antioxidants

MDPI

Systematic Review

Coenzyme Q10 and Dementia: A Systematic Review

Félix Javier Jiménez-Jiménez [1,*], Hortensia Alonso-Navarro [1], Elena García-Martín [2] and José A. G. Agúndez [2]

[1] Section of Neurology, Hospital Universitario del Sureste, Arganda del Rey, Ronda del Sur 10, E-28500 Arganda del Rey, Spain
[2] University Institute of Molecular Pathology Biomarkers, Universidad de Extremadura, E-10071 Cáceres, Spain
* Correspondence: fjavier.jimenez@salud.madrid.org or felix.jimenez@sen.es; Tel.: +34-636-968395; Fax: +34-91-328-0704

Abstract: It is well known that coenzyme Q_{10} (CoQ_{10}) has important antioxidant properties. Because one of the main mechanisms involved in the pathogenesis of Alzheimer's disease (AD) and other neurodegenerative diseases is oxidative stress, analysis of the concentrations of CoQ_{10} in different tissues of AD patients and with other dementia syndromes and the possible therapeutic role of CoQ_{10} in AD have been addressed in several studies. We performed a systematic review and a meta-analysis of these studies measuring tissue CoQ_{10} levels in patients with dementia and controls which showed that, compared with controls, AD patients had similar serum/plasma CoQ_{10} levels. We also revised the possible therapeutic effects of CoQ_{10} in experimental models of AD and other dementias (which showed important neuroprotective effects of coenzyme Q_{10}) and in humans with AD, other dementias, and mild cognitive impairment (with inconclusive results). The potential role of CoQ_{10} treatment in AD and in improving memory in aged rodents shown in experimental models deserves future studies in patients with AD, other causes of dementia, and mild cognitive impairment.

Keywords: coenzyme Q_{10}; tissue concentrations; therapeutics; Alzheimer's disease; dementia; vascular dementia; Lewy body dementia

check for updates

Citation: Jiménez-Jiménez, F.J.; Alonso-Navarro, H.; García-Martín, E.; Agúndez, J.A.G. Coenzyme Q10 and Dementia: A Systematic Review. *Antioxidants* **2023**, *12*, 533. https://doi.org/10.3390/antiox12020533

Academic Editor: Yan-Zhong Chang

Received: 27 January 2023
Revised: 9 February 2023
Accepted: 17 February 2023
Published: 20 February 2023

Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

The 1,4-benzoquinone ubiquinone or coenzyme Q_{10} (CoQ_{10}), which is present in the majority of tissues in the human body, is an important component of the mitochondrial electron transport, participating in the generation of cellular energy through oxidative phosphorylation, and can be present in tissues in three different redox states: fully reduced (ubiquinol), fully oxidized (ubiquinone), and partially oxidized (semiquinone or ubisemiquinone). In addition to mitochondria, CoQ_{10} is present in peroxisomes, lysosomes, and the Golgi apparatus. CoQ_{10} has important antioxidant properties, with both a direct antioxidant effect of scavenging free radicals, and an indirect one of participating in the regeneration of other antioxidants such as ascorbic acid and alpha-tocopherol, offering protection to cells against oxidative stress processes [1,2].

It is well known that one of the most important pathogenetic mechanisms of Alzheimer's disease (AD) and other neurodegenerative disorders is oxidative stress [3–5]. Due to the important antioxidant functions of CoQ_{10}, several publications over the last two decades have addressed the issues of both determinations of CoQ_{10} levels in different tissues of patients diagnosed with AD or other types of dementia and on the potential therapeutic role of CoQ_{10} in these diseases (considering experimental studies in animal models of dementia in humans suffering from AD or other dementias). This systematic review and meta-analysis aims to analyze the results of studies addressing the tissular concentrations of CoQ_{10} in patients diagnosed with AD and other dementia syndromes compared with healthy controls, and the results of therapeutic trials of CoQ_{10} in AD (including experimental models of this disease) and in other causes of dementia.

2. Methods

2.1. Search Strategy and Criteria for Eligibility of Studies

We undertook a literature search using 3 well-known databases (PubMed, EMBASE, Web of Science-WOS-Main Collection) from 1966 until 31 December 2022. We crossed the term "coenzyme Q_{10}" with "Alzheimer's disease" (188, 403, and 171 items found in PubMed, EMBASE, and WOS, respectively), "dementia" (222, 79, and 86 items found in PubMed, EMBASE, and WOS, respectively), "vascular dementia" (13, 9, and 8 items found in PubMed, EMBASE, and WOS, respectively), "Lewy body dementia" (9, 8, and 11 items found in PubMed, EMBASE, and WOS, respectively) "Lewy body disease" (9, 15, and 25 items found in PubMed, EMBASE, and WOS, respectively), and "mild cognitive impairment" (68, 19, and 34 items found in PubMed, EMBASE, and WOS, respectively). The search retrieved 477 references which were examined one by one by the authors in order to select exclusively those strictly related to the proposed topic. Duplicated articles and abstracts were excluded. We did not apply any language restrictions. Figure 1 represents the flowcharts for the selection of eligible studies which analyzed tissue CoQ_{10} concentrations in patients with different types of dementia, and therapeutic trials with CoQ_{10} in experimental models of dementia or in patients with AD or other dementias according to the PRISMA guidelines [6].

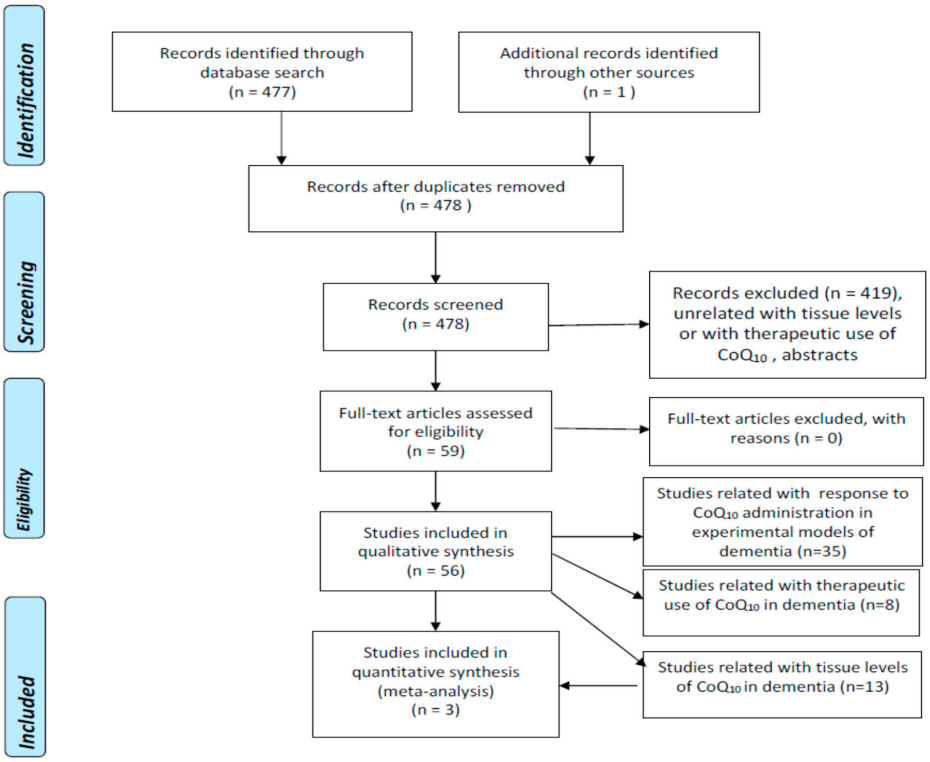

Figure 1. Flowchart for studies assessing tissue concentrations of coenzyme Q10 in dementia (PRISMA) (6, 17).

2.2. Selection of Studies and Methodology for the Meta-Analyses

We performed a meta-analysis of observational eligible studies assessing the concentrations of CoQ_{10} in tissues of patients diagnosed with AD and/or other causes of dementia and in controls. We extracted the following information: first author, year of publication, country, study design, and quantitative measures. We analyzed the risk for bias with the Newcastle–Ottawa Scale [7]. Table 1 summarizes data from selected studies analyzing tissular concentrations of CoQ_{10} in patients diagnosed with AD, Lewy body dementia (LBD), vascular dementia (VD), and dementia without specification of etiology compared with controls (with the exception of one study that compares the serum/plasma CoQ_{10} of patients with dementia with reference values).

Table 1. Coenzyme Q_{10} concentrations in several tissues from dementia patients and healthy controls (HC).

