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Review

Enhancing the Absorption and Bioavailability of Exogenous Coenzyme Q_{10}: Novel Approaches and Mechanisms

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Abstract: Coenzyme Q_{10} (CoQ_{10}) is a vital antioxidant and cellular energy facilitator with significant therapeutic potential, yet its clinical effectiveness is frequently limited by poor bioavailability due to its hydrophobic nature and large molecular size. Enhancing CoQ_{10} absorption has become a research focus, yielding various innovative formulation and delivery strategies aimed at improving solubility, permeability, and overall bioavailability. This review examines the latest advancements in CoQ_{10} delivery, including nanoparticle-based formulations, such as liposomes, micelles, and nano-emulsions, as well as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) that protect CoQ_{10} from gastrointestinal degradation. Cyclodextrin complexes, self-emulsifying drug delivery systems (SEDDS), and the development of CoQ_{10} derivatives, like ubiquinol, further demonstrate promising improvements in bioavailability and pharmacokinetics. We also explore the underlying mechanisms contributing to enhanced absorption, including improved cellular uptake, enhanced permeability, and potential involvement of specific transport proteins and metabolic pathways. Comparative data from clinical trials indicate that these novel formulations significantly increase CoQ_{10} bioavailability, supporting their potential in therapeutic settings. Future research should focus on personalized CoQ_{10} delivery systems tailored to individual metabolic profiles and disease states, as well as emerging technologies for targeted and controlled release. This review provides a comprehensive overview of current bioavailability enhancement strategies for CoQ_{10} and highlights future directions to optimize its clinical efficacy.

Keywords: Coenzyme Q_{10} (CoQ_{10}); Bioavailability enhancement; Nanoparticle-based formulations; Liposomes; Self-emulsifying drug delivery systems (SEDDS); Solid lipid nanoparticles (SLNs); Cyclodextrin complexes; Ubiquinol; Absorption mechanisms; Controlled-release technology.

Citation: To be added by editorial staff during production.

Academic Editor: Firstname Lastname

Received: date
Revised: date
Accepted: date
Published: date

1. Introduction

Coenzyme Q_{10} (CoQ_{10}) is a lipid-soluble antioxidant essential for cellular energy production and antioxidative defence mechanisms. First elucidated in the 1957 “Isolation of a Quinone from Beef Heart Mitochondria”by Frederick Crane and colleagues, the nomenclature "coenzyme Q_{10}" is predicated upon its chemical configuration—a benzoquinone ring conjoined to a side chain comprising 10 isoprene units [1,2]. Known as “ubiquinone” due to its widespread presence in nature, this endogenous compound manifests in three oxidation states: the fully oxidized ubiquinone iteration (CoQ_{10}), the radical semiquinone intermediate ($CoQ_{10}H.$), and the fully reduced ubiquinol form ($CoQ_{10}H_2$; Figure 1). Despite structural similarities to certain vitamins, such as vitamin K, CoQ_{10} is distinguished

and delineated from being classified as vitamin due to its endogenous synthesis, in contrast to vitamins that necessitating exogenous acquisition from dietary sources [1].

Synthesized endogenously, CoQ_{10} is localized predominantly within the mitochondria, where it plays a critical role in the mitochondrial respiratory chain by facilitating electron transport. This electron-shuttling function is central to adenosine triphosphate (ATP) synthesis, enabling the energy transfer necessary for vital cellular processes [2,3]. Specifically, CoQ_{10} serves as an electron carrier, transferring electrons from complexes I and II to complex III, thus maintaining cellular energy homeostasis [2]. Additionally, CoQ_{10} exhibits potent antioxidant activity, preventing oxidative damage to cellular lipids, proteins, and DNA. The reduced form of CoQ_{10}, ubiquinol, supports cellular antioxidant capacity by regenerating other antioxidants such as vitamins C and E, thereby exerting protective effects on cellular membranes and circulating lipoproteins [4,5].

