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Recent Advances in the Neuroprotective Potential of Coenzyme Q10 (Ubiquinone) and its Analogues

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Abstract

Many neurodegenerative diseases share the same pathophysiology and etiologies, this led us to search for a product that may fit in the treatment of most of diseases, including neurological, cardiovascular, cancers, etc. Coenzyme Q10 is a natural product found in many kinds of beings like fish, beef, organ meat (liver, heart), whole grains, etc. Many studies on different animal models have concluded that coenzyme Q10 has neuroprotective effects against neurological disorders, improves mitochondrial functions, prevents oxidative stress and cellular death, stimulates cell growth, inhibits inflammation, and enhances neurogenesis. In addition, it decreases cerebral infarct size, inhibits platelet aggregation and blood thrombosis, and improves endothelial dysfunction. Coenzyme Q10 has important roles in different body systems ranging from cardioprotection, hepatoprotection, gastroprotection and nephroprotection to a documented function in slowing the aging processes. This article aims to summarize and discuss up-to-date experimental findings related to the mechanisms by which coenzyme Q10 and its analogs assist in treatment and thus improvement of many conditions in animals and human.

Introduction

The search for new treatments of ischemic stroke, neurodegenerative diseases, their risk factors, and their complications has always been the focus in neurology. Although each neurodegenerative disease has a specific pathology, they all share several pathophysiological similarities on the sub-cellular level. Those similarities include increased levels of oxidative injury, mitochondrial dysfunction, neuroinflammation, protein aggregation and apoptosis that contribute to neuronal loss [1]. In the late 1950s, Frederick Crane isolated Coenzyme Q10 (CoQ10) from lipid extracts of beef heart [2], and since then, more research projects have been performed to uncover information about its potential uses in medicine. CoQ10 also known as coenzyme Q, ubidecarenone, ubiquinone, and 2-methyl-5,6-dimethoxy-1,4-benzoquinone [3], is a fat-soluble vitamin-like compound [4] and an essential constituent of the mitochondrial respiratory chain (MRC) in almost all human cells. CoQ10 is found in nature as a biological tissue-extract (ubiquinone-10), a chemically-synthesized ubiquinone [5, 6], and as a byproduct of microbial fermentation [7]. Other natural sources of CoQ10 include fish oil, organ meats (liver, heart), and whole grains [8]. CoQ10 consists of a substituted quinone headgroup combined with an isoprenoid chain that has different lengths in different species. In human, the chain contains ten isoprenoid units [9], while in most rodents it contains 9 units (CoQ9) [10]. CoQ10 has three redox states, these include: oxidized ubiquinone, semiquinone (ubisemiquinone), and reduced (ubiquinol, $CoQ10H_2$) [11] that acts as a powerful antioxidant protecting membrane lipids from peroxidation [12]. Reduced CoQ10 (ubiquinol) achieves many-fold higher serum levels compared to oxidized CoQ10 [13,14]. However, processes of oxidation and reduction of coenzyme Q10 can also take place in Golgi apparatus, lysosomes and plasma membranes [15]. Several researchers have focused on the human metabolism and pharmacokinetics of CoQ10, and showed that exogenous CoQ10 is safe for human use with no reported serious side effects [16]. This is attributed to the fact that CoQ10 is synthesized endogenously, mainly by the mevalonate pathway [17–19]. Gastrointestinal discomfort is one of the most occurring adverse events in both animals and human [20]. CoQ10 therapy is available as an over-the-counter dietary supplement and as an add-on therapy to assist in the treatment of different diseases in many countries [21]. In human, CoQ10 status is recognized by measuring serum CoQ10 concentration [22]. However, CoQ10 levels in blood and tissues are decreased with both normal aging and disease conditions such as cardiovascular diseases [23], neurodegenerative disorders, myopathies and cancers [14, 24]. Not only CoQ10 causes scavenging of free radicals [19], but also enhances the availability of other antioxidants such as vitamin A, vitamin C, vitamin E, and β-Carotene [25, 26]. Many studies on different animal models have concluded that CoQ10 has neuroprotective effects against neurological disorders, such as stroke and other neurodegenerative diseases, owing to its roles in improving mitochondrial functions, preventing oxidative stress [27] and cellular death, stimulating cell growth [28], inhibition of inflammation, and enhancing neurogenesis [29–31]. In addition to its roles in decreasing the cerebral infarct size, inhibiting platelet aggregation and blood thrombosis and improving endothelial dysfunction [32], it also offers great assisting benefits in the treatment of ischemic strokes, myocardial infarction (MI) and ameliorating their associated post-onset changes [33, 34]. In addition to its neuroprotective functions, CoQ10 has important roles in different body systems ranging from cardioprotection [23, 35], hepatoprotection [26, 36, 37], gastroprotection [38, 39], and nephroprotection [25, 40], to documented functions in slowing the aging processes [41, 42], fighting obesity, enhancing immunity [43], and improving the general health. Table 1 lists some conditions that may benefit from CoQ10 treatment.

Coenzyme Q10 nanoparticles (CoQ10-NPs) were recently formulated using nano-technology. They are superior to the native CoQ10 form in different aspects, including their greater hepatoprotective effects. Their superiority is due to their higher solubility and oral bioavailability. It is important to mention that CoQ10 nanoparticles are safe for human usage [44, 45]. Mitoquinone (MitoQ) [46–48] and Idebenone (IDE) are neuroprotective, synthetic analogs of coenzyme Q10 [49, 50]. Idebenone (IDE), (2-(10-hydroxydecyl)-5,6-dimethoxy-3-methyl-cyclohexa-2,5-diene-1,4-dione) [51], was initially developed for the treatment of cognitive disorders and Alzheimer's disease (AD). Later on, IDE was approved for the management of Friedreich's ataxia [52], Duchenne muscular dystrophy (DMD) [53] and Leber hereditary optic atrophy (LHON: a mitochondrial inherited degeneration of retinal ganglia and their axons) [54]. CoQ10 might hold a great value in the future management of many disabling neurological disorders, including ischemic stroke, AD, PD, HD, demyelinating and seizure disorders and their neuropsychiatric consequences

ranging from anxiety and depression to even dementia disorders. This article aims to summarize and discuss up-to-date experimental findings related to the mechanisms underlying CoQ10 and its analogs in ischemic stroke, neurodegenerative diseases, epilepsy, multiple sclerosis (MS), depression, Gaucher disease (GD), myocardial infarction (MI), and diabetes mellitus (DM). CoQ10 will refer specifically to Coenzyme Q10, ubidecarenone, ubiquinone, ubiquinone-10 in our further writings.

