International Journal of
*Molecular Sciences*

MDPI

*Review*

# Coenzyme $Q_{10}$: Novel Formulations and Medical Trends

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Received: 18 October 2020; Accepted: 7 November 2020; Published: 10 November 2020

**Abstract:** The aim of this review is to shed light over the most recent advances in Coenzyme $Q_{10}$ ($CoQ_{10}$) applications as well as to provide detailed information about the functions of this versatile molecule, which have proven to be of great interest in the medical field. Traditionally, $CoQ_{10}$ clinical use was based on its antioxidant properties; however, a wide range of highly interesting alternative functions have recently been discovered. In this line, $CoQ_{10}$ has shown pain-alleviating properties in fibromyalgia patients, a membrane-stabilizing function, immune system enhancing ability, or a fundamental role for insulin sensitivity, apart from potentially beneficial properties for familial hypercholesterolemia patients. In brief, it shows a remarkable amount of functions in addition to those yet to be discovered. Despite its multiple therapeutic applications, $CoQ_{10}$ is not commonly prescribed as a drug because of its low oral bioavailability, which compromises its efficacy. Hence, several formulations have been developed to face such inconvenience. These were initially designed as lipid nanoparticles for $CoQ_{10}$ encapsulation and distribution through biological membranes and eventually evolved towards chemical modifications of the molecule to decrease its hydrophobicity. Some of the most promising formulations will also be discussed in this review.

**Keywords:** Coenzyme $Q_{10}$; ubiquinone; mitochondria

## 1. Introduction

Coenzyme $Q_{10}$ ($CoQ_{10}$) was first identified back in the fifties by two groups, Festenstein et al. (1955) [1] and Crane et al. (1957) [2]. Its name was chosen due to the fact that it is an ubiquitous quinone present in all cells and that its chemical structure comprises a quinone group with a variable number of isoprenyl units, being ten in the case of humans [3]. Its reduced form is known as ubiquinol and the oxidized one as ubiquinone. Both forms coexist and through sequential redox reactions serve to regenerate each other (Q cycle) [4]. The biological relevance of this vital molecule is related to its functions as a lipophilic antioxidant (scavenges free radicals inhibiting the initiation and progression of lipid peroxidation in cell membranes) [5]. Moreover, the intracellularly produced ubiquinone is a potent endogenous antioxidant and acts as an electron carrier in the mitochondrial electron transport chain, being involved in electron transport between complexes I or II and complex III [6]. Ubiquinol, meanwhile, presents antioxidant behavior in cell and organelle membranes. Apart from these main functions, $CoQ_{10}$ plays an important role in uncoupling proteins' activation [7], cell signaling [8], cell growth [9] and apoptosis through the modulation of the mitochondrial permeability transition

pore [10]. This molecule has traditionally been used clinically as an enhancer of mitochondrial function or an antioxidant intended to either palliate or diminish the oxidative damage that may worsen the physiological outcome of a wide range of diseases. For this purpose, it is commonly administered orally as a dietary supplement. However, this may compromise the effectivity of treatment, since the intestinal absorption of the molecule is poor. In fact, studies in rats demonstrate that only about 3% of the orally administered $CoQ_{10}$ can be absorbed [11]. In this case, increasing the dosage is not a feasible solution due to the toxicity associated with the traditional vehicles used for its delivery at high concentrations. The acceptable daily intake (ADI) of $CoQ_{10}$ has been set at 12 mg/kg/day. This is calculated from the no-observed-adverse-effect level (NOAEL) by applying a safety factor of 100 (i.e., ≥600 mg/day for adults weighing 50 kg) [12].

$CoQ_{10}$ is indispensable for the proper functioning of any cell type, hence, its absence or its reduced synthesis has severe consequences. The diverse phenotypes associated with low $CoQ_{10}$ concentration are provoked by an abnormal respiratory chain function in addition to increased generation of free radicals, leading to inadequate cellular energy production and consequent degradation of mitochondria by mitophagy [13]. The repercussions of these failures are various diseases that range from cerebellar ataxia, severe infantile multisystemic failure, and encephalomyopathy or nephropathy to isolated myopathy or nephrotic syndrome with or without sensorineural hearing loss, these latter being the most common ones [14].

In the present review, the most recent $CoQ_{10}$ applications of therapeutic and scientific interest will be examined (Figure 1 and Table 1), as well as the state-of-the-art $CoQ_{10}$ formulations (Figure 2). To conclude, future perspectives associated with the use of this versatile molecule will be discussed to give a general overview of the promising advances that the field can undergo.

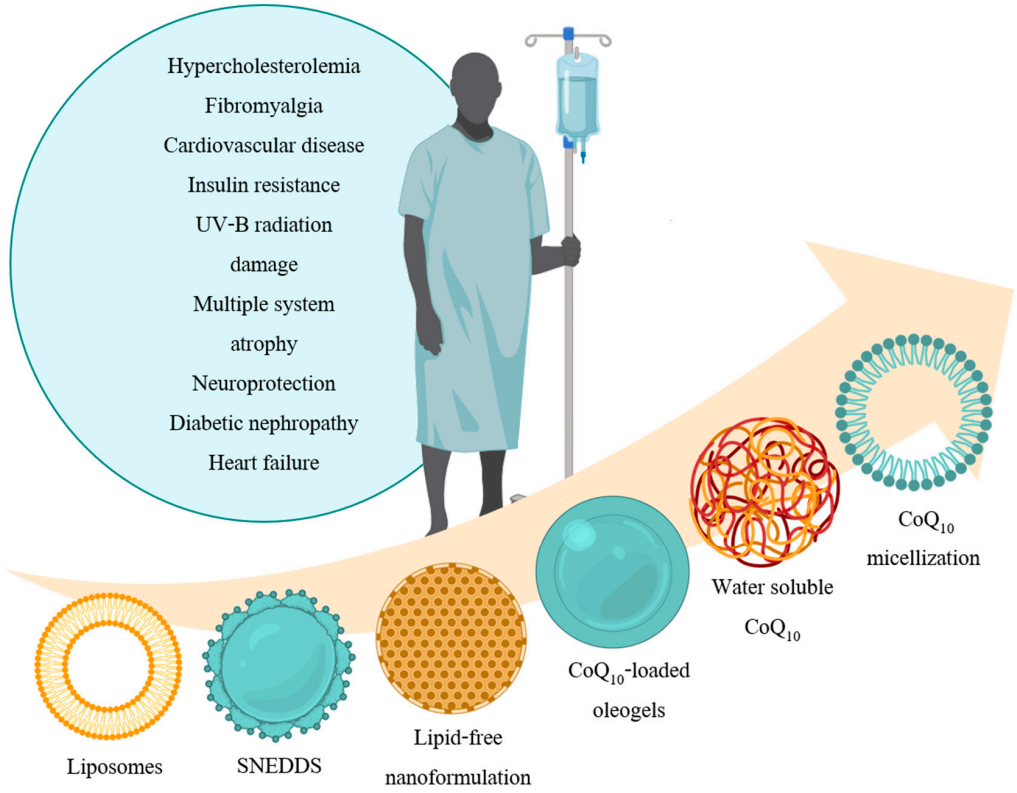


**Figure 1.** $CoQ_{10}$ applications in the medical field. Traditionally, $CoQ_{10}$ has been used as a therapeutic agent for diabetic cardiovascular diseases, diabetic nephropathy, neuroprotection, and heart failure owing to its antioxidant activity. In fact, it is widely known that the excessive generation of ROS is a

underlying factor of all these diseases which severely worsens the outcome for the patients. More recently, several studies have proved $CoQ_{10}$'s potential application against ultraviolet B (UVB) radiation damage, multiple system atrophy (MSA), or as an immunity and inflammatory marker. Both in MSA and inflammation, $CoQ_{10}$ levels are below the normal range in patients, the reason why its supplementation led to an improvement in their development and well-being. Furthermore, due to its ROS-scavenging function, $CoQ_{10}$ has proved to be significantly beneficial for skin cells' protection against UVB radiation and insulin sensitivity. Surprising though it may seem, it is also highly beneficial for familial hypercholesterolemia patients who, in general, present a secondary $CoQ_{10}$ deficiency derived from their disease. Finally, it has shown a remarkable membrane stabilizing property, since it increases the lipid packing order and the mechanical stability of the IMM-mimicking membranes, the reason why it could potentially be used as a therapy for Barth syndrome patients.

