Current Nutrition Reports
https://doi.org/10.1007/s13668-024-00568-2

REVIEW

# Therapeutic Effects of Coenzyme Q10 in the Treatment of Ischemic Stroke

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Accepted: 20 August 2024


## Abstract

**Purpose of Review** Ischemic stroke is the second deadly disease worldwide, but current treatment is very limited. The brain, rich in lipids and high in oxygen consumption, is susceptible to damage from oxidative stress after ischemic stroke. Thus, antioxidants are promising neuroprotective agents for treatment and prevention of ischemic stroke. Coenzyme Q10 is the only lipophilic antioxidant that can be synthesized de novo by cells and plays a key role as an electron carrier in the oxidative phosphorylation of the mitochondrial electron transport chain. However, the reduced form of coenzyme Q10 (Ubiquinol) levels are significantly deficient in the brain. The aim of this article is to review the therapeutic effects and mechanisms of coenzyme Q10 in ischemic stroke.

**Recent Findings** Current studies have found that coenzyme Q10 protects and treats ischemic stroke through multiple mechanisms based on the evidence from in vitro experiments, in vivo experiments, and clinical observations.

**Summary** For the first time, we reviewed the neuroprotective effects of coenzyme Q10 in ischemic stroke. Coenzyme Q10 exerts neuroprotective effects after ischemic stroke through anti-oxidative stress, anti-nitrosative stress, anti-inflammation, and anti-cell death. Here, we provided the evidence on the therapeutic and preventive effects of coenzyme Q10 in ischemic stroke and suggested the potential value of coenzyme Q10 as a medication candidate.

**Keywords** Coenzyme Q10 · Ischemic stroke · Antioxidant · Neuroprotective effect · Atherosclerosis · Blood-brain barrier

## Introduction

Stroke is a common disease with high incidence, high mortality and high disability, and the burden of stroke ranks the second in the world [1]. Stroke includes hemorrhagic stroke and ischemic stroke (IS), with IS accounting for more than 80% [2]. IS is a common disease in the elderly and tends to occur at a younger age in recent years. Currently, about 80 million people worldwide suffer from IS [3]. As the population ageing processes, more than a quarter of the world's population will be over 65 years old by 2050, which will further increase the number of IS patients [4]. Therefore, sequelae of IS has brought heavy burden to patients, families and society.

Currently, thrombolysis and mechanical thrombolysis are effective treatments for IS, but their clinical application is limited by strict contraindications, narrow treatment time windows, and severe side effects, resulting in only a small number of patients benefiting from them [5]. In addition, the incidence of hemorrhagic transformation (HT) following the treatment of thrombolysis and mechanical thrombolysis was close to 10% [6]. HT is an important factor in the exacerbation of brain injury and death in IS patients. Preventive strategies for IS have greatly reduced the chance of IS, however, there is still a large number of patients with risk factors such as smoking, alcoholism,

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Published online: 04 September 2024

diabetes, hypertension, especially in developing countries. Therefore, it is important to develop affordable drugs for the treatment of IS.

The pathological mechanism of IS is complex, and oxidative stress plays an important role in the pathological progression of IS. Thus, there is a trend to develop effective antioxidants for the treatment of IS [7]. Coenzyme Q10 (CoQ10) is a fat-soluble antioxidant and is widely synthesized in the body. However, in vivo synthesis of CoQ10 is often inadequate. CoQ10 plays a key role in oxidative phosphorylation in mitochondria, where it protects cell membranes from free radical-induced oxidative damage. It also plays important roles in other organelles, including lysosome, Golgi apparatus, endoplasmic reticulum, and among others. For example, CoQ10 maintains the pH in lysosomes [8]. In addition, CoQ10 can be obtained from a normal diet of about five mg per day [9]. However, the daily requirement for CoQ10 is estimated to be about 500 mg per day [10]. Therefore, CoQ10 is likely to be necessary through dietary supplementation.

Many studies have reviewed the role of CoQ10 in neurological disorders, such as Parkinson's disease [11], cerebral hemorrhage [12], epilepsy [13], migraine [14], and multiple sclerosis [15]. In addition, recent studies have found that serum CoQ10 levels are significantly lower in patients after IS and associated with clinical outcomes [16]. However, the treatment of IS with CoQ10 has not been reviewed. For the first time, we reviewed the therapeutic effects of CoQ10 for IS. Herein, we aim to provide evidences for the treatment of IS with CoQ10.

## The Role of CoQ10 in the Treatment for IS

CoQ10 plays important roles in the treatment of IS. The detailed information are shown in Table 1. A study has found that in IS patients, the serum CoQ10 levels were significantly lower, and serum CoQ10 levels were significantly negatively correlated with National Institutes of Health Stroke Scale (NIHSS) scores and Modified Rankin Scale (mRS) scores, suggesting the serum CoQ10 could be an indicator for the clinical neurological outcomes after IS [16]. Also, a recent clinical study has found that the intake of 300 mg/day of CoQ10 for one month has significantly improved IS outcomes, and increased NIHSS scores [17].