Selection of articles

The search for articles was performed on Medline, PubMed, and ScienceDirect databases using keywords such as coenzyme Q10, ubidecarenone, ubiquinone, ubiquinone-10, ubiquinol, MitQ, Idebenone, and IDE. This yielded a wide range of articles, including cell cultures, animal models and human trials. Recent articles on animal models or cell cultures directly assessing any involved mechanism of CoQ10 beneficial effects on different neurological conditions as ischemic stroke, neurodegenerative diseases, demyelinating diseases (MS), epilepsy, or psychiatric disorders as depression, cardiovascular conditions as diabetes, myocardial infarction, hypertension, and obesity were included in this review paper. Other conditions as the primary CoQ10 deficiency, Gaucher disease and cancer were also selected.

Primary CoQ10 deficiency

Primary CoQ10 deficiency, a rare genetic disorder, is defined as an autosomal recessive disease [55–57], caused by mutations in genes that are required for endogenous synthesis of CoQ10. Ataxia with cerebellar atrophy is the most common form. This indicates that the cerebellum is selectively sensitive to declined levels of CoQ10 [58]. Findings as seizures, cognitive deficits, muscular weakness, neuropathy, and hypogonadism may co-exist with ataxia in some cases [59]. However, this condition responds effectively to treatment with CoQ10 [60]. The clinical deterioration in individuals with CoQ10 deficiency was reported following treatment with idebenone, indicating that IDE cannot be used as an alternative for CoQ10 [61]. In newborns, fatal neonatal multi-organ dysfunction can be present in CoQ10 deficiency and can be reversed by the early CoQ10 administration. In preterm infants, CoQ10 was shown to protect erythrocytes from hemolysis by H_2O_2 [62]. Here in the following sections, we summarized the primary deficiency able to recognize the secondary deficiencies as well.

CoQ10 and ischemic stroke

Ischemic stroke is a serious health problem with high morbidity and mortality rates worldwide [63]. This implies that stroke treatment; minimizing tissue damage, and decreasing post-ischemic neuronal loss, and most importantly prevention of its occurrence and recurrence virtually define the goals of modern management [64–66]. Many studies have stated the benefits of CoQ10 in the prevention and management of ischemia in animals' stroke models. It has been shown that CoQ10 administration leads to elevation of endogenous CoQ10 content in rat brain [67–70]. Recent experimental results indicate that CoQ10 could be used as a primary medication in the acute phase of stroke [71] since it exhibited beneficial effects against experimental cerebral ischemia/reperfusion (I/R) injury [72–74], and was also reported by many studies to decrease size of cerebral ischemic or infarction zones [71, 75, 76], resulting in improvement of both functional and morphological indices of brain damage [71], thus improving neurological and neurobehavioral outcomes [48]. The mechanisms by which CoQ10 ameliorates ischemic stroke injury are described in this section.

Antiplatelet aggregation and antithrombotic effects

The diminished incidence of platelet aggregation, the decreased vascular endothelial injury and the prevention of thrombotic complications are all thought to be among the multiple beneficial clinical effects of CoQ10 in prevention and treatment of cerebral ischemia [77, 78]. CoQ10 is able to cross the blood-brain barrier (BBB) and can accumulate in the brain [65, 71]. However, it's supplementation in swine had shown a significant inhibition of adenosine diphosphate (ADP)-induced platelet aggregation, a decrease in plasma fibronectin, prostaglandin I2 (PGI2), thromboxane B2 (TXB2), and endothelin-1 (ET-1) levels [79], and in human, CoQ10 was shown to significantly inhibit the platelet vitronectin receptor expression [80–82]. Endothelial dysfunction plays a basic role in the pathogenesis of acute ischemic stroke (AIS), and prevention of such damage by CoQ10 therapy is thought to be due to its well-known ability to improve endothelial nitric oxide (NO) bioavailability [83–85], and maintain the endothelial intracellular calcium concentration. Additionally, it suppresses the gene expression of the "nuclear factor kappa-light-chain-enhancer" of activated B cells (NF-κB) [82], thereby inhibiting the

release of cytochrome C (Cyto C) [85] and deactivating the proapoptotic protein caspase 3(CASP3). Endothelium-derived- relaxing factor (EDRF) is deactivated by free radicals, the latter are inhibited by CoQ10 therapy [86].

An study showed that CoQ10 enhances the antioxidant capacity of both glutathione-disulfide reductase (GSR) and superoxide dismutase (SOD) [87]. SOD converts free superoxide radicals (O^{2-}) into hydrogen peroxide (H_2O_2), which is converted into oxygen (O_2) and water (H_2O). Moreover, the activity of extracellular superoxide dismutase (SOD3) and endothelium-dependent vasodilation are remarkably improved by CoQ10 supplementation [88]. In hypercholesterolemia, it was found that treatment with CoQ10 suppressed the oxidized low-density lipoprotein (oxLDL)-induced down-regulation of endothelial nitric oxide synthase (eNOS) and up-regulation of inducible nitric oxide synthase (iNOS). It also reduced the levels of nitrotyrosine and decreased the release of reactive oxygen species (ROS) [85, 89]. Furthermore, its daily supplementation results in decline in plasma LDL concentrations as well as rise in HDL concentration [86, 90]. Together, these findings demonstrate the antiplatelet and vascular endothelial-protective functions of CoQ10, which can be decisive in the management outcome of ischemic stroke patients and might establish an essential field for further therapeutic options.

