



Applied nutritional investigation

Bioavailability of coenzyme Q10 supplements depends on carrier lipids and solubilization



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ARTICLE INFO

Article History:

Received 19 January 2018

Received in revised form 17 April 2018

Accepted 22 May 2018

Keywords:

Ubiquinol

Ubiquinone

Bioavailability

Human

Coenzyme Q10

ABSTRACT

Objectives: Bioavailability of supplements with coenzyme Q10 (CoQ₁₀) in humans seems to depend on the excipients of formulations and on physiological characteristics of the individuals. The aim of this study was to determine which factors presented in CoQ₁₀ supplements affect the different response to CoQ₁₀ in humans.

Methods: We tested seven different supplement formulations containing 100 mg of CoQ₁₀ in 14 young, healthy individuals. Bioavailability was measured as area under the curve of plasma CoQ₁₀ levels over 48 h after ingestion of a single dose. Measurements were repeated in the same group of 14 volunteers in a double-blind crossover design with a minimum of 4 wk washout between intakes.

Results: Bioavailability of the formulations showed large differences that were statistically significant. The two best absorbable formulations were soft-gel capsules containing ubiquinone (oxidized CoQ₁₀) or ubiquinol (reduced CoQ₁₀). The matrix used to dissolve CoQ₁₀ and the proportion and addition of preservatives such as vitamin C affected the bioavailability of CoQ₁₀. Although control measurements documented that all formulations contained 100 mg of either CoQ₁₀ or ubiquinol, some of the participants showed high and others lower capacity to reach high increase of CoQ₁₀ in blood, indicating the participation of individual unknown physiological factors.

Conclusion: This study highlights the importance of individually adapted selection of best formulations to reach the highest bioavailability of CoQ₁₀ in humans.

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Introduction

Coenzyme Q10 (CoQ₁₀) is an essential component of the human electron transport chain (ETC) in mitochondria and also an important lipid-soluble antioxidant that protects cell membranes and lipoproteins against oxidative damage [1–3]. CoQ₁₀ (in its oxidized form, ubiquinone) can be reduced by many oxidoreductases to maintain a redox cycle [3]. In its reduced form, CoQ₁₀ H₂ (ubiquinol) is able to transfer electrons to acceptors such as complex III in the mitochondrial ETC or, for example, to α -tocopherol in other

cellular membranes [3]. In this reaction, CoQ₁₀H₂ is oxidized back to CoQ₁₀. In mitochondria, oxidoreductases that reduce CoQ₁₀ are complex I and II in the ETC, but also dihydroorotate dehydrogenase, acyl-coenzyme A (CoA) dehydrogenase, sulfide:quinone oxidoreductase, choline, and proline dehydrogenases, whereas in other membranes, cytochrome b₅ reductase and NQO1 are the main oxidoreductases that maintain CoQ₁₀ in its reduced form [4–8].

In blood, CoQ₁₀ is located in lipoproteins. Many studies have demonstrated that there is a clear relationship between the levels of total cholesterol or low-density lipoprotein (LDL) and CoQ₁₀ in plasma [9]. In LDL, CoQ₁₀ shows a clear antioxidant function because it is the first antioxidant to be depleted when these lipoproteins are exposed to oxidative stress [10]. The proportion of CoQ₁₀H₂ to total CoQ₁₀ in plasma varies from 97% to 98% to 90%, depending on the study and the age of the individuals [11–13]. Older individuals show an impaired CoQ₁₀ status with lower serum CoQ₁₀ concentration and higher proportion of the oxidized form

GL-L and PN conceived and designed the experiments, analyzed the data, and wrote the paper. JP-C, AS-C, and ABC-R supervised extractions and performed the determinations in blood plasma.

All the authors revised and approved the manuscript. The authors have received funding and were supplied with the compounds used in this study by Pharma Nord, Denmark.

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[14]. Reduced levels of CoQ₁₀ in plasma also have been associated with the progression of sarcopenia [15]. In agreement with these findings, my colleagues and I have proven that higher physical capacity in older individuals shows a direct relationship with CoQ₁₀ levels in plasma, whereas higher body mass index shows an inverse relationship [16,17]. In older individuals, higher CoQ₁₀ levels in plasma were associated with lower LDL oxidation [16]. These results all indicate that the maintenance of CoQ₁₀ levels in plasma is important in preventing LDL oxidation, thereby reducing risk for cardiovascular disease and preventing muscle deterioration during aging.