In addition to clinical observations, the animal model also demonstrated the role of CoQ10 in the treatment for IS. Middle cerebral artery occlusion (MCAO) model is the most commonly used animal model for IS. In a 10-min MACO model, 10 mg/kg CoQ10 has significantly decreased neurological deficit scores, brain infarct volume, and blood glucose levels [18]. The pretreatment of CoQ10 at 10 mg/kg alleviated the biochemical changes in both brain and serum, and the hippocampal damage in CA1 region after 60-min MACO model [19, 20]. With the supplement at 30 mg/kg, CoQ10 has significantly decreased neurological deficit scores, mortality, and brain infarct volume, and attenuated motor impairment brain edema, cognitive impairment, and blood-brain barrier integrity in a 60-min MACO model [21–23]. Additionally, the 200 mg/kg CoQ10 has also reduced neurological deficit score and improved cerebral infarction in a 60-min MACO model [24]. In a bilateral common carotid artery occlusion (BCCAO) model, the post-IS treatment with CoQ10 at 200 mg/kg has significantly reduced brain edema, and improved anxiety and depression-like behavior, and cognitive impairments [25]. Additionally, in a photothrombotic stroke model for neonatal rats, pretreatment with 200 mg/kg CoQ10 decreased cerebral ischemic injury and brain infarct volume, while post-stroke treatment with CoQ10 improved motor function and reduced brain infarct volume, with a better treatment effect than the pretreatment [26].

There are very limited studies using CoQ10 in the treatment of IS with the in vitro models. A study reported that CoQ10 could protect neural stem cells against hypoxia-reperfusion by increasing cell viability and decreasing formation of free radicals in an oxygen glucose deprivation/re-oxygenation (OGD/R) model [27].

## The Effects and Potential Mechanisms of CoQ10 in the Treatment for IS

Here, we focus on the beneficial effects of CoQ10 on the prevention of IS etiology (i.e. atherosclerosis, atrial fibrillation, cerebral small vessel disease), pathogenesis (i.e. oxidative stress, inflammation, endothelial damage, etc.) and other interventional risk factors of IS.

The therapeutic mechanisms of CoQ10 in IS are not clearly understood. Current studies suggest that the mechanisms of CoQ10 involves anti-oxidative stress, anti-nitrosative stress, anti-inflammatory effect, anti-apoptotic effect, and anti-autophagy, mainly focusing on the beneficial effects of CoQ10 on the prevention of IS pathogenesis. The specific mechanism and information are shown in Fig. 1.

CoQ10 has been clinically proven effective in protecting ischemic stroke. Now, one of the clear therapeutic mechanisms of CoQ10 over IS is through the miRNA-149-5-p and the NF-κB to reduce inflammation factors, such as MMP-2, MMP-9, IL1β, IL6, TNF-α, and iNOS. Therefore, the integrity of blood-brain barrier has improved, and brain edema and hemorrhagic transformation are reduced. In addition, CoQ10 can reduce oxidative stress to regulate apoptosis and autophagy, and increase the survival of nerve cells after IS, including through increasing the levels of glutathione and antioxidants, reducing reactive oxygen species (ROS),

**Table 1** Details of included studies and results of CoQ10 in the treatment of IS

| Year | Species | Dose | Model | IS Time | Evidence | References |
|---|---|---|---|---|---|---|
| 2020 | Rats | 30 mg/kg/day | MCAO | 60 min | Neurological deficit scores↓, mortality↓, coenzyme Q10↑ | 22 |
| 2020 | Rats | 100 mg/kg/day | Photothrombosis | 7 d | Activated microglia↓, ROS↓, motor function↑, Neurological deficit scores↓, Brain Infarct Volume↓, IL-1β↓, TNF-α↓ | 26 |
| 2018 | Human | 300 mg/day | | 30 d | coenzyme Q10↑, NIHSS↑, MMSE↑ | 17 |
| 2012 | Neural stem cells | 0.01, 0.1, 1, 10 μM | OGD/R | 8 h | ROS↓, Akt↑, GSK3β↑, Bcl-2↑,Bax↓, cleaved caspase-3↓ | 27 |
| 2019 | Rats | 200 mg/kg/day | MCAO | 60 min | Neurological deficit scores↓,IL-6↓, TNF-α↓, caspase-3↓, caspase-9↓ | 24 |
| 2021 | Rats | 30 mg/kg/day | MCAO | 60 min | Neurological deficit scores↓, Brain Infarct Volume↓, Blood-brain barrier permeability↓, miRNA-149-5p↑, MMP2↓, MMP9↓, TNF-α↓, IL-6↓, tissue damage volume↓ | 21 |
| 2017 | Rats | 10 mg/kg/day | MCAO | 30 min | Neurological deficit scores↓, Brain Infarct Volume↓, blood glucose↓, Lc3-II/Lc3I↓ | 18 |
| 2022 | Rats | 200 mg/kg/day | BCCAO | 20 min | Brain edema↓, depressive and anxiety-like behavior↓, cognitive impairments↓, BDNF↑, SOD↑ | 25 |
| 2010 | Rats | 10 mg/kg/day | MCAO | 60 min | LDH↓, $Ca^{2+}$↓, MDA↓, glutathione↑ | 19 |
| 2015 | Rats | 30 mg/kg/day | MCAO | 60 min | Neurological deficit scores↓, mortality↓, motor function↑, coenzyme Q10↑, Brain Infarct Volume↓ | 23 |
| 2017 | Rats | 10 mg/kg/day | MCAO | 60 min | cytochrome C↓, caspase-3↓, Bax↓, Bcl-2↑, p-Akt↑, p-FOXO3A↑, JNK3↓, c-Jun↓,TNF-α↓, ICAM-1↓, MPO activity↓, NF-κBp65↓, iNOS↓, Bim↓ | 20 |

↑ = increased, ↓ = decreased

*OGD/R* Oxygen glucose deprivation/reoxygenation, *MCAO* Middle cerebral artery occlusion, *Time* Time of ischemic stroke model

regulating the expression of Caspase3, Caspase9 and other proteins. The above are the specific molecular mechanisms by which CoQ10 protects IS from reducing neurological deficits, infarct volume, and promoting motor function and intellectual recovery.