Effects on neuronal cell apoptosis

The antiapoptotic potential of CoQ10 is demonstrated in both *in vivo* [91, 92] and *in vitro* [33, 93]. Antiapoptotic function of CoQ10 is believed to be through activation of the phosphatidylinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway, which is confirmed by the decreased number of apoptotic cells and increased viability of neural stem cells [94]. B-cell-lymphoma-2 (Bcl-2) family is a group of regulator proteins that possess both mediatory and inhibitory roles and are considered essential anti-apoptotic proteins [95]. Experimental studies showed an increased expression of B-cell lymphoma 2 (Bcl-2) [96], phosphorylated glycogen synthase kinase 3-β (pGSK3-β), and phosphorylated Akt (pAkt), coupled with reduced expression of caspase-3 [94], caspase-9, and Bcl-2-associated X protein (BAX) after administration of CoQ10 [69]. Suppressed activity of phosphatidylinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway results in dephosphorylation of Forkhead box O3 (FOXO3, FOXO3a), resulting in its nuclear translocation and the enhancement of Bcl-2 interacting mediator of cell death (Bim) expression. The last-mentioned promote apoptosis by the activation of caspase-3 and cytochrome C release from the mitochondria [97]. Recent studies suggest that CoQ10 is able to induce Forkhead box O3 (FOXO3, FOXO3a) through the activation of phosphatidylinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway [92, 98]. CoQ10 can inhibit neuronal death via inhibition of c-Jun N-terminal kinase 3 (c-JNK3) [92, 99, 100]. Together, the above findings support the claimed beneficial effect of CoQ10 in the management of stroke by reducing or inhibiting neuronal cell apoptosis.

Effects on mitochondrial function

As a basic element of the mitochondrial electron transport chain (ETC), CoQ10 transfers electrons from respiratory complex I and II to complex III, driving oxidative phosphorylation to produce ATP needed to maintain functions of the brain [17,101–103]. Brain mitochondrial and plasma levels of CoQ10 are decreased in cerebral I/R injury in rat models, resulting in the suppression of mitochondrial activity [104–106]. However, this reduction was reversed after supplementation of intravenous (IV) injection of solubilized exogenous CoQ10 [71], and its levels in mitochondria were significantly increased [107]. Glutamate excitotoxicity results from excessive release of glutamate in the brain under pathological CNS conditions, such as stroke and other neurodegenerative diseases [108]. Glutamate excitotoxicity is associated with failure to maintain calcium homeostasis in the cell, mitochondrial dysfunction, overproduction and generation of oxidants, such as ROS and reactive nitrogen species (RNS), and a loss of mitochondrial membrane potential [108]. CoQ10 was reported earlier to prevent glutamate toxicity by preserving mitochondrial structure [30]. The mitochondrial dysfunction associated neurotoxicity could be ameliorated by CoQ10 [109]. CoQ10 prevents mitochondrial dysfunction-induced activation of apoptosis [33, 110]. Orally delivered water soluble CoQ10 (Ubisol-Q10) was shown to block dynamin-related protein (Drp1) [111] and prevent formation of mitochondrial permeability transition pore (MPTP or mPTP) protein, which once stimulated, can result in mitochondrial swelling, and may even cause cell death [112]. Additionally, ubisol-Q10 prevents potential loss of mitochondria and restores their calcium capacity. In addition, it inhibits the release of

Apoptosis Inducing Factor (AIF), and improves cell survival [111,113,114].

Studies have also shown that the expression of peroxisome proliferator-activated receptor (PPAR) coactivator-1α (PGC-1α) is upregulated by CoQ10, leading to the activation of mitochondrial biogenesis [42, 115]. On one hand, mitochondrial fission can enhance the release of cytochrome C, that eventually results in cell death. On the other hand, mitochondrial fusion may contribute to the mitochondrial network maintenance, thus enhancing survival. However, the expression of mitochondrial fission 1 protein (FIS1) was decreased, and expression of mitofusin-2 (Mfn2) was increased following treatment with CoQ10, resulting in a well-balanced mitochondrial fission/fusion and amelioration of cerebral I/R injury [74].

Effects on oxidative stress

Oxidative stress (OS) leads to CoQ10 deficiency, as the latter is consumed by reactive oxygen species (ROS) generation [104, 106]. Early experimental results showed that dietary supplementation with ubiquinol could lead to a significant decline in the senescence grading scores along with a significant increase in body weight and improvement of behaviors and appearance in accelerated senescence-prone-1 (SAMP-1) mice [116]. Parameters of oxidative stress such as the glutathione disulfide /glutathione (GSSG/GSH) ratio, malondialdehyde (MDA), or antioxidant (AOX) activities could be involved in its beneficial effects [116]. In the brain, CoQ10 can effectively inhibit the production of (ROS), thereby minimizing ischemic neuronal damage and providing neuroprotection [33, 117]. In the Ischemia/Reperfusion (I/R) model, the elevated levels of malondialdehyde (MDA) were significantly decreased in rats treated with CoQ10 [30, 118]. That is attributed to its powerful antioxidant effects, and the role that it plays in inhibiting lipid peroxidation [119–121]. Twendee X (TwX) is an antioxidant mixture results from combining CoQ10 with other powerful antioxidants, as: ascorbic acid and cystine [122]. Recently, (TwX)'s mechanisms of action during oxidative stress in ischemic models have been better clarified. In mouse stroke model, it's administration showed a significant reduction in oxidative stress (OS) by inhibiting its markers: 8-hydroxy-2'-deoxyguanosine (8-OHdG), and N(6)-carboxymethyl lysine (CML). In addition, brain sections have also shown a reduction in 4-hydroxynonenal (4-HNE), a marker for lipid peroxidation [122]. All the findings above suggest that CoQ10 possesses preventive and therapeutic effects against ischemic stroke. Also, a better outcome may be granted by combining CoQ10 with other powerful antioxidants, such as: vitamin C, cysteine and vitamin E as in TwX.

Anti-inflammatory effects

Cytokines are produced by different kinds of cells in the brain, such as immune cells, neurons [123], and astrocytes [124]. However, peripherally-derived cytokines can also provoke inflammation of the central nervous system (CNS) [125]. In humans, administration of (CoQ10) has shown to significantly decrease the serum levels of (TNF-α) [126]. CoQ10 plays an important role in decreasing the production of pro-inflammatory cytokines by inhibiting the gene expression of (NF-κB) of activated B cells [127]. There is substantial evidence that pro-inflammatory cytokines such as tumor necrosis factor- alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin 6 (IL-6) are released by microglial cells once activated by ischemia [128–130]. Treatment with CoQ10 results in suppression of both (TNF-α) and (IL-6) levels in rat stroke model [69, 131]. These results are supported by previous findings that showed a decreased hepatic mRNA expression of (IL-6) and (TNF-α) after CoQ10 supplementation in mice [132]. *In vitro*, ubiquinol-10 was shown to reduce the expression of monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein 1-alpha (MIP-1α) in cultured cells [133]. Another recent study showed that ionized calcium-binding adapter molecule1 (IBA1) was significantly reduced by TwX in mouse stroke model [122]. Post-ischemic neuroinflammatory changes result in exacerbation of cerebral injury by causing cerebral edema, neuronal cell death and dysfunction of the blood-brain barrier (BBB). Therefore, therapeutic targeting of the neuroinflammatory pathways in acute ischemic stroke patients with the administration of CoQ10 may have benefits alleviating the neurological ischemic injuries, obtained by decreasing production and release of pro-inflammatory markers [69, 134].