Alzheimer's Disease (AD)							
Tissue	**Author, Year [Ref]**	**Parameter**	**AD N**	**AD Mean ± SD**	**HC N**	**HC Mean ± SD**	**Difference in Means (95% C.I.), *p***
Serum/plasma	De Bustos et al., 2000 [8]	Total CoQ_{10} (nmol/L)	44	1262 ± 389	21	1209 ± 457	53.00 (−165.26 to 271.26); 0.629
	Battino et al., 2003 [9]	Total CoQ_{10} (nmol/L)	18	1216 ± 69	53	1278 ± 104	−62.00 (−114.55 to −9.45), 0.021
	Giavarotti et al., 2013 [10]	Total CoQ_{10} (nmol/L)	23	130 ± 30	42	115 ± 20	15.00 (2.57 to 27.43), 0.019
	Total series	**Total CoQ_{10} (nmol/L)**	**85**	**945.95** ± 573.50	**116**	**844.42** ± 588.71	**Random effects model *p* = 0.911**
	De Bustos et al., 2000 [8]	Total CoQ_{10} / cholesterol (µmol/mmol)	44	0.24 ± 0.05	21	0.23 ± 0.05	0.01 (−0.02 to 0.04), 0.454
CSF	Isobe et al., 2009, 2010 [11,12]	Oxidized CoQ_{10} (nmol/L)	30	5.2 ± 1.5	30	1.9 ± 1.3	3.30 (2.69 to 3.91), <0.0001
	Isobe et al., 2009, 2010 [11,12]	Reduced CoQ_{10} (nmol/L)	30	1.4 ± 0.6	30	2.7 ± 0.7	−1.30 (−1.64 to −0.96), <0.0001
	Isobe et al., 2009, 2010 [11,12]	Total CoQ_{10} (nmol/L)	30	6.6 ± 1.2	30	4.6 ± 1.0	2.00 (1.43 to 2.57), <0.0001
	Isobe et al., 2009, 2010 [11,12]	Oxidized/total CoQ_{10}	30	0.782 ± 0.188	30	0.413 ± 0.104	0.37 (0.29 to 0.45), <0.0001
Lewy Body Dementia (LBD)							
Tissue	**Author, Year [Ref]**	**Parameter**	**LBD N**	**LBD Mean ± SD**	**HC N**	**HC Mean ± SD**	**Difference in Means (95% C.I.), *p***
Serum/plasma	Molina et al., 2002 [13]	Total CoQ_{10} (nmol/L)	18	960.6 ± 359.1	20	1205.2 ± 362.2	−244.60 (−482.30 to −6.90 to); 0.044
	Molina et al., 2002 [13]	Total CoQ_{10}/cholesterol	18	4.67 ± 1.75	20	5.05 ± 1.52	−0.38 (−1.46 to 0.70); 0.478
Vascular Dementia (VD)							
Tissue	**Author, Year [Ref]**	**Parameter**	**VD N**	**VD Mean ± SD**	**HC N**	**HC Mean ± SD**	**Difference in Means (95% C.I.), *p***
Serum/plasma	De Bustos et al., 2000 [8]	Total CoQ_{10} (nmol/L)	17	1130 ± 452	21	1209 ± 457	−79.00 (−379.92 to 221.92), 0.598
	De Bustos et al., 2000 [8]	Total CoQ_{10}/cholesterol (µmol/mmol)	44	0.22 ± 0.06	21	0.23 ± 0.05	−0.01 (−0.04 to 0.02), 0.511
Dementia without Specific Etiologic Diagnosis (DEM)							
Tissue	**Author, Year [Ref]**	**Parameter**	**DEM N**	**DEM Mean ± SD**	**HC N**	**HC Mean ± SD**	**Difference in Means (95% C.I.), *p***
Serum/plasma	Yamagishi et al., 2014 [14]	Total CoQ_{10} (nmol/L)	65	731 ± NA	130	762 ± NA	*p* = 0.32 (according to the authors, SD not provided)
Serum/plasma	Chang et al., 2022 [15]	Total CoQ_{10} (nmol/L)	80	410 ± 21	NA	NA	73% of patients showed low CoQ_{10} status using as reference values 500–1700 nmol/L
Serum/plasma	Yamagishi et al., 2014 [14]	Total CoQ_{10}/cholesterol (µmol /mmol)	65	0.14 ± NA	130	0.15 ± NA	*p* = 0.15 (according to the authors, SD not provided)
Serum/plasma	Chang et al., 2022 [15]	Total CoQ_{10}/cholesterol (µmol/mmol)	80	0.09 ± 0.04	NA	NA	73% of patients showed low CoQ_{10} status using as reference values 500–1700 nmol/L

We converted plasma/serum and CSF CoQ_{10} concentrations to nmol/mL when necessary. The meta-analyses were carried out using the R software package meta [16] and following both the PRISMA [6] (Table S1) and the MOOSE guidelines [17] (Table S2). Because of the high heterogeneity across studies, we applied the random-effects model and used the inverse variance method for the meta-analytical procedure, the DerSimonian–Laird as an estimator for Tau^2 [18], the Jackson method for the confidence interval of tau^2 and tau [19], and the Hedges' g (bias-corrected standardized mean difference) [20]. The statistical power to detect differences in mean values (alpha = 0.05) for the pooled samples was calculated when stated in the text. The meta-analysis was finally only applicable to three studies on serum/plasma CoQ_{10} concentrations in patients with AD compared with controls.

3. Results

3.1. Studies Assessing Tissular CoQ_{10} Concentrations

3.1.1. Alzheimer's Disease

A total of three studies that assessed the serum/plasma levels of CoQ_{10} in patients with AD and controls failed to detect significant differences between the two study groups (Table 1, Figure 2) [8–10]. One of these studies showed a similar serum/plasma CoQ_{10}/cholesterol ratio between AD patients and controls [8].

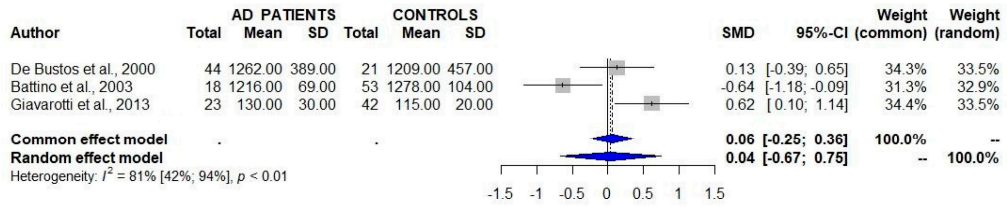

Figure 2. Studies assessing the serum/plasma levels of CoQ_{10} in patients with Alzheimer's disease (AD) and controls show a lack of significant differences between the two groups. 95% CI 95% confidence intervals; SMD standard mean difference [8–10].

Isobe et al. [11,12] reported increased total CoQ_{10} and oxidized CoQ_{10} concentrations in the cerebrospinal fluid from AD patients compared with controls, and a negative correlation between oxidized/total coenzyme Q_{10} and duration of the disease.

To date, only two studies have addressed brain CoQ_{10} concentrations in patients with AD. Edlund et al. [21] described the mean values (without SD) of CoQ_{10} in frontal, precentral, temporal, and occipital cortex, and in nucleus caudate, hippocampus, pons, cerebellum, and medulla oblongata of AD patients and controls. They reported a 30–100% increase in CoQ_{10} concentrations in most of these regions; however, the number of AD patients and controls involved in the study was not stated. Kim et al. [22] described a decreased activity of the 25 kDa subunit nicotinamide adenine dinucleotide + hydrogen (NADH):ubiquinone oxidoreductase (complex I) in the temporal and occipital cortex and of the 75 kDa subunit of this enzyme in the parietal cortex of patients with AD compared with controls, but specific measures of CoQ_{10} were not performed.

Santa-Mara et al. [23] reported the presence of CoQ_{10} in paired helical filaments (aberrant protein aggregates containing tau protein) and in Hirano bodies (neuronal inclusions that are mainly observed in hippocampal neurons and are composed of actin either associated with or not associated with tau) in brain patients with AD, and state that CoQ_{10} was able to induce the formation of aggregates when it was mixed with tau and actin.

3.1.2. Other Causes of Dementia

Serum CoQ_{10} concentrations and CoQ_{10}/cholesterol ratios from patients diagnosed with LBD [13] and VD [8] did not differ significantly from those of controls according to two single studies.

Yamagishi et al. [14], in a community-based cohort study in Japan involving 6000 Japanese participants aged 40–69 years at baseline, described an inverse association between serum CoQ_{10} concentrations and the risk for disabling dementia, although serum CoQ_{10} levels and serum CoQ_{10}/cholesterol ratio did not differ significantly between 65 incident cases and 130 controls.

Finally, Chang et al. [15] reported "low CoQ_{10} status" in 73% of 80 patients diagnosed with dementia (they used reference values of their laboratory of 0.5-1-7 μM). In addition, they described a correlation between CoQ_{10} status and values of total antioxidant capacity, MiniMental State Examination, amyloid β-42 (Aβ-42), and Aβ-42/40 ratio, but not with tau protein.

3.2. Studies Assessing Therapeutic Response to CoQ_{10} Administration in Experimental Models of AD and Other Dementias

The results of studies assessing the response to the administration of COQ_{10} in different experimental models are summarized in Table 2.

Table 2. Studies on the effects of coenzyme Q_{10} in different experimental models of Alzheimer's disease.