**Table 1.** Novel medical applications of $CoQ_{10}$.

| Disease | $CoQ_{10}$ Application | References |
| --- | --- | --- |
| Diabetic cardiovascular diseases and diabetic nephropathy | Significant reduction in adverse cardiovascular events | [11,15–22] |
| Multiple system atrophy | Accurate biomarker for MSA when found in low levels in cerebrospinal fluid | [20,23–30] |
| Immunological disorders | Significant improvement of the T cell function<br>Reduction of circulating inflammatory markers | [14,31–50] |
| Neuropathies | Neuroprotection via $Ca_2^+$ buffering and antioxidant activity | [35,51–79] |
| UVB radiation damage | Treatment of damaged skin | [66,80–85] |
| Heart failure | Supplementation required for improving patient condition | [82,86–93] |
| Barth syndrome and membrane instability-related diseases | $CoQ_{10}$-based treatment for Barth syndrome patients<br>Development of cholesterol-free liposome-based drug delivery systems | [94–106] |
| Insulin resistance | Increase in insulin sensitivity by scavenging mitochondrial oxidants | [107–115] |
| Fibromyalgia | Pain alleviation | [116–121] |
| Familial hypercholesterolemia and atherosclerosis | Supplementation required for improving patient condition | [122–126] |

Coenzyme $Q_{10}$ has been extensively used in the clinic due to its potent antioxidant properties. However, less known $CoQ_{10}$ properties have gained importance in the medical field in the past few years. Now that the physiological barriers of $CoQ_{10}$ delivery have virtually been overcome, this quinone could prove an invaluable ally for the treatment of a wide spectrum of diseases. This table lists some of the most recent clinical applications of $CoQ_{10}$ and the diseases that would benefit from them.

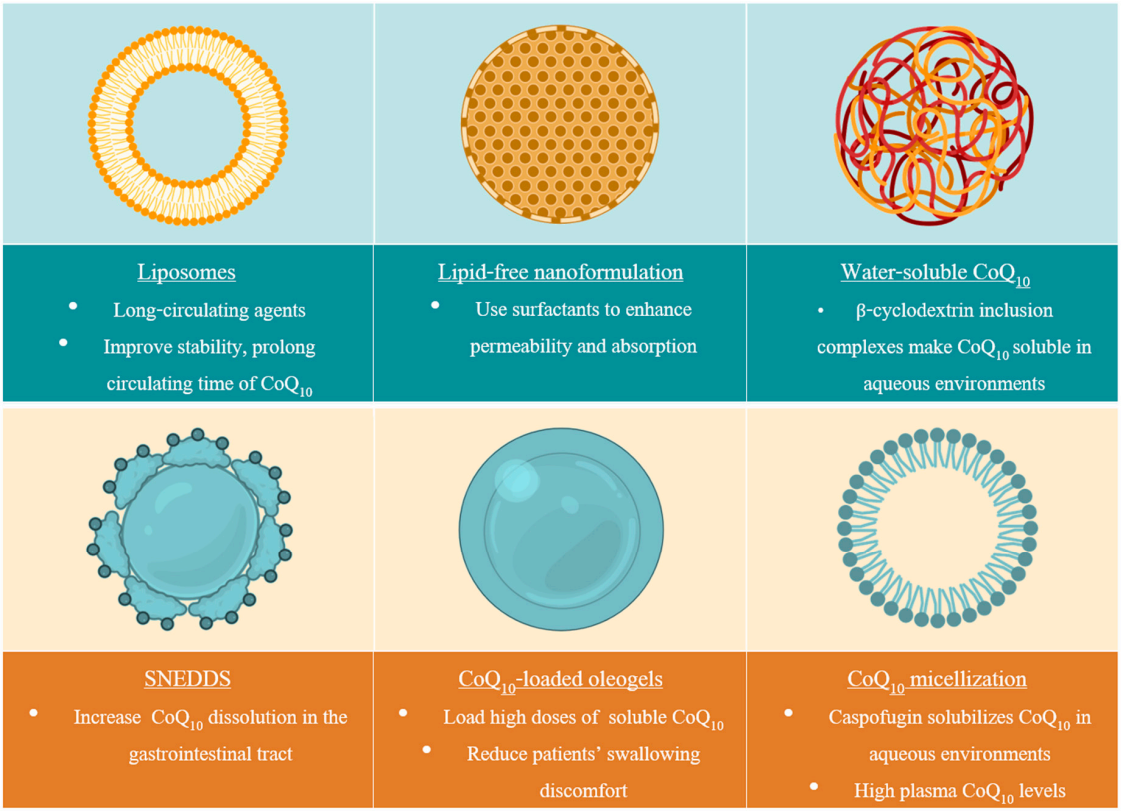


**Figure 2.** Highlights of $CoQ_{10}$ formulations. The initial trend in $CoQ_{10}$ formulations' design was to use non-polar agents as delivery systems due to several advantages they present (increase drug solubility in intestines, recruit lymphatic drug transport, or modify enterocyte-based drug transport and disposition). However, there is rising interest in the development of water-soluble delivery mechanisms in order to prevent the common drawbacks of lipid-based formulations, such as rate of dispersion, degree of emulsification, particle size, or drug precipitation from the formulation upon dispersion. The first attempts towards this goal include the development of lipid-free $CoQ_{10}$ nanoformulations, micellar $CoQ_{10}$ solutions, and hydrophilic $CoQ_{10}$ inclusion complexes.

## 2. $CoQ_{10}$ Applications in the Medical Field

### *2.1. Diabetic Cardiovascular Diseases and Diabetic Nephropathy*

Diabetes mellitus is a metabolic disorder characterized by impaired insulin production and reduced insulin sensitivity. This disorder leads to inadequate glucose storage and deficient glycogenolysis and gluconeogenesis pathways. As a result, patients suffer from chronic hyperglycemia and, subsequently, from long-term micro- and macrovascular complications. The microvascular complications affect small blood vessels and include nephropathy, neuropathy, and retinopathy, while the macrovascular complications comprise cardiovascular, cerebrovascular, and peripheral artery diseases [15].

Macrovascular complications of diabetes, such as diabetic cardiovascular disease (CVD), occur through a number of hyperglycemia-induced mechanisms that trigger generation of oxidative stress. The generation of reactive oxygen species (ROS) by diabetic cardiac cells can be mediated by several pathways, such as, among other things, activation of the receptor for advanced glycation end products (RAGE) by advanced glycation end products (AGEs), xanthine oxidase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, activation of protein kinase C (PKC) [11]. Given that these factors interact, profound overproduction of ROS takes place, leading to diabetic CVD. The symptoms of this lateral disease include, among other things, alterations in cardiac morphology, increased blood pressure, and chest pain [16].