## The Effect of CoQ10 Against Oxidative Stress

Oxidative stress is critical in the pathology of IS, and excess ROS is a key mechanism in the development of IS. In the clinical studies, CoQ10 reduced ROS levels in IS patients, and improves prognosis [17]. In addition, both in vivo and in vitro experiments found that CoQ10 increased glutathione levels and superoxide dismutase (SOD), and decreased ROS, lactate dehydrogenase (LDH), and malondialdehyde (MDA) levels [19, 25–27].

In addition to the direct evidence of CoQ10 against IS, CoQ10 also displayed protection against atherosclerosis (AS), which is the most common factor leading to IS. There are two mechanisms by which AS triggers IS. One is a stable atherosclerotic plaque that gradually increases in size

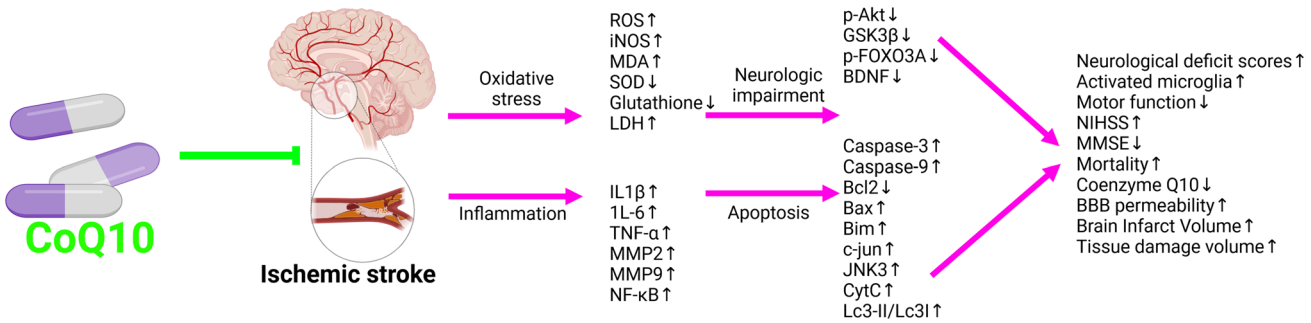


**Fig. 1** Schematic illustration of the therapeutic effects of CoQ10 for IS. CoQ10 improves brain tissue damage and function after IS through anti-inflammatory, anti-oxidative stress, anti-apoptosis and anti-autophagy

and encroaches on the lumen of the vessel, blocking blood flow and causing hypoperfusion or even complete ischemia. These patients were usually with symptoms and detected through examinations, often without serious consequences. In the other case, the plaque dislodgement leads to the formation of a blood clot, which blocks the blood vessel and usually causes an acute IS with serious consequences.

ROS are essential for vascular homeostasis, but excess ROS cause vascular damage [28]. The imbalance of oxidative stress leads to oxidative damage to endothelial cells and production of oxidized LDL (ox-LDL). The release of chemotactic proteins from damaged endothelial cells leads to migration of immune cells to the endothelium [29]. Further, ox-LDL increases the expression of cell adhesion molecules, leading to the aggregation of immune cells. Subsequently, monocytes differentiate into macrophages that mediate phagocytosis of ox-LDL, and these lipid-rich macrophages are known as foam cells. This is also a hallmark of early AS. These immune cells release a variety of cytokines that promote ROS production, further leading to oxidative stress. ROS and inflammatory factors stimulate migration of smooth muscle cell and deposition of collagen, and the atherosclerotic plaque increases in size and invades the medial arterial. Eventually, the atherosclerotic plaque completely forms, leading to a decrease in arterial elasticity.

Recent study was found that the serum CoQ10 level was significantly decreased, and the 8-hydroxy-2' -deoxyguanosine/deoxyguanosine ratio, MDA level, and glutathione peroxidase (GPX) were significantly increased in patients with AS and hyperlipidemia [30]. It suggests that CoQ10 may play an important role in the pathological process of AS. CoQ10 can reduce LDH and MDA levels, and increase SOD and GSH levels, suggesting that CoQ10 exerts protective effects through anti-oxidative stress in AS [31].

Elevated levels of LDL and ox-LDL and decreased levels of high-density lipoprotein (HDL) are key factors in the development and progression of AS. Macrophage phagocytosis and uptake of ox-LDL are the basis for AS formation. Oxidation of HDL has multiple functions, including reverse cholesterol transport and blocking LDL from becoming ox-LDL. CoQ10 may be involved in inhibiting oxidative stress via miR-378, promoting macrophage cholesterol efflux and reducing ox-LDL-induced foam cell formation [32]. In addition, myeloperoxidase levels are elevated in patients with AS, and myeloperoxidase is involved in the oxidation of LDL, HDL and nitric oxide (NO) [33]. CoQ10 may have reduced myeloperoxidase levels after IS [20]. NO can be considered as a powerful antioxidant that protects cells and mitochondria during oxidative stress [34].