Experimental Model	Author, Year [Ref]	Main Findings
AGED RATS	McDonald et al., 2005 [24]	Coadministration of CoQ_{10} and alpha-tocopherol (but not administration of each of these compounds alone) improved learning and memory tasks (assessed by a test that required the mice to rapidly identify and remember the correct arm of a T-maze, and to respond preemptively in order to avoid an electric shock).
AGED MICE	Wadsworth et al., 2008 [25]	Administration of CoQ_{10} decreased protein carbonyls in the brain but had no effect on lipid peroxidation, brain ATP levels, and mitochondrial membrane potential.
	Sumien et al., 2009 [26]	Intake of a low-CoQ_{10} diet did not change age-associated decrements in muscle strength, balance, coordinated running, or learning/memory, whereas intake of CoQ_{10} at a higher amount increased spontaneous activity, worsened age-related losses in acuity to auditory and shock stimuli, and impaired spatial learning/memory of old mice.
	Shetty et al., 2013 [27]	Intake of a low-CoQ_{10} diet did not change age-associated decrements in tests for spatial learning (Morris water maze), spontaneous locomotor activity, motor coordination, and startle reflex. However, intake of high-CoQ_{10} improved spatial learning and decreased protein oxidative damage in the heart, liver, skeletal muscle, and to a lesser extent, in the brain mitochondria.
	Shetty et al., 2014 [28]	Administration of α-tocopherol or α-tocopherol + CoQ_{10} diets improved coordinated running performance. The α -tocopherol + CoQ_{10} diet improved performance in a discriminated avoidance task (α-tocopherol and CoQ_{10} diets alone improved this task to a lesser degree). Both α-tocopherol and CoQ_{10} diets decreased protein damage, this effect being more marked with the α-tocopherol + CoQ_{10} combination.
HYPERCHOLESTE-ROLEMIA-INDUCED AD IN RATS	Ibrahim Fouad, 2020 [29]	Treatment with omega-3 and CoQ_{10} alone or in combination decreased markers of brain oxidative stress and inflammation and serum Aβ levels, regulated cholinergic functioning, and enhanced the functional outcome.
ALUMINIUM-INDUCED AD IN RATS	Ali et al., 2019 [30]	Treatment with CoQ_{10} in combination with vinpocetine partially reversed the changes induced by aluminium chloride (AlCl3) by decreasing malonyl-dialdehyde (MDA), increasing superoxide dismutase (SOD) and total antioxidant total capacity, decreasing IL1β, TNFα, chitinase, β-secretase, Aβ, tau protein, acetyl-cholinesterase, increasing catecholamine and brain-derived neurotrophic factor (BDNF) levels in brain tissue.
	Attia et al., 2020 [31]	Treatment with CoQ_{10} alone or in combination with biotin attenuated the changes induced by AlCl3 (impaired memory, a significant increase in Aβ, lipid peroxides, inflammatory markers—TNFα, IL6, IL1, nuclear factor κB-, caspase-3, and pSer-IRS-1, significant reduction in the antioxidants reduced glutathione and SOD-, pTyr-IRS-1, and p-Akt, reflecting Aβ-induced inflammation and defective insulin signaling, focal aggregations of inflammatory cells and neuronal degeneration).

Table 2. *Cont.*

Experimental Model	Author, Year [Ref]	Main Findings
	Ali et al., 2022 [32]	Treatment with CoQ_{10} reversed changes induced by aluminium by decreasing Aβ and acetylcholinesterase expression, increasing monoamine levels, restoring levels of total antioxidant capacity and superoxide-dismutase, and decreasing MDA, TNFα, and IL6.
FOREBRAIN LESIONED RATS	Nitta et al., 1994 [33]	Administration of CoQ_{10} to forebrain lesioned rats caused an increase in nerve growth factor (NGF) protein and mRNA and in choline acetyltransferase activity, and improved memory tasks such as behavioral deficits in habituation, water maze, and passive avoidance tasks in these animals.
INTRACEREBRO-VENTRICULAR INFUSION OF Aβ(1-42) IN RATS	Yamada et al., 1999 [34]	Coadministration of CoQ_{10} prevented some learning and memory deficits (Y-maze and water maze, but not passive avoidance tasks) in this model without affecting lipid peroxide levels in the hippocampus and cerebral cortex.
INTRAHIPPO-CAMPAL INJECTION OF Aβ(1-42) IN RATS	Singh et al., 2015 [35]	Treatment with CoQ_{10} and minocycline alone improved cognitive performance (reduced transfer latency and increased time spent in the target quadrant in the Morris Water Maze), reduced acetyl–cholinesterase activity, decreased oxidative damage (by reducing lipoperoxide and nitrite level and restoring superoxide, catalase, and reduced glutathione levels), decreased TNFα level, and restored mitochondrial respiratory enzyme complex activities and histopathological alterations induced by Aβ(1-42) in a dose-dependent and synergistic manner.
	Komaki et al., 2019 [36]	Treatment with CoQ_{10} reversed the decreased excitatory postsynaptic potential (EPSP) slope and population spike (PS) amplitude in the hippocampal dentate gyrus after induction of long-term potentiation (LTP) induced by injection of Aβ, reversed the decrease in serum MDA levels and total oxidant levels induced by injection of Aβ, and increased total antioxidant capacity levels.
INTRACEREBRO-VENTRICULAR INFUSION OF STREPTOZOTOCIN IN RATS	Ishrat et al., 2006 [37]	Coadministration of CoQ_{10} prevented learning and memory deficits (loss of cognitive performance in Morris water maze and passive avoidance tests), the increase in markers of oxidative damage (thiobarbituric acid reactive substances, reduced glutathione, protein carbonyl, activities of glutathione peroxidase and glutathione reductase), the decline of ATP in the hippocampus and cerebral cortex, the decrease in choline-acetyl-transferase activity and the increase in acetyl-cholinesterase activity induced by this neurotoxin.
	Sheykhhasan et al., 2022 [38]	Administration of CoQ10-loaded exosomes derived from adipose-derived stem cells improved memory impairment (assessed with the Morris water maze and passive avoidance task), increased BDNF expression, and increased cell density and the transcription factor *SOX2* gene expression in comparison with the administration of CoQ_{10} exosomes derived from adipose-derived stem cells alone.
TRANSGENIC MICE: AD PRESENILIN 1 MUTATION L235P	Yang et al., 2008 [39]	CoQ_{10} administration partially attenuated Abeta overproduction and intracellular Aβ deposit, partially decreased MDA increase, and up-regulated the decreased activity of SOD [24].
	Yang et al., 2010 [40]	CoQ_{10} administration reduced the burden of the amyloid plaques (assessed by immunohistochemistry and magnetic resonance imaging)
TRANSGENIC MICE: TG19959 MUTATION	Dumont et al., 2011 [41]	CoQ_{10} administration improved cognitive performance during Morris water maze testing, decreased brain levels of protein carbonyls (a marker of oxidative stress), decreased brain Aβ42 levels and Aβ protein precursor (AβPP), β-carboxyterminal fragments, and decreased plaque area and number in the hippocampus and the overlying cortex (assessed by immunostained with an Aβ42-specific antibody).
TRANSGENIC MICE: P301 TAU MUTATION (FRONTO-TEMPORAL DEMENTIA)	Elipenahli et al., 2012 [42]	CoQ_{10} administration improved survival and behavioral deficits (it increased locomotor activity and anxiety in open field testing), caused a modest reduction in phosphorylated tau, a significant increase in complex I activity and protein levels, and a reduction in lipid peroxidation in the cortex.
DOUBLE TRANSGENIC MICE: MUTATIONS *TGAPESWE* AND *PSEN1DE9*	Muthukumaran et al., 2018 [43]	Administration of ubisol-Q_{10} (a water-soluble form of coenzyme Q_{10}) improved long-term memory, preserved working spatial memory, and inhibited Aβ plaque formation in 18-month-old transgenic mice compared to an untreated transgenic group.

