Graphical Review

Border between natural product and drug: Comparison of the related benzoquinones idebenone and coenzyme Q_{10}

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A B S T R A C T

Coenzyme Q_{10} is a ubiquitous component of cellular membranes and belongs to the class of benzoquinones that mainly differ with regards to the length and composition of their hydrophobic tail. The characteristic quinone group can accept electrons from various biological sources and is converted by a one electron transfer to the unstable semiquinone or by a two electron transfer to the more stable hydroquinone. This feature makes CoQ_{10} the bona fide cellular electron transfer molecule within the mitochondrial respiratory chain and also makes it a potent cellular antioxidant. These activities serve as justification for its popular use as food supplement. Another quinone with similarities to the naturally occurring CoQ_{10} is idebenone, which shares its quinone moiety with CoQ_{10}, but at the same time differs from CoQ_{10} by the presence of a much shorter, less lipophilic tail. However, despite its similarity to CoQ_{10}, idebenone cannot be isolated from any natural sources but instead was synthesized and selected as a pharmacologically active compound in the 1980s by Takeda Pharmaceuticals purely based on its pharmacological properties. Several recent clinical trials demonstrated some therapeutic efficacy of idebenone in different indications and as a consequence, many practitioners question if the freely available CoQ_{10} could not be used instead. Here, we describe the molecular and pharmacological features of both molecules that arise from their structural differences to answer the question if idebenone is merely a CoQ_{10} analogue as frequently perpetuated in the literature or a pharmaceutical drug with entirely different features.

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Abbreviations: CoQ, coenzyme Q; DMD, Duchene Muscular Dystrophy; ETC, electron transport chain; NQO1, NAD(P)H-quinone oxidoreductase 1; ROS, reactive oxygen species

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Introduction

Universally present in human cells, coenzyme Q_{10} (CoQ_{10}) is a ubiquitous component of all cellular membranes. However, its best studied function lies within the mitochondrial energy producing system as an electron transport molecule. With only some rare exceptions CoQ_{10} is therefore essential to life. CoQ_{10} belongs to a class of compounds that are characterized by their quinone moiety but differ in length and composition of their hydrophobic tail (Fig. 1). The characteristic quinone group can accept electrons from various biological sources and is converted by a one electron transfer to the unstable semiquinone or by a two electron transfer to the more stable hydroquinone (Fig. 2). This feature makes CoQ_{10} the bona fide cellular electron transfer molecule within the mitochondrial respiratory chain. In addition, CoQ_{10} is also described as a potent cellular antioxidant. This activity, together with lower CoQ_{10} levels during ageing and some diseases serve as justification for its common use as food supplement. It is of interest that CoQ_{10} is only one among a large range of very similar molecules that are involved in a multitude of cellular functions. Many 1,4-benzoquin none-containing molecules similar to CoQ_{10} are selectively synthesized by cells from bacteria to eukaryotic cells. These molecules harbour different tail length ranging from 0 (CoQ_{0}) to 10 (CoQ_{10}) isoprenyl units. For example, the predominant form of coenzyme Q in rats is CoQ_{8} compared to CoQ_{10} in humans (Fig. 1). While the ubiquinone moiety present in CoQ_{10} is the major quinone in cells of animal origin, plants use an entirely different quinone moiety (plastoquinone) for photosynthesis, while still using CoQ_{10} within their mitochondria.

A synthetic quinone with similarities to the naturally occurring CoQ_{10} is idebenone (Fig. 1). Idebenone shares its quinone moiety with CoQ_{10}, but at the same time differs from CoQ_{10} by the presence of a much shorter, less lipophilic tail. However, despite its similarity to CoQ_{10}, idebenone is not synthesized by any organism and can therefore not be isolated from any natural sources. Thus, idebenone is a novel chemical entity, which was selected from a medicinal chemistry programme conducted in the 1980s by Takeda Pharmaceuticals as a pharmacologically active compound purely based on its pharmacological properties. Here, we describe the molecular and pharmacological features of idebenone that are shared with and at the same time separate it from CoQ_{10} to answer the question if idebenone is merely a CoQ_{10} analogue as frequently perpetuated in the literature or a drug with entirely different pharmacological properties.

