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Research Article

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Inhibitory interactions of Coenzyme Q10 with selected key enzymes of glucose metabolism: An *in silico* approach

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ABSTRACT

Loss of glycemic control plays an important role in the induction of short and long term diabetic complications that have a wide prevalence around the globe. Hence, it is necessary to explore the effectiveness of synthetic and natural compounds as inhibitors of key enzymes in diabetes. The aim of current study is to screen the in silico inhibitory activity of CoenzymeQ10on enzymes such as human xanthine oxidoreductase, human glycogen synthase kinase 3-β, α-glucosidase, human aldose reductase and alpha amylase. Docking experiments were carried out on Patch Dock server and the docked complexes were analyzed using PyMol molecular viewer. The in silico experiments revealed that Coenzyme Q10 showed 3 hydrogen bond interactions with human glycogen synthase kinase 3 beta (PDB Id.:3SAY) which is an important target in the treatment of obesity-associated insulin-resistance in type 2 diabetes.

Keywords: Diabetes, enzymes, coenzyme Q10, docking

INTRODUCTION

Diabetes mellitus has both acute and chronic complications which account for morbidity and mortality[1]. It is the major metabolic disease of the world and one of the major health issues in developing countries. India lies in the first place for the prevalence of diabetes in which thirty million people are suffering due to diabetes[2]. It has been predicted that about 366 million people worldwide will be affected due to diabetes at the end of 2030[3].

CoenzymeQ10, an endogenous lipid antioxidant is being widely used as food supplement and also in cosmetics. CoQ10 is distributed in the cell membrane which helps in enhancing the production of free radical scavenging antioxidants[4,5]. Due to stress and advancing age, the level of CoQ10 would decrease gradually. Hence, CoQ10 supplementation would aid fight against ageing and ageing-associated disorders[6]. It has been proven to be effective against ulcer, diabetes, hypercholesterolemia, cardiovascular disorders and obesity[7–9]. Considering the previously proven beneficial effects of this food supplement, we intend to determine the interactions of coenzyme Q10 with enzymes significant in diabetes.

Docking of ligand into receptor and knowing the binding affinity of the molecule is much helpful in drug designing process[14]. Docking can specify the binding site of ligand to protein. Computational approach is the first step for drug discovery which also helps in reducing the cost involved[15]. The aim of current study is to screen the *in silico* inhibitory activity of CoenzymeQ10on enzymes such as human xanthine oxidoreductase, human glycogen synthase kinase 3-β, alpha-glucosidase, human aldose reductase and alpha amylase.

EXPERIMENTAL SECTION

Receptor Modeling

PDB structures of the receptor proteins used in present study were obtained from RCSB (Research Collaborator for Structural Bioinformatics) protein data bank (http://www.rcsb.org/pdb/home/home.do). The receptor proteins were prepared for docking by adding polar hydrogen atoms and eliminating water molecules.

Table 1: Receptors used for molecular docking

S. No.	Receptor	PDB Id.
1	Human xanthine oxidoreductase	2EIQ
2	Human glycogen synthase kinase 3 beta	3SAY
3	Alpha-glucosidase	3WY1
4	Human Aldose Reductase	4PR4
5	Alpha amylase	4W93

Active site prediction

The residues of ligand binding sites were predicted by submitting the pdb file in 3dligand site server (http://www.sbg.bio.ic.ac.uk/3dligandsite/). The server predicted the residues of binding site by conservation at CASP8 and homologous structures[16,17].

Ligand Modeling

PubChem database (http://pubchem.ncbi.nlm.nih.gov) was used to obtain the SMILES format of CoQ10. The 3-dimensional structure of the compound was generated by submitting the SMILES of C0Q10 on CORINA molecular networks(https://www.molecular-networks.com/online_demos/corina_demo).The files used for docking were saved in pdb format.

Table 2: Physico-chemical characteristics of coenzyme Q10

Molecule Name	Molecular formula	Molecular weight	PubChem compound Id.
Coenzyme Q10	$C_{59}H_{90}O_4$	863.34 g/mol	5281915

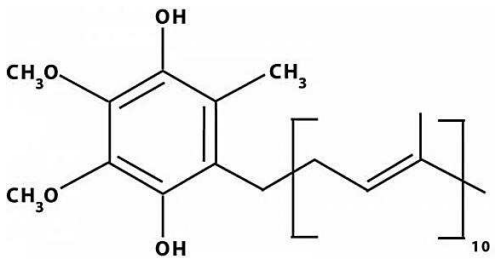

Figure 1: Coenzyme Q10

In silico docking

The PDB files of receptor and ligand were submitting on PatchDock automatic server for molecular docking(http://bioinfo3d.cs.tau.ac.il/PatchDock/).The results were retrieved through the user's e-mail address.