Effects on neurogenesis

The development of new therapeutic strategies to enhance neurogenesis should gain more attention by researchers, since improving neurogenesis will ameliorate neurological functions in patients with ischemic brain injury [64]. Adult neural stem cells (NSCs) in the subventricular region of the lateral ventricle and the dentate gyrus of the hippocampus can be activated after stroke, differentiate into astrocytes [135, 136], proliferate and produce

neuroblasts that migrate to the infarcted area and contribute to the repair of the infarcted brain tissues, as well as the formation of glial scar tissue [137–141]. However, under ischemic stroke, NSCs themselves can also be damaged by hypoxia [142]. Therefore, it is important to provide protection for NSCs against stroke in order to replace damaged brain cells [144]. Phosphatidylinositol 3-kinase (PI3K) pathway is activated by CoQ10, which has been reported to enhance the proliferative activity of neural stem cells (NSCs) by significantly increasing the expression of a number of survival-related proteins such as p85a PI3K, protein kinase B (Akt), phosphorylated Akt (pAkt), phosphorylated glycogen synthase kinase 3-β (pGSK3-β), and B-cell lymphoma 2 (Bcl-2), and inhibiting the expression of death-related proteins such as cytochrome C and active caspase-3 [94, 143, 144]. Additionally, a study observed that astrocytes viability *in vitro* was increased with CoQ10 treatment [33]. Inhibition of ROS production, and restoring cellular antioxidants, such as alpha-tocopherol and ascorbic acid were also observed following CoQ treatment [93]. In rats, intravenous CoQ10 administration has shown protective effects on the penumbral region, and has been confirmed to limit the infarction diameter [65].

CoQ10 and neurodegenerative diseases

CoQ10 and Alzheimer's disease

Alzheimer's disease (AD), the most common in the family of neurodegenerative disorders, is a chronic, fatal, incurable age-related disorder with irreversible and progressive deteriorations in cognition and behavior [145]. Although it is the most common form of dementia, pathogenesis of AD is still not completely understood, but selective pyramidal neuronal death [146] and plaque accumulation of misfolded amyloid beta (Aβ) and tau proteins in the hippocampus are strongly accepted as the most common pathological alterations [147]. Mitochondrial dysfunction and oxidative stress are the primary events in AD pathophysiology [148, 149]. Other documented mechanisms include: excitotoxicity, neuroinflammation, neurotransmitter deficits and even apoptosis and neuronal loss [150]. Earlier results showed that ubiquinol [151] and MitoQ have protective roles in Alzheimer's disease [46, 152, 153]. Up-to-date, several experimental studies have concluded that CoQ10 possesses a beneficial multi-targeted approach in different mouse models of Alzheimer's disease. An early study reported that CoQ10 can significantly reduce plaque pathology in the APP/PS1 mouse model of AD [154]. In Tg19959 mouse model of AD, CoQ10 was reported to decrease the levels of Aβ42 and AβPP β-carboxyterminal fragments (sAβPPβ) [155]. It was also shown to mitigate sevoflurane-induced cognitive impairment in young mice by rescuing related mitochondria [156, 157].

The effective antioxidant role that CoQ10 plays against oxidative stress (OS) in hippocampal tissues is related to its capacity in the replenishment of the hippocampal glutathione (GSH) and superoxide dismutase (SOD), and the suppression of nitrogen oxide (NOX) subunits [92, 132, 158–160]. The beneficial effects of CoQ10 on human umbilical vein endothelial cells (HUVECs) was found to prevent β-amyloid-induced oxidative stress by decreasing the elevated superoxide (O^{2-}), H_2O_2, and Ca^{2+}, and restoring normal values of NOX in endothelial cells. It also prevented β-amyloid opening of the mitochondrial permeability transition pores (mPTP) in endothelial cells and partially inhibited β-amyloid entry and gathering into endothelial cells' mitochondria [161]. Ubisol-Q10 was also shown to delay premature aging in presenilin-1(PS-1)-mutated cells [162]. A double transgenic study on ubisol-Q10 indicated a significant prevention of the Aβ deposition in the APP/PS1 transgenic mice model of AD. The mechanism is believed to be through enhancing mitochondrial stability and decreasing the levels of ROS [163]. A recent study revealed that chronic administration of CoQ10 in Aβ (1-42) model of AD showed a significant improvement in memory deficits and spatial learning, and also an attenuation in TNF-α levels and AChE activities, plus the restoration of mitochondrial activities, implying its anti-inflammatory, anti-oxidant, and mitochondrial-restoring functions [67].

A study on Aβ25–35-injured PC12 cells showed that CoQ10 exerts anti-inflammatory effects through its inhibitory action on NF-κB. It also suppressed the upregulated protein expression of cyclooxygenase-2 (COX-2) and the levels of prostaglandin E2 (PGE-2). Most importantly, CoQ10 inhibits Aβ25-35- induced-nuclear-factor of kappa-light-polypeptide-gene-enhancer in B cells inhibitor, IκB degradation, and NF–κB translocation [164]. This finding indicates that CoQ10 plays, through blocking NF-κB signaling pathway, a crucial role against AD-related neuroinflammation. Another study on PC12 cells showed that CoQ10 has a protective effect against H_2O_2-induced oxidative cytotoxicity through the nuclear factor erythroid 2-derived factor 2 (Nrf2)

signaling pathway [165, 166]. CoQ10, by multi-mechanisms, improves survival and behavioral abnormalities present in the transgenic mice with P301S tau mutation. Reducing the levels of phosphorylated tau in the cortex, upregulating the major enzymes of the electron transport chain (ECT), and inhibiting lipid peroxidation (evidenced by decreased levels of MDA) are all suggested mechanisms responsible for the mentioned preferable results of CoQ10 treatment in AD models [167].