CoQ10 treatment increased serum lipocalin, NO, HDL, glutathione, and eNOS levels, and decreased lipid profile, creatine kinase activity, inducible nitric oxide synthase (iNOS), ox-LDL and lipid peroxidation [35, 36]. Interestingly, the clinical effects of CoQ10 in combination with simvastatin are controversial. One study found that 400 mg daily of CoQ10 combined with simvastatin for eight weeks did not appear an additional augmentation effect compared to simvastatin treatment [37]. In contrast, another study found that simvastatin only combined with CoQ10 can achieve normalization of plasma NO levels [38]. This difference may need to be explained by future clinical studies with larger samples.

In addition, CoQ10 may be involved in the treatment of AS through other mechanisms. One study found that lipid changes in patients treated with CoQ10 were inconsistent with a general improvement in antioxidative status, suggesting that the anti-atherosclerotic effects of CoQ10 may be mediated by other mechanisms to regulate antioxidative pathway. For example, paraoxonase 1 (PON1) was originally found to hydrolyze toxic metabolites of a variety of organophosphorus pesticides. PON1 is now also found to mediate the enzymatic protection of LDL. PON1 binds tightly to HDL and destroys ox-LDL by hydrolyzing lipid peroxides. PON1 activity was significantly increased during CoQ10 treatment and PON1 activity was positively correlated with HDL levels and negatively correlated with atherosclerotic coefficient [39, 40]. In addition, the role of HIF1α is important in IS and AS, and CoQ10 reduces oxidative stress by inhibiting HIF1α [41].

As the pathological process of AS develops, atherosclerotic plaques form calcification. The mechanisms of atherosclerotic plaque formation are discussed further in the inflammation section below. ROS generated by oxidative stress may be involved in instability and rupture of atherosclerotic plaque, and ROS are involved in AS by promoting proliferation and migration of vascular smooth muscle cell. Also, ROS induce apoptosis in vascular smooth muscle cells, which may cause instability and rupture of atherosclerotic plaque [42]. CoQ10 can inhibit the excessive release of ROS, increase ATP content, improve mitochondrial function, control the development of AS, and facilitate the stability of atherosclerotic plaques [31, 36].

## The Effect of CoQ10 Against Nitrosative Stress

Nitrosative stress is an important disorder of oxygen metabolism that is closely associated with the pathological processes of AS and IS. However, the role of nitrosative stress in the development of AS and IS pathology is often overlooked. This may be due to the fact that nitrosative stress and oxidative stress are very similar, and the ROS include superoxide anion ($\cdot O^{2-}$), hydroxyl radical, hydrogen peroxide ($H_2O_2$), and NO, which are overlapped with the formation and scavenging pathways of reactive nitrogen species

(RNS) [43, 44]. The difference is that nitrosative stress refers to the combination of NO and $\cdot O^{2-}$ to generate peroxynitrite anion ($ONOO^-$) when the body undergoes a disturbance in oxygen metabolism. $ONOO^-$ can nitrate biomolecules such as proteins, lipids and DNA [44]. Nitrosative stress-generated $ONOO^-$ promotes protein tyrosine nitration, leading to lipid peroxidation, DNA strand breaks, and cell death in macrophages and smooth muscle cells, and promotes the formation of lipid-rich necrotic cores in AS [45]. And nitrosative stress is also an important factor in the outcome of IS patients. Since the penetration ability of $ONOO^-$ to lipid membrane is about 400 times higher than $\cdot O^{2-}$, it has more ability to damage DNA and more likely to cause neuronal cell death in the ischemic semidark zone [46]. The mechanism of CoQ10 against atherosclerotic nitrosative stress, DNA damage and repair is unclear. It may be related to the inhibition of $O^{2-}$ to further reduce the production of $ONOO^-$ by CoQ10, which needs to be confirmed in future experiments [47]. The specific mechanism of anti-oxidative stress and anti-nitrosative stress was shown in Fig. 2.

## The Effect of CoQ10 Against Inflammation

Neuroinflammation plays a key role in the pathogenesis of IS, and the post-IS inflammatory response is initiated by the activation of microglia. CoQ10 can inhibit inflammation by reducing Interleukin-1β (IL-1β), Interleukin- 6 (IL-6), iNOS, nuclear factor-kappaB (NF-κB) and tumor necrosis factor alpha (TNF-α) levels after IS [24, 26]. In addition, CoQ10 protects blood-brain barrier integrity by resisting autophagy and reducing matrix metalloproteinase-2 (MMP-2) and metalloproteinase-9 (MMP-9) expression [18, 21]. These effects are inextricably linked to the anti-inflammatory and anti-oxidative stress mechanisms of CoQ10.

The nature of AS is a chronic vascular inflammatory disease characterized by the accumulation of lipids and inflammatory cells [48]. Therefore, the pathogenesis of AS in addition to oxidative stress, also includes activation of pro-inflammatory signaling pathways and enhanced immune response. Moreover, oxidative stress and inflammation are inextricably linked, and both are causally involved in regulating the pathological process of IS and AS. CoQ10 can reduce the release of multiple cytokines in AS, including CD11, CD35, CD62, CD63, CD40, PF4, β-TG, CCL5 [40, 49], sP-selectin, C-reactive protein [50], THP-1 [36], ICAM-1, VCAM-1, IL-1, IL-6, TNF-α, and NLRP3 [31].