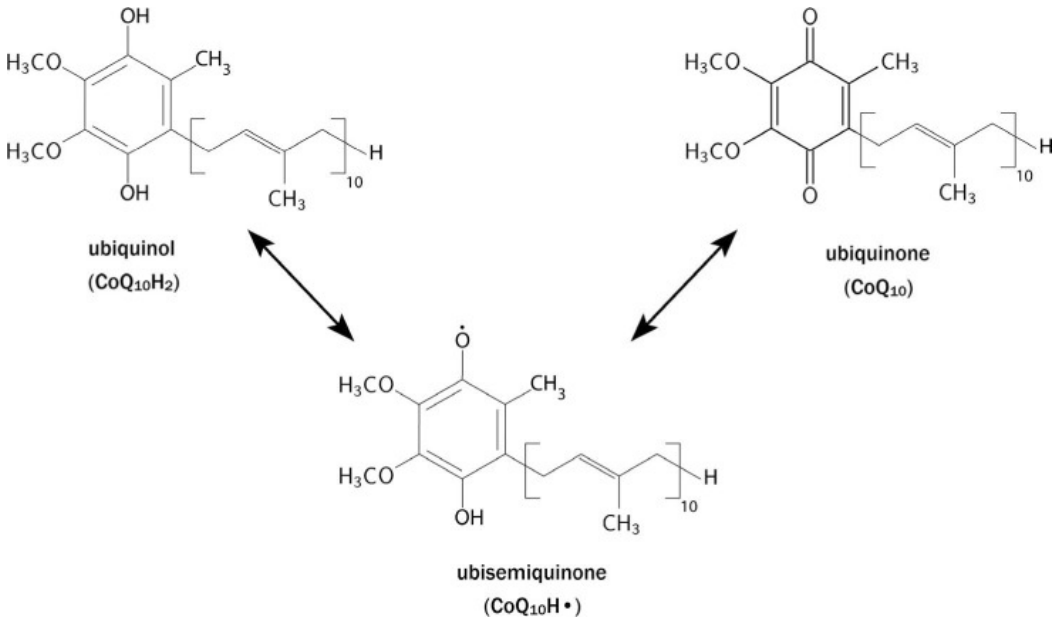

Figure 1. Three oxidative states of CoQ_{10}: the fully oxidized ubiquinone form (CoQ_{10}), the radical semiquinone intermediate ($CoQ_{10}H.$), and the fully reduced ubiquinol form ($CoQ_{10}H_2$).

The estimated daily requirement for CoQ_{10} is approximately 500 mg, which is met through endogenous synthesis and, to a lesser extent, dietary intake. Dietary contributions to CoQ_{10} levels are relatively modest, averaging around 5 mg per day. The majority of CoQ_{10} is synthesized internally via pathways involving 4-hydroxybenzoate and the mevalonic acid pathway, critical for isoprenoid side chain synthesis [6,7]. However, the body's ability to produce CoQ_{10} declines with age, particularly after the mid-twenties, with marked reductions in tissues that demand high energy levels, such as the heart, liver, and kidneys [8]. Age-related decreases in CoQ_{10} are further associated with chronic diseases, including cardiovascular and neurodegenerative conditions, where CoQ_{10} deficiency contributes to increased oxidative damage and impaired energy production [8,9]. This reduction is attributed to a biosynthesis process that relies on at least 13 genes, requiring amino acids, vitamins, and trace elements as cofactors for effective synthesis [6]. Consequently, CoQ_{10} supplementation is advocated to counteract diminished endogenous synthesis, particularly in elderly populations and in individuals with oxidative stress-related disorders [7].

CoQ_{10} has established therapeutic roles in the management of oxidative stress-related diseases. Oral supplementation of CoQ_{10} has demonstrated clinical benefits in conditions such as cardiovascular disease, diabetes, and neurodegenerative disorders, including

Parkinson's and Alzheimer's diseases [4,6,10]. Due to its role in reducing mitochondrial oxidative stress, CoQ_{10} is considered a promising therapeutic agent for mitigating neurodegeneration and cardiovascular risk [11]. Its antioxidant properties make it particularly valuable as an adjunct therapy in conditions characterized by elevated oxidative stress, including atherosclerosis, hypercholesterolemia, and hypertension. Additionally, CoQ_{10} supplementation is beneficial in cases of primary CoQ_{10} deficiencies caused by genetic mutations in CoQ_{10} biosynthesis pathways. However, its therapeutic efficacy is often limited by poor blood-brain barrier penetration and irreversible neuronal damage in these conditions [12].

The bioavailability of CoQ_{10} is limited by its physicochemical properties. Structurally, CoQ_{10} consists of a benzoquinone head and an isoprenoid tail, rendering it highly lipophilic and practically insoluble in water (<4 ng/mL) [8,13]. This hydrophobicity, combined with a substantial molecular weight (863.3 g/mol), contributes to its poor gastrointestinal absorption and low oral bioavailability, generally less than 3% [13,14]. During digestion, CoQ_{10} is absorbed in the small intestine in a manner akin to other lipid-soluble compounds, such as vitamin E, requiring bile salts and micelle formation for optimal absorption [13]. Despite these mechanisms, CoQ_{10}'s limited water solubility and complex transport requirements hinder its systemic availability. Following intestinal absorption, CoQ_{10} is transported through lymphatic circulation via chylomicrons and subsequently distributed within lipoproteins, including very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) [14,15]. The absorption process of CoQ_{10} is nonlinear, influenced by formulation type and dosage, highlighting the need for bioavailability-enhancement strategies [14,15]. Current formulations of CoQ_{10} supplements include the oxidized ubiquinone and the reduced ubiquinol forms. While standard ubiquinone remains the most widely used, recent advancements have introduced reduced ubiquinol formulations, potentially offering superior bioavailability in older adults and individuals with specific absorption challenges [8]. Nonetheless, achieving optimal plasma levels through standard supplementation remains challenging due to CoQ_{10}'s low solubility and rapid systemic clearance.

Traditional CoQ_{10} supplementation faces significant challenges in achieving effective plasma concentrations, primarily due to its limited oral bioavailability, solubility, and extensive first-pass metabolism [13,15]. Although absorption rates increase when CoQ_{10} is ingested with high-fat meals, this strategy alone is insufficient to overcome its absorption challenges. Moreover, the dose-dependent decline in CoQ_{10} absorption further complicates supplementation efforts; increased dosages do not correlate with proportionally higher absorption rates [14]. Clinical studies on CoQ_{10}'s therapeutic efficacy yield mixed results, often due to inconsistencies in bioavailability, which underscores the urgent need for novel formulations aimed at enhancing CoQ_{10} absorption and sustaining plasma concentrations.

