World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Original Article

In silico drug designing studies on dengue virus envelope protein

[1]Sushmitha H.S, [2]Balasubramanian Sathyamurthy

[1]Department of Biochemistry, Ramaiah College of Arts, Science and Commerce, Bangalore
[2]Professor, Department of Biochemistry, Ramaiah College of Arts, Science and Commerce, Bangalore

Received: 16-07-2018 / Revised Accepted: 22-08-2018 / Published:29-08-2018

ABSTRACT

The key proteins involved in causing dengue are seven major proteins, which are considered as major therapeutic targets for dengue drug development. Recent studies have reported positive for dengue virus envelope protein in dysregulation of causing dengue process in humans. Dragon fruit seed phytochemicals are reported to have antioxidant and antiviral properties. In the present study we studied the binding efficiency of 11 compounds that are present in the dragon fruit seeds with dengue virus envelope protein through *in silico* method. By our virtual screening and docking result, we found that the Compound A and Compound C have highest binding affinity with the dengue virus envelope protein and also we predicted the binding site amino acid residues and the nature of hydrogen bonding. However more *in vivo* experimental validation of our results with animal models will enlighten the development of more potent drugs from these compounds for treatment of dengue.

Key words: Envelope protein, Binding interaction, molecular docking, dengue

Address for Correspondence: Dr. Balasubramanian Sathyamurthy, **Professor, Department of Biochemistry**, Ramaiah College of Arts, Science and Commerce, Bangalore – 560054.

How to Cite this Article: Sushmitha H.S, Balasubramanian Sathyamurthy. In silico drug designing studies on dengue virus envelope protein. World J Pharm Sci 2018; 6(9): 138-143.

INTRODUCTION

*Hylocereus*the generic name of the commonly called "Dragon Fruit" belongs to the family of *cactaceae*. It is called as "Buah Naga" in Malay [1]. Dragon fruit is the native of Mexico which is now being cultivated in other parts of the world including India. Three varieties of dragon fruit are available based on the difference in the fruit pulp and peel; *Hylocereusundatus* (red peel with white pulp), *Hylocereuspolyrhizus* (red peel with red pulp) and *Hylocereusmeghalanthus*(yellow peel with white pulp) [2]. The fruit is oval in shape with small black edible seeds interspersed in the pulp [3]. In the recent times, this fruit has provoked interest as studies have proven that the fruits contain antioxidant and antimicrobial properties [4]. They have also been used in the treatment of various infectious diseases and are also used as preservatives [5]. Dragon fruit seeds were found to contain high amounts of fatty acids like linolenic acid [6]. The GC/MS studies on *Hylocereusundatus* seeds was found to possibly contain S-(-)-1,2,4-butanetriol, 2-acetate propanoic acid, tetradecanoic acid, nonanoic acid, octadecanoic acid, n-hexadecanoic acid, 9,12,15-octadecatrienoic acid, methyl-8,11,14-heptadecatrienoate, phytol, 9,12,15-octadecatrienoic acid, methyl ester, 7,10,13-hexadecatrienoic acid, 9,17-octadecadienal, 8-hexadecyne, 2-chloroethyl linoleate, 9,12-octadecadienoic acid, Cis-7-dodecen-1-yl acetate and Methyl-8,11,14-heptadecatrienoate. All of these compounds have many biological activities such as anti-microbial, anti-malarial, anti-filariasis, anti-cancerous, anti-inflammatory, anti-arthritic, anti-histamic, anti-eczemic, anti-depressant, anti-asthamatic, hypocholestremic effect and are also effective in the treatment of neurodegenerative diseases [7].

Four main serotypes of the dengue virus which are responsible for dengue are DENV-1, DENV-2, DENV-3 and DENV-4 [8]. All the serotypes of dengue contain three structural proteins and seven non-structural proteins [9]. Envelope protein is a structural protein which is involved in the viral assembly. The protein utilized for the study is the envelope protein domain III of the dengue type 4 viruses (strain Dominica/814669/1981). It is classified under structural protein immune system [10]. The envelope protein is involved in various biological activities including fusion and entry into host cells and binding to host cell receptors. The domain III of the envelope protein stimulates host immune responses by neutralizing antibodies. Hence, envelope protein is an important protein to develop vaccines [11].