Pharmacokinetics

Despite the structural relatedness of CoQ_{10} and idebenone, both molecules differ significantly in their physicochemical properties (Fig. 1) (Table 1). The ten isoprenyl units of the tail (50 carbon atoms) of CoQ_{10} make this molecule practically insoluble in aqueous solutions, which is represented by a partition coefficient of nearly 20 [1]. Idebenone on the other hand has a much shorter tail (10 carbon atoms) and unlike CoQ_{10}, also harbours a terminal hydroxyl group which provides the molecule with polarity. Both of those features are responsible for a partition coefficient of 3.9 for idebenone, which leads to a much higher solubility in aqueous solution. It is this difference in solubility that is largely responsible for all the functional differences between two molecules that are discussed in detail below.

It has to be stressed that CoQ_{10}, unlike idebenone, is a physiological molecule that is synthesized by all cells of the body. The biosynthesis of CoQ_{10} is complex and shares some of the early steps with the cholesterol synthesis pathway [2]. Due to the very high lipophilicity of CoQ_{10} eleven specialized enzymes are presently known. These enzymes are crucial for the biosynthesis of the lipophilic CoQ_{10} and hand the synthetic intermediates of CoQ_{10} from one enzyme to the next. As a final step, these enzymes ensure that CoQ_{10} is effectively inserted into cellular membranes as no soluble form of CoQ_{10} exists [2]. Consequently, dietary CoQ_{10} faces a number of hurdles with regards to transport to reach its proposed site of action in cellular membranes. Despite its frequent use as food supplement, there are only few reports on the pharmacokinetics of CoQ_{10} in humans. Dietary CoQ_{10} is slowly absorbed from the intestinal tract, evidenced by a plasma T_{max} of 6–8 h [3] and it is eliminated with a half-life of about 33 h [4]. A second plasma peak was described to occur about 24 h after oral administration, which likely reflects enterohepatic recycling. There is some suggestion that using chronic ingestion of high doses via the diet can increase CoQ_{10} concentrations at least in heart and brain tissue of rodent models [5], although it has to be noted that CoQ_{10} and not CoQ_{10} is the predominant form found in rodents. In rodents CoQ_{10} levels are kept at about 10% of those of CoQ_{9} under physiological conditions and it is long known that dietary CoQ_{10} is converted back to CoQ_{9} in rats [6]. Furthermore, there is some evidence for metabolism of dietary CoQ_{10}, which highlights that the results described above cannot be easily translated to the human situation where CoQ_{10} is the predominant quinone. Consequently, due to the lack of data of CoQ_{10} metabolite production, reliable information on tissue levels for dietary CoQ_{10} is not available.

Based on the synthetic nature of idebenone, detailed investigations that took metabolic conversion into account by separately measuring the intact idebenone and metabolites provided reliable data for unmodified idebenone levels in plasma and tissues. Studies in animal models have demonstrated a wide biodistribution of intact, unmetabolized idebenone with the highest levels found in liver and kidney and the lowest in heart and brain [7]. In patients, idebenone is rapidly absorbed with a t_{max} of 1–3 h and also eliminated faster than CoQ_{10}, with a half-life between 10 to 13 h [8]. Although there is uncertainty around the relevance and accuracy of CoQ_{10} measurements and metabolism, the reported pharmacokinetic differences between idebenone and CoQ_{10} are likely a direct consequence of the major difference in solubility of both molecules.