Table 2. *Cont.*

Experimental Model	Author, Year [Ref]	Main Findings
TRIPLE TRANSGENIC MICE: MUTATIONS *PS1M146V*, *APPSWE*, AND *TAUP301L*	Sui et al., 2014 [44]	The administration of CoQ_{10} altered changes in the differentially expressed serum proteins in the transgenic compared with wild-type mice by up-regulating 10 proteins and down-regulating another 10 proteins. Among the proteins modulated by CoQ10, clusterin and α-2-macroglobulin were validated via ELISA assay.
CELL CULTURES: HUMAN SKIN FIBROBLASTS FROM PS1 MUTATED FAMILIAL AD	Ma et al., 2014 [45]	CoQ_{10} treatment decreased reactive oxygen species generation, increased population doublings, and postponed stress-induced premature senescence. CoQ_{10} treatment increased proliferating cell nuclear antigen expression, and decreased levels of manganese-SOD (MnSOD), p21, p16Ink4A and cell cycle regulatory protein retinoblastoma (suggesting a resumption of autophagy).
	Vegh et al., 2019 [46]	Administration of ubisol-Q_{10} caused enhanced expression autophagy-related genes such as *beclin-1* (a major autophagy regulator) and *mitogen-activated protein kinase 8* (*MAPK8/JNK1*, a major activator of beclin-1) avoiding resumption of premature senescence. Withdrawal of ubisol-Q10 treatment led to the return of the senescence phenotype in AD fibroblasts.
CELL CULTURES: HUMAN SH-SY5Y NEUROBLASTOMA CELLS	Qi et al., 2005 [47]	Exposure of these cells to Aβ(1-42) caused, among other effects, enhanced lipid peroxidation and protein oxidation and significant reductions in the total contents of phospholipids, ubiquinone-10, and alpha3 and alpha7 subunit proteins of nicotinic acetylcholine receptors.
CELL CULTURES: HUMAN MC65 NEUROBLASTOMA CELLS	Wadsworth et al., 2008 [25]	Administration of CoQ_{10} showed a neuroprotective effect on the neurotoxic effects induced by the Aβ protein precursor C-terminal fragment (APP CTF).
CELL CULTURES: HUMAN UMBILICAL VEIN ENDOTHELIAL CELLS (HUVECS)	Durán-Prado et al., 2014 [48]	CoQ_{10} pretreatment delayed Aβ incorporation into the plasma membrane and mitochondria, reduced the influx of extracellular Ca^{2+} and Ca^{2+} release from mitochondria due to opening the mitochondrial transition pore after Aβ administration, decreasing O_2^- and hydrogen peroxide (H_2O_2) levels, prevented Aβ-induced necrosis and apoptosis, and restored the ability to proliferate, migrate and form tube-like structures in vitro.
CELL CULTURES: RAT BRAIN ENDOTHELIAL CELLS	Frontiñán-Rubio et al., 2021 [49]	CoQ_{10} pretreatment protected endothelial brain cells from Aβ(25–35)-induced damage, preventing nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and reducing both reactive oxygen species generation and increase in free cytosolic Ca^{2+} induced by Aβ(25–35) (this prevented apoptosis and necrosis).
CELL CULTURES: PRIMARY CULTURED RAT CORTICAL NEURONS	Choi et al., 2012 [50]	CoQ_{10} protected neuronal cells against Aβ(25–35)-induced neurotoxicity in a concentration-dependent manner by increasing the expression levels of proteins related to neuronal cell survival (p85aPI3K, phosphorylated protein kinase B–Akt-, phosphorylated glycogen synthase kinase-3β, and heat shock transcription factor), and decreasing the levels of proteins associated with neuronal death (cytosolic cytochrome c and cleaved caspase-3). This protective effect was blocked by a phosphatidylinositol 3-kinase (PI3K) inhibitor.
	Wang et al., 2020 [51]	CoQ_{10} pretreatment significantly prevented neurons from Aβ-induced collapse of mitochondrial bioenergetics and perturbations of the protein kinase A (PKA)/cAMP response element-binding protein (CREB) signaling.
CELL CULTURES: CULTURED NEURAL STEM CELLS	Choi et al., 2013 [52]	Co-administration of CoQ_{10} restored the Aβ(25–35) oligomer-inhibited proliferation of neural stem cells by increasing the expression levels of proteins related to the PI3K pathway (p85α PI3K, phosphorylated Akt-Ser473-, phosphorylated glycogen synthase kinase-3β-Ser9-, and heat shock transcription factor). This protective effect was blocked by a phosphatidylinositol 3-kinase (PI3K) inhibitor.
CELL CULTURES: PRIMARY CULTURED HIPPOCAMPAL NEURONS FROM FETAL MICE	Yang et al., 2020 [53]	Administration of CoQ_{10} reversed all the effects induced by sevoflurane anesthesia (decrease in ATP and SOD levels, increase in apolipoprotein E (ApoE) mRNA, total ApoE protein, full-length ApoE, and ApoE fragments, increase in phosphorylated tau and neuroinflammatory factor (TNFα, IL6, and IL1β) expression levels.
CELL CULTURES: BRAIN MITOCHON-DRIA ISOLATED FROM AGED DIABETIC RATS	Moreira et al., 2005 [54]	CoQ_{10} treatment attenuated the decrease in oxidative phosphorylation efficiency and avoided the increase in H_2O_2 production induced by Aβ1-40.

Table 2. *Cont.*

Experimental Model	Author, Year [Ref]	Main Findings
CELL CULTURES: RAT PHEOCHROMO-CYTOMA (PC12) CELL LINE	Li et al., 2017 [55]	CoQ_{10} treatment suppressed the protein expression of COX-2 and the level of PGE2 in Aβ(25–35)-injured PC12 cells (this effect was correlated with the suppression of NF-κB activation by CoQ_{10}, attenuating neuroinflammation).

In general, the administration of CoQ_{10} alone or in combination with other substances (mainly other antioxidants) has been useful to improve the results of clinical tasks related to learning and memory and to improve or prevent oxidative stress, inflammation and cellular death in different models of AD and frontotemporal dementia including aged rodents [24–29], aluminium-induced AD in rats [30–32], forebrain lesioned rats [33], intracerebroventricular infusion of Aβ-42 [34] or streptozotocin [37,38] or intrahippocampal injection of Aβ-42 [35,36] in rats, transgenic mice with different mutations inducing AD [39–41,43–46] or frontotemporal dementia [42], and cell cultures using different human [25,45,46,48] or rodent cells [49–55]. On the other hand, Aβ(1-42) decreased CoQ_{10} concentrations in human SH-SY5Y neuroblastoma cells in culture [47].

3.3. Studies Assessing Therapeutic Response to CoQ_{10} Administration in Patients with Dementia

3.3.1. Alzheimer's Disease

Table 3 summarizes the results of the eight eligible studies addressing the therapeutic response to CoQ_{10} administration in patients with AD [56–63], although in one of them, an important percentage of patients included were diagnosed with mixed dementia [61]. Two of these studies used an open-label design [56,61] while the others were randomized clinical trials [33].

Table 3. Studies describing the effects of COQ_{10} supplementation in patients with AD. AD: Alzheimer's disease; ADAS: Alzheimer's Disease Assessment Scale; ADAS-Cog: ADAS cognitive score; ADAS-Noncog: ADAS non-cognitive scores; ADCS-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living; ADL: activities of daily living; CGI-I: clinical global impression improvement; CGI-C: clinical global impression change; CMT: Central macular thickness; DAT: dementia of Alzheimer type; DSS: Digit Symbol Substitution test; GCIPL: Ganglion cell-inner plexiform layer; MMSE: MiniMental State Examination; OCT: optic coherence tomography; RNFL: Retinal nerve fiber layer; SCT: Subfoveal choroidal thickness.

Authors, Year [Ref]	Study Setting	Type of Study	Main Findings	Level of Evidence (Quality Score)
Imagawa et al., 1992 [56]	Combined therapy with CoQ10, iron, and vitamin B6 in 27 AD patients.	Open-label study	• Treatment was as effective as mitochondrial activation therapy in 27 AD patients. • Treatment induced significant clinical improvement in two genetically confirmed AD patients.	II (NA)
Weyer et al., 1997 [57]	Three hundred patients with mild to moderate degree DAT were prescribed idebenone 30 mg t.i.d. (n = 100), idebenone 90 t.i.d. (n = 100), or placebo (n = 100). Evaluation at baseline, 1, 3, and 6 months including a total score of the ADAS-Total, ADAS cognitive (ADAS-Cog) and noncognitive scores (ADAS-Noncog), CGI-I, MMSE, Digit Symbol Substitution test (DSS) and several scales for the assessment of daily activities (the self- and observer-rating scales NAA and NAB of the Nuremberg Age Inventory NAI and Greene's Assessment).	Multicenter, randomized, double-blind, placebo-controlled, dosage-ranging trial	• Idebenone 90 mg t.i.d. improved significantly and was superior to placebo and idebenone 60 mg t.i.d. in ADAS-Total, ADAS-Cog, ADAS-Noncog, and CGI-global improvement. • Safety results (adverse events, vital signs, ECG, and clinical laboratory parameters) were similar for the three groups.	I (>50%)