Bioinformatics is an interdisciplinary branch of science, which uses statistics, computer and mathematics to analyse the biological data [12]. Protein Data Bank (PDB) is a bioinformatic tool which has large number of proteins and macromolecules stored in them [13]. Interaction of the ligand with the protein is important to develop the drugs in a pharmaceutical basis. Docking analysis gives the data for the interaction profile of the protein and the ligand [14].

This study aims to provide binding studies using computational methods on the compounds of the dragon fruit seeds and the envelope protein of the dengue virus. The main objective of this study is to obtain the best binding pose of the ligands to the protein and to compare the binding affinities of each ligand. This study could be an initiative for the formulation of the drugs against dengue virus.

MATERIALS AND METHODOLOGIES

Preparation of macromolecule envelop protein: The protein data bank (PDB) was used to obtain the three-dimensional structure of the macromolecule. PDB contains large number of proteins which are experimentally determined and stored in this site. The structures are downloaded and saved either in mm CIF or pdb format. Envelop protein of dengue virus was used for this study. The 3D structure of this protein was downloaded from PDB and saved in pdb format. The downloaded protein was viewed in Py-Mol viewer.

Preparation of ligands: Ligands selected were from the previous studies on this fruit seeds. 11 ligands were used for the study. Ligands were constructed using ChemSketch[15]. The constructed ligands were optimized to add the hydrogen bonds and the obtained structures were saved in mol for docking analysis.

Docking study: Docking studies were conducting using iGEMDOCK software. IGEMDOCK (Generic Evolutionary Method for molecular DOCKing) is a graphical-automatic drug design system for docking, screening and post-analysis [15]. The protein and the ligands were loaded and the out path was set. Standard docking parameters were used for docking (population size=200, generations=70 and no.of solutions=2). The docking process was initiated. After the docking process, the best docking pose for the individual ligands can be obtained. The best binding pose, the binding affinity and the total binding energy values were saved in the output folder. The saved files were visualized in Py-Mol viewer.

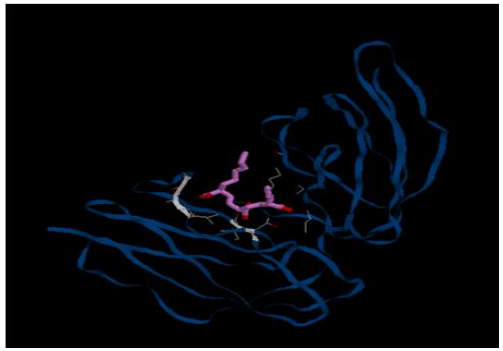
RESULTS AND DISCUSSION

Ligand	Compound name	Total Binding Energy (kcal/mol)	VanderWaal's Force (kcal/ mol)	H -Bond Energy (kcal/mol)	Electrostatic Force (kcal/mol)	AverCon Pair (kcal/mol)
A	7,10,13-hexadecatrienoic acid	- 103.4	- 62.6	- 35.0	- 5.68	- 17.64
B	9,12,15-octadecatrienoic acid	- 88.5	- 79.6	- 8.9	0	- 18.14
C	9,12-octadecadienoic acid	- 101.6	- 76.9	- 23.3	- 1.30	- 19.95
D	9,17-octadecadienal	- 71.6	- 62.7	- 8.9	0	- 20.0
E	methyl-8,11,14-heptadecatrienoate	- 77.1	- 74.2	- 2.8	0	- 23.25
F	n-hexadecanoic acid	- 75.8	- 67.8	- 8.4	- 0.52	- 23.94
G	Nonanoic acid	- 67.9	- 52.7	- 15.1	0	- 32.72
H	Octadecanoic acid	- 82.0	- 68.8	- 13.1	0	- 20.80
I	Phytol	- 75.6	- 69.0	- 6.5	0	- 22.80
J	S-(-)-1,2,4-Butanetriol	- 53.1	- 39.1	- 14.0	0	- 35.14
K	Tetradecanoic acid	- 76.8	- 57.8	- 14.9	- 4.16	- 24.56