Dietary contribution of CoQ₁₀ is minimal, with daily intakes around 3 to 5 mg/d [18]. For this reason, supplementation with CoQ₁₀ can be recommended in cases of deficiency in order to restore, at least, the antioxidant capacity and to avoid LDL oxidation. However, studies of bioavailability show that response of individuals to CoQ₁₀ supplementation is very variable. Furthermore, the causes of the low bioavailability of CoQ₁₀ have been associated with its large molecular weight, high lipophilicity, and poor aqueous solubility [19]. For this reason, considerable research has been carried out to increase its bioavailability including the use of different types of liposomes or new surfactants [20–24]. The different procedures carried out to manufacture CoQ₁₀ to increase bioavailability and stability have been revised recently [19].

To determine which factors presented in CoQ₁₀ supplements affect the different response to CoQ₁₀ in humans, we determined the bioavailability of seven different CoQ₁₀ formulations differing in the composition of matrix, crystal structure, and additives, in the same group of 14 healthy individuals.

Material and methods

Participants

This study comprised 14 healthy young (18–33 y) participants (see Supplementary Table 1). All participants signed an informed consent document and all procedures performed in this study were in accordance with the ethical standards of the Pablo de Olavide University research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Study design

The investigation was performed as a double-blind crossover design, with a washout period of at least 4 wk between each test. Participants were selected from young volunteers who had not taken drugs to reduce fat or statins or vitamin supplements (including vitamin E) during the previous month, and who maintained a normal lifestyle avoiding the intake of any drugs or alcohol during the 48 h of each determination. Participants were required to fast for 8 h before donation of the first peripheral venous blood sample from the antecubital vein. Baseline CoQ₁₀ level was measured at time –1 h before supplementation. Immediately after the intake of any preparation, the volunteers had a normal Spanish breakfast including fruit juice, milk, yogurt, and cakes; and ~5 h later a standard Spanish-type lunch including vegetables and meat. Volunteers were asked to maintain the same type of diet during the 48 h of the study. Blood extractions were performed at 2, 4, 6, 8,

24, and 48 h after CoQ₁₀ sample intake. Blood was placed in a test tube containing heparin (BD Vacutainer LH PSTTM II, Becton Dickinson, Franklin Lakes, NJ, USA). After each round of extractions, tubes were immediately centrifuged at 3000g using an Eppendorf benchtop centrifuge (Model 5810 R, Eppendorf North America, Hauppauge, NY, USA) for 10 min at room temperature, and plasma fraction was rapidly separated and stored at –80°C until analysis.

Participants remained in the Centro Andaluz de Biología del Desarrollo research facility from the baseline blood sampling until the 8-h blood sample collection. Collection of the 24- and 48-h blood samples was performed at separate visits. No adverse events (subjective symptoms) or any change in the concomitant medications were recorded at any visit.

Formulations tested

The formulations, prepared by Pharma Nord using the same CoQ₁₀ raw material, differed in matrix, crystal structure and additives and, in the case of NYD formulation, in capsule type (Table 1). Actual CoQ₁₀ (ubiquinone)/CoQ₁₀ H₂ (ubiquinol) content was measured in addition to individual dose variation of three capsules per preparation. The content of CoQ₁₀ of the 100 mg capsules was determined against CoQ₁₀ CRS European Pharmacopoeia, standard using high-performance liquid chromatography (HPLC)-ultraviolet (UV) normal-phase chromatography. The CoQ₁₀ was detected at a wavelength of 273 nm. The HPLC system applied was qualified and the method was validated in accordance to International Council for Harmonisation (ICH) guideline Q2. The content of CoQ₁₀ H₂ was measured by a similar method, but with ubiquinol as reference standard. The dose variation in all cases was <2 mg CoQ₁₀/CoQ₁₀ H₂. Two formulations are indicated by the trade name (Pharma Nord); the other five are identified by preparation codes because they are not commercialized and also were prepared by Pharma Nord only for this study.

The researchers were blinded to characteristics of the formulations until the end of the study; samples were codified in origin and received by the researchers without any indication of their composition, including the already commercialized formula. The nature of the formulations was only revealed after final analysis of the data.

Coenzyme Q determination in plasma

Plasma CoQ₁₀ levels were determined no later than 1 wk after the procedure from 100 µL plasma samples. CoQ6 was used as an internal standard at ~100 pmol per sample as previously indicated [25]. A more detailed and adapted procedure is indicated in supplementary information. CoQ₁₀ levels were quantified via electrochemical detection, and expressed as mg/L.