Diverse antioxidant molecules have been tested for possible therapeutic use. Among them, $CoQ_{10}$ has shown promising results. A recent randomized controlled trial has proven that its use as an adjunct therapy for chronic heart failure is associated with a significant reduction in adverse cardiovascular events [17]. For this reason, $CoQ_{10}$ can be considered a potential treatment for CVD patients.

Diabetic nephropathy (DN) is one of the most recurrent microvascular complications associated with hyperglycemia. A recent approach towards this disease's treatment involves the combination of $CoQ_{10}$-loaded liposomes with ultrasound-targeted microbubble destruction (UTMD) [18]. As previously mentioned, excessive ROS are found in the mitochondrial respiratory chain in high-glucose environments [19]. High ROS concentrations are the most advanced and upstream factor in the pathogenesis of diabetic vascular disease [20] and hence of diabetic nephropathy. Thereby, $CoQ_{10}$ with its antioxidant function could be a potential treatment for early DN. Nevertheless, $CoQ_{10}$ has limited clinical application owing to its low bioavailability. In order to resolve this problem, liposome-mediated delivery systems might be the best option, not only because they enable the transport of $CoQ_{10}$ to the target tissue, but also because they achieve a successful release of the cargo, reduce drug toxicity, and improve drug stability thanks to their good cell compatibility [21]. Yet, $CoQ_{10}$ delivery would be inefficient and non-specific. Aiming to ameliorate the delivery system, liposomes are combined with UTMD. Previous studies confirm that this combination increases local renal interstitial capillary permeability [22], facilitating the entrance of $CoQ_{10}$ in the tissue. This delivery method proved highly satisfactory to treat impaired kidney. The authors of the study believe that the success of the technique can be attributed to the use of UTMD, since it impelled the $CoQ_{10}$-charged liposomes to the target kidney in a non-invasive fashion [17].

### 2.2. Multiple System Atrophy

Multiple System Atrophy (MSA) is an incurable and progressive neurodegenerative condition. Clinically, it is grouped with atypical parkinsonism since its main symptoms are parkinsonism or ataxia plus dysautonomia [23]. Up to the moment, the diagnose of such disease could only be confirmed neuropathologically, being misdiagnoses relatively common [24,25]. Recent studies have proposed low $CoQ_{10}$ levels in cerebrospinal fluid (CSF) as an accurate biomarker for MSA since mutations on the coenzyme Q2 (*COQ2*) gene and an abnormally low cerebellar $CoQ_{10}$ concentration have been reported in all MSA patients. The overlap in the levels of $CoQ_{10}$ in plasma and serum [26,27] and the dependence on other modifiers or confounders like cholesterol [20], were the key aspects leading researchers to hypothesize CSF as an alternative and reliable source to assess a possible MSA biomarker [28]. Interestingly, there is a significant lowering of $CoQ_{10}$ levels in CSF from MSA patients in comparison with other Parkinsonism sufferers and healthy individuals; irrespective of the presence of other confounders [22]. In this line, there is available evidence that $CoQ_{10}$ deficiency is more specifically related to MSA than to other neurodegenerative diseases [29]. Therefore, ubiquinol, a reduced form of $CoQ_{10}$, has been used to treat patients suffering from MSA due to COQ2 mutations with satisfactory results [30].

### 2.3. Immunity and Immunological Disorders

The clinical outcomes of $CoQ_{10}$ deficiency are variable depending on the genetic heterogenicity involving either $CoQ_{10}$ biosynthetic pathways (primary defect) or other pathways (secondary defect) [31]. Recent studies have related impaired immune function with $CoQ_{10}$ deficiency in a case report [14]. The patient showed no mutations of the genes known to be linked to primary or secondary $CoQ_{10}$ deficiency (*COQ2*, *COQ9*, *COQ8A*, *ETFDH*, and *PDSS2*), however, she presented extremely low levels of muscular $CoQ_{10}$ (0.02 μg/mg in comparison to the normal levels of 0.14–0.29 μg/mg protein). Additionally, abnormal T cell proliferation was reported, together with a decreased fraction of plasmablasts, which contributed to the poor humoral response noted in the patient [14]. Proliferating immune cells have a high energy demand [32]. Leukocytes, in particular, are rich in $CoQ_{10}$ and require a reliable mitochondrial network [33]. Thereby, $CoQ_{10}$ supplementation was administered, with the

results being highly satisfactory, since a significant improvement of the T cell function was detected. Moreover, the patient was subject to an immunoglobulin replacement treatment which, combined with $CoQ_{10}$ supply, resulted in a reduced number of infections, less hospitalizations, and, overall, a better quality of life.

It would be convenient to carry out further investigation on the impact of $CoQ_{10}$ deficiency over immune function so as to elucidate whether functional T cell deficiency may be linked to $CoQ_{10}$ deficiency in patients with recurrent infections. This would explain the improvement of the CD4 T cell counts in acquired immune deficiency syndrome (AIDS) patients following a $CoQ_{10}$ supplementation treatment [34,35].

Surprising though it may seem, $CoQ_{10}$ supplementation has also been proven to reduce the levels of circulating inflammatory markers [36]. According to previous studies, inflammation plays a deleterious role in numerous diseases, such as, among other diseases, type 2 diabetes [37], CVD [38], chronic obstructive pulmonary disease [39], and cancer [40]. Elevated levels of inflammatory markers, such as C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α), increase the risk of chronic disease development and contribute to enhance disease pathogenesis [41]. Oxidative stress is one of the main factors that trigger inflammation [42], therefore, antioxidants that target oxidative stress and inflammation like $CoQ_{10}$ may be highly effective in disease prevention or treatment [30,43]. The anti-inflammatory effect of $CoQ_{10}$ is already widely known [42], nonetheless, the most recent approaches are aimed at examining the impact of $CoQ_{10}$ over inflammatory mediators CRP, IL-6, and TNF-α. The ability of $CoQ_{10}$'s to lower these inflammatory mediators was reported in a systematic review and meta-analysis carried out in the past few years [30]. This is deeply interesting since the data show that the accumulation of such mediators has detrimental consequences on our health. As a matter of fact, elevated CRP, product of hepatic stimulation under IL-6 regulation, is a notable risk for CVD and diabetes [44,45]. Furthermore, IL-6 and TNF-α are closely related to chronic kidney disease [46], type 2 diabetes [47], and CVD [48]. Presumably, $CoQ_{10}$ anti-inflammatory potential is related to the downregulation of nuclear factor-ϰβ (NF-ϰβ)-dependent gene expression [49], which is known to be activated by reactive oxygen species [50]. With NF-ϰβ inhibited, no expression of pro-inflammatory cytokines could take place. Bearing this in mind, further studies should be encouraged to translate these findings into clinical applications for the improvement of patients' well-being.

### 2.4. Neuroprotection

Neurodegeneration, the progressive loss of neuronal function, electrical activity, and structure in the central nervous system (CNS) is the main triggering feature of acute and chronic neurodegenerative diseases, such as, among other diseases, Alzheimer's disease, Parkinson's disease, paraneoplastic disorders, or multiple sclerosis [51]. The most common neurodegeneration-promoting factors are neuroinflammation, oxidative stress, mitochondrial dysfunction, protein aggregation and misfolding, excitotoxicity, cell death pathways, and the loss of trophic factors [52].