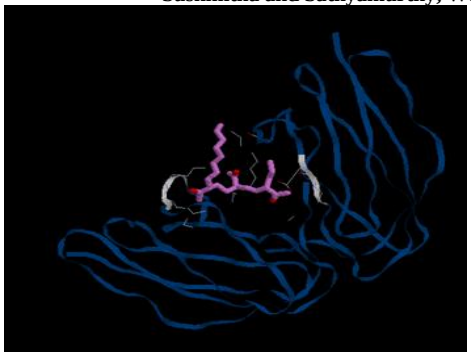
Table – 1: The fitness and the interaction profile of the envelope protein with the ligands

Ligand	Compound name	Total Binding Energy (kcal/mol)	H - Bond	Amino acid position	H - Bond Energy (kcal/mol)
A	7,10,13-hexadecatrienoic acid	- 96.94	H – M	Ile (630)	- 6.9
			H – S	Arg (619) /Lys (625)	- 7.0
B	9,12,15-octadecatrienoic acid	- 82.43	H – M	Gly (628) /Arg (629)	- 3.5
C	9,12-octadecadienoic acid	- 91.05	H – M	Ile (630)	- 6.7
			H – S	Lys (625)	- 3.5
D	9,17-octadecadienal	- 86.94	H – S	Arg(672)	- 8.9
E	methyl-8,11,14-heptadecatrienoate	- 79.49	H – M	Ile(618)	- 2.9
F	n-hexadecanoic acid	- 71.57	H – M	Glu (638)	- 3.5
			H – S	Ser(642)	- 2.5
G	Nonanoic acid	- 63.71	H – M	Ser (664)	- 7.0
			H – S	Ser (664)	- 4.7
H	Octadecanoic acid	- 75.07	H – M	Ala(610)	- 3.5
			H – S	Thr (640)	- 5.0
I	Phytol	- 86.24	H – M	Lys (625)	- 3.1
			H – S	Arg (619)	- 3.5
J	S-(-)-1,2,4-Butanetriol	- 75.54	H – M	Lys (673)	- 3.5
			H – S	Arg (672)	- 6.7
K	Tetradecanoic acid	- 75.51	H – S	Arg (619)	- 5.6

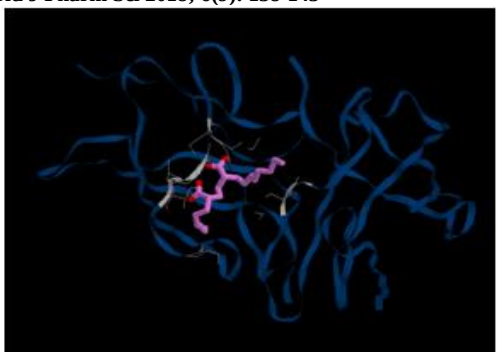
Table – 2: The cluster interaction table for the envelope protein with the ligands