Fig. 1. Chemical structure of the two quinones CoQ_{10} and idebenone. The ten isopren unit-containing side chain of CoQ_{10} is responsible for major differences in solubility and molecular weight and as a consequence bioactivation. MW: molecular weight; LogD: partition coefficient at physiological pH.
described that the respiratory and phosphorylating activities of
brate. However, when using a complex II substrate, the authors
centration-dependent manner when using a complex I sub-
brain mitochondria that idebenone decreased state 3 respiration in
also demonstrated that in line with CoQ10, reduced idebenone is
roles in the electron transport chain

The most prominent role of CoQ10 is as an electron carrier in
the mitochondrial electron transport chain (ETC). Under physio-
nical conditions, CoQ10 accepts electrons mainly from complexes
and II and transports them to complex III. Upon donating the
electrons to complex III, CoQ10 is able to be reduced by complexes
negatively impact on cellular energy levels, which is evidenced by
spiratory activity used isolated mitochondria. Since we now know
that idebenone also facilitates important redox-functions outside
ponents of the reported CoQ10-deficiency disorders. Biochemical evidence suggests that throughout this cyclic electron
transport process CoQ10, due to its highly lipophilic nature, is
firmly anchored to and embedded within in the inner mitochon-
drial membrane.

Given the structural similarity to CoQ10 at the level of the
quinone moiety (Fig. 1), it was always assumed that idebenone
also has similar properties with regards to cellular electron
transport. Contrary to this notion however, there is evidence that
in the presence of physiological levels of mitochondrial CoQ10,
idebenone directly modulates mitochondrial respiration and en-
ergy production, which suggest that idebenone has characteristics
that are distinct from those of CoQ10. It has to be noted that the
majority of reports that observed effects of idebenone on res-
spiratory activity used isolated mitochondria. Since we now know
that idebenone also facilitates important redox-functions outside
the mitochondria [9], these studies using isolated mitochondria
not only misrepresent the activity of idebenone but are also re-
sponsible for many conflicting reports, Therefore only the most
relevant studies will be mentioned briefly below.

Roles in the electron transport chain

Sugiyama et al. [10] were the first to observe in isolated rat
brain mitochondria that idebenone decreased state 3 respiration in
a concentration-dependent manner when using a complex I sub-
strate. However, when using a complex II substrate, the authors
described that the respiratory and phosphorylating activities of
isolated mitochondria were left unchanged. Sugiyama et al. [10]
also demonstrated that in line with CoQ10, reduced idebenone is
rapidly converted back to the oxidized quinone form through
oxidation by complex III of the respiratory chain. Although ide-
benone markedly inhibited complex I–III (NADH-cytochrome c
reductase) activity in this system, the authors also reported a
surprising stimulation of complex I activity by idebenone.
However, given the low basal NADH-ubiquinone reductase activity
observed, rather than measuring mitochondrial complex I activity,
it is more likely that other quinone oxidoreductases such as NQO1
were detected, which co-purified with the mitochondrial pre-
paration [9]. Overall, despite the use of different experimental
systems by different investigators, there is consensus that idebe-
none is an efficient substrate for the complexes II and III and in
contrast to CoQ10, a relatively slow substrate for complex I [10–12];

Idiebenone as complex I inhibitor

In fact, more than just being an inefficient substrate, multiple
studies consistently detected inhibition of complex I by idebenone,
in contrast to the function of CoQ10 [10–17,19,20]. Recent data
confirm this inhibitory activity of idebenone using the sophisti-
cated electrochemical detection of proton translocating activity
of isolated mitochondrial membranes [16]. This inhibition of complex
I by idebenone is thought to be based on the slow release of re-
duced idebenone from the CoQ10 binding site within complex I,
which therefore interferes with the physiological reduction of
CoQ10 [15]. One possible explanation for this inhibitory activity is
based on the size of the quinone binding pocket of complex I. The
long lipophilic tail of CoQ10 safely secures the molecule in the
mitochondrial membrane, while still allowing the quinone moiety
to enter into the quinone binding pocket of complex I. Idebenone
on the other hand can be expected by its much shorter tail to
completely enter the binding pocket, which likely results in a
much longer time within the pocket [15]. This difference in tail
size and the arising difference in its interaction with complex I
make idebenone, quite contrary to CoQ10, a competitive inhibitor
of complex I.

