Original Research Article

Investigation into the prophylactic and therapeutic activity of coenzyme Q10 against COVID-19

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Abstract

Purpose: To evaluate the anti-SARS CoV-2 effect of Coenzyme Q 10, Ubiquinol-10, and idebenone, which have beneficial therapeutic applications against diverse virus types, using molecular docking approach.
Methods: The potential activity of Coenzyme Q10, Ubiquinol-10, and Idebenone against viral infections was explored through the collection of data from relevant literature, and by modelling these compounds virtually, using in silico investigation methods.
Results: Coenzyme Q10 and ubiquinol-10 showed significant docking performance. They interacted with numerous amino acid residues of the main protease of SARS-CoV-2 ACE2 (7C8J), Alpha thrombin (1AE8), TYRO (4TS1) protein targets sides, SARS-coronavirus Orf7a accessory protein (1XAK), TNF (1RJ8), and Cytokine/receptor (1I1R).
Conclusion: The findings of our study showed promising inhibitory activities of the selected compounds against the main proteases of SARS-CoV-2. Consequently, these compounds have theoretical effects on inhibiting the viral entry, reproduction, and ultimately the prevention and/or treatment of the SARS-CoV2 infection.

Keywords: SARS-CoV-2, Docking, Coenzyme Q10, Ubiquinol-10, Idebenone

INTRODUCTION

The recently emerged virus, SARS-CoV-2, is categorized under the family of coronaviruses and has been found to be responsible for the recent severe acute respiratory syndrome [1]. The infectious nature of this novel virus is attributed to its ability to invade the human respiratory system besides other body systems, and cause infectious symptoms [2]. After a series of investigations, scientists discovered that after the virus binds to the protein receptor, the pathological cascade commences. The receptor was confirmed to be the angiotensin-

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converting enzyme-2 (ACE2) [1]. This highly transmissible virus needs to bind to its receptor in order to fulfil its entry, function, and pathogenic effects on the host by a yet unknown mechanism. The virulent characteristics of this individual coronavirus are responsible for the recent pneumonia pandemic [3]. The virus invades the human respiratory system after inhalation of the contaminated air with its droplets, and afterwards, it binds itself to the cells receptors (ACE2) with the aid of its spike proteins and the cellular protease (TMPRSS2) for priming. Inside the host's cells, un-coating, genome transcription, translation, and eventually the replication processes are activated [4]. The ACE2 and TMPRSS2 receptors are distributed in the gastrointestinal system include the upper part of the esophagus, large intestines, and the liver. This might explain the vast discrepancies in the symptoms as well as the organ systems hit by SARS-COV-2. Symptoms might range from asymptomatic to mild/moderate, to even severe life-threatening scenarios [5]. Viral activation leads to the appearance of inflammation markers and interferon's type I (IFNs), which is widespread and also accelerates the phagocytosis of the viral antigens [6]. Many therapeutic modalities that interfere with these inflammatory pathways have been developed to mitigate the symptoms of SARS-COV-2. The repositioning of this natural product is a challenging strategy that could help find a novel therapeutic lead compound with minimal side effects [7]. While searching several potential antiviral candidates, Coenzyme Q10 (CoQ10) appears to be one of the promising phytomedicines possessing biological properties capable of tackling SARS-COV-2. CoQ10 is a natural Quinone which occurs in biosynthesized form, is in abundance, exists in variable aerobic microorganisms and most importantly, also exists in mammals. This valuable substance serves as a cofactor in the mitochondrial respiratory process, and shares the same activity with vitamin E with regards to skin integrity boost and regeneration. Moreover, CoQ10 enhances energy, strengthens immunity, and has anti-oxidation activity. A recent study found that patients who suffer from acute influenza had lower concentrations of CoQ10 compared to patients in the control group. It was also found that CoQ10 concentration in influenza cases are linked somehow to numerous inflammatory biomarkers such as IL-6, which have been taken in consideration in studying the pathogenesis of influenza [8].