Differentiation of macrophages is the most important mechanism in the development of AS, and later various types of immune cells in atherosclerotic arteries were discovered one after another [51]. Macrophages play a crucial role in the development and progression of AS by phagocytosing ox-LDL through scavenger receptors, triggering inflammation and subsequent formation of foam cells. These

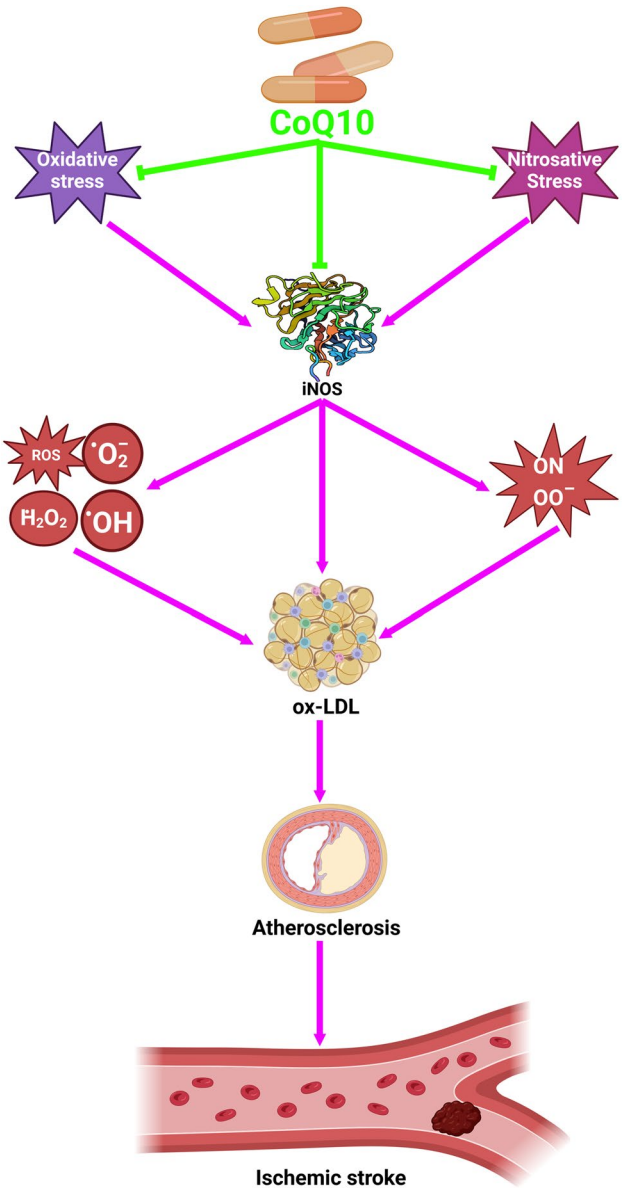


**Fig. 2** Schematic illustration of the anti-oxidative stress effect of CoQ10 after IS. Oxidative stress and nitrosative stress promote ROS and RNS release. Further, the combination of $O^{2-}$ and NO generates $ONOO^-$, leading to DNA damage. CoQ10 prevents IS by inhibiting the development of AS through anti-oxidative stress, regulation of RNS, ROS

lipid-laden macrophages are important in plaque rupture by producing various pro-inflammatory factors. CoQ10 has multiple regulatory effects on immune cells. CoQ10 treatment increases tocopherol levels of monocyte and decreases CD11 and CD35 levels [40].

At the onset of AS, endothelial cells release signals to recruit monocytes, which enter the intima and differentiate into macrophages to phagocytose ox-LDL, exacerbating the inflammatory response and releasing chemokines, which increase plaque volume causing hemodynamic changes

and further promoting plaque formation. The role of macrophages is to remove pro-inflammatory ox-LDL from the endothelium. Macrophages become foam cells once they phagocytize ox-LDL [52]. These macrophages also increase the expression of lectin-like oxidized LDL (LOX-1) and ATP-binding cassette transporter proteins, such as ATP-binding cassette protein G1 (ABCG1), which are involved in reverse cholesterol transport [52]. CoQ10 may be involved in atherosclerotic protection by inducing ABCG1 expression and enhancing HDL-mediated cholesterol efflux from macrophages [53].

The metabolic status of immune cells is significantly altered during atherosclerotic pathology. Metabolic reprogramming plays an important role in the development of AS, and inflammation promotes metabolic reprogramming of macrophages. This metabolic reprogramming promotes phagocytosis, cytokine release and ROS production, exacerbating inflammation, oxidative stress and immune responses [54]. Under physiological conditions, monocytes and lymphocytes rely primarily on oxidative phosphorylation for energy production. The accumulation of lipids in macrophages leads to a reprogramming of cellular metabolism and a metabolic shift towards glycolysis, which enhances their pro-inflammatory activity. This process includes reduced phagocytosis of macrophages and increased production of pro-inflammatory cytokines. The ox-LDL also induces increased glucose uptake by macrophages in a dose- and time- dependent manner, accompanied by an increase in lactate production [55]. Glucose over-utilization promotes IL-6 and IL-1β secretion by monocytes and macrophages, and increases inflammation [56].