Table 3. *Cont.*

Authors, Year [Ref]	Study Setting	Type of Study	Main Findings	Level of Evidence (Quality Score)
Gutzmann and Hadler D, 1998 [58]	Four hundred and fifty patients with mild to moderate degree DAT were prescribed placebo for 12 months, followed by idebenone 90 mg for another 12 months (n = 153) or idebenone 90 mg tid for 24 months (n = 148) or 120 mg ti for 24 months (n = 149). Evaluation included a total score of the Alzheimer's Disease Assessment Scale (ADAS-Total), ADAS cognitive (ADAS-Cog) and noncognitive scores (ADAS-Noncog), CGI-Improvement), the SKT neuropsychological test battery, and the Nurses' Observation Scale for Geriatric Patients (NOSGER-Total and IADL subscale).	Prospective, randomized, double-blind multicentre study in three parallel groups	• During the placebo-controlled period, idebenone showed statistically significant dose-dependent improvement in all the efficacy variables. • A further improvement of most efficacy variables was determined in the second year in comparison to the results at the 12-month visit, with a clear dose–effect relationship (placebo < idebenone 90 mg < idebenone 120 mg). • Safety results (adverse events, vital signs, ECG, and clinical laboratory parameters) were similar for the three groups.	I (>50%)
Gutzmann et al., 2002 [59]	Two hundred and three patients with mild to moderate degree DAT were prescribed idebenone 360 mg/day (n = 104) or tacrine up to 160 mg/day (n = 99) for 60 weeks. Evaluation included the Efficacy Index Score (EIS, a combination of improvement in cognitive function, activities of daily living, and global function), the ADAS-Cog score, the NOSGER-IADL score, and the CGI-I.	Prospective, randomized, double-blind, parallel-group multicenter study	• A total of 28.8% of the patients on idebenone and 9.1% of the patients on tacrine finalized the follow-up. • A total of 50% of the patients on idebenone and 39.4% of the patients on tacrine showed an improvement in at least one of the other (secondary) outcome variables. • Patients on idebenone showed a higher benefit from treatment than patients on tacrine.	I (>50%)
Thal et al., 2003 [60]	Five hundred and thirty-six patients diagnosed with probable AD aged over 50 with MMSE scores between 12 and 25 were prescribed idebenone 120, 240, or 360 mg, or placebo (n = 136, 138, 133, and 126, respectively) during 1 year. Evaluation included ADAS-Cog, CGIC (primary outcome measures), and measurements of ADL, Behavioral Pathology in Alzheimer's Disease Rating Scale, and MMSE (secondary outcomes).	Multicenter, double-blind, placebo-controlled, randomized trial	• The study was completed by 95, 94, 92, and 96 of the patients assigned to idebenone 120, 240, or 360 mg, or placebo, respectively. • Primary outcome measures did not differ significantly between the four groups. • In an exploratory two-group analysis comparing all three treated groups combined with a placebo, drug-treated patients performed better on the ADAS-Cog, although CGIC scores did not differ significantly.	I (>50%)
Voronkova and Meleshkov, 2009 [61]	Thirty-five patients were diagnosed with AD (n = 9), mixed dementia (n = 21), or memory impairment not reaching dementia (n = 5). Treatment with CoQ_{10} 120 mg/day for 6 months. Assessment with the Luriya method (memory and especially auditory-speech memory), Clinical Dementia Rating scale (CDRS), CGIC, and MMSE.	Open-label study	• Improvement in the MMSE score in patients with mild and moderate dementia. • Improvement in daily activities in 27% of patients, including improvement in short-term and long-term memory and attention, speech functions, the performance of kinesthetic, spatial, and dynamic praxis tests, visuospatial gnosis, thought, and writing. • Improvement on the CGI scale in 37% of patients.	II (NA)

Table 3. *Cont.*

Authors, Year [Ref]	Study Setting	Type of Study	Main Findings	Level of Evidence (Quality Score)
Galasko et al., 2012 [62]	Seventy-eight patients with mild to moderate AD (66 of them provided serial CSF specimens adequate for biochemical analyses). Random assignment to treatment for 16 weeks with 800 IU/d of vitamin E (α-tocopherol) plus 500 mg/d of vitamin C plus 900 mg/d of α-lipoic acid (E/C/ALA); 400 mg of coenzyme Q_{10} 3 times/day; or placebo (26 to each group; 24, 20, and 12, respectively, provided CSF). Evaluation at baseline and 16 weeks of MMSE and ADCS-ADL scale, and CSF biomarkers related to AD.	Monocenter, randomized, placebo-controlled, double-blind clinical trial	• Accelerated decline in MMSE scores occurred in the E/C/ALA group. • Changes in CSF Aβ42, tau, and P-tau(181) levels did not differ between the three groups. • Cerebrospinal fluid F2-isoprostane levels decreased on average by 19% from baseline to week 16 in the E/C/ALA group but were unchanged in the other groups. • Drugs used were well tolerated.	I (>50%)
Karakahya and Özcan, 2020 [63]	Sixty-two patients diagnosed with AD (31 randomized to the treatment group and 31 to the observational group), and 31 healthy controls. The treatment group received topical application of CoQ10 on the retina and choroids. Assessment of CMT, RNFL thickness, GCIPL thickness, and SCT with OCT at baseline and after 6 months.	Monocenter, randomized clinical trial	• Increased RNFL thickness in all quadrants in the treatment group, but only significant in the temporal sector (inversely correlated with AD duration). • Increased GCIPL thickness in the treatment on average and superonasal sector (inversely correlated with AD severity). • Increased ganglion cell-inner plexiform layer in the treatment group.	I (>50%)

Imagawa et al. [56], after a preliminary report indicating that therapy with CoQ10, iron, and vitamin B6 was effective as mitochondrial activation therapy in 27 AD patients, reported a significant clinical improvement with this therapy in two genetically confirmed AD patients. Three of the randomized clinical trials showed improvement in neuropsychological assessments in patients treated with CoQ_{10} compared, respectively, with placebo [57,58] or with tacrine [59], while the other two did not show any improvement in comparison with placebo [60,62], although in one of them, the patients treated with CoQ_{10} showed a better outcome than those treated with a combination of α-tocopherol, vitamin C, and α-lipoic acid [62].

Karakahya and Özcan [63], in a study using optic coherence tomography (OCT), reported an improvement in retinal ganglion cell loss related to AD with short-term topical administration of CoQ10. Finally, an open-label study showed some degree of improvement in the MMSE score and other neuropsychological tests in patients with AD or mixed dementia [61].

3.3.2. Vascular Dementia (VD)

Kawakami et al. [64] measured CSF levels of homovanillic acid (HVA), 5-hydroxyindole acetic acid (5-HIAA), 3-methoxy-4-hydroxyphenylethylenglycol (MHPG), and noradrenalin (NA) in six patients with cerebrovascular dementia. CoQ_{10} administration during 1–2 months returned to normal CSF levels of HVA, 5-HIAA, and MHPG, which had been previously decreased compared to control values.

Qi et al. [65], in a randomized clinical trial involving 88 patients diagnosed with VD (44 of them assigned to treatment with butylphthalide plus idebenone as the observational group, and 44 to idebenone as the control group), showed a higher degree of improvement in MMSE, clinical dementia rating scale (CDRS), and ability of daily life (ADL), and a higher decrease in serum IL6, C reactive protein, TNFα, IL1β, CD31+, CDl44+, and endothelin-1 levels in the observational group compared with the control group.

3.3.3. Mild Cognitive Impairment and Normal Aging

García-Carpintero et al. [66], in a 1-year randomized, double-blind, placebo-controlled observational analytical study involving 69 patients diagnosed with mild cognitive impairment (MCI) assigned to CoQ_{10} 200 mg/day (n = 33) or placebo (n = 36) showed that although CoQ_{10} treatment improved cerebral vasoreactivity (assessed by transcranial Doppler sonography) and inflammatory markers, it did not display any significant improvement in the results of an extensive neuropsychological assessment.

Finally, Stough et al. [67] designed a 90-day randomized, double-blind, placebo-controlled, parallel group clinical trial involving 104 healthy subjects aged 60 years and over randomized to either CoQ_{10} 200 mg/day or placebo (52 per group), aiming to evaluate the effects of CoQ_{10} in the amelioration of cognitive decline that it should be undergoing. Interestingly, a recent study described a significant association of plasma CoQ_{10} concentrations with cognitive functioning and executive function in elderly people [68].

4. Discussion and Conclusions

The possible role of CoQ_{10} in the pathogenesis of AD and other causes of dementia, if any, is far from established with the current evidence. The studies addressing the serum/plasma levels of CoQ_{10}, which are scarce and based on a relatively small sample size, were similar for AD patients and controls [8–10]. The increased values of total and oxidized CoQ_{10} concentrations in the cerebrospinal fluid from patients [11,12] and in certain brain areas from patients with AD [13], described in single studies, have not had further replication studies and await confirmation. Studies on human AD brain are restricted to a single report of a 30–100% increase in CoQ_{10} concentrations in most of the regions studied (which included the frontal, precentral, temporal and occipital cortex, nucleus caudate, hippocampus, pons, cerebellum, and medulla oblongata) in an unspecified number of AD patients compared with controls [18]. The possibility of induction of aggregates of tau protein and actine by CoQ_{10} and the finding of the presence of this coenzyme in paired helical filaments and Hirano bodies in the hippocampus [23] lends support to the hypothesis of the possible role of CoQ_{10} in AD. Studies reporting on CoQ_{10} concentrations in other causes of dementia are restricted to the measurements in serum/plasma from patients with Lewy body dementia (LBD) [13], vascular dementia [8], and dementia without specification of etiologic diagnosis [14,15].

Because of their antioxidant actions, it was proposed that CoQ_{10} administration could be a potential protective therapy in AD [69,70]. Moreover, an important number of studies have shown a significant neuroprotective and/or clinical effect of the administration of CoQ_{10} in different experimental models of AD, as was previously commented in more detail in the Section 3 [24–46,49–55] (Table 2). Interestingly, most of the studies performed using cell cultures including human neuroblastoma SH-SY5Y [47] and human MC 65 neuroblastoma cells [25], human umbilical vein endothelial cells [48], rat endothelial [49], cortical [50,51] and brain stem cells [52], hippocampal neurons from fetal mice [53], brain mitochondria isolated from aged diabetic rats [54], and rat pheochromocytoma (PC12) cells [55] have shown a protective effect of CoQ_{10} on the neurotoxic effects of different types of Aβ. In addition, it has been shown that oral administration of CoQ_{10} results in an important increase in serum/plasma CoQ_{10} concentrations in humans [71–73] and in rats [73].