This review aims to systematically assess recent advancements in CoQ_{10} bioavailability enhancement methods. The focus is on emerging delivery technologies, including nanoparticle-based formulations, liposomes, micelles, and self-emulsifying drug delivery systems (SEDDS), which have shown promise in addressing CoQ_{10}'s solubility and absorption limitations. Additionally, this review will explore the mechanistic foundations of these novel delivery systems, examining their roles in improving gastrointestinal uptake, cellular transport, and stability. By synthesizing findings from contemporary research, this review aims to provide insights into optimal CoQ_{10} formulations for clinical application, highlighting areas where further innovation is necessary to maximize CoQ_{10} bioavailability and therapeutic efficacy.

2. Physicochemical Barriers to CoQ10 Absorption

CoQ10 faces significant absorption challenges due to its high molecular weight and strong lipophilicity, which limit its water solubility and bioavailability. Its large, hydrophobic structure hinders efficient dissolution and permeation through the gastrointestinal

tract, while absorption relies on micelle formation and lipid transport—mechanisms less effective for such hydrophobic molecules. Additionally, CoQ10's bioavailability fluctuates with dietary fat intake, further complicating absorption. Overcoming these physicochemical barriers is essential for developing formulations that improve CoQ10 solubility, stability, and absorption efficiency.

2.1 Molecular Characteristics and Solubility Constraints

Coenzyme Q10 (CoQ10) is a lipophilic molecule, comprising a benzoquinone ring structure attached to an isoprenoid side chain. The number of isoprenyl units in this chain varies among species, influencing the bioavailability and physiological roles of CoQ10. In humans, CoQ10 contains 10 isoprenyl units, whereas in species like Saccharomyces cerevisiae, it comprises only 6 units, of which variation contributes to the molecule's unique functionality in different biological systems [3]. The isoprenoid tail confers high lipophilicity to CoQ10, resulting in low water solubility (<4 ng/mL) and necessitating specific absorption mechanisms in the gastrointestinal (GI) tract, where hydrophilic properties generally facilitate nutrient uptake [3].

The fully oxidized ubiquinone form of CoQ10 is generally more stable than the fully reduced ubiquinol form (CoQ10H2) and is less susceptible to environmental degradation. In contrast, ubiquinol, while crucial as an antioxidant within cellular membranes, is particularly vulnerable to oxidative degradation when exposed to light, oxygen, or heat, reverting to the more stable ubiquinone form [7]. This sensitivity is exacerbated in aqueous or atmospheric environments, necessitating specific storage and handling conditions to preserve ubiquinol's bioactive form. Structurally, ubiquinone and ubiquinol have distinct physicochemical characteristics, with ubiquinol exhibiting a hydroxyl group that enhances its antioxidative properties but also contributes to its susceptibility to oxidation [5,6].

The structural form in which CoQ10 is provided further impacts its bioavailability. CoQ10 raw material typically exists as polymorphic crystals, which are structurally rigid and require dissociation into single molecules for absorption [5,16]. In this crystalline state, CoQ10 is not readily solubilized, limiting its ability to form the micelles necessary for lipid-based absorption in the GI tract. For absorption to occur, CoQ10 crystals must first dissociate into individual molecules to enable their incorporation into micelles, which facilitate transport through the intestinal epithelium. However, not all manufacturers have demonstrated the capability to maintain CoQ10 in a dissociated, bioavailable form throughout the product's shelf life, resulting in variability in the effectiveness of CoQ10 supplements [16].

Modern supplemental CoQ10 is manufactured via yeast fermentation, yielding the bioidentical trans-form that is chemically identical to endogenously produced CoQ10. Kaneka Corporation, a primary supplier, produces CoQ10 for supplement formulations, yet achieving consistent and sustained dissociation of the crystalline form remains a challenge in the industry [17]. Polymorphic crystals have a high level of structural stability, making them difficult to dissolve in biological fluids. Studies show that formulations subjected to processes like thermal crystal dispersion can significantly improve CoQ10's bioavailability by enhancing crystal dissociation, thereby allowing better integration into micelles and subsequent absorption [5,16].

The stability of CoQ10 formulations is a critical aspect of its efficacy as a supplement. The design of CoQ10-based therapeutics and supplements must account for the instability of ubiquinol under environmental conditions, as degradation reduces its bioavailability and therapeutic effectiveness. For instance, when exposed to light and oxygen, ubiquinol can degrade into byproducts like ubichromenol, which can adversely affect cellular structures and diminish CoQ10's intended benefits [5]. To ensure the stability of CoQ10, formulation research often incorporates protective strategies such as encapsulation, complexation with cyclodextrins, or microencapsulation. Cyclodextrins, for example, form inclusion complexes with CoQ10, enhancing its solubility and protecting it from oxidative

degradation. Microencapsulation provides a physical barrier, stabilizing ubiquinol against environmental factors and extending its shelf life, especially under adverse storage conditions [4,5].

The poor aqueous solubility, large molecular structure, and hydrophobic isoprenoid tail of CoQ10 are major barriers to its GI absorption. Enhancing CoQ10 bioavailability depends on addressing these molecular challenges through innovative formulation techniques rather than relying on the ubiquinol form alone, as early studies have suggested.