Activation of alternative pathways by idebenone

Given the importance of complex I for energy production, it
appears counterintuitive that inhibition of complex I by idebenone
could be associated with any beneficial therapeutic effects, unless
idebenone could compensate this inhibition by utilizing other
metabolic pathways to generate energy. In fact, there is evidence
from several studies that idebenone can activate different complex
I-independent metabolic pathways. One of those idebenone-

Fig. 2. Schematic representation of quinone bioactivation mainly by two-electron reduction (two red circles). While activation of CoQ10 preferentially occurs via the mi-
tochondrial electron transport chain (mETC), idebenone is activated to the hydroquinone by the cytoplasmic NQO1 reductase. In contrast, one electron reduction (one red
circle) to the unstable semiquinone is mostly done by the Cyp450 family in the absence of two-electron-transferring reductases and is not a favourable pathway as it
remains in these cells.
preferred pathways facilitates complexes II–III based respiration; a mechanism that could support mitochondrial energy production in the presence of dysfunctional complex I [11]. Indeed, this activity was substantiated and later extended by several reports illustrating that idebenone utilizes and activates further complex I-independent metabolic pathways in the presence of CoQ₁₀ [1,9,17,18] (Fig. 3). One of those is the glycerophosphate (G3PDH) shuttle. This mechanism supplies extra energy from a non-mitochondrial source into the mitochondria and is predominantly active in tissues with high energy demand. First described by James et al. [12] and studied in more detail by Rauchova et al. [17,19,20], idebenone efficiently activates this metabolic pathway in vitro and in vivo in the presence of physiological levels of CoQ₁₀ by a so far unknown mechanism.

An additional idebenone-dependent metabolic pathway that transfers energy equivalents from the cytosol directly into the mitochondrial respiratory chain, was reported recently [1,9,18]. Here, upon entering the cell, idebenone is efficiently reduced by the cytoplasmic enzyme NADH-quinone oxidoreductase 1 (NQO1) as part of the cellular response to detoxify quinones and to prevent production of ROS. The resulting active form of idebenone subsequently enters the mitochondria to become re-oxidized by complex III of the mitochondrial electron transport chain. In line with this “catalytic” model of repeatedly donating electrons derived from the cytosol directly to complex III, idebenone is able to directly circumvent complex I–III-dependent electron transport [9,18] (Fig. 3). Indeed, under conditions of acute rotenone treatment, which efficiently inactivates complex I function and abolishes cellular energy levels, this NQO1-dependent activation of idebenone is able to increase mitochondrial membrane potential and restore cellular ATP levels in the presence of physiological levels of CoQ₁₀ (Table 1) [1,9,18].

Overall, in the presence of CoQ₁₀, idebenone treatment leads to a shift away from complex I-dependent respiration towards alternative pathways that either use complex II dependent substrates or utilize cytoplasmic electron equivalents, which are fed directly into complex III. The combined results of this idebenone-modified metabolism lead to a largely complex I-independent form of respiration. It is again important to state that the ability of idebenone to activate these alternative pathways is absolutely dependent on a balanced solubility that allows it to shuttle between cytosol and mitochondrial membranes [1]. Consequently, at present there is no evidence to suggest that dietary CoQ₁₀ can activate the alternative modes of energy production described for idebenone above. Given that complex I dysfunction is the major cause of mitochondrial dysfunction in a multitude of disorders ranging from classic mitochondrial diseases to neuromuscular disorders such as Duchene Muscular Dystrophy (DMD) and neurological disorders such as glaucoma [21], this functional difference between CoQ₁₀ and idebenone rationalizes the use of idebenone.

### Antioxidative activities of idebenone and CoQ₁₀

The naturally occurring CoQ₁₀ is described by numerous reports as a potent physiological antioxidant (reviewed by Littarru and Tiano [22]). Within the cell, CoQ₁₀ can detoxify radicals and is important to protect cellular membranes against lipid peroxidation. This information is based on the study of human CoQ₁₀ deficiency disorders that are associated with low levels of CoQ₁₀, high levels of ROS and most importantly, which can be treated with exogenous CoQ₁₀ supplementation. Consequently, CoQ₁₀ is widely used in indications that are thought to be associated with

