, hyper-inflammatory state and critical stages of illnesses like septic shock share some features with COVID19 in pathophysiology. The following statements describe this shared features and possible effects of CoQ_{10} supplementation in COVID19 patients.

Coenzyme Q_{10} and its potential cardioprotective effects

Coenzyme Q10 has a pivotal role in myocyte bioenergetics, exerts anti-inflammatory effects, and reduces oxidative stress. CoQ10 could be beneficial for a wide spectrum of cardiovascular diseases including: heart failure, hypertension, myocardial infarction, viral myocarditis, arrhythmias, and drug-induced or idiopathic cardiomyopathies(94).

The action mechanism of this supplement, according to Greenberg and Ferishman (95), is to not only enhance the cellular aerobic metabolism but also exert cardiovascular effects including: the modification of endothelial dysfunction, preserving the function of the NA^+/K^+ ATPase, stabilizing the cellular membrane, reducing blood viscosity, modulating the immune system, and suppressing systemic inflammation. CoQ_{10} could be helpful for heart disease patients by increasing mitochondrial phosphate/oxygen ratio, alleviating reperfusion injury after hypoxic conditions, modifying QRS duration abnormalities, and improve NYHA function class in heart failure patients (96). Moreover, CoQ_{10} improves extracellular superoxide dismutase (ecSOD) and flow-mediated-dilation (97), and protect against progressive left ventricular remodeling and fibrosis (98). Ultimately, CoQ_{10}can reduce total cardiac events and could be protective against myocardial infraction, congestive heart failure, and dilated and drug-induced types of cardiomyopathies(99).

The protective role of CoQ_{10} in improving viral myocarditis and drug induced cardiotoxicity introduces this supplement as an appropriate choice for the prevention of COVID19 cardiovascular complications which is generally influenced by two factors: cytokine storm, and drugs side-effects (32). The hypercytokinemia caused by SARS-COV-2 infection could lead to fulminant myocarditis(100), a lethal condition mostly caused by hyper-inflammatory state and cytokine storms, particularly during a viral infection(101). Evidence has demonstrated that the blood levels of inflammatory cytokines in critically ill patients in the ICU are higher than the patients not admitted to the ICU; additionally, the level of IL-6 has shown to be higher in patients with cardiac injury(102). The anti-inflammatory, antioxidant, and immunomodulatory effects of CoQ_{10} could suppress the hyper-inflammatory state, particularly through reducing IL-6, TNF-α and other inflammatory cytokines resulting in the prevention of cardiovascular events in COVID19 patients and the alleviation of the cardiac complications caused by the cytokine storm in this disease(78,99).

Despite the fact that no definitive treatment for COVID19 has yet been discovered, several curative and supportive medications have been suggested; the most fundamental of which include: Chloroquine, hydroxyl chloroquine, lopinavir/ritonavir, and potent antibiotics preventing bacterial super infections(104). Among the adverse effects of these drugs, particularly hydroxyl chloroquine, cardiovascular complications are of great importance (105). These drugs induce cardiotoxicity through increasing oxidative stress, triggering endothelial dysfunction and elevating tissue inflammation(106). CoQ_{10} counteracts the cardio-toxic effects of these drugs by improving the mechanism of oxidative phosphorylation, reducing oxidative stress and decreasing the inflammation of the myocardium(112).

Coenzyme Q_{10}, primary hypertension and endothelial dysfunction

The pathophysiology of primary hypertension is generally associated with the oxidative stress in the endothelium which leads to decreased available NO for the cells of vascular intima layer, mitochondrial dysfunction of the endothelium, and eventually endothelial dysfunction(109). CoQ_{10} could improve hypertension through decreasing vascular oxidative stress, improving the function of mitochondria, moderating the effects of AngII, and reducing the level of Aldosterone(94). As mentioned, in the pathophysiology of COVID19, the RAS system is disturbed due to the interference caused by the protein-protein interaction of the virus spikes and ACE2, leading to the down-regulation of ACE2 which could enhance the pathologic effects of AngII and frustrate the AngII/$Ang_{(1-7)}$ ratio resulting in the severe complications of COVID19 disease(110). Supplementation with Q10 could improve the interference in the RAS system caused by COVID19 infection through exerting anti-AngII effects and decreasing oxidative stress(93). The antihypertensive effects of CoQ_{10} are not entirely confirmed and more well-designed clinical trials are suggested to confirm it(116). Studies have demonstrated that CoQ_{10} could not solely reduce blood pressure but could be beneficial against hypertension in the context of metabolic diseases like diabetes as an adjunctive therapy to adjust blood pressure(112).