2.2 Gastrointestinal Absorption Pathways

CoQ10 absorption is a complex process involving multiple stages as it travels from ingestion through the GI tract to systemic circulation and eventually into cells. This pathway includes key steps such as micelle formation, lymphatic transport, and enterohepatic recycling, each of which supports CoQ10's transition from a lipid-soluble compound to an accessible nutrient in the body.

Once ingested, exogenous CoQ10, typically dissolved in a carrier lipid like soy or palm oil and encapsulated in gelatin, enters the acidic environment of the stomach, where the capsule dissolves within minutes, releasing CoQ10 into the gastric fluid. Given its lipophilic nature, CoQ10's solubility remains low in this aqueous environment, even as it moves from the stomach toward the duodenum as part of the chyme. In this acidic transit, any CoQ10 in its reduced form (ubiquinol) undergoes oxidation to ubiquinone, a transformation that typically completes within 90 minutes under gastric conditions [18]. Despite attempts to make CoQ10 water-soluble, the molecule's lipid solubility remains intrinsic, rooted in its isoprenoid chain, which requires lipid-based formulations for effective absorption.

Upon reaching the duodenum, CoQ10 becomes exposed to bile and pancreatic secretions, which facilitate the process of micellization. Bile salts aid in forming micelles, spherical lipid-based structures that encapsulate CoQ10 along with other lipid-soluble compounds such as monoglycerides, fatty acids, and fat-soluble vitamins. These micelles, typically about 20 nanometers in diameter, help transport CoQ10 through the intestinal lumen toward the enterocyte cells lining the intestinal wall. Notably, micelles themselves are not absorbed; they continuously break apart and reform, releasing individual CoQ10 molecules at the surface of enterocytes for absorption [19].

The enterocyte cells absorb CoQ10 primarily via passive facilitated diffusion, a process that does not require energy. This absorption may involve specific carrier proteins, although these remain unidentified. Some studies suggest that NPC1L1 (Niemann-Pick C1 Like 1) could serve as a transporter, though further investigation is needed [20,21]. Once within the enterocytes, CoQ10 is incorporated into chylomicrons, lipid-based particles that facilitate its transport through the lymphatic system. Chylomicrons, being too large for direct entry into the bloodstream, first enter the lymphatic circulation, where they pass through the subclavian vein and then enter systemic circulation.

During this lymphatic transport, CoQ10 undergoes a redox transformation from ubiquinone to ubiquinol, aligning with the form in which it predominantly circulates in the blood. Although some CoQ10 supplements are available in the reduced ubiquinol form to potentially enhance bioavailability, studies suggest that ubiquinone naturally reduces to ubiquinol during absorption. As such, the stability challenges associated with ubiquinol supplements question its practical advantage over ubiquinone [3].

In the bloodstream, CoQ10 is incorporated into lipoproteins following its initial transport within chylomicrons to the liver. It is then primarily integrated into low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) particles, with smaller amounts found in high-density lipoproteins (HDL). The peak plasma concentration (Cmax) of ingested CoQ10 is typically reached about six hours after ingestion, with a half-life of approximately 33 hours, allowing it to maintain therapeutic plasma levels with

regular dosing [8]. CoQ10's role as an antioxidant is significant within LDL particles, where it helps inhibit lipid peroxidation, a factor in the pathogenesis of atherosclerosis [22,23].

Once delivered to tissues, CoQ10's lipid nature facilitates its diffusion into cell membranes, with the highest concentrations appearing in organs with high energy demands, such as the heart. Cellular uptake of CoQ10 likely depends on maintaining higher plasma concentrations, which enhances passive diffusion from the bloodstream. Clinical studies have shown that CoQ10 supplementation can elevate cellular CoQ10 levels, especially in energy-demanding tissues, which supports its therapeutic use in conditions requiring enhanced mitochondrial function [9]. Within cells, CoQ10 primarily resides in the mitochondria, reflecting its role in energy production, though it is also present in other organelles such as the endoplasmic reticulum and lysosomes. The intracellular transport of CoQ10 among organelles is an active area of research, with some evidence suggesting that saposin B may function as a binding and transfer protein within this process [24,25].

3. Innovative Strategies for Enhanced Bioavailability

Given CoQ10's poor water solubility and limited bioavailability, significant research has been dedicated to developing novel delivery systems that can enhance its absorption and stability. These strategies leverage advances in nanotechnology, lipid-based systems, and chemical modification to improve CoQ10's solubility, permeability, and cellular uptake. Below, we outline some of the most promising techniques used to enhance CoQ10 bioavailability. (Table 1)

Table 1. Overview of Conventional and Nanotechnology-Based Manufacturing Techniques for Coenzyme Q10 (CoQ10).