The correlation pattern between CoQ10 on the one hand and the inflammatory markers on the other hand, reflects the link between the injury and the response in acute influenza patients. It is concluded therefore that CoQ10 is a pivotal therapeutic agent in treating influenza [9]. CoQ10 is a nutraceutical with good acceptance, due to its anti-oxidant activity and protective function in various biological processes, either physiological or pathological. Up to this point, numerous studies confirmed the anti-inflammatory properties of CoQ10 [9]. Therefore, finding safe and effective treatments for SARS-COV-2 is crucial. In this paper, we investigate the possibility of the prophylactic and therapeutic activity of Coenzyme Q10 against SARS-COV-2.

This study aims to explore Coenzyme Q10 as a prophylactic and a probable therapeutic agent against SARS-COV-2, and to review literature that supports the prophylactic use of Coenzyme Q10 for its immunomodulatory action, to combat the cytokine storm, and to aid anti-viral activity as well as anti-inflammatory effects.

METHODS

Primary data

Retrieval and preparation of the target structures

A different receptor and target binder were selected in this study; where the structure of 3-chymotrypsin-like cysteine protease (3CLpro), and protein (PDB ID: 6WQF) were placed in a resolution of 2.30 Å, the spike receptor-binding domain of the target virus (SARS-COV-2) to bat the angiotensin-converting enzyme-2 (ACE2, PDB ID: 7C8J) in a resolution of 3.18, Human α-thrombin inhibition (EOC-D-PHE-PRO-AZALYS-ONP) was put in a resolution of 2.00 Å, and the crystalline structure of the enzyme tyrosyl-T/RNA synthetase (mutation with deletion) in a complex with tyrosine and at a resolution of 2.50 Å, were obtained from Research Collaborator for Structural Bioinformatics (RCSB) protein databank (http://www.rcsb.org).

To start with, protein preparations were analyzed using different parameters, including the assignment of their charge, solvation, and the volume of their fragments using the UCSF Chimera Version 1.15 [9]. Further optimization of the protein molecules took place using the AutoDock4 Tool for molecular docking [9].

Preparation of ligands

Coenzyme Q10, Ubiquinol-10, and Idebenone (Table 1 and 2), were acquired from PubChem

compound database in the Inch key (InChI) format.:

- https://pubchem.ncbi.nlm.nih.gov/compound/Coenzyme-Q10;
- https://pubchem.ncbi.nlm.nih.gov/compound/9962735;
- https://pubchem.ncbi.nlm.nih.gov/compound/3686.

ACD/Chemsketch program was used to generate the two-dimensional (2D) structured ligand, and it was saved in the mol-file format. Using the Open Babel toolbox, the ligands were converted into three-dimensional structures [10].

Molecular docking

The docking was done using the Swiss Dock Tool (the molecular docking program) [11] to identify the possible inhibitors within the different target sites. A genetic algorithm (Lamarckian) with predetermined parameters was used to assess the docking for interactions between the protein and the ligand. A 257 was set as an overall number of poses. Poses were extra clustered via an all-atom RMSD limit of 0.3 Å to eliminate redundancy along with, on average. All additional parameters for both docking and scoring were set as default. The rigid protein structure was saved at every step, and UCSF Chimera was used to perform all the docking poses and interaction analysis [11].