The phosphatidylinositol 3-kinase (PI3K) pathway is not only highly involved in adult neurogenesis, but also plays a crucial role in controlling tau protein phosphorylation in AD brains. Initial studies showed that CoQ10, through activation of PI3K signaling pathway and inhibition of ROS production, exhibits protective effects against amyloid beta 25–35 (Aβ25–35)-induced neuronal cell death [168]. In neural stem cells (NSCs), it was shown that treatment with CoQ10 could significantly elevate the expression of numerous survival proteins, such as: phosphoinositide 3-kinase subunit p85a (PI3K p85a), protein kinase B (Akt), pAkt (Ser473), glycogen synthase kinase-3 beta (GSK-3b), pGSK-3b (Ser9), and heat shock transcription factor-1 (HSTF-1). On the other hand, CoQ10 remarkably inhibited the expression of death signals, such as: active caspase-3 and cytochrome C [143]. CoQ10 was also shown to reverse age-associated functional impairments in mice, and since AD is an age-related disease, it can benefit from this characteristic feature of CoQ10 [169]. These findings, altogether, show that CoQ10 plays an important multi-facet role in preventing memory loss and cognitive impairment by decreasing amyloid beta and tau proteins accumulation, and fighting oxidative stress, preventing mitochondrial imbalance, enhancing neurogenesis and anti-inflammatory effects.

CoQ10 and Parkinson's disease

Parkinson's disease (PD), a slowly progressive neuropsychiatric disorder, is considered as the 2nd most common neurodegenerative disorder. The main pathological alterations in PD include loss of dopaminergic neurons from substantia nigra pars compacta (SNpc) [170]. Several studies assessing the effectiveness of CoQ10 on PD have been carried out. MitoQ was reported early on to reduce aspects of mitochondrial fission in the 6-OHDA cell model of Parkinson's disease [46]. An increase in brain-derived neurotrophic factor (BDNF) levels following CoQ10 treatment was observed in a rat model of PD indicating its favorable role in improving neurogenesis [171]. A recent study showed that water-soluble CoQ10 protects murine neuronal HT22 cells from rotenone-induced cytotoxicity and ameliorates mitochondrial dynamics by reducing (Drp1) and (Fis1) proteins to pre-rotenone levels. Additionally, it reduces (ROS) accumulation, inhibits Apoptosis Inducing Factor (AIF) translocation and subsequent apoptosis [172]. An experimental study involving haloperidol-induced PD Wistar rats indicated that CoQ10 nanoemulsion, when compared to traditional CoQ10, was more effective in lowering MDA content and increasing GSH concentration. Thus, effectively improving muscular coordination and locomotor activity, and decreasing cataleptic behaviors. These favorable effects are due to its smaller droplet size, hence its enhanced absorption after oral administration and easier penetration into the brain [14]. In a paraquat (PQ)-induced PD model, CoQ10 was able to restore dopamine to normal levels in the brain [173]. A nanomicellar formulation of CoQ10 (Ubisol-Q10) was tested for its possible use as an add-on therapy for PD and was proven to be superior to typical CoQ10 therapy. Results indicated that treatment with ubisol-Q10 could block ongoing neurodegeneration and enhance neuroprotection through astrocytic activation in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-treated mice brain. [174]. A recent study has explored the effect of CoQ10 on aged mice and found that oral supplementation of CoQ10 to old mice could restore the mitochondrial oxygen consumption rate (OCR) and the vesicular glutamate transporter 1 (VGLUT1) to their normal levels. Additionally, it decreased the raised accumulation of ser129-phosphorylated α-synuclein (α-syn) in the motor cortex of these mice [175]. These findings suggest that CoQ10 has anti-aging effects, and hence can be administered as a prophylactic therapy for PD [176]. It is important to mention that behavioral improvement was shown following chronic administration of CoQ10 in transgenic mice P301S and other animals, suggesting its benefits for most neurodegenerative disorders [167]. These studies above suggest that CoQ10 can be a candidate drug of choice for the treatment of PD. More experimental studies are needed to explore other benefits of CoQ10 treatment in PD and the possibility of other mechanisms contributing to its ameliorating effects.

CoQ10 and Huntington's disease (HD)

Huntington's disease (HD) is an incurable, inherited and a progressive neurodegenerative disorder caused by mutations in the gene huntingtin (HTT) [20]. It is

believed that excitotoxicity, increased brain lactate levels, and bioenergetic disturbances are included in the pathogenesis of HD [177, 178]. Previous studies have indicated that treatment with CoQ10 leads to reduction in brain lactate levels [30, 121, 179]. In R6/2 mice model of HD, CoQ10 therapy seems to extend survival, improve rotarod performance, decrease brain and striatal neuronal atrophies, and lessen the appearance of both striatal (HTT) aggregates and macrophage antigen-1 (MAC-1)-positive microglia [180]. Additionally, CoQ10 reduces plasma levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) in both R6/2 mice model and individuals with (HD), implying its function in reducing oxidative stress in HD [20, 181]. Importantly, CoQ10 is thought to be more beneficial if administered in early stages of HD [182, 183]. These above findings suggest that CoQ10 might be an effective additive for the treatment of HD. However, due to scarcity of experimental and clinical studies, more exploration of this promising field is needed.

CoQ10 and other neurological and psychiatrical disorders

CoQ10 and multiple sclerosis

Multiple sclerosis (MS) is an autoimmune, demyelinating and a progressive disorder of the central nervous system (CNS) with extremely disabling consequences. It is characterized by chronic inflammatory changes and axonal loss. Oxidative stress and mitochondrial dysfunctions are also involved in the progression and pathogenesis of MS. Recently, CoQ10 was presented as an antioxidant that is capable of suppressing the inflammatory pathways of MS [184]. MitoQ can readily cross the blood-brain barrier, plasma, and mitochondrial membranes [152]. In models of MS, MitoQ exerted neuroprotective effects and decreased axonal inflammation and oxidative stress, thus decreasing neurological disabilities [185]. MitoQ was reported to protect demyelinated axons from additional degeneration. It attenuates the neuronal toxicity that is induced by lipopolysaccharide-activated microglia. It also reduces IL-6 and improves mitochondrial function [185]. More studies are needed to explore the role of CoQ10 in alleviating demyelinating disease.