Pharmacokinetics parameters

The area under the curve (AUC_{0–48}) corresponding to the 48-h investigation period was computed using the trapezoidal rule by using the SigmaPlot 12.5 software (Systat Software, San Jose, CA, USA). Maximal concentration (C_{max}) and time to maximal concentration (T_{max}) were determined for each of the CoQ₁₀ samples.

Statistics

Statistical analysis was performed using SigmaPlot 12.5 software. Comparison between two groups was determined by using the paired *t* test, applying the Shapiro–Wilk normality test. Analysis of more than two groups was performed by one-way analysis of variance with Bonferroni post hoc, applying the Kolmogorov–Smirnov normality test. Statistical significance was determined at *P* ≤ 0.05.

Table 1
Preparation characteristics.

Preparation	Type	Matrix	Measured CoQ ₁₀ /CoQH10 content
Myoqinon	Softgel	Soy oil matrix, drug specification heat/cooling recrystallization procedure*	100.6 mg/
KOJ, CoQ ₁₀	Soft gel	Same as Myoqinon but without heat/cooling procedure	100.6 mg/
ICT, CoQ ₁₀	Soft gel	Olive oil, cocoa butter produced accordingly normal soft-gel filling technology	98.9 mg/
ERG, CoQ ₁₀	Soft gel	Olive oil, cocoa butter, 25 mg vitamin C produced accordingly normal soft-gel filling technology	100.5 mg/
Ubiquinol QH	Soft gel	MCT oil, 12 mg vitamin C, patented [†]	0.5 mg/102 mg
NYD, CoQ ₁₀	Hard gel	Finely ground (micronized) CoQ ₁₀ powder	98.3 mg/
SMF, CoQ ₁₀	Soft gel	Olive oil/soy oil matrix produced accordingly normal soft-gel filling technology	100.6 mg/

CoQ₁₀, coenzyme Q10; ERG; ICT; KOJ; MCT, medium-chain triglyceride; NYD; SMF,

*Full manufacturing procedure patented WO 2016038150 A1.

[†]Full manufacturing procedure patented DK 2008 00040 U3.

Results

Figure 1 shows the profile of CoQ₁₀ increase in plasma after the intake of 100 mg CoQ₁₀ of different formulations. Clearly, the change in plasma CoQ₁₀ levels was higher with Myoquinon when compared with all the other formulations. This increase was apparent after 4 h of CoQ₁₀ intake, reaching a peak at 8 h and decreasing afterwards toward normal levels at 48 h (Fig. 1).

Myoquinon and Ubiquinol QH induced similar plasma profiles (Fig. 1). A significant incorporation with Ubiquinol QH was found 6 h after intake, also reaching a maximum at 8 h. In the case of Ubiquinol QH, C_{max} was around half of the C_{max} seen with Myoquinon. In the five remaining formulations, incorporation was very low. NYD, ICT, and KOJ showed a similar pattern of incorporation, with a peak at 24 to 48 h around 0.2 to 0.3 mg/L over the baseline levels of CoQ₁₀. In the case of these compounds, C_{max} was around 0.35 mg/L, which is very low compared with Myoquinon or Ubiquinol QH. In the case of SMF and ERG, the response was even lower (Fig. 1, Tables 2 and 3).

AUC_{0–48 h} was determined as mg·L·48 h⁻¹ (Table 2). Clearly, Myoquinon showed the highest mean AUC_{0–48 h} of CoQ₁₀ in plasma followed by Ubiquinol QH. As indicated in Figure 2, the relative presence of CoQ₁₀ in the case of Ubiquinol QH in plasma was around half of Myoquinon. With the other compounds, CoQ₁₀ incorporated less into plasma. With KOJ, ICR, and NYD mean AUC_{0–48 h} was about 30% of the levels reached with the best compound. ERG and SMF did not show any meaningful incorporation (Table 2, Fig. 2).

In general, the bioavailability of the different compounds indicated a great variability among the different participants (Fig. 3; Supplementary Table 2). Among the different formulations tested, KOJ and ERG showed less variability, whereas the best formulations, Myoquinon and Ubiquinol QH, showed the highest variability.

Among the two best formulations, Myoquinon and Ubiquinol QH presented a similar incorporation profile, showing a peak at 8 h after intake and a slow decrease up to and beyond 48 h. Lag phase with Ubiquinol QH was longer than with Myoquinon. C_{max} obtained

with Ubiquinol QH was significantly lower than in the case of Myoquinon (Fig. 1, Supplementary Fig. 1). A clear difference in the mean and median AUC_{0–48 h} (Table 2) of the two formulations was found. However, Ubiquinol QH showed a lower rate of decrease after reaching C_{max} (Fig. 1).

