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Molecular docking analysis of embelin and its metal complexes as human aldose reductase (HAR) inhibitor

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ABSTRACT

In recent years regulation of the enzymatic activity of human aldose reductase (HAR) has been the main focus of investigation, due to its potential therapeutic application in Diabetes mellitus (DM). In the present study, the docking behaviour of human aldose reductase (HAR) with seven different ligands namely embelin, copper-embelin complex, zinc-embelin complex, vilangin and quercetin were evaluated along with their putative binding sites using Discovery Studio Version 3.1. Docking studies and binding free energy calculations revealed that vilangin has maximum interaction energy (-48.94 kcal/mol) and metformin with the least interaction energy (-19.52 kcal/mol) as compared to the other investigated ligands. Interestingly, copper-embelin complex fails to dock; this might be due poor protein-ligand interaction. Embelin, vilangin and quercetin showed interaction with Ser 2 amino acid residue respectively. Therefore, it is strongly suggested that the present study outcomes might provide new insight in understanding these seven ligands, as potential candidates for human aldose reductase (HAR) inhibitory activity & for the prevention of Diabetes mellitus (DM) associate disorders.

Keywords: human aldose reductase, diabetes mellitus, embelin, metformin, docking

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by insulin deficiency [1]. Mainly it is characterized by high amount of circulating glucose. In particular, type II diabetes is a serious health concern due to its escalating prevalence throughout the world. In India it is proving to be a major health problem, especially in the urban areas. In spite of all the advances in therapeutics, the high morbidity and mortality rates associated with chronic diabetic complications [2-3]. Throughout the globe, people have been affected by increased blood glucose level. Even though energy delivering body fuel is glucose, but, accumulation of glucose to unhealthy levels may lead to all life threatening problems. Treatment with natural drugs may help them to improve their life style.

The potential uses of therapeutic drugs, which are derived from plants have accelerated in recent years. Plants are rich in a wide variety of secondary metabolites, such as tannins, terpenoids, alkaloids, and flavonoids, which have been found to possess various therapeutic uses in medical and pharmaceutical fields. *Embelia ribes* is one of the most extensively researched ethnomedicinal plants for a number of years with different pharmacological actions. Bright orange embelin was isolated from *Embelia ribes* berries and it belongs to the family myrsinaceae. The plant *Embelia ribes* in addition to embelin, it contains quercitol, and fatty ingredients; an alkaloid, christembine, a resinoid, tannins and minute quantities of a volatile oil [4-6]. One of the major attractions among researchers towards quinone compounds is their color and biological activities [7]. Among all quinones, benzoquinone and its

analogues are most widely used to elicit pharmacological action. Embelin is a natural benzoquinone (2, 5-dihydroxy-3-undecyl-p-benzoquinone), found to be the active principle of *Embelia ribes* and reported to possess a wide spectrum of biological activities [8]. Bhandari and co-workers [9-10] have reported the antidiabetic, antidiyslipidemic and antioxidant activity of *Embelia ribes* Burm in streptozotocin-induced diabetes in rats. In our earlier studies, we reported the antimicrobial [11] and UVB inhibitory activity of embelin [12]. Furthermore, biological properties of Zinc and Copper (II) embelin complexes have been evaluated and reported by us [13-14]. Recently, embelin has been reported to bind with collagen [15], tyrosinase [16], human neutrophil elastase [17] and human pancreatic alpha amylase [18] using molecular docking studies.

Under the long-term hyperglycaemic condition, several possible mechanisms have been proposed to explain the pathogenesis of diabetic complications, including retinopathy, cataractogenesis, nephropathy, and neuropathy. These mechanisms include increased aldose reductase-related polyol pathway, increased advanced glycation end product formation, and excessive oxidative stress [19]. Aldose reductase is a multifunctional enzyme that reduces aldehydes. Aldose reductase (aldo-keto reductase) is the enzyme considered to play a key role in the development of secondary diabetic complications via polyol pathway. Under diabetic conditions aldose reductase converts glucose into sorbitol, which is then converted to fructose by utilizing NADPH as a cofactor and then sorbitol dehydrogenase enzyme for conversion [20-22]. This protein has been chosen because extremely high resolution x-ray structure is available. Furthermore, this protein is a target for diabetes control as it is responsible for many of the side effects of diabetes; as a result many classes of inhibitors are available. The primary emphasis in this study is on the inhibitory action of Aldose reductase, the first enzyme of the polyol pathway, which sits high in the biochemical cascade that follows the entry of excess glucose into the body [23]. *In silico* docking studies of an Human Aldose Reductase (HAR) with selected ligands was performed using Discovery Studio 3.1 software.