Secondary data

Attention was mostly focused on existing Coenzyme Q10, Ubiquinol-10, and Idebenone, preclinical and clinical results from diverse databases as PubMed and EMBASE. The search terms for all databases were Coenzyme Q10, Ubiquinol-10, and Idebenone, SARS-COV-2. The search terms for PubMed and EMBASE, selected in various combinations, were Anti-inflammatory effect of Coenzyme Q10, Ubiquinol-10, and Idebenone, Anti-viral activity of Coenzyme Q10, Ubiquinol-10, and Idebenone, Immunomodulatory action of Coenzyme Q10, Ubiquinol-10, and Idebenone, and Cytokine storm of SARS-Cov-2, and SARS-COV-2. We included published articles, without limitations, that evaluated the Anti-inflammatory and anti-viral activity of Coenzyme Q10. Figure 1 shows the present work scope where we are interested in the interventional use of Coenzyme Q10 as a prophylactic agent against SARS-COV-2.
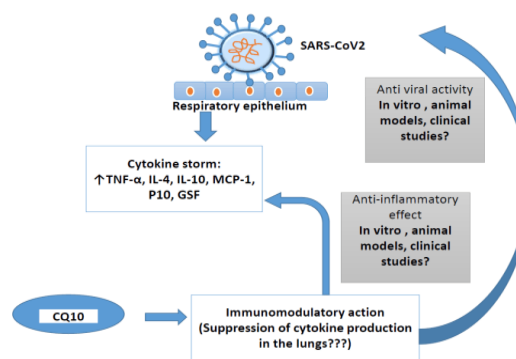

Figure 1: The scope of the present study

RESULTS

Based on the binding affinities ΔG (kcal/mol), of Coenzyme Q10, Ubiquinol-10, and Idebenone in the protein target sites, were found to be different across Alpha thrombin (1AE8), Main protease SAR-CoV-2, SARS-CORONAVIRUS (1XAK), TNF (1RJ8), and Cytokine/receptor (1I1R) with $F_{(2, 768)}$ = 1316.458, 14.645, 5.051, 9.067 and 52.622 respectively, with P value= <0.001, and .007 for SARS-CORONAVIRUS (1XAK). Tukey multiple comparisons, which was performed at a significant level of 0.05, determined that the mean average binding affinity for the Ubiquinol-10 towards Main protease SAR-COV-2 (M = -8.4862, SD = .36415, N = 257) was significantly lower compared with the Coenzyme Q10 (M = -7.2063, SD = .36284, N = 257) and Idebenone (M = -7.0223, SD = .32882, N = 257), while the mean average binding affinity for the Ubiquinol-10 towards Alpha thrombin (1AE8) (M = -7.5033, SD = .42944, N = 257) was significantly lower than that for the Idebenone (M = -7.3150, SD = .40251, N = 257). Additionally, main average binding affinity of Coenzyme Q10 towards SARS-CORONAVIRUS (1XAK), Cytokine/receptor (1I1R), and TNF (1RJ8) was significantly lower than that of Idebenone, while there were no significant differences between Coenzyme Q10 and Ubiquinol-10. While there were no significant differences in binding affinity between Ubiquinol-10 and Coenzyme Q10 towards Alpha thrombin (1AE8), there were also no significant differences in binding affinity between Coenzyme Q10, Ubiquinol-10 and Idebenone towards TYRO (4TS1) and ACE2 (7C8J). The actively interacted amino acid residues with the model ligands are shown in Tables 1 and 2 and Figure 2.

Physicochemical characteristics, bioavailability and the GIT absorption of the possible inhibitors are shown in Table 3. Where data showed

Table 1: Details of molecular docking analysis

Compound Name	CAS No.	Main protease (Mpro) (6WQF)) Amino acid residues	ACE2 (7C8J) Amino acid residues	Alpha thrombin (1AE8) Amino acid residues	TYRO (4TS1) Amino acid residues	SARS-CORONAVIRUS (1XAK) Amino acid residues	TNF (1RJ8) Amino acid residues	Cytokine/receptor (1I1R) Amino acid residues
Coenzyme Q10	303-98-0	PHE^{264}, THR^{111}, PRO^{252}	CYS^{337}, PHE^{338}, GLY^{339}	GLU^{39}, GLN^{38}, LYS^{36}	PRO^{129}, VAL^{132}, ILE^{76}	GLY^{27}	LEU^{354} PRO^{328}, ALA^{357}	ARG^{137}, VAL^{145}
Ubiquinol-10	992-78-9	THR^{111}, PHE^{264}, ARG^{105}	ASP^{494}, LYS^{676}, ILE^{679}	MET^{32}, ARG^{67}, ILE^{82}	VAL^{132}, ASP^{131} ALA^{72}	TRP^{5}, HSE^{4}	LEU^{354} PRO^{328}, PHE^{329}	ARG^{137}, PHE^{47}
Idebenone	58186-27-9	THR^{26}, THR^{25}, THR^{24}	LEU^{673}, MET^{640}, LEU^{642}	MET^{84}, GLU^{89}, SER^{48}, TRP^{51}	VAL^{132}, ASP^{131}, THR^{165}	GLY^{27}	PRO^{328}, MET^{279}	ILE^{46}