Figure 4 provides a direct comparison of the individual AUC_{0–48 h} of the two best responding formulations Myoquinon and Ubiquinol QH. Participants showed a significant 1.7-fold better absorption with Myoquinon in comparison with Ubiquinol QH (Table 3). The distribution of the AUC_{0–48 h} for different individuals (the difference between minimal and maximal values) was also more disperse with Ubiquinol QH than with Myoquinon (Fig. 4). Interestingly, some of the individuals that showed lower AUC_{0–48 h} with Myoquinon presented similar or higher uptake of Ubiquinol QH, whereas other individuals showing high bioavailability with Myoquinon showed low uptake with Ubiquinol QH. In general, most of the individuals showed lower uptake with Ubiquinol QH (Fig. 4). These results indicate that the response of each individual is independent of the redox nature of CoQ₁₀.

Discussion

This study determined the bioavailability of seven different formulations of CoQ₁₀ from the same origin (in which matrix, oil suspensions, crystal structure, and additives varied) in an analysis lasting 48 h after the intake of one single capsule containing 100 mg CoQ₁₀. The same cohort tested all the seven formulations. To avoid external factors, the CoQ₁₀ used in this study was from the same source and prepared by the same company. Our results show a great variability in CoQ₁₀ absorption between individuals in agreement with many previous studies about acute bioavailability of CoQ₁₀ indicating the participation of individual physiology factors [26–30].

The low bioavailability of CoQ₁₀ has been associated with its large molecular weight, high lipophilicity, and poor aqueous

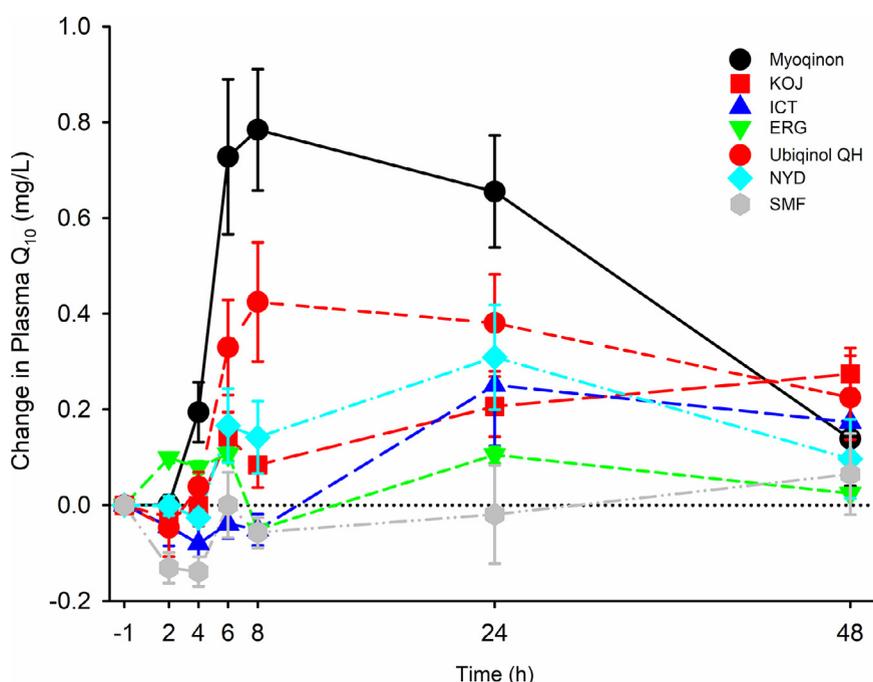


Fig. 1. Absorption curves of the kinetics of plasma CoQ₁₀. Changes in mean plasma CoQ₁₀ concentrations \pm SEM over 48 h after administration of a single dose of one 100-mg capsule of CoQ₁₀ differing in matrix and crystal structure. CoQ₁₀, coenzyme Q10; ERG, ICT; KOJ; NYD; SMF.