Category	Method	Techniques
Solid Dispersion (SD) Methods	Melting Solvent Method	Melt evaporation
	Melting Methods	Solution, Suspension
	Kneading Method	Hot melt extrusion, Meltrex™, Melt agglomeration
	Solvent Evaporation Method	Solvent evaporation in vacuum, Spray drying, Freeze drying, Lyophilization, Supercritical fluid, Co-precipitation
Nanotechnology Methods (NM)	Nanoemulsion	High pressure homogenization, Microfluidization, Ultrasonication, Phase inversion emulsification, Self-nanoemulsification
	Nanoparticles	Emulsion-diffusion-evaporation, Nanoprecipitation, Rapid expansion of supercritical solution, High pressure homogenization, Solvent diffusion technique, Polymer method
	SNEEDS	Spontaneous nanoemulsification of oil, surfactants, co-surfactants, and co-solvents in an aqueous medium
	Liposomes	Sonification, Dry-film dispersion, Extrusion, Freeze drying lipid hydration, Ether/ethanol injection, Reverse phase evaporation method
	Nanomicelles	Spontaneous emulsification, Dialysis, Solvent evaporation method, Spray drying

3.1. Conventional Method: Solid Dispersion (SD)

Improving the bioavailability and solubility of poorly water-soluble drugs, such as CoQ10, is a common challenge in pharmaceutical development. Solid dispersion (SD) is a promising technique to enhance these properties, offering an effective and relatively simple method to improve the dissolution rate of hydrophobic substances. SD involves dispersing one or more hydrophobic active compounds in a hydrophilic carrier matrix in the solid state, which enhances the compound's interaction with aqueous environments, thereby promoting solubility and absorption [26,27]. SD methods are broadly categorized based on the carriers and preparation techniques used, including solvent evaporation, melting, and melting-solvent methods (Olsen et al., 2007) [27,28]. The melting method, also known as the fusion method, was among the first SD preparation techniques, but it is unsuitable for thermolabile substances due to the high temperatures required. In contrast, solvent evaporation, the most commonly used SD method in the pharmaceutical industry, is especially suitable for heat-sensitive compounds. This method involves dissolving the drug and carrier in a volatile solvent to create a homogeneous mixture. The solvent is then evaporated, leaving behind a solid dispersion that is subsequently crushed and sieved for use [15,27,29].

SD techniques have shown significant promise in enhancing the solubility and bioavailability of CoQ10. For instance, Nazzal et al. prepared an SD formulation of CoQ10 using the solvent evaporation method with Eudagrit® L 100-55 as the carrier [26]. Solubility tests using surfactants like Labrasol and Cremophor EL achieved a solubility of 562 μg/mL, attributed to microemulsion formation. Dissolution testing of the SD tablet containing 100 mg CoQ10 demonstrated a 100% release over 24 hours, compared to a 26.5% release from a physical CoQ10-Eudagrit mixture and 12.5% from pure CoQ10 [26]. However, while the photostability of the formulation was maintained in ambient light, exposure to UV light led to decomposition, highlighting a limitation in stability [26]. Further advancements in SD formulation include Olsen et al.'s patented method combining dry blending with solvent-phase spray drying, resulting in reduced CoQ10 particle size and improved dispersion. Increasing the PVP (polyvinylpyrrolidone) content in this method prevented CoQ10 crystallization, achieving up to 80% dissolution. Similarly, Rosenberg et al. patented a CoQ10 SD formulation using polymers like Kollidon® VA 64 and Cremophor RH40, though high-temperature processing led to some CoQ10 recrystallization, impacting solubility [15]. Another approach, demonstrated by Bhandari et al., involved a binary solid dispersion (BSD) using the low-temperature melting method. Poloxamer 188 (P188) was identified as a potent solubilizing agent, with a CoQ10:P188 BSD formulation achieving a 37.73% dissolution rate, compared to <3% for pure CoQ10. The enhanced dissolution rate was likely due to improved wettability and dispersibility of CoQ10 in the SD matrix [30].

In subsequent studies, Nepal et al. utilized a combination of Aerosil 200 and Poloxamer 407 to stabilize CoQ10 SD. The study found that the melting method achieved higher solubility than solvent evaporation, with formulations containing Aerosil 200 demonstrating improved stability and flow properties over 30 days. Stability testing showed effective inhibition of CoQ10 recrystallization, with a maximum dissolution rate of around 85% achieved in 24 hours [31]. Onoue et al. introduced a novel nanocrystalline SD method using cold wet-milling (CWM) to preserve CoQ10's crystalline form, improving photostability and dissolution. Although in vitro dissolution rates remained low, in vivo testing demonstrated a 13-fold increase in oral bioavailability, along with hepatoprotective effects in a rat model, suggesting that further investigation into CWM's pharmacokinetic and therapeutic benefits is warranted [32].

Finally, Yang et al. explored supercritical fluid technology to create a CoQ10 SD formulation with fumed silica as the carrier. This technique yielded CoQ10 in an amorphous state, enhancing dissolution rates to 78.8% compared to 0.16% in commercial CoQ10 tablets. Although the dissolution rate improved, the study's value was limited by the absence of stability testing [33].

Overall, SD represents a viable approach for enhancing the solubility of CoQ10, as shown in various studies demonstrating substantial improvements in dissolution rates. However, many formulations use surfactants or solvents that may artificially boost solubility in dissolution tests, necessitating more rigorous assessments in distilled water for a reliable comparison. In vivo studies are also needed to evaluate long-term bioavailability and cellular-level effects of CoQ10 SD formulations [34].

3.2. Nanoparticle-Based Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

Nanotechnology has made significant strides in the pharmaceutical industry, offering innovative solutions for enhancing the pharmacokinetics and pharmacodynamics of poorly water-soluble drugs, including CoQ10. By reducing particle size to the nanometer range (1–100 nm), nanoparticles can improve solubility, stability, and bioavailability. Nanoparticles for medical applications are typically categorized as polymeric, inorganic, or lipid-based, with lipid-based systems particularly beneficial for hydrophobic molecules like CoQ10 [35].