Visualization and analysis of docked complexes

Interactions of the molecules in the docked complexes were visualized and analyzed using PyMol molecular viewer (https://www.pymol.org/).The interacting residue and atom were differentiated by labeling the same. The hydrogen bond length was also labeled.

RESULTS AND DISCUSSION

The predicted active site residues of 4W93 are ASN-100, ARG-158, ASP-167, HIS-201. Figure 2 represents the predicted active site residue of 4W93.

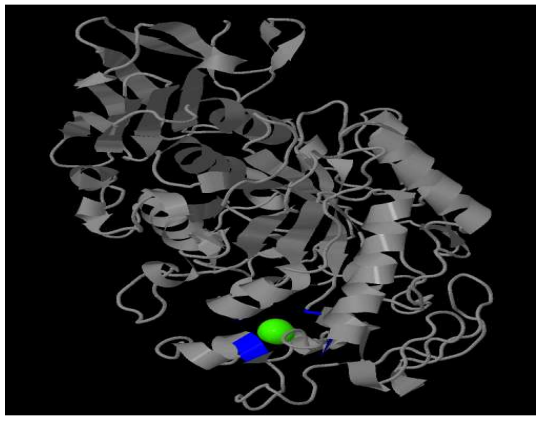

Figure 2: Active site of 4W93(Note: Predicted binding site-blue; other residues-grey)

The predicted active site residues of 4PR4 are GLY-18, THR-19, TRP-20, LYS-21, ASP-43, TYR-48, LYS-77, HIS-110, TRP-111, SER-159, ASN-160, GLN-183, TYR-209, SER-210, PRO-211, LEU-212, GLY-213, SER-214, PRO-215, ASP-216, LEU-228, ALA-245, ILE-260, PRO-261, LYS-262, SER-263, VAL-264, THR-265, ARG-268, GLU-271, ASN-272, CYS-298. Figure 3 represents the predicted active site residue of 4PR4.

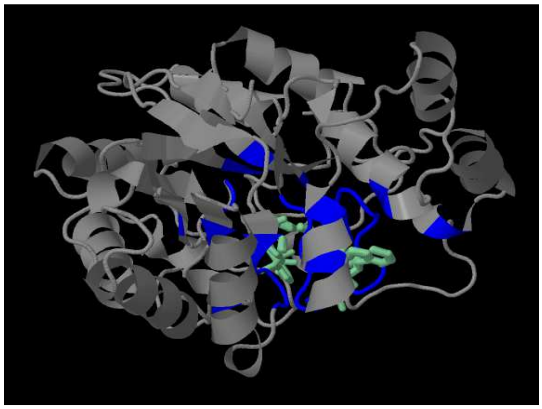

Figure 3: Active site of 4PR4(Note: Predicted binding site-blue; other residues-grey)

Table 3: Score, ACE and interacting residues of docked complexes

Receptor	Ligand	Score	Area	ACE	No. of Bonds	Residue
2E1Q	Co Q10	10176	1495.20	-290.34	Nil	
3SAY		8866	1134.20	-282.51	3	SER-147, GLY-253, GLN-254
3WY1		8186	1348.20	-435.30	1	ALA-514
4PR4		6002	931.70	-399.44	1	PHE-276
4W93		6890	897.30	-409.75	2	SER-219, ASN-220