Table 2
Pharmacokinetic parameters after administration of a single 100 mg dose of CoQ₁₀ of 7 different formulations

Preparation	AUC _{0–48}			ΔC _{max} (mg/L)	T _{max} (h)
	Mean	Median	Range		
Myoquinon	25.15 ± 4.07	24.54	(2.40 to 52.81)	0.95 ± 0.16	8
KOJ, CoQ ₁₀	6.89 ± 1.66*	5.62	(–2.04 to 15.67)	0.33 ± 0.05*	48
ICT, CoQ ₁₀	6.28 ± 3.07*	2.47	(–5.28 to 35.52)	0.35 ± 0.10*	24
ERG, CoQ ₁₀	2.45 ± 1.64*	2.92	(–7.88 to 10.79)	0.26 ± 0.05*	6
Ubiquinol QH	14.75 ± 3.71 [†]	14.196	(–5.55 to 49.96)	0.49 ± 0.11 [†]	8
NYD, CoQ ₁₀	8.94 ± 3.33*	5.15	(–3.38 to 41.58)	0.38 ± 0.09*	24
SMF, CoQ ₁₀	–0.73 ± 3.01*	–2.78	(–11.78 to 26.02)	0.18 ± 0.10*	48

AUC, area under the curve; ERG; ICT; KOJ; NYD, not significant; SMF.

AUC_{0–48} is indicated as mg•L⁻¹•48 h⁻¹ as the mean ± SEM. C_{max} is indicated as mg/L above baseline as the mean ± SEM and T_{max} as h.

*Significantly different, $P \leq 0.01$ vs Myoquinon.

[†]Significantly different, $P \leq 0.05$ vs Myoquinon.

solubility [19]. Some studies have demonstrated that modifications in excipient composition markedly affects CoQ₁₀ bioavailability [31,32]. In general, the results of the present study indicate that the nature of the oil used as matrix for solubilizing CoQ₁₀ is essential for the bioavailability of CoQ₁₀. In the present study, soy oil matrix was the best excipient because other combinations, such as olive oil and cocoa butter in the ICT and ERG formulations or olive oil and soy oil in the SMF formulation, showed lower bioavailability despite showing the same content of CoQ₁₀ as KOJ, which only differed in the composition of the oil matrix.

Furthermore, our results indicated that a higher surface-to-volume ratio in CoQ₁₀ crystals was important to improve bioavailability. Myoquinon and KOJ only differed by a specific heat and cooling procedure of recrystallization of CoQ₁₀, which gives a higher surface-to-volume ratio in Myoquinon, as indicated in patent WO 2016038150 A1. AUC_{0–48 h} with KOJ was only one-fourth of the mean AUC_{0–48 h} reached with Myoquinon and ΔC_{max} was around one-third with a delay in the incorporation of CoQ₁₀ into plasma. Furthermore, nearly all of the participants showed a clear decrease in the AUC_{0–48 h} with KOJ compared with Myoquinon, with the exception of three of the participants who showed low incorporation with both formulations (Supplementary Fig 2).

CoQ₁₀ is better absorbed from aqueous or emulsified vehicles than from powder-filled formulations [28,33,34]. However, in the present study, the bioavailability of the NYD preparation (the micronized CoQ₁₀ preparation used in this study) was similar to the bioavailability of KOJ, ICT and ERG, and significantly higher to the bioavailability of SMF. Only Myoquinon showed significant

Table 3
Magnitude of the difference in mean AUC for a single 100-mg dose of the 7 formulations

Factor X/Y X↓ Y→	Myoquinon	KOJ	ICT	ERG	Ubiquinol	NYD	SMF
Myoquinon	1	0.275*	0.251*	0.098*	0.590 [†]	0.357 [†]	0.029*
KOJ	3.630*	1	1.097 [†]	0.371 [†]	2.141 [†]	1.297 [†]	0.106 [†]
ICT	3.981*	1.100 [†]	1	0.407 [†]	2.348 [†]	1.422 [†]	0.116 [†]
ERG	10.218*	2.815 [†]	2.567 [†]	1	6.025*	3.650 [†]	0.298 [†]
Ubiquinol	1.696 [†]	0.467 [†]	0.426 [†]	0.173*	1	0.606 [†]	0.049*
NYD	2.800*	0.771 [†]	0.703 [†]	0.286 [†]	1.651 [†]	1	0.082 [†]
SMF	34.340*	9.459 [†]	8.626 [†]	3.509 [†]	20.25*	12.266 [†]	1

AUC, area under the curve; ERG; ICT; KOJ; NYD; SMF

*Significantly different, $P \leq 0.01$.

[†]Difference significantly different, $P \leq 0.05$.

[‡]Not significant.

higher bioavailability than this micronized preparation, probably explaining the differences found in other studies [27].