One of the widely researched approaches involves the development of CoQ10-incorporated nanoparticles (CoQ10-NPs) using lipid-based systems. Hsu et al. formulated CoQ10-NPs by cooling microemulsion precursors of emulsifying wax, CoQ10, Brij 78, and Tween 20, resulting in nanoparticles with a high incorporation efficiency (74%) and a particle size range of 50 to 100 nm. The nanoparticles exhibited a slow-release profile in vitro, releasing only 14% of CoQ10 over 250 hours. This sustained-release mechanism could enhance bioavailability by allowing a gradual and extended uptake in the gastrointestinal tract. Additionally, lyophilization with disaccharide cryoprotectants was shown to stabilize CoQ10-NPs, preventing particle aggregation during storage [35].

Ankola et al. explored the therapeutic potential of CoQ10-loaded polymeric nanoparticles for hypertension management. Using the emulsion-diffusion-evaporation technique with poly(lactide-co-glycolide) (PLGA) and a stabilizer, DMAB, they created nanoparticles with high CoQ10 loading (up to 75%) and a slow-release profile [36]. This nanoparticle formulation showed increased intestinal uptake and higher bioavailability in animal studies compared to commercial CoQ10 formulations. Furthermore, CoQ10 nanoparticles demonstrated significant antihypertensive effects, proving 50% more effective than CoQ10 suspension at a reduced dose, likely due to prolonged circulation time and controlled release [36]. Polymeric nanoparticles without surfactants have also shown promise. Nehilla et al. developed surfactant-free PLGA nanoparticles encapsulating CoQ10 via nanoprecipitation [37]. The nanoparticles, with an average size below 200 nm, provided a sustained-release profile, with 45% of the total CoQ10 released over 60 days. This prolonged release suggests potential benefits for sustained antioxidant therapy, offering gradual CoQ10 delivery over extended periods [37]. For conditions linked to oxidative stress, such as hyperlipidemia and cardiovascular diseases, CoQ10 co-encapsulation with other antioxidants has been investigated. Ratnam et al. developed Nano-Co-Encapsulated Antioxidant Particles (NanoCAPs) containing CoQ10 and ellagic acid using the emulsion technique [38]. In vivo studies on hyperlipidemic rats showed that NanoCAPs significantly reduced plasma glucose, LDL cholesterol, total cholesterol, and triglyceride levels. These results highlight the therapeutic potential of nanoparticle formulations in addressing oxidative stress-related conditions [38].

The rapid expansion of supercritical solutions (RESS) has also been applied to CoQ10 nanoparticle formulation [39]. This technique micronizes CoQ10 to submicron levels

without using toxic organic solvents. In a study using supercritical CO2, CoQ10 nanoparticles displayed a nonspherical morphology and significant improvement in solubility, achieving 0.19 mg/mL in water compared to 0.4 μg/mL for unprocessed CoQ10. Pharmacokinetic studies in rats revealed that CoQ10-NPs achieved a Tmax of 3 hours, compared to 4 hours for CoQ10 powder, with a 1.96-fold increase in Cmax and AUC, underscoring the potential of RESS to improve bioavailability [39]. Lipid nanocapsules (LNCs) have been explored as another lipid-based nanoparticle system for CoQ10 delivery. Zhou et al. prepared CoQ10-LNCs with medium-chain triglycerides, achieving high stability and a particle size of approximately 56 nm [40]. Bioavailability studies in mice demonstrated that CoQ10-LNCs provided a 1.8-fold higher AUC compared to a conventional CoQ10 tablet suspension, confirming the bioavailability advantage of LNCs for CoQ10 [40]. A novel lipid nanoparticle formulation combining solid and liquid lipids was developed by Nanjwade et al., using solvent diffusion in an aqueous system [41]. This method yielded CoQ10-loaded nanoparticles below 90 nm with a sustained-release profile. The lipid matrix effectively controlled CoQ10 release, aligning with the Higuchi diffusion model, and exhibited stable antioxidant activity, suggesting potential as a supplementary therapy for oxidative stress-related diseases [41].

Nanoparticle formulations represent an innovative approach to improving the solubility and bioavailability of CoQ10. By leveraging lipid or polymeric materials and advanced manufacturing techniques, these systems address the inherent challenges of CoQ10 delivery, offering sustained-release profiles, enhanced intestinal absorption, and extended circulation times. Although in vitro and in vivo studies show promise, further research is needed to establish clinical efficacy and optimize these formulations for commercial use.

3.2. Self-Emulsifying Drug Delivery Systems (SEDDS)

Self-Emulsifying Drug Delivery Systems (SEDDS) have emerged as a promising approach to improve the oral bioavailability of poorly water-soluble drugs, such as CoQ10. SEDDS formulations consist of a mixture of oils, surfactants, and cosurfactants or cosolvents that spontaneously emulsify upon exposure to aqueous gastrointestinal fluids. This process results in either microemulsions or nanoemulsions, providing a larger interfacial surface area for drug dissolution and subsequent absorption [42]. The small oil droplet size (<5 μm) and high polarity of these emulsions facilitate faster dispersion in the gastrointestinal tract, enhancing drug release and absorption [42].

