Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(2):679-682

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

HPAA inhibitory effect of embelin and its metal complexes on diabetic complications: An approach with molecular docking studies

Saba Maanvizhi[1], Radhakrishnan Narayanaswamy[2], Lam Kok Wai[3] and Arumugam Gnanamani[4*]

[1]*Faculty of Pharmacy, Sri Ramachandra University, Porur, Chennai, Tamil Nadu, India*
[2]*Laboratory of Natural Products, Institute of Bioscience (IBS), Universiti Putra Malaysia (UPM), Serdang, Selangor, Malaysia*
[3]*Faculty of Pharmacy, Universiti Kebangsaan Malaysia (UKM), Jalan Raja Muda Abdul Aziz, Kuala Lumpur, Malaysia*
[4]*Microbiology Division, Central Leather Research Institute, Adyar, Chennai, Tamil Nadu, India*

ABSTRACT

The occurrence of diabetes mellitus in the world's population is increasing every year. Most of the currently available synthetic therapeutic agents are associated with undesirable side effects. Moreover, inhibitors of pancreatic alpha-amylase are gaining much attention among the researchers owing to its therapeutic application in diabetic control and treatment. The primary objective of this study was to investigate the docking behaviour of human pancreatic alpha-amylase (HPAA) with Embelin, Vilangin, 5-O-methyl embelin, Quercetin, Metformin, Copper & Zinc embelin complexes and studying their putative binding sites using Discovery Studio Version 3.1. Docking studies and binding free energy calculations revealed that Zinc-embelin complex has maximum interaction energy (-44.6 kcal/mol) and Metformin with the least interaction energy (-13.1 kcal/mol) as compared to the other investigated ligands. Interestingly, Copper-embelin complex fails to dock with that of human pancreatic alpha amylase. Therefore, it is strongly suggested that the present study outcomes might provide new insight in understanding these six ligands, as potential candidates for human pancreatic alpha-amylase inhibitory activity.

Keywords: Diabetes mellitus, Herbal Ligands, Inhibitors, Docking,Metal Complexes

---

INTRODUCTION

More than 80% of the population of our country is dependent on medicinal plants for its primary health care.*Embeliaribes* commonly known as Vidanga,is a highly valuable medicinal plant with various pharmacological activities [1]. The plant *Embeliaribes*(Myrsinaceae)contains embelin, quercitol, and fatty ingredients; an alkaloid, christembine, a resinoid, tannins and minute quantities of a volatile oil [2-4].Embelin was isolated from *Embeliaribes* berries and one of the major attractions among researchers towards quinone compounds is their color and biological activities [5]. Bhandari and co-workers [6-7] have reported the antidiabetic, antidyslipidemic and antioxidant activity of *Embeliaribes*Burmin streptozotocin-induced diabetes in rats, using gliclazide as the positive control drug. In our earlier studies, we reported the antimicrobial [8] and UVB inhibitory activity of embelin [9]. Similarly, embelin has been reported to bind with collagen [10], tyrosinase [11], human neutrophil elastase [12] and human glutamate pyruvate transaminase [13] using molecular docking studies.

Diabetes mellitus [14] is a chronic metabolic disease affected a wide range of population all over the world and leads to development of many severe long term complications.Family history, genetic makeup, low muscle or body activity, junk food or unhealthy diet, and excess body weight usually increase the risk of a person getting affected with stress and diabetes [15]. Some of the long-term symptoms include deterioration of normal health, atherosclerosis, myocardial infarction and hyperosmolar nonketotic diabetic coma [16]. So Diabetes mellitus is one

of the major life threatening diseases worldwide and progressing at an incremental rate every year and number of research works are going on to control the disease by targeting its enzymes or proteins.