In the present study, the most effective compositions were Myoquinon and Ubiquinol QH. These compositions differ in the nature of the fat used to dissolve CoQ₁₀ and in the redox nature of CoQ₁₀. Considering the importance of oil matrix and the presence of liposomes by the presence of soya bean oil, the difference in oil composition probably explains why the mean AUC_{0–48 h} of Myoquinon was higher than the mean of Ubiquinol QH (Table 1 and Supplementary Fig. 1). Another important factor could be the presence of vitamin C in the Ubiquinol QH preparation. When we compared the mean AUC_{0–48 h} of ICT with ERG formulations, which differs only in the presence of vitamin C as additive, the mean AUC_{0–48 h} with ERG was 50% lower than with ICT, although both formulations were prepared with the same procedure and oil matrix (Supplementary Fig. 3). Taking this effect of vitamin C into consideration, the presence of 12 mg of vitamin C in the formulation of Ubiquinol QH might have affected the net incorporation of CoQ₁₀ into blood plasma. Other studies have shown that the addition of antioxidants decrease the AUC of a generic CoQ₁₀ preparation, which is the case with the addition of vitamin E [35]. Furthermore, a previous study compared a commercial solubilized preparation containing 100 mg CoQ₁₀ in soy oil with a solubilized preparation containing 100 mg CoQ₁₀ with polysorbate 80, medium chain triacylglycerols (MCTs) and 300 mg of non-esterified soybean phyosterols (Sterol CoQ₁₀) in a soft gelatin capsule. In this case, a lower, although not significant AUC was found with the Sterol CoQ₁₀ formulation [30].

To our knowledge, the only study that compared the bioavailability of the oxidized and the reduced forms of CoQ₁₀ in humans studied the chronic accumulation of CoQ₁₀ in plasma after a daily intake of 200 mg/d of CoQ₁₀ or CoQ₁₀ H₂ for 4 wk [36]. In this study, almost all CoQ₁₀ found in plasma was in the reduced form, independently of the redox nature of the compound used as a supplement [37]. Langsjoen et al. used the same oil in both formulations (diglycerol monooleate, bee wax, soy lecithin, and canola oil), whereas in our preparation, soy oil was the matrix used to solubilize CoQ₁₀ in Myoquinon, and MCTs with the addition of vitamin C for Ubiquinol QH; probably explaining our differences in bioavailability.

We cannot exclude the possibility that CoQ₁₀ H₂ can reach the liver and be retained for a longer time than CoQ₁₀. The longer lag phase found with Ubiquinol QH compared with Myoquinon could be explained by a higher retention time in both enterocytes and hepatocytes. Furthermore, after reaching C_{max}, plasma CoQ₁₀ levels with Ubiquinol QH treatment showed a slower decrease than with Myoquinon treatment (Supplementary Fig. 1). In fact, a recent study performed in diabetic rats, in which ubiquinol-10 was better absorbed in the liver and pancreas, suggests a longer retention time in these organs, which could explain the decrease found in the AUC in comparison with ubiquinone in the present study [37]. In another study performed in mice showing CoQ synthesis deficiency by mutation in the COQ9 gene, the use of water-soluble formulations of ubiquinol-10 or ubiquinol-10 showed a better incorporation of ubiquinol-10 in tissues [38]. These studies indicate the necessity to go in depth into the physiology of CoQ bioavailability to improve its incorporation into tissues.

We wanted to compare our results with previous acute bioavailability studies using CoQ₁₀; however, this is a complex task because the different time periods and doses used in the literature make a correct comparison impossible. In the present study, we found that there was a direct and very strong correlation between AUC_{0–48 h} and ΔC_{max} with independence of the compound used

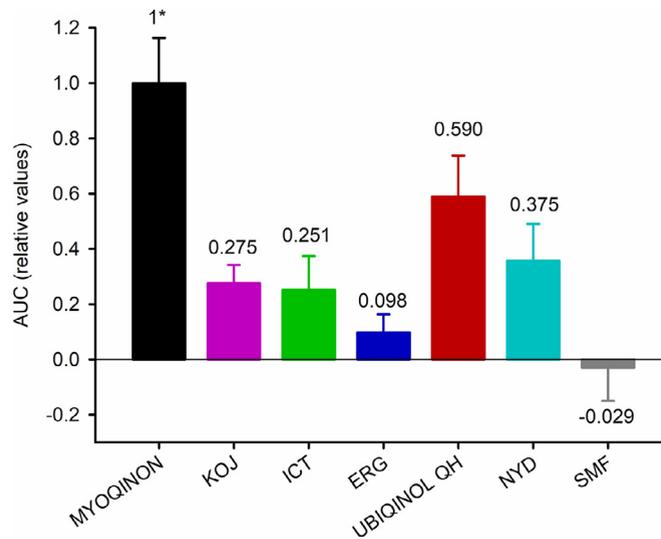


Fig. 2. Comparative relative absorption as the area under the curve (mean AUC_{0-48h}) between seven 100 mg coenzyme CoQ_{10} compositions. The highest AUC was found with Myoqinon. Values of other compounds are indicated in relative to the mean AUC_{0-48h} of Myoqinon. Error bars represent SEM. CoQ_{10} , coenzyme Q10; ERG; ICT; KOJ; NYD; SMF. *Significantly different vs. the rest of the compounds, $p \leq 0.05$.