MATERIALS AND METHODS

Ligand structure preparation

The compounds exhibiting similar moiety were selected from the database. Chemical structures of ligands namely Quercetin [CID no: 5280459], Embelin [CID no: 3218], Vilangin [CID no: 417182], 5-O-methyl embelin [CID no: 171489] and Metformin [ChemSpider ID: 3949] were retrieved from Pubchem [24] and ChemSpider [25] compound database respectively. Unavailable three dimensional structures of Copper-embelin complex & Zinc-embelin complexes were generated using ACD [26].

Protein preparation

Crystal structures of Human aldose reductase (HAR) protein (PDB ID: 1 US0 with resolution 0.66 Å) was downloaded from the Protein Databank (PDB) (<http://www.pdb.org/>) (Figure 1). Considering all these criteria, the 3D structure of human aldose reductase protein (PDB ID: 1 US0 with resolution 0.66 Å) were prepared by removing the heteroatoms and cleaned (clean geometry) using Discovery Studio 3.1 (DS) software (Accelrys Software Inc, USA.).

Docking Studies using Discovery Studio (DS)

Docking studies were carried out on the crystal structure of HAR retrieved from Protein Data Bank using the CDOCKER protocol under the protein-ligand interaction section in Discovery Studio® 3.1 (Accelrys, San Diego, USA) [27]. In general, CDOCKER is a grid-based molecular docking method that employs CHARMM force fields. This protein was firstly held rigid while the ligands were allowed to flex during the refinement. Two hundred random ligand conformations were then generated from the initial ligand structure through high temperature molecular dynamics, followed by random rotations, refinement by grid-based (GRID 1) simulated annealing, and a final grid-based or full force field minimisation [15]. In this experiment, the ligand was heated to a temperature of 700 K in 2000 steps. The cooling steps were set to 5000 steps with 300 K cooling temperature. The grid extension was set to 10 Å. Hydrogen atoms were added to the structure and all ionisable residues were set at their default protonation state at a neutral pH. For each ligand, ten ligand binding poses were ranked according to their CDOCKER energies, and the predicted binding interactions were analysed. Furthermore, best among the ten ligand binding pose was chosen and carried out *in-situ* ligand minimization using standard protocol.

RESULTS AND DISCUSSION

DM is the most prevalent chronic disease in the world affecting most of the people in the world. DM has been proposed that the essential trace elements such as zinc, chromium or manganese, are deficient. Chronic hyperglycemia may cause alterations in the status of trace elements in the body. Therefore, trace elements may play important functions for glucose and lipid metabolisms, particularly insulin function in DM [28].

Docking studies were performed using software in order to evaluate the inhibitory effects of embelin and its metal complexes against aldose reductase, an enzyme involved in diabetic complications. Human aldose reductase [29] protein was chosen as the target protein due to their vital role in regulation of blood glucose concentration.

Docking studies and binding free energy calculations revealed that vilangin has maximum interaction energy (-48.94 kcal/mol) and metformin with the least interaction energy (-19.52 kcal/mol) as compared to the other investigated ligands. Interestingly, copper-embelin complex fails to dock; this might be generally due to poor binding phenomenon [30].