Carbohydrates and sugars are the major energy storage molecules used by living organisms. Human pancreatic alpha-amylase is one of the major enzyme (biomarker) which play a vital role in Diabetes mellitus. Alpha-amylase hydrolyzes bonds between glucose repeats. Alpha –amylase also known as 1, 4-a-D-Glucan glucanohydrolase. The structure of human pancreatic alpha-amylase has been determined to 1.8 A resolution using X-ray diffraction techniques [11]. This enzyme is found to be composed of three structural domains. Human Pancreatic α-Amylase is considered to be an important antidiabetic target [17]. Compounds inhibiting human alpha amylase have been implicated as potential therapeutic agents in the treatment of Diabetes mellitus and its related diseases. The molecular docking studies of the major bioactive compound of this *Embeliaribes* and its metal complexes like copper and zinc with Human pancreatic alpha amylase inhibiting activity has been studied in our laboratory. The present study mainly focuses on the binding affinity of embelin and its metal complexes towards alpha amylase. To check this, binding of four different quinone and its analogs to human pancreatic alpha-amylase have been studied by molecular modeling and docking. The mode of interactions of compounds with strong binding are discussed and reported here.

EXPERIMENTAL SECTION

Ligand 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 [18] &ChemSpider [19] compound database respectively. Unavailable three dimensional structures of Copper-embelin complex and Zinc-embelin complex were generated using ACD [20].

Protein preparation

The protein data bank (PDB) is a repository contains information about experimentally- determined 3-D structural data of macromolecules (such as proteins and nucleic acids) [21]. The 3D structure of Human pancreatic alpha-amylase (PDB ID: 4GQR with resolution 1.2˚A) was retrieved from Protein Data Bank (PDB) (http: /www.pdb.org/pdb/home/home.do) [22]. The protein was pre-processed separately by deleting the ligand as well as the crystallographically observed water molecules (water without Hydrogen bonds).

Docking studies

Docking studies were carried out on the crystal structure of human pancreatic alph-amylase using the CDOCKER protocol under the protein-ligand interaction section in Discovery Studio® 3.1 (Accelrys, San Diego, USA) [23]. In every docking experiment, 10 ligand conformations were generated for each ligand respectively. Highest CDOCKER interaction energy pose was chosen. And further, all the complexes were minimized using Smart Minimizer method with Generalized Born with a Simple Switching (GBSW) implicit salvation model. CHARMm force filed was used in the simulation. Binding energy of each complex was then calculated using Generalized Born with Molecular Volume Integration (GBMV) implicit solvation model with *in situ* ligand minimization.

RESULTS AND DISCUSSION

Human pancreatic alpha-amylase is an important enzyme involved in anti diabetic activity and the docking studies was carried out for an isolated compound embelin from the berries of *Embeliaribes* and its metal complexes.In the present docking studies, we identified that the effective binding site of Human pancreatic alpha-amylase with Quercetin, Embelin, Vilangin, 5-O-methyl embelin and Metformin which were retrieved from Pubchem & Chem Spider compound database was used as ligands. Among the ligands used, Metformin is considered to be synthetic standard drug and Quercetin as naturally occurring standard anti diabetic drug. Docking analysis was performed using Discovery Studio 3.1 suite to know about the favorable molecular interactions, docking score and interaction energy value. Virtual Screening has been done for all selected ligands and the best pose having highest binding energy was chosen for further *in situ* ligand minimization studies. This pose was selected as best docking result. These docking results compared that the Metformin (standard antidiabetic drug) and with Quercetin (natural compound). Metformin &quercetinhave been reported to exhibit alpha-amylase inhibitory activity [24-25]. However, until today there is no report available with regard to their docking studies.

Table 1 shows the docking studies and binding free energy calculations in which Zinc-embelin complex exhibited the maximum interaction energy (-44.6 kcal/mol). However, it did not exhibit any interaction with any of active site amino acid residues (Table 1 and Figure 1). In contrast, Metformin showed very least interaction energy (-13.1