The potential beneficial effects of CoQ_{10} administration, its good absorption, and the lack of important adverse effects led to some initial short-term randomized clinical trials that showed improvement in several neuropsychological tests in patients with AD treated with CoQ_{10} in comparison with those assigned to placebo [57,58] or the anticholinesterase drug tacrine [59]. However, a further short-term randomized clinical trial failed to determine any benefit except a mild improvement in the ADAS-Cog scores [60].

In conclusion, according to the data from the results presented in this review, there are still important knowledge gaps regarding both the suitability of CoQ_{10} as a biomarker of AD and other causes of dementia (studies on this issue in brain, cerebrospinal fluid, and

other tissues are scarce) and the possible usefulness of treatment with CoQ_{10} in patients with AD (controversial results of randomized controlled trials with a maximum of 1 year of follow-up) despite the promising neuroprotective effects of CoQ_{10} detected in different models of AD. The design of further studies with a longer-term follow-up period is needed.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/antiox12020533/s1, Table S1: PRISMA Checklist; Table S2: MOOSE Checklist.

Author Contributions: F.J.J.-J.: Conceptualization, Methodology, Investigation, Validation, Formal analysis, Investigation, Writing—original draft, Writing—review and editing, Project administration. H.A.-N.: Conceptualization, Methodology, Investigation, Validation, Formal analysis, Investigation, Writing—original draft, Writing—review and editing, Project administration. E.G.-M.: Conceptualization, Methodology, Investigation, Validation, Formal analysis, Investigation, Writing—original draft, Writing—review and editing, Project administration, Obtaining funding. J.A.G.A.: Conceptualization, Methodology, Investigation, Validation, Formal analysis, Investigation, Writing—original draft, Writing—review and editing, Project administration, Obtaining funding. All authors have read and agreed to the published version of the manuscript.

Funding: The work at the authors' laboratory is supported in part by Grants PI18/00540 and PI21/01683 from Fondo de Investigación Sanitaria, Instituto de Salud Carlos III, Madrid, Spain, and IB20134 and GR21073 from Junta de Extremadura, Mérida, Spain. Partially funded with FEDER funds.

Acknowledgments: We thank James McCue for assistance with the English language. We also appreciate the efforts of the personnel of the Library of Hospital Universitario del Sureste, Arganda del Rey, who retrieved an important number of papers for us.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Crane, F.L. Biochemical functions of coenzyme Q10. *J. Am. Coll. Nutr.* **2001**, *20*, 591–598. [CrossRef]
2. Mantle, D.; Heaton, R.A.; Hargreaves, I.P. Coenzyme Q10, Ageing and the Nervous System: An Overview. *Antioxidants* **2021**, *11*, 2. [CrossRef] [PubMed]
3. Jiménez-Jiménez, F.J.; Alonso-Navarro, H.; Ayuso-Peralta, L.; Jabbour-Wadih, T. Estrés oxidativo y enfermedad de Alzheimer. *Rev. Neurol.* **2006**, *42*, 419–427. [CrossRef] [PubMed]
4. Kumaran, K.R.; Yunusa, S.; Perimal, E.; Wahab, H.; Müller, C.P.; Hassan, Z. Insights into the Pathophysiology of Alzheimer's Disease and Potential Therapeutic Targets: A Current Perspective. *J. Alzheimers Dis.* **2023**, *91*, 507–530. [CrossRef] [PubMed]
5. Jurcau, A. Insights into the Pathogenesis of Neurodegenerative Diseases, Focus on Mitochondrial Dysfunction and Oxidative Stress. *Int. J. Mol. Sci.* **2021**, *22*, 11847. [CrossRef]
6. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G.; Group, P. Preferred reporting items for systematic reviews and meta-analyses, the PRISMA statement. *PLoS Med.* **2009**, *6*, e1000097. [CrossRef]
7. Wells, G.A.; Shea, B.; O'Connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality If Nonrandomized Studies in Meta Analyses. Available online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed on 3 January 2023).
8. de Bustos, F.; Molina, J.A.; Jiménez-Jiménez, F.J.; García-Redondo, A.; Gómez-Escalonilla, C.; Porta-Etessam, J.; Berbel, A.; Zurdo, M.; Barcenilla, B.; Parrilla, G.; et al. Serum levels of coenzyme Q10 in patients with Alzheimer's disease. *J. Neural. Transm.* **2000**, *107*, 233–239. [CrossRef]
9. Battino, M.; Bompadre, S.; Leone, L.; Devecchi, E.; Degiuli, A.; D'Agostino, F.; Cambiè, G.; D'Agostino, M.; Faggi, L.; Colturani, G.; et al. Coenzyme Q, Vitamin E and Apo-E alleles in Alzheimer Disease. *Biofactors* **2003**, *18*, 277–281. [CrossRef]
10. Giavarotti, L.; Simon, K.A.; Azzalis, L.A.; Fonseca, F.L.; Lima, A.F.; Freitas, M.C.; Brunialti, M.K.; Salomão, R.; Moscardi, A.A.; Montaño, M.B.; et al. Mild systemic oxidative stress in the subclinical stage of Alzheimer's disease. *Oxid. Med. Cell. Longev.* **2013**, *2013*, 609019. [CrossRef]
11. Isobe, C.; Abe, T.; Terayama, Y. Increase in the oxidized/total coenzyme Q-10 ratio in the cerebrospinal fluid of Alzheimer's disease patients. *Dement. Geriatr. Cogn. Disord.* **2009**, *28*, 449–454. [CrossRef]
12. Isobe, C.; Abe, T.; Terayama, Y. Levels of reduced and oxidized coenzyme Q-10 and 8-hydroxy-2'-deoxyguanosine in the CSF of patients with Alzheimer's disease demonstrate that mitochondrial oxidative damage and/or oxidative DNA damage contributes to the neurodegenerative process. *J. Neurol.* **2010**, *257*, 399–404. [CrossRef] [PubMed]
13. Molina, J.A.; de Bustos, F.; Ortiz, S.; Del Ser, T.; Seijo, M.; Benito-Léon, J.; Oliva, J.M.; Pérez, S.; Manzanares, J. Serum levels of coenzyme Q in patients with Lewy body disease. *J. Neural. Transm.* **2002**, *109*, 1195–1201. [CrossRef]