### Table 1
Summary of structural and mechanistic differences between CoQ₁₀ and idebenone.

| Parameter                        | CoQ₁₀         | Idebenone     |
|----------------------------------|---------------|---------------|
| **Chemical formula**             | C₂₀H₃₆O₄      | C₁₉H₃₀O₅     |
| **Molecular weight (g/mol)**     | 863.49        | 338.44        |
| **Solubility; log D (pH 7.4)**   | 19.12         | 3.91          |
| **Ability to cross membranes**   | No            | Yes           |
| **In vivo t<sub>max</sub>**      | 6–8 h         | 1–3 h         |
| **In vivo t<sub>1/2</sub>**      | About 33 h    | 10–15 h       |
| **Complex I inhibitor**          | No            | Yes           |
| **Complex II substrate**         | Yes           | Yes           |
| **Complex III substrate**        | Yes           | Yes           |
| **Reduction by NQO1**            | very low      | Yes           |
| **Activation of G3PDH shuttle**  | Not reported  | Yes           |
| **Rescue of ATP levels in the absence of functional complex I (the higher the better)** | 93 ± 5% | 45 ± 7% |
| **Reduction of lipid peroxide levels (the lower the better)** | 0%  | 106%        |
| **Effect on mitochondrial membrane potential (APₜₚᵣ) (ΔΨ) ** | 106% | 116%        |
| **Proposed mode(s) of action**   | Membrane-localized antioxidant, electron transport activity in mitochondrial respiratory chain | Antioxidant in multiple cellular compartments; redox function and energy rescue via alternative pathways |

Fig. 3. Schematic representation of the different electron transport pathways favoured by the two quinones CoQ₁₀ and idebenone. Black arrow: favoured pathway; grey arrow: minor pathway.
liped peroxidation impaired the activity of complexes II, III and V, reported a direct anti-oxidative activity of idebenone treatment with both molecules. This obviously harbours the pos-
markers of oxidative stress in intact organisms in response to
duced mitochondrial dysfunction was also tested in human tissue
idebenone also protected complex II activity against ROS-induced injury in this system [37]. The authors noted that this protective effect was dependent on the conversion of idebenone into the reduced quinol form by the respiratory chain.

It is important to point out that evidence for the antioxidant activity of both idebenone and CoQ10 are largely derived from in vitro and ex vivo studies. The few studies that looked at anti-
activity in vivo did so by demonstrating reduced bio-
makers of oxidative stress in intact organisms in response to
in treatment with both molecules. This obviously harbours the pos-
sibility that both molecules could prevent oxidative stress by in-
direct mechanisms such as the upregulation of endogenous anti-
oxidative defence mechanisms. However, at least one paper has
reported a direct anti-oxidative activity of idebenone in vivo using
electron spin resonance in the presence of CoQ10 [26], which
suggests that at least idebenone can act as a bona fide antioxidant in vivo.

Overall, most biochemical studies agree that both CoQ10 and idebenone can inhibit the generation of reactive oxygen species (ROS), however, given the differences in solubility and therefore cellular localization of both molecules, no information is available if their antioxidative activities are restricted to only certain cellular compartments. In this context, it is important to point out that nearly all described antioxidant effects of idebenone have been demonstrated in systems that display physiological levels of CoQ10. Positive effects of CoQ10 administration in cells with physiological levels of CoQ10 could suggest that the amount or localization of quinone, CoQ10 or idebenone, are the rate limiting factors for de-
toxification of ROS and that the quinone-dependent antioxidative activity is not saturated under physiological conditions. However, it could also suggest that idebenone is able to detoxify ROS in a manner distinct from that of CoQ10 or that the conditions for bioactivation of both molecules differ significantly based on their significant physicochemical differences described above.