Metabolic reprogramming also plays an important role in the regulation of macrophage polarization. Macrophages are mainly classified into pro-inflammatory M1 and anti-inflammatory M2 phenotypes. M1 macrophages are mainly dependent on glycolysis, whereas M2 cells are more dependent on oxidative phosphorylation [57]. Inhibition of glycolysis reduces the M1 phenotype of macrophages. However, monocyte glycolytic enzyme expression levels appear elevated in patients with AS, exhibiting a pro-inflammatory phenotype [58]. CoQ10 plays a key role in electron transfer in mitochondrial oxidative phosphorylation [59]. Thus, CoQ10 may be useful in the metabolic reprogramming of AS.

In addition to monocytes, multiple cell types are active in AS, such as neutrophils, lymphocytes, smooth muscle cells and endothelial cells, and they are also involved in the formation of AS. Due to the specificity of endothelial cells (endothelial damage is the earliest event of AS), the main role of endothelial cells is discussed in the next section.

In atherosclerotic lesions, there is also a differentiation of foam cells from smooth muscle cells (SMCs), which make up the majority of the cells, and they are mainly involved in intimal thickening. As time progresses, foam cells infiltrate into the intima, which disrupts the elastic layer of the arterial intima, and calcification of the artery occurs as vascular SMCs and extracellular matrix increase in mass and volume. This is a biomineralization process manifested by the deposition of insoluble calcium in the form of calcium salts in the atherosclerotic plaque, which eventually leads to arterial stiffness. This process may be mediated by proteoglycans that have the ability to bind calcium [60]. In addition, glycolysis is also involved in the proliferation, migration and calcification of SMCs [61]. High rates of glycolysis and low rates of glucose oxidation are observed during atherosclerotic calcification. The Warburg effect refers to the switch in energy metabolism from oxidative phosphorylation to glycolysis, and the Warburg effect can induce SMCs proliferation, leading to AS [62]. Stimulation of SMCs by ox-LDL causes a Warburg effect, resulting in increased glucose uptake and lactate formation. SMCs exhibit higher rates of glucose metabolism and lactate production than normal cells [63]. There are no studies related to the effect of CoQ10 on IS and AS glycolysis, and CoQ10 may have beneficial effects on metabolic reprogramming. Recent studies found that CoQ10 can reduce the expression of glycolysis-related genes, but future studies are still needed to reveal the regulatory mechanism of CoQ10 on metabolic reprogramming [64].

Over time, neutrophils undergo apoptosis, reducing the inflammatory process. However, if macrophages are not able to phagocytose neutrophils in time, then neutrophils become necrotic, which exacerbates inflammation. At this point, cells can experience activation and release of neutrophil extracellular traps (NETs), a defense mechanism, but may exacerbate the inflammatory response with detrimental effects. NETs are also important in IS and AS pathology, and recent studies have found that NETs are elevated in IS and AS patients and are associated with poor IS outcomes [65, 66]. CoQ10 treatment improved neutrophil extracellular traps and differentiation of pro-inflammatory T cell [67].

The main role of dendritic cells is to initiate antigen-specific adaptive immune responses, and in the early formation of atherosclerotic lesions, dendritic cells become foam cells through uptake of lipoproteins and lipid-loaded apoptotic cells, but dendritic cells have a poor efferocytosis, which AS produce adverse effects [51]. However, there are no studies on the effect of CoQ10 on dendritic cells.

Calcification is important in the development of the pathological process of AS and can determine the outcome of IS. Plaque calcification is mainly caused by dysregulated calcium ion deposition and impaired clearance, also known as biomineralization. Rupture-prone atherosclerotic plaques usually have a thin fibrous cap. In contrast, plaques with limited lipid accumulation and a thick fibrous cap are often referred to as stable plaques. The inflammatory process

reduces collagen in atherosclerotic plaques. And MMPs released by inflammatory cells degrade the extracellular matrix, promoting AS plaque progression and rupture [68]. In addition to ROS, inflammatory and immune responses also determine atherosclerotic plaque stability. For example, plaques formed by the M1 phenotype of macrophages are unstable, while the M2 phenotype is stable [51]. Moreover, the predominant phenotype of symptomatic patients is M1 macrophage, while M2 phenotype is predominant in asymptomatic patients [51].

There are no clinical studies on the effects of CoQ10 on the stability of atherosclerotic plaques in the middle veins. A clinical study found that CoQ10 was beneficial for vascular stiffness. Animal studies found that CoQ10 treatment of atherosclerotic rabbit for 36 weeks has increased stability of atherosclerotic plaque [69]. CoQ10 may also increase stability of atherosclerotic plaque by elevating collagen concentrations [70].

The regulation of CoQ10 on stability of atherosclerotic plaque may be due to multiple factors, including the reduction of glycolysis, oxidative stress, inflammatory and immune response to ROS, release of MMPs, modulation of ox-LDL and HDL levels, reduction of angiogenesis and apoptosis, and increase in collagen levels to maintain the extracellular matrix by CoQ10. These need to be confirmed in future experiments. The schematic diagram of CoQ10 for prevention of AS progression is shown in Fig. 3.