Oxidative stress results from the accumulation of free radicals due to either the overproduction of ROS or the failure of cellular buffering mechanisms. In line with this, it has been reported that the CNS cells of most Parkinson's disease (PD) patients show high oxidative damage in their proteins, nucleic acid, or lipids [53]. The excessive production of ROS occurs as a consequence of either dopamine metabolism [54], mitochondrial dysfunction mostly caused by impaired complex I in the nervous system of PD sufferers [55], or environmental factors (exposure to ultraviolet radiation).

For instance, the neuronal ganglion cells of the retina are highly exposed to sun radiation, being therefore subject to acute oxidative stress [56]. Hence, $CoQ_{10}$ with its antioxidant properties is a crucial molecule for their protection against the oxidative damage perpetrated by ROS [57]. Nonetheless, concentrations of $CoQ_{10}$ in the human retina are reported to decline with age [58], meaning that an external supplementation of the molecule is necessary to maintain optical health as a person ages. Topically active formulations of $CoQ_{10}$ have successfully been developed [59,60], but their efficacy is compromised by poor aqueous solubility of this molecule and its low bioavailability. It is widely known

that the multi-drug efflux pump P-glycoprotein (P-gp) has a lot to do with this limited bioavailability [61]. Ergo, the novel approaches aimed at enhancing the topical delivery and the pharmacological effects of $CoQ_{10}$ consider the administration of this drug together with a P-gp inhibitor [62]. One of the tested inhibitors has been α-tocopherol polyethylene glycol 1000 succinate (TPGS), which formulated into micelles with $CoQ_{10}$, successfully increased its delivery [63]. Recent studies have gone deeper in the subject by trying to demonstrate the neuroprotective activity of $CoQ_{10}$/TPGS compared to $CoQ_{10}$ alone. According to their results, $CoQ_{10}$/TPGS micelles are significantly more neuroprotective against retinal ganglion cell (RGC) loss [61]. This is in agreement with the previous work in the field which proved that co-administration of $CoQ_{10}$ with an α-tocopherol derivative enhances the neuroprotective activity of $CoQ_{10}$ in vitro [64,65]. The postulated mechanisms through which $CoQ_{10}$ is thought to elicit its neuroprotective function are its antioxidant activity [66] and its $Ca^{2+}$ buffering activity [67], due to the fact that accumulation of intracellular $Ca^{2+}$ is known to signal for apoptosis induction [68].

Another fundamental application of Coenzyme $Q_{10}$ in the field of ocular health is the therapeutic potential of this molecule to treat glaucoma. Glaucoma is the leading cause of irreversible blindness worldwide [69]. There is compelling evidence to suggest that apart from optic nerve degeneration and retinal ganglion cell death, glutamate excitotoxicity and oxidative stress are key pathophysiological mechanisms in mitochondrial dysfunction-mediated glaucomatous neurodegeneration [70,71]. $CoQ_{10}$, with its ability to maintain the mitochondrial membrane potential while supporting ATP synthesis and inhibiting reactive oxygen species' generation, has proven to be an invaluable therapeutic tool for the protection of neuronal cells against oxidative stress in neurodegenerative conditions like glaucoma. Indeed, intraocular $CoQ_{10}$ administration had a potent neuroprotective effect on the established animal models of retinal ischemia [72]. According to the authors of the study, it prevented high intraocular pressure-derived optic nerve degeneration and RGC death [73]. Moreover, recent approaches have proven that dietary supplementation with $CoQ_{10}$ not only promotes RGC survival in DBA/2J mice, but also reduces the expression of proapoptotic protein Bax in the retina of glaucomatous mice. Based on the available evidence, it is now clear that $CoQ_{10}$ prevents retinal ganglion cell death by diminishing oxidative stress and glutamate excitotoxicity and by inhibiting the activation of the Bax-mediated apoptotic pathway [74]. In light of the success of Coenzyme $Q_{10}$ supplementation to treat glaucoma in mice, it would be reasonable to expect its incorporation to the clinic to be nothing but a matter of time.

Patients with vascular disorders affecting the retina also benefit from $CoQ_{10}$ supplementation, as proven in a retrospective clinical case study with 48 patients. The interruption of $CoQ_{10}$ treatment resulted in a pronounced decrease of the patients' visual field index, which was recovered once the treatment was restored [75].

Neuroinflammation has been identified as a primary mechanism involved in neurodegenerative diseases' pathogenesis. In this regard, activation of microglia has been detected in the nervous system and striatum from postmortem PD patients' brains. Moreover, pro-inflammatory cytokines' levels have been reported over the mean values in the CSF and basal ganglia of neurodegenerative diseases' patients [52]. Active microglia cells release cytokines, including interleukin 1β (IL-1β) and TNF-α, which promote inflammation. Thereby, microglia inhibitory compounds or anti-inflammatory substances represent promising neuroprotective strategies [76].

Several diseases have been related to abnormal microglial activation (microgliosis) [42]. One of them is epilepsy, whose pathophysiology is characterized by both a severe mitochondrial dysfunction and neuroinflammation [77]. $CoQ_{10}$ with its ability to downregulate nuclear factor-ϰβ (NF-ϰβ)-dependent gene expression prevents production of pro-inflammatory cytokines [35]. Furthermore, recent studies [78] have demonstrated the effectivity of $CoQ_{10}$ as a treatment for epilepsy due to its interaction with minocycline, a second generation tetracycline which suppresses microglial activation and reduces TNF-α release, being beneficial to treat various neurological problems [79].

The outcome of the combined treatment of patients with both $CoQ_{10}$ and minocycline has revealed the synergistic effect of both molecules and their potential as a cocktail against cognitive

dysfunction-related diseases [53]. These findings also suggest that they might share overlapping mechanisms of action, a topic which deserves further in-depth research.

### 2.5. Against UVB Radiation Damage

UVB radiation triggers major alterations in skin cells, with ROS overproduction being one of the most deleterious. In fact, several pathologic changes in the skin, such as erythema, edema, sunburn, immune suppression, or cancer occur as a consequence of the excessive production of reactive oxygen species [80,81]. The most common and widespread protective method against ultraviolet (UV) radiation damage is the topical application of regular sunscreens, which absorb, reflect, or scatter radiation. However, they are not capable of repairing cutaneous injuries. For this reason, there is a growing search for antioxidant molecules' formulations that can alleviate cytotoxic events derived from ROS intracellular accumulation [82]. $CoQ_{10}$ and vitamin E are both known to be highly antioxidant molecules that play fundamental roles in most biological systems. Hence, their combination was hypothesized as a promising strategy to boost their cytoprotective potential [83]. The challenge that researchers had to face in this regard was the implementation of a viable delivery system. In the past few years, nanocapsules have emerged as promising mechanisms for topical substance delivery due to their ability to control drug release and improve drug stability [84]. Thereafter, the newest approaches towards an effective skin repair treatment have been based on the formulation of $CoQ_{10}$ and vitamin E nanocapsules. In the process, the novel association between $CoQ_{10}$ and vitamin E nanocapsules via gellan gum, an amicrobial polysaccharide with gelling properties [85], was demonstrated [66]. The relevance of this study lies in the formulation of a semisolid nanoparticle system thanks to the addition of gellan gum. This is interesting due to the fact that a semisolid texture would enable the direct cutaneous application of the drug-containing nanoparticles. Furthermore, the anti-edematogenic, anti-inflammatory, and antioxidant activities of these semisolid formulations were tested in an animal model of UVB radiation inflammation and yielded promising results [66].