The emulsification ability of SEDDS formulations is influenced by the composition and concentration of oils and surfactants. For example, Kommuru et al. developed a CoQ10 SEDDS using Captex-200 and Myvacet 9-45 as oils, Labrasol as a surfactant, and lauroglycol as a cosurfactant [43]. The optimized formulation demonstrated a twofold increase in bioavailability compared to a standard CoQ10 powder, evidenced by significant increases in both AUC and Cmax values. This study highlights the role of SEDDS in enhancing oral absorption by facilitating a finer emulsion with improved gastrointestinal dispersion [43]. Similarly, Balakrishnan et al. evaluated the bioavailability of a novel CoQ10 SEDDS based on solubility studies in various oils, identifying Labrafil M 1944 CS and Labrafil M 2125 CS as suitable carriers [44]. The optimized formulation, containing 65% Labrasol, 25% Labrafil, and 10% Capryol 90, achieved nearly 90% CoQ10 release in aqueous media. In vivo studies in rats showed a twofold increase in AUC and Cmax values over traditional CoQ10 suspensions, suggesting that SEDDS technology enhances CoQ10's aqueous solubility and bioavailability by promoting rapid and efficient dispersion [44].

SEDDS formulations also include advanced versions such as Self-Microemulsifying (SMEDDS) and Self-Nanoemulsifying Drug Delivery Systems (SNEDDS), which offer even smaller droplet sizes for enhanced absorption. Agrawal et al. developed a CoQ10 SNEDDS with hepatoprotective properties by combining CoQ10 with ethyl oleate,

Cremophor RH 40, and Transcutol P. The SNEDDS formulation exhibited 90% drug dissolution within 30 minutes and demonstrated antioxidant and hepatoprotective effects in vivo, significantly reducing ALT, AST, and ALP levels in a rat liver injury model. This SNEDDS was also converted into solid nanostructures (S-SNEDDS) for easier administration, which showed stability over three months [45]. Further development in SNEDDS formulations was demonstrated by Khattab et al., who formulated a CoQ10 SNEDDS using isopropyl myristate as the oil and Cremophor EL as the surfactant. These formulations displayed small droplet sizes (11.7–13.5 nm) and rapid release, with complete CoQ10 dissolution achieved within 30 minutes. In vivo pharmacokinetic studies in rabbits revealed a 2.1-fold increase in Cmax and AUC values over simple CoQ10 suspensions. Additionally, the formulation showed significant hepatoprotective effects, as evidenced by improved liver biochemical markers [46]. Jain et al. explored a SNEDDS co-loaded with CoQ10, α-tocopherol, and resveratrol, aiming for a prophylactic effect against breast cancer [47]. This antioxidant-loaded SNEDDS showed enhanced stability, antioxidant activity, and bioavailability in vitro and in vivo. In a rat breast cancer model, the formulation reduced tumor growth and angiogenesis markers compared to free antioxidants, suggesting the formulation's potential as a preventive therapy in cancer due to the synergistic effects of its components [47].

SEDDS and its advanced variants, SMEDDS and SNEDDS, have shown significant promise in improving CoQ10's bioavailability and therapeutic efficacy. By enhancing CoQ10's dissolution and absorption in the gastrointestinal tract, these formulations provide a practical solution for overcoming the solubility challenges associated with lipophilic compounds. The simplicity of SEDDS technology and its compatibility with commercial production make it a viable option for delivering CoQ10 in therapeutic contexts, particularly for conditions requiring enhanced antioxidant protection.

4. A proposal of an innovative SEDDS CoQ10

This innovative proposal centers around developing an advanced Self-Emulsifying Drug Delivery System (SEDDS) for CoQ10 that is specifically designed to optimize its bioavailability and cellular utilization. The proposed SEDDS composition combines ubiquinol, ubiquinone, and mitoquinol mesylate, along with essential oils, surfactants, and a carefully selected blend of bioactive components, to address challenges related to solubility, stability, and bioavailability of CoQ10. This formulation represents a strategic approach to enhance CoQ10's pharmacokinetics, as well as its antioxidant and energy-enhancing properties, providing a comprehensive system to support mitochondrial function and cellular health.

4.1 Core CoQ10 Components

The primary active ingredient in this proposed SEDDS is a combination of 100 mg of CoQ10, which includes 75 mg of ubiquinol processed through a patented thermal crystal dispersion process, 20 mg of mitoquinol mesylate, and 5 mg of ubiquinone. Ubiquinol, in its reduced form, is prone to oxidation; thus, a patented thermal dispersion process dissociates CoQ10 crystals into individual molecules, increasing their absorption and bioavailability by 75% . Mitoquinol mesylate, a mitochondrial-targeted antioxidant conjugated to a triphenylphosphonium cation, facilitates CoQ10 accumulation within mitochondria, enhancing its antioxidative effects [48,49]. Additionally, the inclusion of a small amount of ubiquinone is intended to balance the redox state, as the ubiquinol-to-ubiquinone ratio in plasma may serve as an indicator of oxidative stress [50].

4.2 Carrier and Surfactant System

The SEDDS formulation includes HCO-60 (polyoxyethylene hydrogenated castor oil-60) and caprylic acid as carrier lipids, in addition to ethylcellulose and sorbitan

monostearate as surfactants. The selection of HCO-60 is based on its ability to form stable micelles that maintain CoQ10 in its dissolved state, both in blood circulation and tissues [51]. Caprylic acid, a medium-chain triglyceride (MCT), has shown potential to enhance the absorption and bioavailability of CoQ10, as MCTs improve solubility and facilitate cellular uptake [8]. Ethylcellulose serves as a gelling agent, creating a thermoreversible oleogel network that improves stability and retention of CoQ10, while sorbitan monostearate stabilizes the emulsion and prevents recrystallization [8].