(Supplementary Fig. 3). Using this relationship, we reviewed the literature about the acute effect of CoQ_{10} supplementation in humans (Table 4). The results shown in the present study agree with the previous study of Weis et al. [29], in which modifications of the Myoqinon formulation impaired the bioavailability of CoQ_{10} in human plasma. Furthermore, in the present study and in Weis' study, Myoqinon showed the highest increase of CoQ_{10} in plasma after a single 100-mg dose. No other preparation reached such a ΔC_{max} concentration with this dose; a similar variation of concentration was reached only with doses such as 150 [44] or 300 mg [41].

The present study also highlighted the fact that the intake of CoQ_{10} strongly depends on the individual. Explanations for this may be different microbiota, different capacity to absorb fats from the gut, or even a different metabolic capacity of the enterocytes. This observation has been confirmed in other studies with many

other formulations [27,44,41]. It seems clear that further studies are needed to clarify the physiological aspects in the different response of high-incorporating populations in comparison with low-incorporating people. This is very important in cases of CoQ_{10} deficiency such as in CoQ_{10} -synthesis deficiency [45], cardiovascular disease [42], aging [2], or sarcopenia [15]. Furthermore, the trials performed to determine the therapeutic effect of CoQ_{10} supplementation in aging and different diseases use very different dosages in small population and with short follow-up periods [46]. Most patients respond to the supplementation with oral CoQ_{10} [47]; however, the different bioavailability of CoQ_{10} requires the use of the best formulation for each individual to reach the highest level of CoQ_{10} in both plasma and tissues. More studies are needed to understand the mechanisms involved in the different bioavailability of CoQ_{10} preparations in humans.

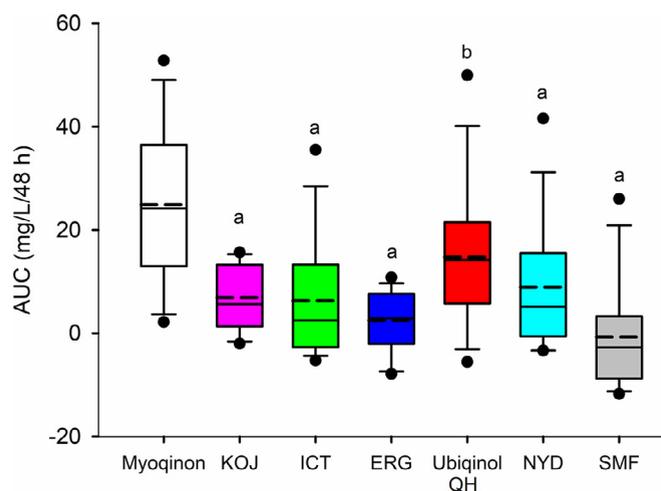


Fig. 3. Comparative AUC_{0-48h} in plasma CoQ_{10} levels in mg/L over 48 h for all formulations. The data represent the maximum, minimum, median (solid line), average, (dotted line) with SD indications for each curve. *Significantly different, $P \leq 0.05$ versus Myoqinon. [†]Significantly different, $P \leq 0.01$ versus Myoqinon. CoQ_{10} , coenzyme Q10; ERG; ICT; KOJ; NYD; SMF.

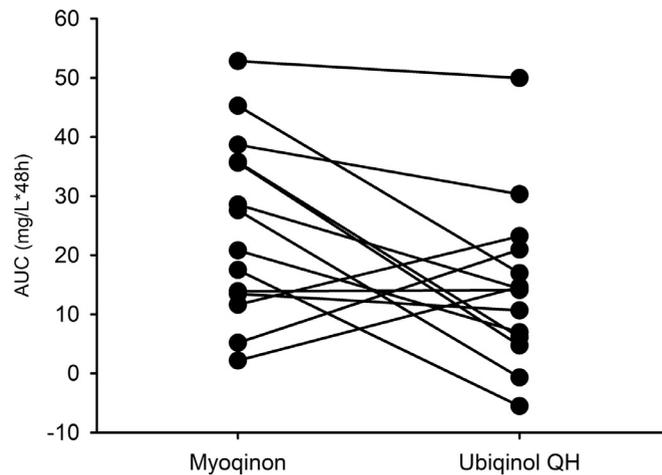


Fig. 4. AUC_{0-48h} for each participant after a single 100-mg oral dose of Myoqinon and Ubiquinol QH. Data represent the AUC_{0-48h} of each participant with both formulations. AUC, area under the curve.