14. Yamagishi, K.; Ikeda, A.; Moriyama, Y.; Chei, C.L.; Noda, H.; Umesawa, M.; Cui, R.; Nagao, M.; Kitamura, A.; Yamamoto, Y.; et al. Serum coenzyme Q10 and risk of disabling dementia, the Circulatory Risk in Communities Study (CIRCS). *Atherosclerosis* **2014**, *237*, 400–403. [CrossRef]
15. Chang, P.S.; Chou, H.H.; Lai, T.J.; Yen, C.H.; Pan, J.C.; Lin, P.T. Investigation of coenzyme Q10 status.; serum amyloid-β.; and tau protein in patients with dementia. *Front. Aging Neurosci.* **2022**, *14*, 910289. [CrossRef]
16. Balduzzi, S.; Rücker, G.; Schwarzer, G. How to perform a meta-analysis with R: A practical tutorial. *BMJ Ment. Health* **2019**, *22*, 153–160. [CrossRef]
17. Stroup, D.F.; Berlin, J.A.; Morton, S.C.; Olkin, I.; Williamson, G.D.; Rennie, D.; Moher, D.; Becker, B.J.; Sipe, T.A.; Thacker, S.B. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **2009**, *283*, 2008–2012. [CrossRef]
18. Der Simonian, R.; Laird, N. Meta-analysis in clinical trials. *Control. Clin. Trials* **1986**, *7*, 177–188. [CrossRef] [PubMed]
19. Jackson, D. Confidence intervals for the between-study variance in random effects meta-analysis using generalised Cochran heterogeneity statistics. *Res. Synth. Methods* **2013**, *4*, 220–229. [CrossRef] [PubMed]
20. Hedges, L.V. Meta-Analysis. *J. Educ. Stat.* **1992**, *17*, 279–296. [CrossRef]
21. Edlund, C.; Söderberg, M.; Kristensson, K.; Dallner, G. Ubiquinone, dolichol, and cholesterol metabolism in aging and Alzheimer's disease. *Biochem. Cell. Biol.* **1992**, *70*, 422–428. [CrossRef]
22. Kim, S.H.; Vlkolinsky, R.; Cairns, N.; Fountoulakis, M.; Lubec, G. The reduction of NADH ubiquinone oxidoreductase 24- and 75-kDa subunits in brains of patients with Down syndrome and Alzheimer's disease. *Life Sci.* **2001**, *68*, 2741–2750. [CrossRef]
23. Santa-Mara, I.; Santpere, G.; MacDonald, M.J.; Gomez de Barreda, E.; Hernandez, F.; Moreno, F.J.; Ferrer, I.; Avila, J. Coenzyme q induces tau aggregation.; tau filaments.; and Hirano bodies. *J. Neuropathol. Exp. Neurol.* **2008**, *67*, 428–434. [PubMed]
24. McDonald, S.R.; Sohal, R.S.; Forster, M.J. Concurrent administration of coenzyme Q10 and alpha-tocopherol improves learning in aged mice. *Free Radic. Biol. Med.* **2005**, *38*, 729–736. [CrossRef]
25. Wadsworth, T.L.; Bishop, J.A.; Pappu, A.S.; Woltjer, R.L.; Quinn, J.F. Evaluation of coenzyme Q as an antioxidant strategy for Alzheimer's disease. *J. Alzheimers Dis.* **2008**, *14*, 225–234. [PubMed]
26. Sumien, N.; Heinrich, K.R.; Shetty, R.A.; Sohal, R.S.; Forster, M.J. Prolonged intake of coenzyme Q10 impairs cognitive functions in mice. *J. Nutr.* **2009**, *139*, 1926–1932. [CrossRef]
27. Shetty, R.A.; Forster, M.J.; Sumien, N. Coenzyme Q(10) supplementation reverses age-related impairments in spatial learning and lowers protein oxidation. *Age* **2013**, *35*, 1821–1834. [CrossRef] [PubMed]
28. Shetty, R.A.; Ikonne, U.S.; Forster, M.J.; Sumien, N. Coenzyme Q10 and α-tocopherol reversed age-associated functional impairments in mice. *Exp. Gerontol.* **2014**, *58*, 208–218. [CrossRef]
29. Ibrahim Fouad, G. Combination of Omega 3 and Coenzyme Q10 Exerts Neuroprotective Potential against Hypercholesterolemia-Induced Alzheimer's-Like Disease in Rats. *Neurochem. Res.* **2020**, *45*, 1142–1155. [CrossRef]
30. Ali, A.A.; Abo El-Ella, D.M.; El-Emam, S.Z.; Shahat, A.S.; El-Sayed, R.M. Physical & mental activities enhance the neuroprotective effect of vinpocetine & coenzyme Q10 combination against Alzheimer & bone remodeling in rats. *Life Sci.* **2019**, *229*, 21–35.
31. Attia, H.; Albuhayri, S.; Alaraidh, S.; Alotaibi, A.; Yacoub, H.; Mohamad, R.; Al-Amin, M. Biotin, coenzyme Q10, and their combination ameliorate aluminium chloride-induced Alzheimer's disease via attenuating neuroinflammation and improving brain insulin signaling. *J. Biochem. Mol. Toxicol.* **2020**, *34*, e22519. [CrossRef]
32. Ali, A.A.; Khalil, M.G.; Abd El-Latif, D.M.; Okda, T.; Abdelaziz, A.I.; Abu-Elfotuh, K.; Kamal, M.M.; Wahid, A. The influence of vinpocetine alone or in combination with Epigallocatechin-3-gallate, Coenzyme COQ10, Vitamin E and Selenium as a potential neuroprotective combination against aluminium-induced Alzheimer's disease in Wistar Albino Rats. *Arch. Gerontol. Geriatr.* **2022**, *98*, 104557. [CrossRef] [PubMed]
33. Nitta, A.; Murakami, Y.; Furukawa, Y.; Kawatsura, W.; Hayashi, K.; Yamada, K.; Hasegawa, T.; Nabeshima, T. Oral administration of idebenone induces nerve growth factor in the brain and improves learning and memory in basal forebrain-lesioned rats. *Naunyn Schmiedebergs Arch. Pharmacol.* **1994**, *349*, 401–407. [CrossRef] [PubMed]
34. Yamada, K.; Tanaka, T.; Han, D.; Senzaki, K.; Kameyama, T.; Nabeshima, T. Protective effects of idebenone and alpha-tocopherol on beta-amyloid-(1-42)-induced learning and memory deficits in rats: Implication of oxidative stress in beta-amyloid-induced neurotoxicity in vivo. *Eur. J. Neurosci.* **1999**, *11*, 83–90. [CrossRef] [PubMed]
35. Singh, A.; Kumar, A. Microglial Inhibitory Mechanism of Coenzyme Q10 Against Aβ (1-42) Induced Cognitive Dysfunctions: Possible Behavioral, Biochemical, Cellular, and Histopathological Alterations. *Front. Pharmacol.* **2015**, *6*, 268. [CrossRef]
36. Komaki, H.; Faraji, N.; Komaki, A.; Shahidi, S.; Etaee, F.; Raoufi, S.; Mirzaei, F. Investigation of protective effects of coenzyme Q10 on impaired synaptic plasticity in a male rat model of Alzheimer's disease. *Brain Res. Bull.* **2019**, *147*, 14–21. [CrossRef]
37. Ishrat, T.; Khan, M.B.; Hoda, M.N.; Yousuf, S.; Ahmad, M.; Ansari, M.A.; Ahmad, A.S.; Islam, F. Coenzyme Q10 modulates cognitive impairment against intracerebroventricular injection of streptozotocin in rats. *Behav. Brain Res.* **2006**, *171*, 9–16. [CrossRef] [PubMed]
38. Sheykhhasan, M.; Amini, R.; Soleimani Asl, S.; Saidijam, M.; Hashemi, S.M.; Najafi, R. Neuroprotective effects of coenzyme Q10-loaded exosomes obtained from adipose-derived stem cells in a rat model of Alzheimer's disease. *Biomed. Pharmacother.* **2022**, *152*, 113224. [CrossRef] [PubMed]
39. Yang, X.; Yang, Y.; Li, G.; Wang, J.; Yang, E.S. Coenzyme Q10 attenuates beta-amyloid pathology in the aged transgenic mice with Alzheimer presenilin 1 mutation. *J. Mol. Neurosci.* **2008**, *34*, 165–171. [CrossRef]