### 2.6. For Heart Failure Treatment

Apart from its antioxidant and electron carrier functions, $CoQ_{10}$ displays a wide range of interesting properties for the treatment of cardiovascular diseases: its positive influence on myocardial $Na^+$–$K^+$ ATPase activity, its protective effect on endothelial cells, its influence on prostaglandin metabolism, and its anti-viscosity effect [86,87]. Concretely, chronic heart failure patients enormously benefit from $CoQ_{10}$ supplementation for the amelioration of their condition. This comes down to the fact that $CoQ_{10}$ levels were found to be significantly decreased in blood and endomyocardial biopsies of heart failure patients. Moreover, such a decrease correlated with severity of the symptoms, the patients whose $CoQ_{10}$ levels were lower being more affected. Based on this finding, the effect of $CoQ_{10}$ supplementation was tested on a group of cardiovascular disease patients. The results backed up the premise of $CoQ_{10}$ effectivity, being beneficial for 69% and 43% of patients with cardiomyopathy and ischemic heart disease, respectively [88]. In order to face heart failure, $CoQ_{10}$ supplementation must be high enough to increase plasma $CoQ_{10}$ concentration to therapeutic levels (>2.5 μg/mL). Studies confirm that 300 mg/day of orally administered $CoQ_{10}$ increases plasma $CoQ_{10}$ concentration to 3.25 ± 1.5 μg/mL [89,90]. The diversity of its beneficial effects as well as the satisfactory results obtained in previous studies set $CoQ_{10}$ as the first treatment to improve survival in heart failure patients ahead of angiotensin-converting enzyme (ACE) inhibitors and β-blockers more than a decade ago [91].

Furthermore, plasma $CoQ_{10}$ levels have been proposed as a reliable biomarker to predict mortality in chronic heart failure (CHF). A recent study with a cohort of 236 chronic heart failure patients demonstrated that reduction in $CoQ_{10}$ levels strongly correlates with worse outcome in CHF [92].

Another interesting $CoQ_{10}$ application for the cardiology field was recently discovered. Several studies claim that $CoQ_{10}$ can be used as a marker of rejection in patients who underwent heart transplantation. Low $CoQ_{10}$ concentrations were observed in the plasma and endomyocardial biopsies of patients who presented signs of histological rejection, whilst patients without a rejection reaction

showed normal $CoQ_{10}$ levels [82]. Furthermore, it was postulated that $CoQ_{10}$ supplementation could be conceived as an option to prevent transplant rejection [93].

### 2.7. Barth Syndrome and Membrane Instability-Related Diseases

Barth syndrome is a cardiomyopathy that includes skeletal muscle weakness, neutropenia, and growth retardation [94]. The locus associated with this disease has recently been mapped to the *Xq28* (tafazzin) gene. The consequence of this gene's mutation is an impairment of the phospholipid metabolism that results in a profound cardiolipin deficiency in patients [95]. Cardiolipin is a dimeric phospholipid that is almost exclusively found in the inner mitochondrial membrane (IMM) of mammalian cells [96]. Its functional relevance arises from its unique ability to interact with proteins and its role in maintaining IMM stability and fluidity [97]. Absence or depletion of cardiolipin translates into mitochondrial dysfunction as documented in a variety of pathological conditions: hypo/hyperthyroidism [98,99], ischemia [100], heart failure [101], aging [102], and Barth syndrome and other related diseases associated with mitochondrial impairment. Reconstituting cardiolipin levels in patients has therefore been the aim of several therapeutic strategies developed against these disorders. One of the most successful approaches proposed the exogenous supplementation of cardiolipin liposomes to restore mitochondrial cytochrome bc1 (complex III) functionality [103]. However, there is an increasing availability of therapeutic options for mitochondrial dysfunction beyond cardiolipin. For instance, detailed studies on both the biological and physiological roles of $CoQ_{10}$ have revealed a mechanical stability enhancing function of this molecule on cell membranes. Among them, a study on the impact of $CoQ_{10}$ on membrane density, permeability, resistance to solubilization by detergents, and promptness to rupture of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) liposomes, liposomes formed by pure lipids, and liposomes supplemented with cholesterol or solanesol is worth pointing out. The results obtained support the hypothesis of a stabilizing role of $CoQ_{10}$ in phospholipid membranes, since POPC nanoparticles became more resistant to rupture and less permeable to hydrophilic solutes in its presence. From the fact that solanesol (a polyisoprenoid alcohol structurally similar to $CoQ_{10}$ with 9 isoprene units rather than 10) [104] had no effect on the analyzed membrane properties, it was elucidated that the quinone moiety is important for the stabilizing function of $CoQ_{10}$. This discovery is of great interest since it implies that $CoQ_{10}$ could be used as a membrane-stabilizing agent for the treatment of such diseases as Barth syndrome, where the lack of cardiolipin compromises the structural integrity and functionality of the mitochondrial membrane.

Moreover, this study reported that the condensing effect of $CoQ_{10}$ was qualitatively similar to that of cholesterol, with a significantly smaller amount of $CoQ_{10}$ needed to produce the same effect on, e.g., lipid packing. In line with this, cholesterol could be substituted by $CoQ_{10}$ for various purposes, for example, the development of cholesterol-free liposome-based drug delivery systems [105].

It must be stressed that the former study was carried out on POPC liposomal membranes, whereas native biological membranes contain, as a rule, a complex mixture of different lipid species. Such alterations in the lipid composition can lead to relevant changes in lipid spontaneous curvature, membrane binding rigidity, and other properties that could affect $CoQ_{10}$'s interaction with or effect on the membrane. In fact, it has been proven that lipid $CoQ_{10}$ interaction depends very much on the lipid species [105]. Nonetheless, the effects observed in the POPC membranes persisted in an alternative research project which made use of membranes with a lipid composition resembling that of the IMM. In fact, it was observed that $CoQ_{10}$ not only increased the lipid packing order and the mechanical stability of the IMM-mimicking membranes, but also improved their barrier properties, which implies that it has a stabilizing role in biological membranes [106].

In this line, the role of acyl chains or intermembrane proteins on membrane stability should be further studied in order to have a better understanding of $CoQ_{10}$'s stabilizing function of the IMM. It must be pointed out that the protein load in the IMM is high. This could be a prominent interfering factor in future experimental approaches, since high protein content is known to lead to lipid segregation and other processes that impact overall membrane structure and dynamics [106].

### 2.8. Insulin Resistance

Mitochondrial oxidants have been reported to play a fundamental role in the development of insulin resistance in adipose [107] and muscle tissue [108]. Supporting this observation, mass spectrometry-based proteome analysis of adipose tissue from insulin-resistant 3T3-L1 mouse adipocytes and adipose tissue from insulin-resistant human cells has revealed downregulation of the mevalonate/$CoQ_{10}$ biosynthetic pathways in both systems. This abnormality eventually leads to a decrease in the mitochondrial $CoQ_{10}$ content. The rationale behind this is that triggering insulin resistance promotes hyperinsulinemia, inflammation, corticosteroids, or caloric excess and prevents the expression of $CoQ_{10}$ biosynthetic enzymes and, hence, lower $CoQ_{10}$ synthesis rates. As a consequence of the reduced $CoQ_{10}$ biosynthesis, the levels of superoxide rise notoriously in cells as proven by highly specific mass spectrometry-based superoxide assays [109]. The majority of the superoxide in mitochondria is derived from flavin sites, including that in complex II (IIF) [110]. Therefore, it is hypothesized that excessive superoxide production from the IIF site occurs as a consequence of increased concentrations of the flavin radical, which is overproduced as a result of scarce electron transfer to the non-abundant $CoQ_{10}$ [109]. It is widely known that scavenging mitochondrial oxidants benefits insulin sensitivity [107,108]. Nevertheless, the mechanism through which oxidants impair insulin action remains uncertain. According to recent studies, it is highly likely that there is a presently undiscovered signal transduction pathway that directly communicates mitochondria and oxidants to the mediators of insulin action in the cytoplasm [109].