CoQ10 and epilepsy

Epilepsy is characterized by seizures that result from spontaneous abnormal electrical discharges in the brain due to molecular and biochemical processes that are still not fully understood [186]. Mechanisms as neuroinflammation [187], oxidative stress (OS) and mitochondrial dysfunction are involved in epilepsy [188, 189]. Up-to-date, many antiepileptic drugs have been developed; however, their disturbing side effects make it so required to develop new antiepileptic drugs with fewer side effects, or with the ability to decrease the side effects if co-administered with conventional antiepileptics [190]. CoQ10 was revealed to have antiepileptic effects, and its combination with l-arginine has resulted in a significant potentiation of their anticonvulsant effects in mice [3]. Early experimental results indicate that pretreatment with CoQ10 has significant ameliorating effects on both pilocarpine-induced seizures, and cognitive impairment related to prolonged use of the anti-epileptic drug phenytoin in rats [191]. The neuroprotective effect of CoQ10 in pentylenetetrazol (PTZ)-induced seizures in mice is explained not only by its role in attenuating oxidative damage, decreasing (TNF-α) levels and thereby reducing neuroinflammation, but also by indirectly inhibiting epileptogenesis through inhibiting microglia and restoring mitochondrial enzyme complex activities (I , II, III and IV) in distinct regions of the brain, implying that CoQ10 acts on multiple targets at different cellular and molecular cascades of complex epilepsy pathogenesis [103]. Another experimental study utilizing the intrahippocampal kainate model of temporal lobe epilepsy (TLE) in rats supported the antiepileptic effect of CoQ10 evidenced by significantly decreasing the elevated MDA and nitrite contents [192]. In the same experiment, CoQ10 was shown to significantly attenuate the intra-hippocampal kainate induced-changes in CA1, CA3 and hilar regions. It lowered mossy fiber sprouting (MFS) intensity in the dentate gyrus of kainite-lesioned rats and significantly decreased seizure severity, and furthermore dropped its incidence rate [192]. CoQ10, by its anti-oxidative and anti-neuroinflammation, seems to decrease side effects associated with anti-epileptics, and more importantly, it showed some favorable anti-epileptic effects in animal models of epilepsy.

CoQ10 and depression

Depression is a major public health problem that is still unsolved properly. Dysfunctional serotonergic system is included in the onset, progression, and course of depression [193]. Different mechanisms such as oxidative stress, neuroinflammation, and decreased antioxidant (AOX) defenses were found to be directly engaged in its pathophysiology [8, 194]. Previously published articles have reported the

contribution of disturbances in the hippocampal neurogenesis and brain-derived neurotrophic factor (BDNF) signaling pathway in the etiology of depression [195–197]. Early studies have addressed that in the chronically-stressed rats or patients with major depression, the activity of the hippocampal glycogen synthase kinase-3β (GSK-3β) enzyme was notably upregulated [198, 199]. CoQ10 and serotonin (5-HT) levels were reported to be significantly decreased in platelets obtained from patients with depression [200], and correlated resistance to antidepressants was also reported [201]. Few studies assessing the effectiveness of CoQ10 in depression have been performed. However, different experimental models showed that CoQ10 could, through its multi-targeted approach, improve depressive-like behaviors in rats. Early results showed that CoQ10 prevents oxidative/nitrosative DNA damage in the hippocampus of rats undergoing chronic restraint stress (CRS) [99]. Prolonged administration of CoQ10 has been shown to induce antidepressant-like activities in Wistar rats, proven by reversal of chronic restraint stress CRS-induced anhedonia, that may be related to its role in reversing mitochondrial disturbances in the frontal cortex (FC) and hippocampus [202]. A recent study supported previously reported anti-depressive effects of CoQ10 therapy [203]. In rat models of depression, CoQ10 was shown to effectively reduce the elevated levels of hippocampal MDA and 4-hydroxynonenal (4-HNE), thus decreasing OS. It also reduced the levels of inflammatory markers, such as: interleukin (IL)-1β, IL-2, IL-6 and (TNF-α). Moreover, CoQ10 could decrease microglial CD68 and increase astrocyte glial fibrillary acidic protein (GFAP) levels in the rat's hippocampus. This could be connected to its ability to reduce indoleamine 2,3-dioxygenase 1 (IDO-1), and thus restoring normal serotonin levels [203]. A recent experimental study demonstrated that Wistar rats that were exposed to chronic unpredictable mild stress (CUMS) protocol exhibited significant drops in 5-HT1A mRNA receptor and a significant increase in 5-HT2A mRNA receptor expression. However, those effects were reversed by CoQ10 treatment with or without the combination with the well-known selective serotonin reuptake inhibitor (SSRI) 'fluoxetine' [203]. This study has also demonstrated that CoQ10 confers preventive antidepressant effects that are in coordination with meaningful upregulation of the hippocampal mRNA expressions of 5-HT1A receptors, pGSK-3β, pCREB and BDNF protein and significant downregulation of mRNA expression of 5-HT2A receptors [203]. These findings together suggest that the anti-deppressant effect of CoQ10 is related to its role in targeting oxidative stress, decreasing inflammatory events, and regulating serotonin levels.

CoQ10 and other conditions

CoQ10 and cardiovascular diseases

Cardiovascular diseases (CVD) is related to conditions including hypertension, atherosclerosis, obesity and diabetes [204]. Increased generation of reactive oxygen species (ROS) are thought to directly contribute to contractile and endothelial dysfunction, myocyte apoptosis and necrosis, and extracellular matrix remodeling in the heart [205, 206]. Oxidative stress plays an important role in the pathophysiology of CVD [207]. Many studies have indicated that CoQ10 has beneficial effects on some cardiovascular diseases such as heart failure and myocardial infarction (MI) via its antioxidative properties and action on the autophagy pathways` in addition to its anti-apoptotic effect on the myocardium [35, 208, 209]. Early study reported that a single dose of CoQ10 could decrease necrotic zone and reduce postinfarction hypertrophy of the left ventricle in rats' model of irreversible myocardial ischemia [210]. Those effects are brought by its positive influence on myocardial Na^+-K^+ ATPase activity and calcium channels plus its role in protecting endothelial cells, ameliorating cardiac bioenergetics, and influencing prostaglandin metabolism. Antiviscosity and antioxidant effects are other important mechanisms involved in cardioprotection brought by CoQ10 [19, 211]. CoQ10 protects against cardiac apoptosis induced by I/R injury by significantly reducing the apoptotic DNA and regulating the expression of Bcl-2 gene [212]. It also induces SOD and GPx, lowers cardiac inflammatory markers like TNF-a and IL-6. and reduced Bax and p53 gene expression in the left ventricle (LV) [34]. CoQ10 also plays a significant role in controlling high blood pressure and can be used as an add-on therapy with other antihypertensive drugs [23].