40. Yang, X.; Dai, G.; Li, G.; Yang, E.S. Coenzyme Q10 reduces beta-amyloid plaque in an APP/PS1 transgenic mouse model of Alzheimer's disease. *J. Mol. Neurosci.* **2010**, *41*, 110–113. [CrossRef]
41. Dumont, M.; Kipiani, K.; Yu, F.; Wille, E.; Katz, M.; Calingasan, N.Y.; Gorras, G.K.; Lin, M.T.; Beal, M.F. Coenzyme Q10 decreases amyloid pathology and improves behavior in a transgenic mouse model of Alzheimer's disease. *J. Alzheimers Dis.* **2011**, *27*, 211–223. [CrossRef]
42. Elipenahli, C.; Snack, C.; Jainuddin, S.; Gerges, M.; Yang, L.; Starkov, A.; Beal, M.F.; Dumont, M. Behavioral improvement after chronic administration of coenzyme Q10 in P301S transgenic mice. *J. Alzheimers Dis.* **2012**, *28*, 173–182. [CrossRef]
43. Muthukumaran, K.; Kanwar, A.; Vegh, C.; Marginean, A.; Elliott, A.; Guilbeault, N.; Badour, A.; Sikorska, M.; Cohen, J.; Pandey, S. Ubisol-Q10 (a Nanomicellar Water-Soluble Formulation of CoQ10) Treatment Inhibits Alzheimer-Type Behavioral and Pathological Symptoms in a Double Transgenic Mouse (TgAPEswe.; PSEN1dE9) Model of Alzheimer's Disease. *J. Alzheimers Dis.* **2018**, *61*, 221–236. [CrossRef]
44. Sui, X.; Ren, X.; Huang, P.; Li, S.; Ma, Q.; Ying, M.; Ni, J.; Liu, J.; Yang, X. Proteomic analysis of serum proteins in triple transgenic Alzheimer's disease mice: Implications for identifying biomarkers for use to screen potential candidate therapeutic drugs for early Alzheimer's disease. *J Alzheimers Dis.* **2014**, *40*, 575–586. [CrossRef] [PubMed]
45. Ma, D.; Stokes, K.; Mahngar, K.; Domazet-Damjanov, D.; Sikorska, M.; Pandey, S. Inhibition of stress induced premature senescence in presenilin-1 mutated cells with water soluble Coenzyme Q10. *Mitochondrion* **2014**, *17*, 106–115. [CrossRef] [PubMed]
46. Vegh, C.; Pupulin, S.; Wear, D.; Culmone, L.; Huggard, R.; Ma, D.; Pandey, S. Resumption of Autophagy by Ubisol-Q_{10} in Presenilin-1 Mutated Fibroblasts and Transgenic AD Mice, Implications for Inhibition of Senescence and Neuroprotection. *Oxid. Med. Cell. Longev.* **2019**, *2019*, 7404815. [CrossRef]
47. Qi, X.L.; Xiu, J.; Shan, K.R.; Xiao, Y.; Gu, R.; Liu, R.Y.; Guan, Z.Z. Oxidative stress induced by beta-amyloid peptide(1-42) is involved in the altered composition of cellular membrane lipids and the decreased expression of nicotinic receptors in human SH-SY5Y neuroblastoma cells. *Neurochem. Int.* **2005**, *46*, 613–621. [CrossRef] [PubMed]
48. Durán-Prado, M.; Frontiñán, J.; Santiago-Mora, R.; Peinado, J.R.; Parrado-Fernández, C.; Gómez-Almagro, M.V.; Moreno, M.; López-Domínguez, J.A.; Villalba, J.M.; Alcaín, F.J. Coenzyme Q10 protects human endothelial cells from β-amyloid uptake and oxidative stress-induced injury. *PLoS ONE* **2014**, *9*, e109223. [CrossRef] [PubMed]
49. Frontiñán-Rubio, J.; Rabanal-Ruiz, Y.; Durán-Prado, M.; Alcain, F.J. The Protective Effect of Ubiquinone against the Amyloid Peptide in Endothelial Cells Is Isoprenoid Chain Length-Dependent. *Antioxidants* **2021**, *10*, 1806. [CrossRef] [PubMed]
50. Choi, H.; Park, H.H.; Koh, S.H.; Choi, N.Y.; Yu, H.J.; Park, J.; Lee, Y.J.; Lee, K.Y. Coenzyme Q10 protects against amyloid beta-induced neuronal cell death by inhibiting oxidative stress and activating the P13K pathway. *Neurotoxicology* **2012**, *33*, 85–90. [CrossRef]
51. Wang, H.; Li, L.; Jia, K.; Wang, Q.; Sui, S.; Lin, Y.; He, Y. Idebenone protects mitochondrial function against amyloid beta toxicity in primary cultured cortical neurons. *Neuroreport* **2020**, *31*, 1104–1110. [CrossRef]
52. Choi, H.; Park, H.H.; Lee, K.Y.; Choi, N.Y.; Yu, H.J.; Lee, Y.J.; Park, J.; Huh, Y.M.; Lee, S.H.; Koh, S.H. Coenzyme Q10 restores amyloid beta-inhibited proliferation of neural stem cells by activating the PI3K pathway. *Stem Cells Dev.* **2013**, *22*, 2112–2120. [CrossRef] [PubMed]
53. Yang, M.; Lian, N.; Yu, Y.; Wang, Y.; Xie, K.; Yu, Y. Coenzyme Q10 alleviates sevoflurane-induced neuroinflammation by regulating the levels of apolipoprotein E and phosphorylated tau protein in mouse hippocampal neurons. *Mol. Med. Rep.* **2020**, *22*, 445–453. [CrossRef] [PubMed]
54. Moreira, P.I.; Santos, M.S.; Sena, C.; Nunes, E.; Seiça, R.; Oliveira, C.R. CoQ10 therapy attenuates amyloid beta-peptide toxicity in brain mitochondria isolated from aged diabetic rats. *Exp. Neurol.* **2005**, *196*, 112–119. [CrossRef] [PubMed]
55. Li, L.; Xu, D.; Lin, J.; Zhang, D.; Wang, G.; Sui, L.; Ding, H.; Du, J. Coenzyme Q10 attenuated β-amyloid$_{25-35}$-induced inflammatory responses in PC12 cells through regulation of the NF-κB signaling pathway. *Brain Res Bull.* **2017**, *131*, 192–198. [CrossRef]
56. Imagawa, M.; Naruse, S.; Tsuji, S.; Fujioka, A.; Yamaguchi, H. Coenzyme Q10.; iron.; and vitamin B6 in genetically-confirmed Alzheimer's disease. *Lancet* **1992**, *340*, 671. [CrossRef] [PubMed]
57. Weyer, G.; Babej-Dölle, R.M.; Hadler, D.; Hofmann, S.; Herrmann, W.M. A controlled study of 2 doses of idebenone in the treatment of Alzheimer's disease. *Neuropsychobiology* **1997**, *36*, 73–82. [CrossRef]
58. Gutzmann, H.; Hadler, D. Sustained efficacy and safety of idebenone in the treatment of Alzheimer's disease: Update on a 2-year double-blind multicentre study. *J. Neural Transm. Suppl.* **1998**, *54*, 301–310.
59. Gutzmann, H.; Kühl, K.P.; Hadler, D.; Rapp, M.A. Safety and efficacy of idebenone versus tacrine in patients with Alzheimer's disease: Results of a randomized, double-blind, parallel-group multicenter study. *Pharmacopsychiatry* **2002**, *35*, 12–18. [CrossRef]
60. Thal, L.J.; Grundman, M.; Berg, J.; Ernstrom, K.; Margolin, R.; Pfeiffer, E.; Weiner, M.F.; Zamrini, E.; Thomas, R.G. Idebenone treatment fails to slow cognitive decline in Alzheimer's disease. *Neurology* **2003**, *61*, 1498–1502. [CrossRef]
61. Voronkova, K.V.; Meleshkov, M.N. Use of Noben (idebenone) in the treatment of dementia and memory impairments without dementia. *Neurosci. Behav. Physiol.* **2009**, *39*, 501–506. [CrossRef]
62. Galasko, D.R.; Peskind, E.; Clark, C.M.; Quinn, J.F.; Ringman, J.M.; Jicha, G.A.; Cotman, C.; Cottrell, B.; Montine, T.J.; Thomas, R.G.; et al. Alzheimer's Disease Cooperative Study. Antioxidants for Alzheimer disease: A randomized clinical trial with cerebrospinal fluid biomarker measures. *Arch. Neurol.* **2012**, *69*, 836–841. [CrossRef]
63. Karakahya, R.H.; Özcan, T.Ş. Salvage of the retinal ganglion cells in transition phase in Alzheimer's disease with topical coenzyme Q10, is it possible? *Graefes Arch. Clin. Exp. Ophthalmol.* **2020**, *258*, 411–418. [CrossRef]

64. Kawakami, M.; Itoh, T. Effects of idebenone on monoamine metabolites in cerebrospinal fluid of patients with cerebrovascular dementia. *Arch. Gerontol. Geriatr.* **1989**, *8*, 343–353. [CrossRef]
65. Qi, F.X.; Hu, Y.; Kang, L.J.; Li, P.; Gao, T.C.; Zhang, X. Effects of Butyphthalide Combined with Idebenone on Inflammatory Cytokines and Vascular Endothelial Functions of Patients with Vascular Dementia. *J. Coll. Physicians Surg. Pak.* **2020**, *30*, 23–27. [CrossRef]
66. García-Carpintero, S.; Domínguez-Bértalo, J.; Pedrero-Prieto, C.; Frontiñán-Rubio, J.; Amo-Salas, M.; Durán-Prado, M.; García-Pérez, E.; Vaamonde, J.; Alcain, F.J. Ubiquinol Supplementation Improves Gender-Dependent Cerebral Vasoreactivity and Ameliorates Chronic Inflammation and Endothelial Dysfunction in Patients with Mild Cognitive Impairment. *Antioxidants* **2021**, *10*, 143. [CrossRef]
67. Stough, C.; Nankivell, M.; Camfield, D.A.; Perry, N.L.; Pipingas, A.; Macpherson, H.; Wesnes, K.; Ou, R.; Hare, D.; de Haan, J.; et al. CoQ_{10} and Cognition a Review and Study Protocol for a 90-Day Randomized Controlled Trial Investigating the Cognitive Effects of Ubiquinol in the Healthy Elderly. *Front. Aging Neurosci.* **2019**, *11*, 103. [CrossRef] [PubMed]
68. Fernández-Portero, C.; Amián, J.G.; Bella, R.; López-Lluch, G.; Alarcón, D. Coenzyme Q10 Levels Associated with Cognitive Functioning and Executive Function in Older Adults. *J. Gerontol. A Biol. Sci. Med. Sci.* **2023**, *78*, 1–8. [CrossRef] [PubMed]
69. Grundman, M.; Grundman, M.; Delaney, P. Antioxidant strategies for Alzheimer's disease. *Proc. Nutr. Soc.* **2002**, *61*, 191–202. [CrossRef] [PubMed]
70. Beal, M.F. Mitochondrial dysfunction and oxidative damage in Alzheimer's and Parkinson's diseases and coenzyme Q10 as a potential treatment. *J. Bioenerg. Biomembr.* **2004**, *36*, 381–386. [CrossRef]
71. Lönnrot, K.; Metsä-Ketelä, T.; Molnár, G.; Ahonen, J.P.; Latvala, M.; Peltola, J.; Pietilä, T.; Alho, H. The effect of ascorbate and ubiquinone supplementation on plasma and CSF total antioxidant capacity. *Free Radic. Biol. Med.* **1996**, *21*, 211–217. [CrossRef]
72. Shults, C.W.; Flint Beal, M.; Song, D.; Fontaine, D. Pilot trial of high dosages of coenzyme Q10 in patients with Parkinson's disease. *Exp. Neurol.* **2004**, *188*, 491–494. [CrossRef] [PubMed]
73. Nukui, K.; Yamagishi, T.; Miyawaki, H.; Kettawan, A.; Okamoto, T.; Belardinelli, R.; Tiano, L.; Littarru, G.P.; Sato, K. Blood CoQ10 levels and safety profile after single-dose or chronic administration of PureSorb-Q40, animal and human studies. *Biofactors* **2008**, *32*, 209–219. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.