For the reasons that have previously been discussed, $CoQ_{10}$ has received considerable attention as a supplement to treat patients suffering from diabetes. However, low oral bioavailability of $CoQ_{10}$ represents a substantial limitation, especially in situations of $CoQ_{10}$ deficiency, where mitochondrial homeostasis needs to be restored in metabolic tissues [111]. Therefore, a pharmaceutical alternative to supplementation would be to target cellular processes that play a part in the regulation of the mitochondrial $CoQ_{10}$ content. Further therapeutic approaches have been proposed, such as targeting complex II as the site of increased superoxide production in response to the loss of mitochondrial $CoQ_{10}$. Up to now, several compounds that prevent oxidant production from complex I [112] and III [113] have been identified. The identification of a similar substance for complex II would be an essential breakthrough to mitigate superoxide production in patients and thus to overcome insulin resistance [109].

Finally, it has been proven that mevalonate pathway-inhibiting statins lower the $CoQ_{10}$ content and trigger insulin resistance in a $CoQ_{10}$-dependent manner. This might shed light on the relationship between statin therapy in humans and insulin resistance [109,114,115].

### 2.9. Pain Alleviation in Fibromyalgia

Fibromyalgia (FM) is a chronic pain syndrome whose pathophysiological mechanisms have not yet been identified. Extensive research in the field has unraveled a direct link between oxidative stress and the pathogenesis of such a disease [116] being therefore mitochondrial dysfunction proposed as one of the main triggering factors of fibromyalgia. In fact, a decrease in mitochondrial mass and $CoQ_{10}$ levels, as well as an overproduction of ROS, was detected in blood mononuclear cells from FM patients [117]. It was also reported that these cells actively remove damaged mitochondria via mitophagy [117] but cannot rely on the normal mitochondrial compensatory mechanisms, since they are impaired. As a consequence, they have a reduced mitochondrial mass and a depleted amount of antioxidant molecules [118], which makes them prone to inflammatory damage. Accordingly, these cells present enhanced activation of the inflammasome owing to $CoQ_{10}$ deficiency, as well as increased serum levels of proinflammatory cytokines, such as IL-1β and interleukin 18 (IL-18) [119]. As it is observed in major metabolic diseases, such as diabetes and insulin resistance, the activation of the inflammasome is a sign of metabolic danger and stress [120].

Interestingly, inflammation has been associated with FM symptoms by means of high positive correlations between IL-1β and IL-18 serum levels and pain scores. This suggests that there is an

inflammatory component in pain induction. It has also been proven that inflammation in FM is dependent on mitochondrial dysfunction, since: (1) a negative correlation has been found between proinflammatory cytokines (IL-1β and IL-18) and $CoQ_{10}$ and (2) a positive one has been found between these cytokines, mitochondrial ROS, and pain scale scores [119]. In brief, the involvement of $CoQ_{10}$ deficiency in the pathological process of inflammasome activation and release of proinflammatory cytokines has been revealed [121]. For this reason, $CoQ_{10}$ presents a potential treatment for pain alleviation in FM patients. Still, further clinical studies should be carried out to corroborate the effectiveness of this antioxidant therapy in such a pathology.

### *2.10. Familial Hypercholesterolemia and Atherosclerosis*

By definition, hypercholesterolemia is a physiological condition at which an abnormally high amount of cholesterol is present in the blood of a patient. This condition can either be triggered by hereditary mutations (familial hypercholesterolemia) on the genes involved in the low-density lipoprotein (LDL) clearance mechanism or by a non-healthy lifestyle, which is especially predominant among the elderly [122]. According to a recent study, patient-derived familial hypercholesterolemia (FH) fibroblasts bearing a mutation on the LDL receptor (LDL-R) are unable to import cholesterol for its metabolism. Since cholesterol uptake is impaired, these fibroblasts synthesize such lipid endogenously in an uncontrolled manner, so that it eventually accumulates within them [123]. The upregulation of cholesterol biosynthesis is directly related to the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) activity, which is itself controlled by lipoproteins binding to the LDL-R [124]. Bearing in mind that these FH fibroblasts have dysfunctional LDL-R or lack them, it is not surprising that such a cholesterogenic enzyme is upregulated. As a consequence, the mevalonate pathway shifts to overproduction of cholesterol in detriment of $CoQ_{10}$ biosynthesis, meaning that these FH patients suffer from secondary $CoQ_{10}$ deficiency. The lack of $CoQ_{10}$ together with cholesterol accumulation is associated with mitochondrial function impairment, which is characterized by an elevated ROS production, reduced ATP levels, low activity of the mitochondrial respiratory complexes, and mitochondrial depolarization. Indeed, mitochondrial dysfunction in these FH fibroblasts with mutations on the LDL-R was corroborated by an abnormal rate of mitophagy events on them [123].

Researchers postulate that mitochondrial dysfunction and $CoQ_{10}$ deficiency could be partly responsible for the pathophysiology of early atherosclerosis by promoting inflammation and enabling increased production of free radicals in the endothelium of blood vessels [125]. The damage infringed by redox imbalance can be extrapolated to other diseases that also involve hyperlipidemia and lipidogenesis, such as diabetes, obesity, and metabolic syndrome [126]. Aiming to ameliorate the conditions of FH patients, treatments targeted at both reducing intracellular cholesterol and raising $CoQ_{10}$ levels should be considered. It has been demonstrated that $CoQ_{10}$ administration can restore increased cholesterol levels and mitochondrial dysfunction in human fibroblasts. Hence, a balanced co-administration of the conventional statin treatment used for hypercholesterolemia patients and $CoQ_{10}$ seems to be the most convenient and accurate approach towards FH therapy [123].

## 3. Recent Formulations

### *3.1. Liposomes*

Owing to its remarkable properties as an anti-fatigue, immunostimulating, and antioxidant molecule [127], $CoQ_{10}$ is nowadays widely used as a functional food, drug, and health supplement. Clinically, it is also prescribed for cardiovascular disease, diabetes, viral hepatitis, cancer and many other patients [128]. However, as previously discussed, traditional $CoQ_{10}$ formulations are not satisfactory, since they fail to increase $CoQ_{10}$'s low oral bioavailability. $CoQ_{10}$'s uptake is compromised due to its poor water solubility, instability to light, and thermolability [129]. For this reason, the development of alternative formulations has been a recurrent topic of study in the past few years. Numerous alternatives to the classic $CoQ_{10}$ formulations have been proposed, like solid dispersion systems [130],

nanoparticles [131], cyclodextrin inclusion compounds and microcapsules [132]. However, one of the most promising approaches has been the preparation of nano-liposomes with long circulating elements that improve the stability, prolong circulation times, and increase the bioavailability of $CoQ_{10}$ [133]. The main drawback of this liposomal formulation is its high instability. As is widely known, lipid-based vectors are prone to aggregating and forming clustered complexes with larger dimensions [134]. Moreover, the encapsulation efficiency was hindered by the constant leakage of cargo through the lipid layers. In order to implement stability, the lyophilization of liposomes through a freeze-drying procedure was suggested. The lyophilized particles showed stable quality characteristics during long-term storage [89].