### The Effect of CoQ10 Against Cell Death

Shortly after IS, the cerebral blood flow reduced, which decreased the access of brain cells to oxygen and glucose, leading to neuronal cell death. CoQ10 reduces neuronal death in IS through regulation of pro-survival and anti-apoptotic pathways, including increased expression of Akt, glycogen synthase kinase 3β (GSK3β), B-cell lymphoma-2 (Bcl-2), and forkhead box O3 (FOXO3A), and decreased expression of BCL2-Associated X (Bax), Bcl-2 interacting mediator of cell death (Bim), cysteinyl aspartate specific proteinase 3 (caspase-3), c-Jun N-terminal kinase (JNK3), C-Jun N-terminal kinase (c-Jun), cytochrome C, caspase-9, and $Ca^{2+}$ content [20, 24, 27]. In addition, CoQ10 protects blood-brain barrier integrity by resisting autophagy and reducing matrix metalloproteinase-2 (MMP-2) and metalloproteinase-9 (MMP-9) expression[18, 21]. These effects are inextricably linked to the anti-inflammatory and anti-oxidative stress mechanisms of CoQ10. CoQ10 improves anxiety and depression-like behavior and cognitive impairment by increasing SOD and BDNF levels [25]. This effect may involve anti-autophagy, with CoQ10 treatment reducing the Lc3-II/Lc3I ratio.

However, the mechanism of CoQ10 in the treatment of IS needs to be revealed in more studies in the future. Furthermore, the role of CoQ10 as an endogenously produced antioxidant may be even more important for the prevention of IS.

## Discussion

Although CoQ10 is often described as a vitamin-like substance, CoQ10 by definition is not a vitamin as it is produced by various tissues in the body. CoQ10 is mainly produced by HMG Co-A reductase. In addition, CoQ10 can also be formed from Coenzyme Q and hydroxyalanine by the catalysis of polyprenyl-4-hydroxy benzoate transferase. The

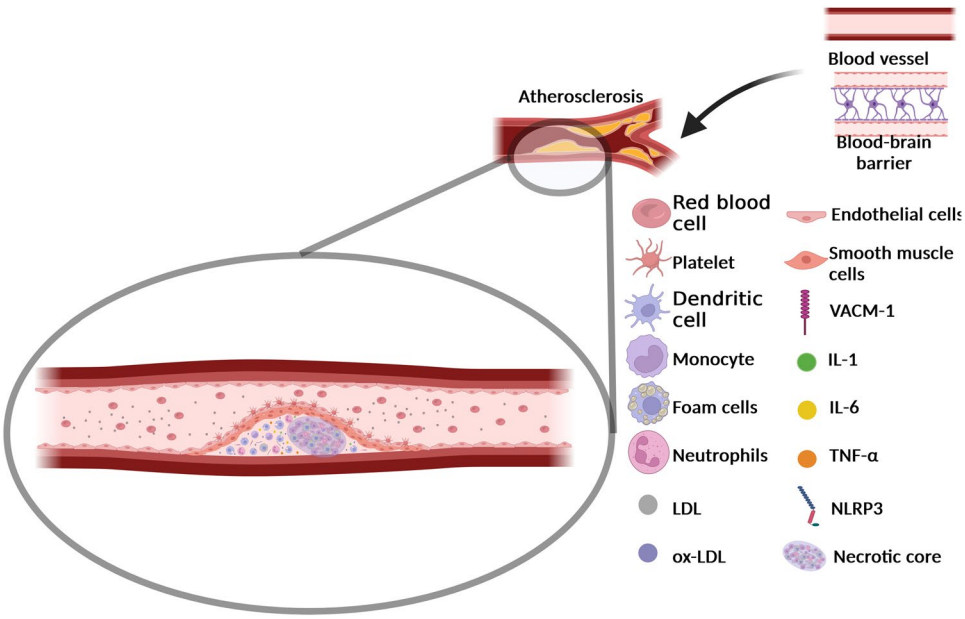


**Fig. 3** CoQ10 inhibits the pathological progression of AS by regulating multiple immune cells and reducing inflammatory responses and cell death. CoQ10 treatment improved neutrophil extracellular traps and pro-inflammatory T cell differentiation. And CoQ10 promotes anti-inflammatory M2 phenotype transformation of macrophages, and promotes ABCG1 expression to enhance HDL-mediated cholesterol efflux from macrophages and among others

decaprenyl diphosphate synthase subunit family gene is an important gene in the regulation of CoQ10 [71]. CoQ10, a key component in the mitochondrial respiratory chain, is involved in the electron transport process where CoQ10 accepts electrons from complexes I and II and transfers them to complex III, thereby driving ATP synthesis. Statin inhibits the 3-hydroxy-3-methylglutaryl coenzyme A reductase, resulting in decreased intracellular concentrations of CoQ10 and cholesterol [72]. This is a potential cause of statin-related muscular symptoms. CoQ10 has many important cellular functions, particularly within the mitochondria. In mitochondria, CoQ10 plays a key role as an electron carrier in the oxidative phosphorylation of the mitochondrial electron transport chain. It is also involved in the metabolism of pyrimidines, fatty acids and mitochondrial uncoupling proteins, as well as in the regulation of mitochondrial permeability. These roles of CoQ10 should not be overlooked [73]. Moreover, CoQ10 inhibits lipid peroxidation in biological membranes and protects mitochondrial proteins and DNA from oxidative damage [74]. Furthermore, it is the only lipophilic antioxidant that can be synthesized from scratch by cells and has an enzymatic mechanism to regenerate its reduced form. However, endogenous CoQ10 levels decrease with age, along with impaired oxidative phosphorylation and antioxidant capacity. It was found that the optimal production of CoQ10 occurs around age 25, with levels at age 65 being only about 50% of those at age 25 [73]. Because of this, CoQ10 has become the third most important nutritional supplement after fish oil and multivitamins. But is CoQ10 supplementation necessary? In this section, we will discuss the scope, dosage and safety of CoQ10.