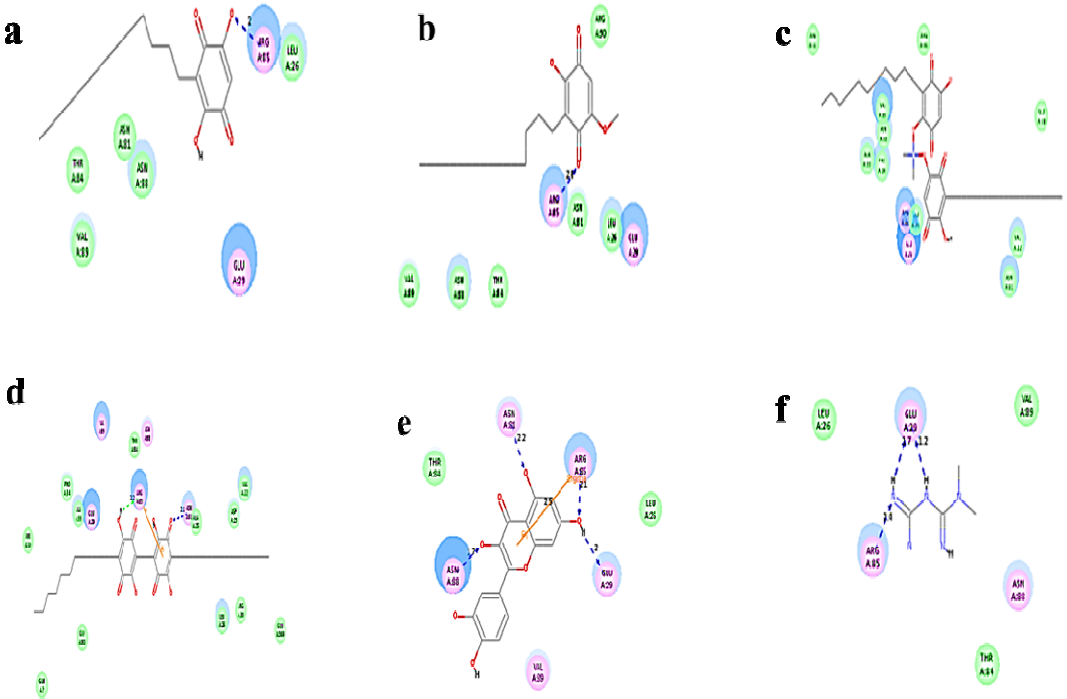
kcal/mol) compared to all other ligands and furthermore exhibited interaction with Glu 29 th&Arg 85 th amino acid residue. Interestingly, we observed that Copper-embelin complex fails to dock with that of human pancreatic alpha amylase, which might be due to poor binding property of ligand.

Table 1. The interaction energy analysis of six ligands (embelin , 5 –O-methyl embelin, zinc-embelin complex, vilangin, quercetin& metformin) with that of human pancreatic alpha-amylase (PDB ID: 4GQR with resolution 1.2 Å) using Discovery Studio® 3.1.

Ligand name	cDocker interaction energy* (kcal/mol)	Interaction amino acid residue	Bond distance (Å)
Embelin	21.3	Arg85	2.0
5-O-methyl embelin	21.7	Arg85	2.4
Copper-embelin complex**	Nil	Nil	Nil
Zinc-embelin complex	44.6	No interaction	Nil
Vilangin	40.9	Arg85 Asn81	2.2 2.1
Quercetin	21.2	Glu29 Arg85 Asn81 Asn88	2.0 2.1 2.2 1.7
Metformin	13.1	Glu29 Arg85	1.2 & 1.7 2.4

*- *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).*

Figure 1. The interaction analysis of the six ligands (a) embelin , b) 5 –O-methyl embelin, c) zinc-embelin complex, d) vilangin, e) quercetin& f) metformin) with that of human pancreatic alpha-amylase



Hydrogen atoms have been omitted in the two dimensional diagram for better clarity.
Pink line indicates the charge interaction. In addition to this, bond distances are indicated in angstroms (Å) unit).

CONCLUSION

Natural products from plants are an excellent source of Human pancreatic α-amylase (HPA) inhibitors which have therapeutic application as oral agents to control blood glucose levels. Crystallographic structure of Human pancreatic alpha-amylase was retrieved from Protein Data Bank (PDBID: 4GQR with resolution 1.2˚A) and docked with the embelinand its metal complexes. The results were analyzed. Computational ligand docking showed that inactivation depends on hydrogen bonding and π-π interactions. From the docking studies reported in this paper, we concluded that the natural products with interesting biological properties and structural diversity have often served as valuable lead drug candidates for the treatment of human diseases and also it replaces the chemically synthesized drugs which cause side effects.