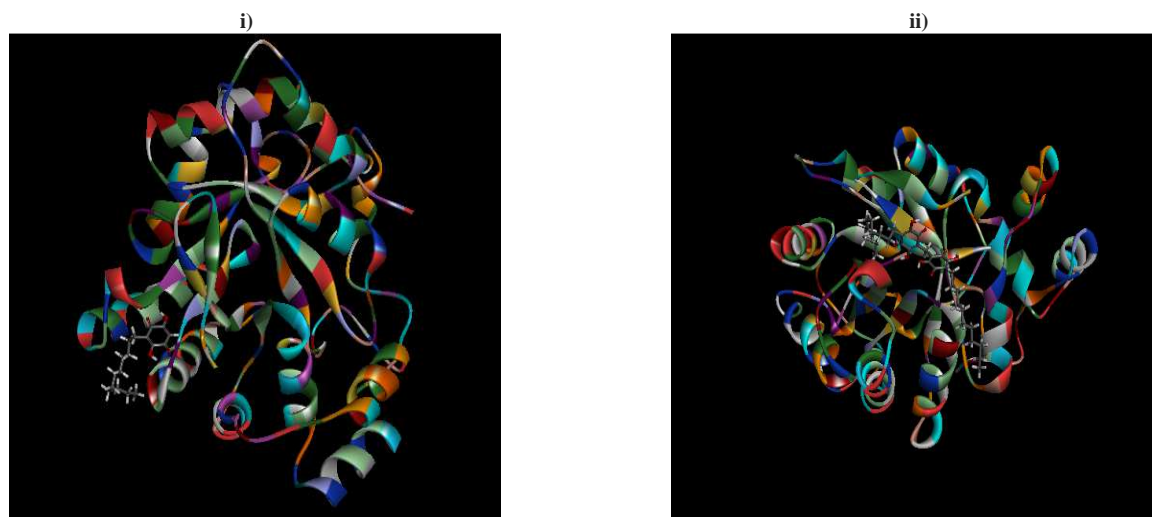
Table 1. The interaction energy analysis of six ligands (embelin, 5-O-methyl embelin, zinc-embelin complex, vilangin, quercetin & metformin) with that of human aldose reductase (PDB ID: 1 US0 with resolution 0.66 Å) using Discovery Studio® 3.1

Ligand name	cDock interaction energy* (kcal/mol)	Interaction amino acid residue	Bond distance (Å)
Embelin	30.8	Ser2	1.7
		Glu71	2.2
		Arg3 [■]	5.5
		Arg40 [▲]	2.7
5-O-methyl embelin	29.34	Arg40	1.9
Copper-embelin complex	F**	Nil	Nil
Zinc-embelin complex	46.0	Arg40 [▲]	2.6
Vilangin	48.94	Ser2	1.9
		Ser2	1.4
		Glu71	2.3 & 2.4
		Arg40	2.0
Quercetin	27.54	Val66	1.7
		Arg40 [■]	5.5 & 4.4
		Glu71	2.2
		Arg40	2.0
Metformin	19.52	Val66	2.3

(Note: *- Calculated interaction energy for the highest ranked, docking pose; after in situ ligand minimization. **- Failed to dock with protein, may be due to poor binding; ▲ - π ---sigma interaction & ■ - π ----+ interaction).

In the present study among the seven ligands studied, three ligands namely embelin, vilangin and quercetin showed interaction with Ser 2 amino acid residue respectively (Table 1). On other hand embelin (Figure 1) and 5-O-methyl embelin exhibited (π ----+) interaction with that Arg 3 amino acid residue. Mahendran et al [31] reported antidiabetic activity of embelin against alloxan induced diabetic rats. Similarly, metformin is also well known synthetic drug for diabetic treatment. However, until the present study, there is no available reported investigation for their HAR inhibitory activity with regard to their docking studies.

Figure 1. Three dimensional schematic representation of the ligands (i- embelin & ii- vilangin) with that of human aldose reductase (HAR)



CONCLUSION

The regulation of the enzymatic activity of Human aldose reductase (HAR) has been the prime focus of investigation due to its potential therapeutic application in medicinal field. Understanding and inhibiting HAR indeed would be significant in therapeutically point of view owing to its clear role in Diabetes mellitus (DM). Hence, it is strongly believed that the results of this present study might provide new insight in understanding these seven ligands as potential candidates for HAR inhibitory agents. Furthermore, the present molecular docking studies could contribute for further development and understanding of HAR inhibitors for the prevention of Diabetes mellitus (DM) associate disorders.

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