### 3.2. Self-Nanoemulsifying Delivery System

$CoQ_{10}$'s low gastrointestinal absorption and low oral bioavailability are a consequence of its low intestinal permeability and high molecular weight. Self-nanoemulsifying $CoQ_{10}$ delivery systems have been developed to face the challenge of this drug's oral administration by increasing its dissolution in the gastrointestinal tract (GIT) [135]. Self-nanoemulsifying drug delivery systems (SNEDDS) can be defined as an isotropic and thermodynamically stable mixture of an oil, a surfactant, a co-surfactant, and a drug that forms nanoemulsion droplets of a reduced size (<100 nm) when subject to dilution in an aqueous medium under gentle agitation, similar to the gastric movements of the GIT [136]. The fundamental standard of these SNEDDS is that when the emulsion is formed in the GIT of the patient, the drug is presented in a solubilized form inside nano-sized droplets that provide a larger surface area for enhancing the drug's release and absorption [137]. This novel approach to increase $CoQ_{10}$'s dissolution and absorption has proven successful in recent studies, in which a daily intake of 100 mg of $CoQ_{10}$ SNEDDS is proposed as a sufficient dietary supplement to compensate for low $CoQ_{10}$ levels in patients suffering from various diseases [106].

### 3.3. Novel Lipid-Free Nanoformulation

As previously mentioned, several formulations have been developed to increase $CoQ_{10}$'s bioavailability: an oil solution and a suspension system [138], a lipid and surfactant-based emulsion [139], and a solid dispersion system [140]. However, the bioavailability of $CoQ_{10}$ in these remains low. Thereafter, the next step forward was to develop lipid-free self-emulsifying drug delivery systems (SEDDS) [106], or nanoemulsions [141]. Traditional $CoQ_{10}$ formulations make use of lipid-based delivery systems, because these present several benefits: they increase drug solubility in intestines, recruit lymphatic drug transport or modify enterocyte-based drug transport and disposition [142]. Nevertheless, many other factors like dispersion rate, degree of emulsification, particle size or drug precipitation upon dispersion have a negative impact on the efficacy of lipid-based delivery methods. For this reason, novel studies have focused on the development of lipid-free nano-$CoQ_{10}$ systems. One of the most promising approaches in the field achieved the development of $CoQ_{10}$ nanoformulations with various surfactants but no other lipids. These nano-$CoQ_{10}$ particles were modified with surfactants using hot high-pressure homogenization (HPH) [131]. Such surfactants were intended to alter cell membrane integrity and tight junctions [143] as well as inhibit efflux transporters like P-gp [144] so that permeability would be enhanced. Subsequent studies in rats demonstrated that the orally administered lipid-free nano-$CoQ_{10}$ significantly improved $CoQ_{10}$ bioavailability in comparison to common $CoQ_{10}$ powder suspensions, mainly due to the action of surfactants. Thereby, lipid-free nano-$CoQ_{10}$ complemented with surfactants like PEG40 hydrogenated castor oil (PHCO) or TPGS are a promising alternative for $CoQ_{10}$'s clinical application.

### 3.4. $CoQ_{10}$-Loaded Oleogels

As previously stated, $CoQ_{10}$ is practically insoluble in aqueous solutions, therefore, its oral or intestinal absorption is slow and extremely inefficient. However, its bioavailability can be substantially modified by using an adequate formulation for its administration. Since $CoQ_{10}$ is fat-soluble [145],

its absorption is enhanced when taken with a meal having a high oil/fat content. In line with this, oil-based formulations, such as emulsions where $CoQ_{10}$ is dissolved in an oil-dispersed phase, have proven to be successful for $CoQ_{10}$ delivery. The research in the field indicates that solubilized $CoQ_{10}$ formulations present a much higher bioavailability than non-solubilized powder-based $CoQ_{10}$ products [11] meaning that a higher $CoQ_{10}$ plasma concentration could be achieved using lower doses of solubilized $CoQ_{10}$ formulations than those used with non-solubilized ones. Another factor supporting the use of solubilized formulations rather than traditional ones is the fact that mitochondrial and neurodegenerative disorders' patients commonly struggle to swallow [146,147]. Therefore, it is hard for them to deal with traditionally big $CoQ_{10}$ tablets or powder-filled capsules. In light of this evidence, the research is now focused on developing formulations with $CoQ_{10}$ solubilized either in liquid or jelly matrixes. Among the studies carried out in this direction, it is worth to point out the development of ethyl cellulose (EC)-oleogels for high-dose $CoQ_{10}$ oral administration (1 g of $CoQ_{10}$ per 5 g oleogel-disk) [148]. Medium-chain triglyceride (MCT) oil was used to dissolve $CoQ_{10}$, since it is known to be the only fat that people with the inability to absorb or digest conventional fats tolerate [149]. Moreover, two surfactants were evaluated to modulate the mechanical properties of the gels. SMS proved to be more convenient than lecithin, since it allowed a higher stability to oxidize the MCT oil and a better enhancement of $CoQ_{10}$ stability while lowering the syneresis in the final oleogels. Moreover, SMS-containing oleogels showed higher thermal stability than lecithin-containing ones.

The novelty of the aforementioned study lies in the fact that the SMS-containing oleogels allowed loading exceptionally high doses of soluble $CoQ_{10}$ in soft gel structures that reduce the swallowing discomfort for patients. Additionally, the number of dosage units per day could be reduced since each of these oleogels provides a high dose of $CoQ_{10}$. According to the authors, the $CoQ_{10}$ dissolved in MCT was stable for 12 months when immobilized into the oleogels. Thereafter, neither storage nor distribution is a problem for the future translation of this formulation to the clinical practice.

### 3.5. Novel Water-Soluble $CoQ_{10}$

The use of $CoQ_{10}$ as a functional food is full of promise, since its properties have the ability to beneficially influence body functions, promoting well-being and health as well as reducing the risk of diseases [150]. However, high lipophilicity of this molecule restrains its use as a food-enriching product, especially in aqueous-based preparations. To overcome this barrier, $CoQ_{10}$'s water solubility has been increased by encapsulating it in β-cyclodextrin inclusion complexes [151]. This novel patented formulation is available as Q10Vital and has proved to be stable and well-soluble in diverse aqueous media. A bioequivalence study has confirmed the improved bioavailability and efficacy of this novel $CoQ_{10}$ material in comparison to the traditional soft gel capsules containing $CoQ_{10}$ in soybean oil, which has been the most widely used formulation up to this moment in Europe [152]. According to that study's results, the mean plasma concentration of $CoQ_{10}$ was highest in the individuals who consumed the liquid Q10Vital formulation, followed by those who took the Q10Vital powder. Moreover, the levels of $CoQ_{10}$ were significantly lower in those who had soft gel capsules. The novel formulation presented higher standard deviations in pharmacokinetics assays owing to its sensitivity to individual pH differences, especially in the gastrointestinal tract. The acidic pH of such an environment may affect the interactions between the guest ($CoQ_{10}$) and the host (β-cyclodextrin) molecules. This inconvenience can be resolved by the co-administration of the formulation with an appropriate food matrix that reduces its pH sensitivity, stabilizes its solution in the GIT, and thereby improves its absorption [117]. All in all, $CoQ_{10}$/β-cyclodextrin complexes have proved to significantly increase water solubilization of $CoQ_{10}$ and, hence, its gastrointestinal absorption. For this reason, this novel formulation, either in its liquid or powder form, represents a more efficient $CoQ_{10}$ delivery method for both the food and pharmaceutical industries.