4.3 Auxiliary Bioactive Ingredients

The proposed SEDDS formulation includes 10 mg of Nicotinamide Adenine Dinucleotide (NADH), which assists in regenerating ubiquinol from ubiquinone within the electron transport chain, thereby optimizing CoQ10 utilization and ATP production. Additionally, 20 mg of bovine colostrum containing 5-10 mg of saposin B is incorporated as a CoQ10 transporter. Saposin B has been identified as a lipid-binding protein with a strong affinity for CoQ10, facilitating its transfer across cell membranes and enhancing cellular uptake [25].

4.4 B-Vitamins for Enhanced CoQ10 Function

B-vitamins, including thiamin (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folate (B9), and cobalamin (B12), are integral to the TCA cycle and oxidative phosphorylation, where CoQ10 plays a pivotal role in energy production. Riboflavin (B2) and pantothenic acid (B5), in particular, are crucial for CoQ10 synthesis, while niacin (B3) improves blood circulation, facilitating efficient CoQ10 delivery to tissues [52]. These B-vitamins enhance CoQ10's bioavailability and antioxidant potential by supporting the enzymes that utilize CoQ10 in mitochondrial energy metabolism.

4.5 Synergistic Antioxidants and Supportive Nutrients

To further support CoQ10's function and protect it from oxidative degradation, the formulation includes 20 μg of selenium, 25 mg of L-carnitine, and 600 IU of vitamin D3. Selenium is required for glutathione peroxidase activity, a selenoprotein that works synergistically with CoQ10 to neutralize free radicals and prevent cellular damage [53]. L-carnitine transports fatty acids into mitochondria for energy production, complementing CoQ10's role in ATP synthesis, while vitamin D3 contributes to cardiovascular health by improving vascular compliance and reducing oxidative stress [54].

4.6 Potential Advantages of the Proposed SEDDS CoQ10 Formulation

The proposed SEDDS formulation offers several benefits over conventional CoQ10 supplements:

1. **Enhanced Bioavailability and Solubility**: By employing a self-emulsifying system, the formulation significantly improves CoQ10's solubility and dissolution rate, ensuring rapid and efficient absorption in the gastrointestinal tract.
2. **Targeted Delivery to Mitochondria**: Mitoquinol mesylate, coupled with NADH and saposin B, targets CoQ10 directly to mitochondria, maximizing its antioxidant effects and enhancing cellular energy production.
3. **Improved Stability and Sustained Release**: The use of thermoreversible oleogels stabilizes CoQ10 against oxidative degradation and allows for sustained release, maintaining therapeutic levels in plasma for extended periods.
4. **Comprehensive Nutritional Support**: The inclusion of B-vitamins, selenium, L-carnitine, and vitamin D3 complements CoQ10's functions and mitigates factors that could limit its effectiveness, such as poor mitochondrial function or oxidative damage.

5. Conclusions

Advancements in enhancing the bioavailability of coenzyme Q10 (CoQ10) have led to promising strategies to improve its absorption, stability, and cellular uptake. Conventional methods, such as solid dispersion (SD), have increased CoQ10's solubility and dissolution rate through techniques like solvent evaporation and supercritical fluid technology. Nanoparticle-based systems, including lipid and polymeric nanoparticles, further enhance CoQ10 bioavailability by reducing particle size and providing a sustained-release profile. Additionally, self-emulsifying drug delivery systems (SEDDS) and cyclodextrin complexes have improved CoQ10's solubility and stability in gastrointestinal fluids, achieving faster dissolution and better pharmacokinetics.

The innovative SEDDS CoQ10 formulation combines ubiquinol, ubiquinone, and mitoquinol mesylate with B-vitamins, selenium, L-carnitine, and NADH to optimize absorption and cellular utilization. This approach leverages a self-emulsifying matrix and auxiliary bioactives, promoting mitochondrial targeting and supporting CoQ10's function as an antioxidant and energy producer.

These advancements have significant clinical potential. Enhanced CoQ10 formulations may support individuals with CoQ10 deficiencies or conditions involving oxidative stress, such as cardiovascular and neurodegenerative diseases. While these formulations show promise, further clinical trials are needed to confirm their efficacy and safety. Continued innovation in CoQ10 delivery could enhance therapeutic options for chronic disease management, particularly for age-related conditions where cellular energy and antioxidant protection are critical.

6. Patents

This section is not mandatory but may be added if there are patents resulting from the work reported in this manuscript.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

Author Contributions: Conceptualization, L.W.L.; writing—original draft preparation, L.W.L.; writing—review and editing, L.W.L., J.-H.C., and X-X.S.. All authors have read and agreed to the published version of the manuscript.

Funding: This APC was funded by Pharma New Zealand PNZ Limited (Hamilton, New Zealand).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.
Data Availability Statement: Data is not publicly available due to privacy.

Acknowledgments: Conceptualization, L.W.L.; writing—original draft preparation, L.W.L.; writing—review and editing, L.W.L., J.-H.C., and X-X.S.. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest

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