Table 4

Comparative study of ΔC_{max} obtained after a single-dose experiment with different preparations of CoQ₁₀ in human studies

Study [Reference]	Participants	Preparation	Dose, mg	ΔC_{max}	SEM
Weber et al., 1997 [39]	Male, age 22 ± 1.1; N = 9	Capsule	30 mg	0.31	
López-Lluch et al. (this study)	M/F, age 18–30; N = 14 (10 M/4 F)	Soft gel Myoqinon	100	1.069	0.177
		KOJ	100	0.238	0.053
		ICT	100	0.351	0.095
		ERG	100	0.258	0.047
		Ubiquinol QH	100	0.473	0.108
		NYD	100	0.381	0.086
		SMF	100	0.181	0.097
Weis et al., 1994 [29]	M/F, age 24–30; N = 10 (5 M/5 F)	Hard gel	100	0.775	0.185
		Soft gel Bioqinon	100	1.454	0.285
		Soft gel	100	0.837	0.186
		Soft gel	100	0.883	0.186
Wajda et al., 2007 [40]	M/F, age 26.71 ± 6.8 (12 M/12 F)	Capsule	100	0.025	
		NanoSolve	100	0.103	
Young et al., 2012 [30]	Male, age 18–40; N = 36	Soft gel	100	0.259	0.025
		Soft gel + sterols	100	0.189	0.034
Molyneux et al., 2004 [27]	Male, age 21–28; N = 10	Q-gel, Soft gel	150	0.506	
		Soft gel	150	0.277	
		Capsule-liquid	150	0.197	
		Capsule-powder	150	0.175	
		Capsule-liquid	150	0.152	
		Capsule-liquid	150	0.149	
		Chewable tablets	150	0.120	
		Q-gel (2 × 30 mg)	60	0.267	
Molyneux et al., 2007 [41]	Male, age 20–26; N = 8	Q-gel (5 × 30 mg)	150	0.802	
		Q-gel (10 × 30 mg)	300	1.010	
		Q-gel (3 × 100 mg)	300	0.518	
		Capsule	250	0.490	0.129
Martinefski et al., 2016 [42]	M/F, age 18–40; N = 6 (3 M/3 F)	Liquid	250	0.980	0.103
		Chewable wafer	600	0.770	
Constantinescu et al., 2007 [35]	M/F, mature; N = 25 (15 M/10 F)	Chewable wafer + vit E	600	0.660	
		Soft gel	600	0.690	
		Hard capsule	600	0.660	
		Powder	333	0.980	
Lucker et al., 1984 [43]	M/F, age 31.9; N = 10 (5 M/5 F)	Kaneka QH, soft gel, ubiquinol	150	1.061	
Hosoe et al., 2007 [44]	Male, age 34.2 ± 4.6; N = 5	Kaneka QH, soft gel, ubiquinol	300	2.506	

ERG; ICT; KOJ; NYD; SMF

Conclusion

The present study demonstrated that the bioavailability of CoQ₁₀ formulations depends on the individual and on the type of excipients used for solubilization of CoQ₁₀. In the present study, the seven tested formulations showed large and significant

differences in bioavailability. Although our results are only applicable to the compositions used in this study, they highlight the complexity of CoQ₁₀ bioavailability in humans. Even in highly effective compositions, individuals show different responses depending on unknown physiological factors probably including lifestyle, weight, body mass index, sex, and age. Special attention must be paid to

the elderly, one of the main target populations for CoQ₁₀ supplementation. Therefore, the present study strongly suggested the necessity of testing the efficacy of any CoQ₁₀ supplementation in humans by the analysis of CoQ₁₀ levels in plasma to find the most effective preparation for each patient.

Acknowledgments

The authors acknowledge Pharma Nord, Denmark for its generous support and for supplying the compounds and the different formulations used in this study. They acknowledge the volunteers for participating in this study and their patience. They also acknowledge the Cell Physiopathology and Bioenergetics Laboratory and especially Juan Carlos Rodríguez-Aguilera for his help in the development of HPLC CoQ₁₀ analysis. The research group is also funded by the Andalusian Government grant BIO177 (FEDER funds of European Commission).

Supplementary data

Supplementary data related to this article can be found at doi:10.1016/j.nut.2018.05.020.

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