REFERENCES

[1] M Mhaskar; S Joshi; B Chavan; A Joglekar; N Barve; A Patwardhan. *Current sci.*,**2011**, 100(4), 547-552.
[2] M Shahid; A Shahzad; F Sobia; A Sahai; T Tripathi; A Singh; HM Khan. *Anti-Infective Agents inMed Chem*., **2009**, 8(3), 211-225.
[3] U Bhandari; M Nazam Ansari; F Islam; CD Tripathi. *Indian J Pharmacol.*,**2008**,40(4), 152-157.
[4] RP Choudhury; A Md. Ibrahim; HN Bharathi; P Venkatasubramanian. *Electronic J Food and Plants Chem*., **2007**, 2(1), 20-24.
[5] H Nohl; W Jordan; RJ Youngman. *Advances in Free Rad Biol Med*., **1986**, 2(1): 211–279.
[6] U Bhandari; N Jain; KK Pillai. *Exp Diabetes Res*., **2007**, 2007, 15803.
[7] U Bhandari; MN Ansari. *Pharma Biol*., **2009**, 47(8), 669-674.
[8] N Radhakrishnan; A Gnanamani; AB Mandal. *Biol Med.*, **2011**, 3(2), 1-7.
[9] N Radhakrishnan; N Rajendra Prasad; A Gnanamani; AB Mandal. *Int. J.Radiat. Biol*., **2010**,88(8), 575-582.
[10] N Radhakrishnan; AGnanamani; S Sangeetha; G Rameshkumar; AB Mandal. *BMC Res Notes*, **2011**, 4, 399.
[11] N Radhakrishnan; S Ashok; V Kavitha; G Rameshkumar; AGnanamani. *J Chem Pharm Res.*,**2013,** 5(10), 320-326.
[12] N Radhakrishnan; Lam KokWai;IntanSafinar Ismail. *J Chem Pharm Res*., **2013**, 5(10), 337-341.
[13] H Cooper; K Booth; G Gill.*Health Educ Res.*,**2003**, 18(2):191-206.
[14] D Giugliano; ACeriello; G Paolisso. *Metabolism*, **1995**, 44, 363–368.
[15] AB Olokoba; OA Obateru; LB Olokoba. *Oman Med J*., **2012**, 27, 269–273.
[16] GD Brayer; L Yaoguang; SG Withers. *Protein Sci.*, **1995**, 4, 1730-1742.
[17] Sudha Ponnusamy; Smita Zinjarde; Shobha Bhargava; Urmila Kulkarni-Kale; Sangeeta Sawant; Ameeta Ravikumar. *The Nat Prod J*., **2013**, 3(1), 15-25.
[18] Anonymous. PubChem Structure. [http://www.pubchem.ncbi.nlm.nih.gov/search/search.cgi].
[19] Anonymous. Chemspider. [http://www.chemspider.com].
[20] Anonymous. ACD, ChemSketch Version 12, Advanced ChemistryDevelopment Inc., Toronto, ON, Canada, 2009 [http://www.acdlabs.com/download/chemsk.html].
[21] CALipinski; F Lombardo; BW Dominy; PJ Feeney. *Adv Drug Delivery Rev*., **2001**, 46, 3–26.
[22] HM Berman. *ActaCryst (Sect A)*.,**2008**, A64, 88–95.
[23] G Wu; DH Robertson; CL 3rd Brooks; M Vieth. *J Comput Chem*., **2003**, 24(13), 1549 -1562.
[24] P Shankaraiah; Y N Reddy. *J Med Sci*.,**2011**, 11(7), 280-284.
[25] E Lo Piparo; H Scheib; N Frei; G Williamson; M Grigorov; CJ Chou. *J Med Chem*., **2008**, 51, 3555-3561.