CoQ10 effect on diabetes mellitus (DM) and it's complications

Acute hyperglycemia was shown earlier to increase the chance of brain damage, activate mTOR pathway, and increase the release of cytochrome C (cyto C) and levels of LC3-phosphatidylethanolamine conjugate (LC3-II) under ischemic conditions [213]. Many studies have reported that CoQ10 can decrease serum glucose levels by suppressing β-cell failure and decreasing insulin resistance [214–217]; in addition, its

supplementation was proved to have lowering effects on the levels of HbA1c in type 2 diabetes [218, 219]. Moreover, CoQ10 works as growth factor in islet precursor cell cultures [220]. CoQ10 beneficial effects on the lipid profile, atherogenic index, and liver enzymes activities were reported in alloxan-induced type 1 diabetic rats [221]. CoQ10 can prevent the reduction in glucose transporter type-4 (GLUT-4) protein levels caused by lipid-lowering therapy [222]. Recent studies showed that CoQ10, through its antioxidant, anti-inflammatory, and anti-apoptotic effects, mitigated diabetic cardiomyopathy [223], ameliorated streptozotocin-induced diabetic encephalopathy [224] and diabetic nephropathy in rats [225, 226]. Ubiquinol protects against renal ischemia and reperfusion injury [227], it also attenuates oxidative stress in rat kidney [228]. CoQ10 ameliorates renal damage by decreasing TNF-α, TGF-β, MPO activity [229]. Pretreatment with CoQ10 was shown to inhibit the expression of the stress factor c-Fos and prevent neuropathic pain [230]. CoQ10 ameliorated high glucose-induced endothelial progenitor cell (EPC) apoptosis, including downregulation of caspase 3, upregulation of Bcl-2, and improving mitochondrial membrane potential [231]. Furthermore, it reduced reactive oxygen species (ROS), increased NO production, enhanced eNOS/Akt activity, and enhanced HO-1 expression in high glucose-treated EPCs through the AMPK pathway [232]. CoQ10 may decrease oxidative stress in the central and peripheral nervous system by acting as an antioxidant and free-radical scavenger that may benefit in conditions as diabetic neuropathy [233]. These results show that CoQ10 can be a promising future anti-diabetic drug, in addition, it's multiple-targeted approach make it a future choice for complications of diabetes mellitus, mainly those with neurological deterioration. CoQ10 may represent a promising therapeutic strategy for both type 1and type 2 diabetes and diabetic neuropathy [234], explained by its roles in the regulation of glucose metabolism [235].

CoQ10 and ischemic retinal injury and glaucoma (optic nerve)

Recent study showed that CoQ10 can ameliorate oxidative stress in ischemic retinal injuries [91], by promoting mitofilin and PGC-1a protein expression, it significantly decreases SOD2 and HO-1 protein expression in the ONH astrocytes [115]. Recent experimental studies indicate that topical CoQ10 is effective in preventing retinal ganglion cell (RGC) apoptosis and loss in glaucoma-related models [236]. CoQ10 may also have some ameliorating effects against glutamate-induced excitotoxicity and oxidative stress in a mouse model of glaucoma [237]. CoQ10 was shown to inhibit mitochondrial depolarization leading to attenuation of cellular apoptosis in corneal fibroblasts [238]. In ethanol-treated corneal fibroblasts, CoQ10 could protect cells from mitochondrial membrane deformity, apoptotic protein translocation, and apoptosis by inhibiting caspase-2 and caspase 3 activities [238]. CoQ10 was recently reported to have protective roles against high-dose radioiodine therapy-associated oxidative damage of lacrimal glands in experimental rats [239]. CoQ10 seems to be a promising therapeutic strategy for ameliorating oxidative stress in retinal injuries including glaucomatous and ischemic retinal neurodegeneration [236].

CoQ10 and arthritis

Rheumatoid arthritis (RA) is defined as an autoimmune disease that results in chronic joint inflammation leading to severe destruction of cartilage and associated movement disabilities [240]. CoQ10 was shown to play anti-arthritic roles on experimental rats [241]. A recent study reported the efficacy of CoQ10 in preventing the narrowing of joint space by inhibiting monosodium urate crystal-induced inflammation in rats [24]. Another study indicated that CoQ10 has significantly decreased MMP-13, IL- 1b, IL-6, IL-15, iNOS, nitrotyrosine, and RAGE expressions in an osteoarthritis animal model [242]. Most recently published work has shown that CoQ10 can inhibit the overexpression of MMP-3, MMP-9, and MMP-13 via inhibition of MAPK signaling pathway in IL-1b- induced inflammatory response -rats model [243]. CoQ10 was shown to mitigate the severity of zymosan-induced arthritis (ZIA) and has been revealed to decrease serum immunoglobulin concentrations [240]. Most recently, the combination of zinc and CoQ10 was reported to ameliorate the development of collagen-induced arthritis (CIA) by blocking the expression of proinflammatory cytokines [244]. These findings support the anti-arthritic and anti-inflammatory effects of CoQ10 in rat models of arthritis, and may be used as an add-on therapy in targetting some rheumatological diseases as osteoarthritis and RA. However, more experimental and clinical trials are needed to support previous results and to target other mechanisms through which CoQ10 plays anti-arthritic effects.

CoQ10 and Gaucher disease (GD)

Gaucher disease (GD), a genetic disorder, is caused by mutations in the GBA1 gene that encodes lysosomal β-

glucocerebrosidase (β-GCase). Few studies of CoQ10 role on GD were executed; however, targeting mitochondrial dysfunction and GCase misfolding by CoQ10 therapy may be beneficial for the treatment of neuronopathic GD [245]. A recent study in support of those findings also showed that CoQ10 could partially restore pathological alterations in a macrophage model of GD by ameliorating the cellular pathological consequences of GlcCer accumulation via targeting mitochondria and oxidative stress plus improving the lysosomal function and reducing inflammasome activation [246]. Conditions that may benefit from CoQ10 treatment are listed in Table 1.