## Indications and Dosage of CoQ10

### AS and IS

The multiple protective effects of CoQ10 have a positive effect on the development and progression of IS and AS. CoQ10 can be used as an adjunctive agent in the treatment of IS and AS.

### Dosage and Safety

The recommended daily dose varies by indication, but is usually around 30 to 100 mg in healthy individuals, and up to 60 to 1200 mg under medical conditions [75]. It was found that 3600 mg/day of CoQ10 remains safe [75]. 2400 mg/day of CoQ10 supplementation reached equilibrium with respect to plasma CoQ10 concentrations [75]. Therefore, 2400 mg/day may provide the best balance between CoQ10 safety and blood levels [75]. CoQ10 is therefore a safe supplement, but the adverse effects and drug co-actions of CoQ10 need to be discovered in more experiments, except for the co-actions with drugs such as warfarin and antihypertensives.

## Limitations and Future Perspectives

### Low Bioavailability

CoQ10 has high molecular weight (863.34 g/mol) and poor water solubility. CoQ10 is almost insoluble in water, slightly soluble in ethanol, and soluble in acetone and ether. This limitation leads to its poor oral bioavailability.

### Storage Difficulties

CoQ10 is a yellow crystalline powder with a melting point of about 48 °C. CoQ10 is unstable and susceptible to the effects of heat, light and oxygen, which limits its use in pharmaceutical and functional food formulations. Moreover, CoQ10 has a low melting point, which makes it difficult to press CoQ10 into tablets because it causes stickiness and adherence to mechanical surfaces when the temperature exceeds its melting point [73]. In addition, CoQ10 should be stored in a cool and dark place, preferably in sealed containers, as it is affected by light, heat and oxidation [73].

### Gradually Increasing Prices

In general, microbial biosynthesis is the preferred and most widespread method for industrial production of CoQ10 [73]. However, microbial bioproduction is not sufficient to meet the current market demand, which leads to higher prices. Tablets are the cheapest processing method, but the physical properties of CoQ10 and the bioavailability limit the use of tablets. As a result, various formulations to improve bioavailability have increased the price of CoQ10 even more.

### The Combined Effect with Other Medications

The combination of CoQ10 with other drugs has both advantages and disadvantages. It was found that CoQ10 and the anticoagulant drug fawarin produced adverse reactions, resulting in reduced anticoagulant effect [76]. In addition, CoQ10 and Vitamin K antagonistic anticoagulants increased the risk of bleeding [77]. CoQ10 in combination with cyclosporine can reduce renal toxicity [78]. Also, CoQ10 may reduce the side effects of statin-related muscular symptoms [79].

The synergistic effect of CoQ10 and vitamin E is not clear, and the combination of CoQ10 and vitamin E

shows different effects in many diseases, such as metabolic syndrome and alcoholism. In preclinical studies, vitamin E combined with coenzyme Q10 was found to be more effective. However, it still needs to be confirmed in future clinical trials [19].

To address these issues, it is necessary to develop lower-cost industrial production systems for CoQ10 and more efficient delivery systems for CoQ10. In addition, more experiments are needed to demonstrate the combined effects of CoQ10 and vitamin E in the future.

## Conclusion

CoQ10, an antioxidant that offers benefits to multiple body systems, has therapeutic and/or positive effects on IS and risk factors, such as AS, diabetes, hyperlipidemia, hypertension, metabolic syndrome, smoking, drinking, infection, occupational exposure, mental illness, menopause, atrial fibrillation, hyperthyroidism, chronic kidney disease, and moyamoya disease. The above people may be suitable for supplementation with CoQ10. First, CoQ10 is already present in the body and exogenous supplementation of CoQ10 does not interfere with endogenous CoQ10 synthesis. Second, CoQ10 is safe and generally does not react adversely with other drugs. Moreover, CoQ10 is affordable and easy to obtain. However, some efficacy, long-term safety and adverse reactions with other drugs of CoQ10 still need more experimental studies.

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This article describes the optimal therapeutic dose and safety of CoQ10.

**Author Contributions** Zhilei Jia contributed to conceptualization, literature search, manuscript writing, and draft preparation. Xiaoya Yu contributed to literature search and manuscript writing. Xu Wang and Jinhua Li contributed to conceptualization, drafting, guidance, and editing of the manuscript. All authors contributed to the article and approved the submitted version.

**Funding** This study was supported by the grants from the National Natural Science Foundation of China (82103892), and the Science and Technology Development Bureau of Jilin Province, China (20220505042ZP).

**Data Availability** No datasets were generated or analysed during the current study. The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

## Compliance with Ethical Standards

**Competing Interests** The authors declare no competing interests.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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