Coenzyme Q_{10} in critically ill and ICU patients

The molecular and cellular mechanism of sepsis has not been entirely discovered and includes different aspects. One of the most crucial elements of sepsis is severe oxidative stress accompanied by the mitochondria dysfunction (113).

The decreased levels of CoQ_{10} during septic shock have also a significant importance(114). The elevated levels of IL-6 and IL-8 which have a negative relationship with CoQ_{10} levels, and the decreased LDL that is the plasma carrier of the coenzyme lead to lower CoQ_{10} levels during the occurrence of septic shock (115). The coenzyme inversely correlates with vascular endothelial biomarkers like VCAM and inflammatory cytokines like IL-10, and its decrease during septic shock, contributes to the organ failure related to the mitochondrial dysfunction(116).

Meanwhile, despite the providing stable and proper hemodynamic conditions along with the optimal oxygenation in the critically ill patients, death rates could not be reduced in these people. This clearly

indicates that the substantial mitochondrial dysfunction in the critically ill patients prohibits using the oxygen to produce intracellular ATP even with proper oxygenation (118). Coenzyme Q10 could not only counteract the oxidative stress in sepsis as a strong mitochondrial and membranous antioxidant, but could also suppress the production of ROS, increase cellular metabolism and enhance the patient's response to oxygenation by alleviating the mitochondrial dysfunction through stabilizing the plasma membrane, sustaining the function of the NA^+/K^+ ATPase, and regulating the oxidative phosphorylation system. Nevertheless, according to evaluations and clinical trials, supplementation with CoQ_{10} could not solely benefit critically ill patients and it is advised to prescribe CoQ_{10} with Selenium as a crucial component of several metabolic enzymes and selenoproteins(78). (Figure4)

Coenzyme Q10 and its potential Neuroprotective effects

Most of neurodegenerative diseases like Alzheimer and Parkinson disease, despite their exclusive neurologic and molecular properties, share some common pathological aspects such as neuro-inflammation, excitotoxicity cascade induced neuronal apoptosis, and mitochondrial dysfunction in affected neurons(123). CoQ_{10} is a nutrients of interest in adjunctive therapy and the prevention of these types of age related diseases(11). CoQ_{10} with anti-inflammatory, antioxidant and immunomodulatory properties, could suppress the CNS inflammation in such diseases in addition to reducing oxidative stress and enhancing mitochondrial function(17). CoQ_{10} could also prevent neuronal apoptosis trough keeping mitochondrial permeability transition pores(MPTP) in closed conformation and blocking the apoptosis pathway induced by N-methyl D-aspartate (NMDA) glutamate receptors or non-NMDA glutamate receptors(122).

The suggested pathophysiology of neurologic involvement in COVID19 patient is based on three events; a retrograde trans-synaptic infection of CNS, hematogenous infection of CNS in the context of disrupted blood brain barrier(BBB) due to hypercytokinemia and a systemic inflammation which causes both endothelium and astrocytes dysfunction in BBB, and the direct impact of systemic inflammation and oxidative stress on CNS and PNS causing neuronal damage and pathologic reactions in the supportive tissue of neurologic system , blood vessels, coagulation cascades and endothelium resulting in the cerebrovascular accidents (CVA)(33,35).

CoQ_{10} as a lipophilic antioxidant which passes easily through BBB, has a direct effect on reducing oxidative stress and modulating the immunologic reactions, which could be beneficial through suppressing the systemic inflammation(11), preventing BBB damage(123), and neuronal

apoptosis(122) in COVID19 patients. Accordingly, CoQ_{10} supplementation could prevent the developing CNS and PNS damage and further deleterious consequences like central respiratory failure, delirium and loss of conciseness, leading to a permanent brain injury and death(34). (Figure1)

Conclusions

COVID19 as a pandemic lethal infection, currently, has no definite treatment. The interaction of virus-spike with ACE2 receptor leads to the down-regulation of ACE2 which could enhance the pathologic effects of AngII and disturb the AngII/$Ang_{(1-7)}$ ratio. It could result in a huge cytokine storm, and an extensive oxidative stress which are the molecular basis of the most coplications induced by COVID19. CoQ_{10} as an essential electron transporter in the phosphorylative oxidation system is a powerful lipophilic antioxidant, anti-apoptotic, immunomodulatory and anti-inflammatory supplement which has been tested for the management and prevention of a variety of diseases specially diseases with inflammatory pathogenesis. CoQ_{10} can decrease the important inflammatory cytokines and prevent the organ damages due to a huge oxidative stress. CoQ_{10} can be also a cardio-protective and neuroprotective agent through reducing the viral toxicity against cardiomyocytes and CNC neurons. Accordingly, CoQ_{10} supplementation could prevent the COVID19-induced morbidities and has a potential protective role against the deleterious consequences of the disease.

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