Table 2: Binding affinity Estimated ΔG (kcal/mol)

Solvent type		Mean± Std	ANOVA P-value	(I) F	Multiple Comparisons Tukey (J) F	Sig.
Main protease SAR-COV-2	A	-7.21±0.3	<0.001	A	B	<0.001
	B	-8.49±0.3			C	<0.001
	C	-7.02±0.3		B	C	<0.001
	-	-		-	-	-
ACE2 (7C8J)	A	-7.42±0.4	.458	-	-	-
	B	-7.41±0.4		-	-	-
	C	-7.35±0.4		-	-	-
	-	-		-	-	-
Alpha thrombin (1AE8)	A	-7.46±0.3	<0.001	A	B	0.410
	B	-7.50±0.4			C	<0.001
	C	-7.32±0.4		B	C	<0.001
	-	-		-	-	-
TYRO (4TS1)	A	-7.02±0.4	.257	-	-	-
	B	-7.02±0.3		-	-	-
	C	-6.96±0.4		-	-	-
	-	-		-	-	-
SARS-CORONAVIRUS (1XAK)	A	-5.73±0.3	.007	A	B	.816
	B	-5.74±0.2			C	.044
	C	-5.66±0.2		B	C	.008
	-	-		-	-	-
Cytokine/receptor (1I1R)	A	-6.90±0.3	<0.001	A	B	.201
	B	-6.85±0.3			C	.032
	C	-6.98±0.3		B	C	<0.001
	-			-	-	-
TNF (1RJ8)	A	-7.20±0.3	<0.001	A	B	.001
	B	-7.09±0.3			C	<0.001
	C	-6.88±0.3		B	C	<0.001
	-			-	-	-

*A; Coenzyme Q10, B: Ubiquinol-10, C: Idebenone; All data are normally distribution according to Shapiro-Wilk normality test; N=257

clearly that the bioavailability of Coenzyme Q10 and Idebenone is 0.85, whereas Ubiquinol-10 has low bioavailability with 0.17. On the other hand, the rate of absorption by the GI was found to be high for Idebenone compared to Coenzyme Q10 and Ubiquinol-10, which have lower absorption rates.

DISCUSSION

The emergence and spread of coronavirus (SARS-CoV-2), due to its harmful effects on health, the economy and other life aspects, led the World Health Organization (WHO) to term it a pandemic. This puts the scientific community worldwide under a considerable challenge, prompting scientists to collaborate and make extraordinary effort to rapidly detect and formulate effective SARS-COV-2 remedies. The main protease enzymes (3CLpro) have been sequenced, and this genetic information is necessary, as the virus requires this protein for