Differences in bioactivation

It is important to point out that both idebenone and CoQ10 are only active as antioxidants or electron donors in the fully reduced hydroquinone form [32]. Therefore, both molecules can be regarded as pro-drugs that require bioactivation to become anti-
oxidants. For their function as electron donors, the same require-
ment applies since only the activated hydroquinones can donate electrons into the electron transfer chain. Consequently, next to tissue distribution and cellular concentrations of both molecules, bioactivation appears to be a rate limiting step for their specific activities. In this context the extreme difference in the solubility of both molecules has to be remembered. As a consequence of its very high lipophilicity, CoQ10 is only present within cellular membranes [38], while idebenone with its much lower lipophilia-
city is found equally distributed in mitochondria and cytoplasm as shown for example in brain tissue [7,39]. This difference in local-
ization determines the access of both molecules to different re-
ductases that localize to different cellular compartments. After
entering the cell, idebenone, with its much higher solubility compared to CoQ10 is rapidly and exclusively activated by NQO1
[9]. On the other hand reduction of CoQ9 within mitochondrial membranes is dependent on the activity of the respiratory com-
plexes I and II. Despite a report that CoQ10 can also be activated by
NQO1, this activity, if at all specific, is at least 1000-fold lower compared to the reduction of idebenone by NQO1 [9,40] and it is
likely that extra-mitochondrial CoQ10 is reduced by another re-
ductase altogether [41]. Therefore, in the context of mitochondrial disorders, it appears likely that efficient reduction of CoQ10 cannot be achieved since this bioactivation is largely dependent on intact mitochondrial activity. On the other hand, based on its mode of
bioactivation by cytoplasmic NQO1, idebenone can still be effi-
ciently reduced under conditions of mitochondrial dysfunction since NQO1 utilizes mitochondria-independent electron equiva-
Ients that are generated for example by glycolysis in the
cytoplasm.

Can idebenone substitute for CoQ10?

As pointed out before, most studies on the activities of idebe-
none have been carried out in cells and tissues that contained physiological levels of CoQ10. Although, reduced CoQ10 levels have been described for the process of ageing, for most mitochondrial disorders and also in nearly all experimental systems where idebe-
none was tested, there is no evidence to suggest that CoQ10 levels are altered. Measurable results of idebenone-treatment therefore indicate that either idebenone has different protective activities compared to those of CoQ10 or that under physiological conditions only suboptimal levels of CoQ10 are available. The latter option would imply that idebenone simply acts by substituting for CoQ10. This possibility was tested and López et al. [42] clearly showed that in cells deficient in CoQ10 biosynthesis, idebenone was unable to substitute for CoQ10 in terms of normalizing elec-
tron flow or restoring ATP levels, which are the main functions of

cellular CoQ10. Similar results were obtained in CoQ10 deficient
cell lines that have a genetic deficiency of only quinone and idebe-
none was also unable to rescue viability [43]. These pre-clinical results are strongly supported by a report of idebenone supplementation in a patient with CoQ10 deficiency syndrome [44]. After switching a young patient with a CoQ10 deficiency syndrome from CoQ10 supplementation to idebenone, his clinical and metabolic symptoms worsened mark-
edly. Only after returning the patient to CoQ10 supplementation did his condition return to the state before idebenone treatment had commenced [44]. In another case, a patient with Leigh disease was treated with CoQ10, which coincided with a worsening of his
condition that only normalized after commencing treatment with idebenone instead [45]. These results highlight that idebenone cannot be used as a CoQ10 replacement and that the protective activities of idebenone are unrelated to the activities shared with CoQ10. Based on these functional differences CoQ10 can therefore also not substitute for idebenone.

Conclusions

Based on their partial structural relatedness, CoQ10 and idebenone share the ability to act as potent antioxidants and to donate electrons to complex III of the ETC. Beyond this however, both in aqueous solutions. This feature leads to different subcellular bioactivation and modulation of cellular energy production mainly dependent on mitochondrial function, while idebenone is bioactivated via complex I-independent pathways. Therefore, based on the current mitochondrial function. As another consequence of different mo- nendent on mitochondrial function, while idebenone is bioacti-

Confl cation of interest

N. Gueven acts as scientific consultant to Santhera Pharmaceuticals (Switzerland) that seeks to obtain market authorization for the use of idebenone in several neuromuscular indications. K. Woolley and J. Smith have no conflicts of interest to declare.

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