### 3.6. Micellization of $CoQ_{10}$ by Caspofungin

Since lipophilicity seems to be the main barrier for the parenteral delivery of $CoQ_{10}$, there is a rising interest in the development of water-soluble $CoQ_{10}$ formulations. One of the most famous advances in the field was the formulation of micellar $CoQ_{10}$ nanoparticles [153]. The formation of these hydrophilic particles was mediated by an FDA-approved drug, caspofungin (CF). Despite its moderate surfactant activity, CF successfully solubilizes $CoQ_{10}$, yielding micellar nanoparticles as a result. These nanoparticles were on average smaller than 200 nm in diameter, being therefore ideal for intravenous delivery, since such a reduced size allows for long circulating times and sufficient extravasation and tissue uptake [154,155]. The critical micelle concentration (CMC) is the parameter that reflects the stability of micelles following their dilution in blood. A CMC in the low millimolar range is desirable in drug-carrying compounds, since it indicates high stability after intravenous administration [156]. The CMC of these CF/$CoQ_{10}$ particles is close to 50 μM, indicating that they are unlikely to dissociate rapidly upon injection. According to the authors of the study, the CF/$CoQ_{10}$ formulation can be safely administered to mice via an injection, $CoQ_{10}$ successfully reaching the desired tissues. The highest plasma $CoQ_{10}$ concentration detected following intravenous CF/$CoQ_{10}$ administration (8.6 mg/kg of body weight) was >160 times higher than the endogenous $CoQ_9$ level ($CoQ_{10}$ being undetectable). The studied tissues (liver, kidney, heart, skeletal muscle, spleen, lung, and brain) also presented significantly higher $CoQ_{10}$ levels after 10 daily intravenous doses of CF/$CoQ_{10}$ (8.612 mg/kg of body weight). Nonetheless, further research on the uptake differences between tissues should be conducted.

Since both CF and $CoQ_{10}$ are already extensively used in clinical practice and have favorable safety profiles, it is hypothesized that there should not be obstacles for CF/$CoQ_{10}$ micelles' clinical development and approval for treatment of $CoQ_{10}$ deficiencies and related diseases. However, patients' discomfort is the main drawback of this therapeutic strategy. As claimed by the authors of the study, $CoQ_{10}$ uptake in organs was cumulative, the reason why several daily injections were required to reach the desired intra-organ $CoQ_{10}$ concentration. Facing the prospect of several injections a day might be an ordeal for many patients [157], the reason why alternative administration procedures should be proposed for this therapy to be unconditionally appealing.

## 4. Conclusions

Coenzyme $Q_{10}$ has always been considered by clinicians and researchers a good ally against a wide range of diseases. Surprising though it may seem, the number of $CoQ_{10}$ applications keeps increasing in our days. Suffice to say that thousands of research teams keep diving into the most remote properties and functions of this molecule, obtaining still surprising results. In the present review, some of the most relevant $CoQ_{10}$ applications have been discussed, as well as the novel formulations for its clinical administration. In addition to its traditional applications (among other diseases, in mitochondrial diseases, Down syndrome, cancer, atherosclerosis, ischemia) $CoQ_{10}$ has proved to be beneficial for diabetic cardiovascular disease and diabetic nephropathy patients, for multiple system atrophy or heart failure treatment, or for epilepsy palliation. Moreover, it has been demonstrated that it can be used as a marker of histological rejection in transplantations or of inflammation. Albeit its most remarkable newborn applications are its protective properties against UV radiation, its highly beneficial effect on familial hypercholesterolemia patients and its neuroprotective potential when administered together with TPGS.

Being aware of $CoQ_{10}$'s clinical interest, numerous research groups have developed promising formulations to ensure a more efficient administration of this drug. Among them, the development of a novel water-soluble $CoQ_{10}$ form should be highlighted. These new delivery systems are intended to overcome the great barrier that prevents $CoQ_{10}$ from becoming a widely used pharmaceutical drug and food complement: its low oral bioavailability.

The unceasing increase in the number of $CoQ_{10}$ applications is flabbergasting, to say the least. Were the bottleneck of its delivery to be overcome by the newly developed formulations, $CoQ_{10}$ would become one of the most widely used molecules for therapeutic purposes.

**Author Contributions:** C.J.P.-M. and J.M.S.-R. wrote the manuscript; M.Á.-C., I.V.-G., M.T.-R., A.S.-C. and M.M.-C. contributed to the literature search; S.P.-C. and J.A.S.-A. revised the manuscript. All authors have read and agreed to the published version of the manuscript.

**Funding:** This work was supported by FIS PI16/00786 and FIS PI19/00377 grants, Instituto de Salud Carlos III, Ministerio de Sanidad, Spain, and Fondo Europeo de Desarrollo Regional (FEDER Unión Europea), Ayudas para la Formación de Profesorado Universitario (FPU), Ministerio de Ciencia e innovación, AEPMI (Asociación de Enfermos de Patología Mitocondrial), and ENACH (Asociación de enfermos de Neurodegeneración con Acumulación Cerebral de Hierro).

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

## Abbreviations

| | |
|---|---|
| $CoQ_{10}$ | Coenzyme $Q_{10}$ |
| ADI | Acceptable daily intake |
| NOAEL | No-observed-adverse-effect level |
| UVB | Ultraviolet B |
| CVD | Diabetic cardiovascular disease |
| ROS | Reactive oxygen species |
| RAGE | Receptor for advanced glycation end products |
| AGEs | Advanced glycation end products |
| NADPH | Nicotinamide adenine dinucleotide phosphate |
| PKC | Protein kinase C |
| DN | Diabetic nephropathy |
| UTMD | Ultrasound-targeted microbubble destruction |
| MSA | Multiple system atrophy |
| CSF | Cerebrospinal fluid |
| COQ2 | Coenzyme Q2 |
| COQ9 | Coenzyme Q9 |
| COQ8A | Coenzyme Q8A |
| ETFDH | Electron transfer flavoprotein dehydrogenase |
| PDSS2 | Decaprenyl diphosphate synthase subunit 2 |
| AIDS | Acquired immune deficiency syndrome |
| CRP | C-reactive protein |
| IL-6 | Interleukin 6 |
| TNF-α | Tumor necrosis factor alpha |
| P-gp | P-glycoprotein |
| TPGS | α-tocopherol polyethylene glycol 1000 succinate |
| RGC | Retinal ganglion cells |
| IOP | Intraocular pressure |
| PD | Parkinson disease |
| NF-β | Nuclear factor beta |
| POPC | Palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine |
| IMM | Inner mitochondrial membrane |
| IIF | Flavin site in complex II |
| FM | Fibromyalgia |
| IL-1β | Interleukin 1 beta |
| UV | Ultraviolet |
| IL-18 | Interleukin 18 |
| FH | Familial hypercholesterolemia |
| GIT | Gastrointestinal tract |
| SNEDDS | Self-nanoemulsifying drug delivery systems |

| | |
|---|---|
| HPH | High-pressure homogenization |
| PHCO | PEG40 hydrogenated castor oil |
| TPGS | Tocopherol polyethylene glycol succinate |
| EC | Ethyl cellulose |
| MCT | Medium-chain triglyceride |
| SMS | SMS detergent |
| CMC | Critical micelle concentration |
| HMGCR | 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase |
| LDL | Low-density lipoprotein |
| LDL-R | Low-density lipoprotein receptor |
| ACE | Angiotensin-converting enzyme |
| CHF | Chronic heart failure |

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