Table 3: Physicochemical analysis of potential inhibitors

| Compound	Molecular formula	ADME properties (Lipinki's rule of five)	Value
Coenzyme Q10		Molecular weight (<500g/mol)	863.3 g/mol
	$C_{59}H_{90}O_4$	LogP (<5)	11.66
		H-bond donor (<5)	0
		H-bond acceptor (<10)	4
		Bioavailability Score	0.85
		TPSA	52.60 Å²
		Molar Refractivity	280.50
Ubiquinol		Molecular weight (<500g/mol)	865.4 g/mol
	$C_{59}H_{92}O_4$	LogP (<5)	11.85
		H-bond donor (<5)	2
		H-bond acceptor (<10)	4
		Bioavailability Score	0.17
		TPSA	58.92 Å²
		Molar Refractivity	284.21
Idebenone	$C_{19}H_{30}O_5$	Molecular weight (<500g/mol)	338.44 g/mol
		LogP (<5)	3.76
		H-bond donor (<5)	1
		H-bond acceptor (<10)	5
		Bioavailability Score	0.85
		TPSA	72.83 Å²
		Molar Refractivity	94.12
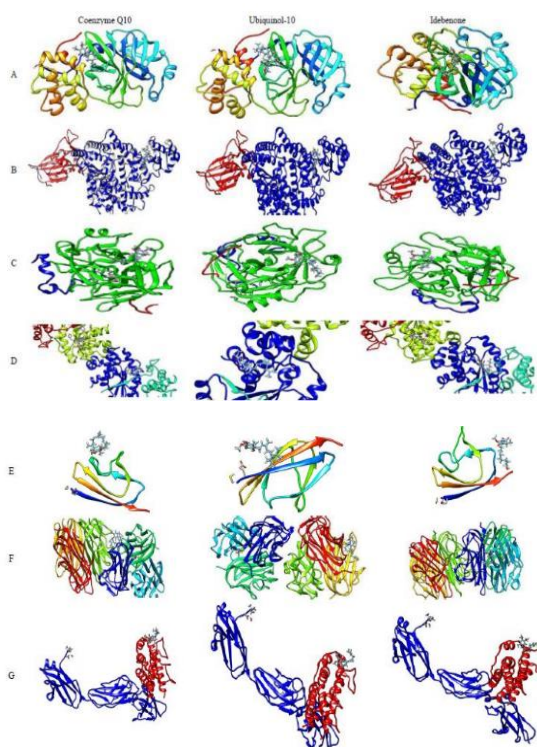
Figure 2: The seven first-rated docking poses Coenzyme Q10, Ubiquinol-10, and Idebenone. A) Snapshots of Main protease SAR-COV-2, B) ACE2 (7C8J), C) Alpha thrombin (1AE8), D) tyrosyl-T/RNA synthetase complexed with tyrosine (4TS1) protein targets sides, E) SARS-coronavirus orf7a accessory protein (1XAK)F) TNF (1RJ8), and G) Cytokine/receptor (1I1R) during the process of docking simulations. Hydrogen bonds, and other intermolecular interactions, are usually represented via yellow dotted lines

its various biological activities, including entrance and replication [2].

Also, early obtained pieces of evidence pointed to ACE2 as a SARS-CoV-2 entry receptor [12]. The importance of IL-6 refers to its role in T-helper 17 (TH17) cell generation as well as the dendritic cell to T-cell interaction. Several kinase inhibitors have been tried in seeking for a treatment for SARS-COV-2, due to their ability to inhibit the phosphorylation of the key proteins that encompass signal transduction, which eventually leads to a stimulation of the immune and inflammatory response as a result of the cellular responses to the released pro-inflammatory cytokines, including interleukin [IL]-6 [7].

The initial screening of coenzyme Q10, ubiquinol-10, and idebenone aids the rapid selection of molecules with promising therapeutic activities against the coronavirus. The annotation and elucidation of the selected compounds' mechanisms of action, and their binding affinity towards the virus were investigated using AutoDock4 software. These three compounds showed anti-viral properties when docked against alpha-thrombin (1AE8), main protease SAR-COV-2, SARS-CORONAVIRUS (1XAK), TNF (1RJ8), and Cytokine/receptor (1I1R)), as shown earlier. Our experimental output confirmed that our selected compounds have both the affinity and strength of a specific ligand. The outputs are a reflection of the numerical binding score. The molecules could interact and bind to the target protein

pocket via outstanding hydrogen bonds. These docking results were a great success despite having the least binding scores. In reading the binding-affinity results; the limits of - 6.5 Kcal/mol, in a maximum reading, are considered suitable inhibitors of enzymatic activities [3]. In the current study, Coenzyme Q10, Ubiquinol-10, and Idebenone showed more spontaneous binding with negative value of ΔG greater than -6.5Kcal/mol except against SARS-CORONAVIRUS (1XAK), which show results lower than -6.5Kcal/mol. Coenzyme Q10, Ubiquinol-10, and Idebenone could potentially inhibit viral proteins, thus preventing viral replication in the infected cells, which could improve patient recovery.