Table 1 List of conditions that may benefit from coenzyme Q10 treatment.

Conditions / Functions
Atherosclerosis [247]
Spinocerebellar ataxia [248]
Friedreich's ataxia [249]
Peripheral neuropathy [250,251]
Enhancing memory [252]
Migraine [253]
Autism [109]
Periodic paralysis [254]
Encephalopathies [255]
Demyelination [256,257]
Fibromyalgia (FM) [258,259]
Male infertility [260–262]
Dental diseases (Periodontitis) [263]
Ulcerative colitis [264–267]
I/R injury in ovarian tissue [268]
Chronic bladder ischemia [269]
Pancreatic fibrosis [270]
Osteoporosis [271–273]
Skin diseases and skin care [274,275]
Hepatic diseases [276–278]
Ototoxicity [279,280]
Cancers as breast cancer [281–283]
Gentamicin-related kidney damage [284]
Ovarian ischemia [285]
Statin induced-adverse effects [289–294]
Hypoxia-induced growth restriction (Neonate) [292]
Eye diseases [293, 294]
Sepsis [295]

Conclusions

The best treatment for diseases that share similar mechanisms is the use of natural products with excluding or decreasing the use of chemical-based medications. However, CoQ10 fulfill the requirement as it is found naturally in human body and other living organisms, plus it works for the treatment of different conditions by using different mechanisms. CoQ10 can assist in the treatment of various diseases of different systems. This conclusion is obtained from the reality that many diseases share same etiologies and pathogenesis.

Abbreviations

AβPP β-carboxyterminal fragments (sAβPPβ)
Acetylcholinesterase (AChE)
Acute ischemic stroke (AIS)
Adenosine diphosphate (ADP)
5-adenosine-monophosphate-activated protein kinase (AMPK)
α-synuclein (α-syn)
Amyloid beta (Aβ)
Apoptosis-inducing factor (AIF)
Bcl-2-associated X protein (BAX)
Bcl-2 interacting mediator of cell death (Bim),
B cell lymphoma-2 (Bcl-2)
Blood-brain barrier (BBB)
cAMP response element-binding protein (CREB),
Cardiovascular diseases (CVDs)
Caspase 3 (CASP3)
c-Jun N-terminal kinase 3 (c-JNK3)
Coenzyme Q10 nanoparticles (CoQ10-NPs)
Cornu Ammonis 1 (CA1)
Cornu Ammonis 3 (CA3)
Cyclooxygenase-2 (COX-2)
Chronic unpredictable mild stress (CUMS)
Cyclic adenosine monophosphate (cAMP)
Duchenne muscular dystrophy (DMD)
Dynamin-related protein 1 (Drp1)
Electron transport chain (ETC)
Endothelin-1 (ET-1)
Endothelial nitric oxide synthase (eNOS)
Endothelium-derived relaxing factor (EDRF)
Endothelial progenitor cell (EPC),
Extracellular superoxide dismutase (SOD3)
First retention transfer latency (1st RTL)
Fission protein 1 (Fis1)
Forkhead box O3 (FOXO3, FOXO3a)
Gaucher disease (GD)
Glial fibrillary acidic protein (GFAP)
Glucose transporter type-4 (GLUT-4)
Glucosylceramide (GlcCer)
Glutathione (GSH)
Glutathione-disulfide reductase (GSR)
Glutathione disulfide (GSSG)
Glycogen–synthase- kinase-3-beta (pGSK-3β)
Heat shock transcription factor-1(HSTF-1)
Hemoglobin A1c (HbA1c)
High-density lipoprotein (HDL)
Hippocampal glutathione (GSH)
Human umbilical vein endothelial cells (HUVECs)
Huntingtin (HTT)
Hypoxia-inducible -factor-1-alpha (HIF-1α)

4-hydroxynonenal (4-HNE)
8-hydroxy-2'-deoxyguanosine (8-OHdG)
Idebenone (IDE)
Indoleamine 2,3-dioxygenase 1 (IDO-1)
Inducible nitric oxide synthase (iNOS)
Ischemia/reperfusion injury (I/R)
LC3-phosphatidylethanolamine conjugate (LC3-II)
Leber hereditary optic atrophy (LHON)
Macrophage antigen-1 (MAC-1)
Macrophage–inflammatory protein 1-alpha (MIP-1α)
Matrix metalloproteinase-13 (MMP-13),
Metalloproteinase-9 (MMP-9),
Mitochondrial respiratory chain (MRC),
p38 Mitogen-actives protein kinases (MAPK)
Monocyte chemoattractant protein- 1 (MCP-1)
Mossy fiber sprouting (MFS)
Multiple sclerosis (MS)
Myeloperoxidase (MPO)
Myocardial infarction (MI)
Neural stem cells (NSCs)
Nuclear factor erythroid 2-derived factor 2 (Nrf2)
Nuclear factor kappa-light-chain-enhancer of Activated B cells (NF-κB)
Optic nerve head (ONH)
Osteoarthritis (OA)
Oxidized low-density lipoprotein (oxLDL)
Oxygen consumption rate (OCR)
Peroxisome proliferator-activated receptor gamma Coactivator 1-alpha (PGC-1α)
Phosphatidylinositide 3-kinase (PI3K)
Phosphorylated Akt (pAkt)
Phosphorylated cAMP responsive element binding protein (pCREB)
Phosphorylated glycogen synthase kinase 3-β (pGSK3-β)
Presenilin-1(PS-1)
Prostaglandin I2 (PGI2)
Protein–kinase- B (Akt)
Reactive -oxygen -species (ROS)
Retinal ganglion cell (RGC)
Second retention transfer latency (2^{nd} RTL)
Selective- serotonin -reuptake -inhibitor (SSRI)
Serotonin (5-HT)
Temporal lobe epilepsy (TLE)
Thromboxane B2 (TXB2)
Transforming- growth- factor -beta (TGF-β)
Tumor necrosis factor- alpha (TNF-α)
Vesicular glutamate transporter 1 (VGLUT1)
Zymosan-induced arthritis (ZIA)

Conflict of interest

The authors declare no competing interests.

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