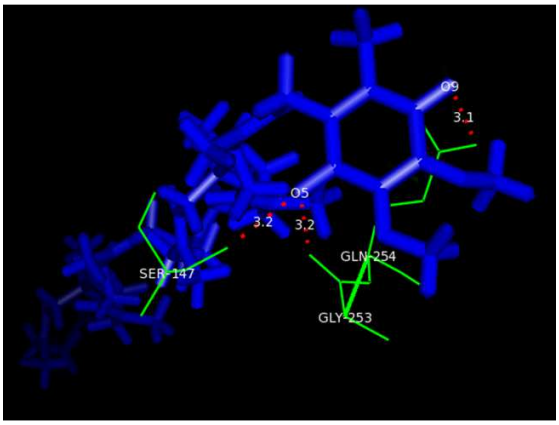

Figure 4:3SAY docked with CoQ10

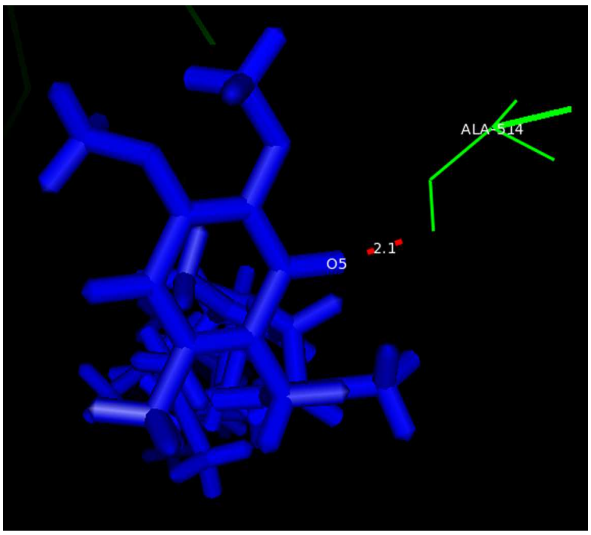

Figure 5: 3WY1 docked with CoQ10

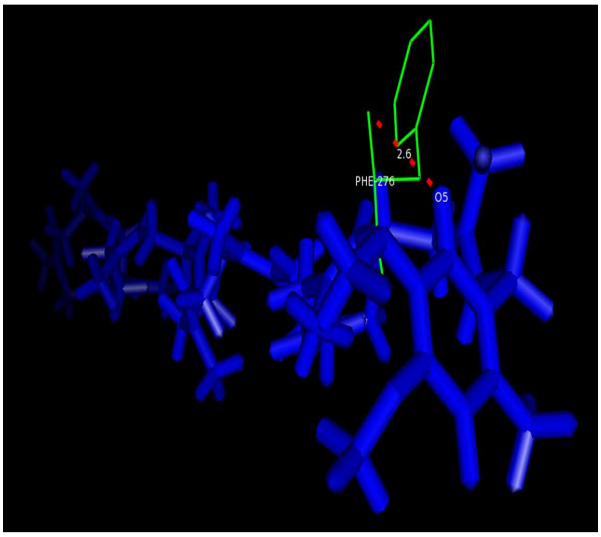

Figure 6: 4PR4 docked with CoQ10

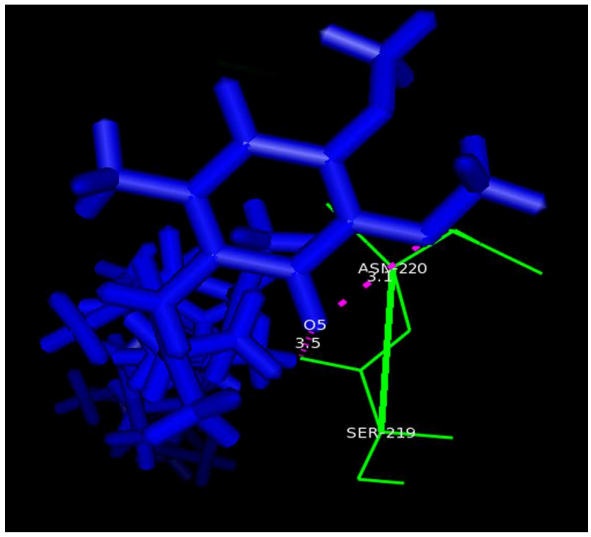

Figure 7: 4W93 docked with CoQ10

Table 4: Interacting residue and bond length of Docked complex

Docked Complex	Residue	Bond length
CoQ10 vs 2E1Q	Nil	
CoQ10 vs 3SAY	SER-147	3.2
	GLY-253	3.2
	GLN-254	3.1
CoQ10 vs 3WY1	ALA-514	2.1
CoQ10 vs 4PR4	PHE-276	2.6
CoQ10 vs 4W93	SER-219	3.5
	ASN-220	3.1

There is no interaction in the docked complex of 2E1Q-CoQ10, where as interaction between CoQ10 and 3SAY (Figure 4) forms three hydrogen bonds, CoQ10 and 3WY1(Figure 5) forms one hydrogen bond, CoQ10 and 4PR4 (Figure 6) forms one hydrogen bond, CoQ10 and 4W93 (Figure 7) forms two hydrogen bonds.The interacting residues of 3SAY-CoQ10 docked complex are namely SER-147, GLY-253, GLN-254. The interacting residues of CoQ10 and 4W93 areSER-219, ASN-220.

CoQ10 is reported to prevent and treat heart ailments, atherosclerosis, heart failure and coronary artery disease[18]. It also helps in decreasing diabetic complications by increasing the response to oxidative stress[19], decreasing serum glutaredoxin 1(Grx1) and total antioxidant capacity[20]. Human glycogen synthase kinase 3-β helps in pathogenesis of oxidative stress, mitochondrial dysfunction and disorders related to central nervous system (CNS). It also plays an important role in alternating cellular function[20,21]. Alpha amylase helps in carbohydrate metabolism[22].

CONCLUSION

Current study reveals the patterns of interaction between the chosen key enzymes of glucose metabolism and the food supplement coenzyme Q10. The 3SAY-CoQ10 docked complex possesses significant inhibitory effect which could be futher studied by specific gene expression studies in models of diabetes.

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