Based on binding affinities of coenzyme Q10, ubiquinol-10, and idebenone in the protein target sites, [i.e., Alpha thrombin (1AE8), main protease SAR-COV-2, SARS-CORONAVIRUS (1XAK), TNF (1RJ8), and Cytokine/receptor (1I1R)], Coenzyme Q10 and Coenzyme Q10 derivatives (Ubiquinol-10, and Idebenone) could help in the management and reduction of the severity of infection in SARS-COV-2 patients.

Ubiquinone or coenzyme Q (CoQ10) is a vitamin-like substance in human cells [8]. It is a fundamental component of the mitochondrial respiratory chain and acts as a potent antioxidant. Also, it can enhance endothelial functions by increasing bioavailability and strengthening non-specific immune responses. Many researchers have suggested that acute and chronic illnesses are associated with depletion of CoQ10 level (as in a septic shock, cardiac arrest, and acute influenza infection) [13]. So we could link the severity of SARS-COV-2 patients with the levels of CoQ10, as research by Chase et al indicated that there is a link between CoQ10 levels and cases of acute influenza, where the level of CoQ10 was found to be lower and insignificant compared to control. Additionally, the measured levels had weak but significant correlations with variable inflammatory biomarkers [8]. In acute or chronic illness, a decrease in cellular energy production and an increase in free radical levels will eventually lead to further mitochondria damage. Besides, the mentioned inflammatory biomarkers (cytokines IL-6, IL-2, and TNF) strongly correlate with SARS-COV-2 pathogenicity [14]. In chronic conditions, CoQ10 has a role in moderating the inflammatory responses related to cytokine production. CoQ10 has the supplementary benefit of suppressing the levels of inflammatory markers,

thereby prohibiting inflammatory signaling cascades [8]. There is a positive even though weak correlation between the vascular endothelial growth factor (VEGF) levels on the one hand, and CoQ10 levels on the other hand in patients who suffer from SARS-COV-2 [15]. This growth factor (VEGF) is associated with severe variable illness, shock cases, and the mortality rate of sepsis [15]. Decreasing oxidative stress is also caused by CoQ10, which can aid in curbing the lethality of myocarditis induced by the virus. In other words, it prevents cardiac damage [16]. This could positively affect SARS-COV-2 patients with severe complications in their cardiovascular systems due to the SARS-COV-2 infection. Nutritional supplements containing CoQ10 alone or added to other antioxidants have shown beneficial effects in patients with recurrent viral dermatoses and myocarditis. In the long run, it would improve the efficacy of conventional therapies and decrease both the viral load and the frequency of relapse. Supplements positively enhance immunity against viral infections and capacity of potential antioxidant activities in different organisms [17,18]. Nonetheless, promising and efficient efficacy was obtained by *in silico* experiments, and further *in-vitro* and *in-vivo* analyses are highly recommended [11].

Therefore, when a compound becomes a drug candidate, studying its pharmacokinetic properties is necessary. The bioavailability of both Coenzyme Q10 and Idebenone compounds was equal to 0.85, while it was much lower (0.17) for the Ubiquinol-10 compound. Idebenone has a higher absorption rate via GIT compared to Coenzyme Q10 and Ubiquinol-10.

CONCLUSION

There is an urgent need worldwide to find solutions to this global coronavirus pandemic, and remedies for its infection. This is now considered a primary health concern all over the world, and communities, in particular scientists, have a social and moral responsibility to combat this disease efficiently. Data from the present study indicate that cQ10, ubiquinol-10, and idebenone possess variable and potential antiviral activity against SARS-CoV-2. They also have promising benefits that could contribute to the development of a potential novel therapy for SARS-CoV-2 patients. These findings need further *in vitro* and *in vivo* investigations to confirm the activity, and develop a novel therapy.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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