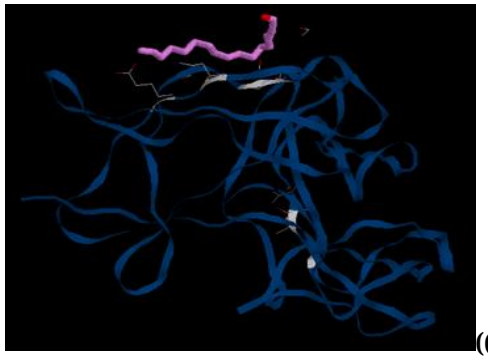
(A) 7,10,13-hexadecatrienoic acid



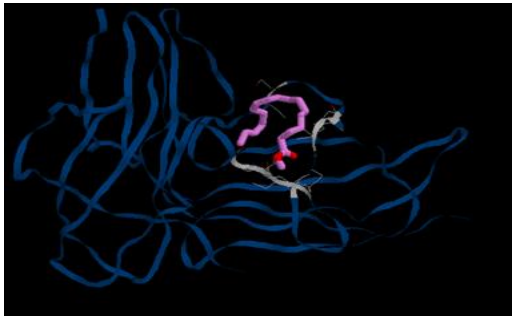
(B) 9,12,15-octadecatrienoic acid



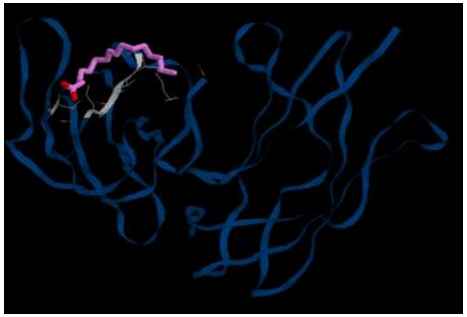
(C) 9,12-octadecadienoic acid



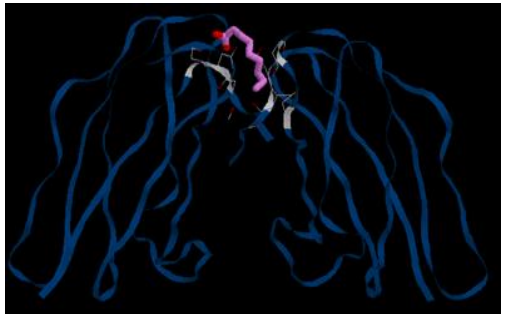
((D) 9,17-octadecadienal



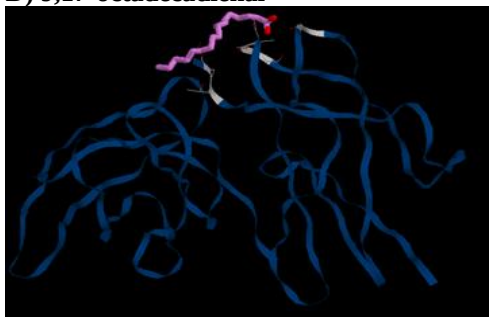
(E) methyl-8,11,14- heptadecatrienoate



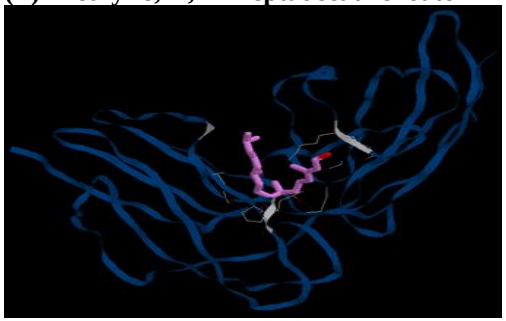
(F) n-hexadecanoic acid



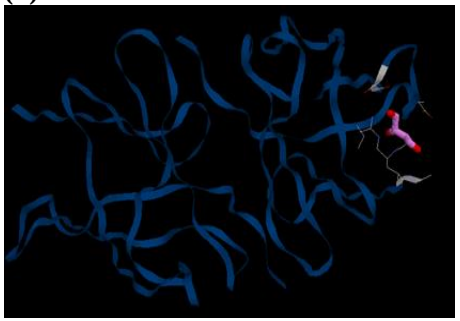
(G) Nonanoic acid



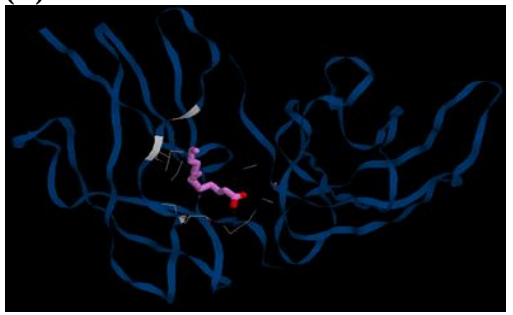
(H) Octadecanoic acid



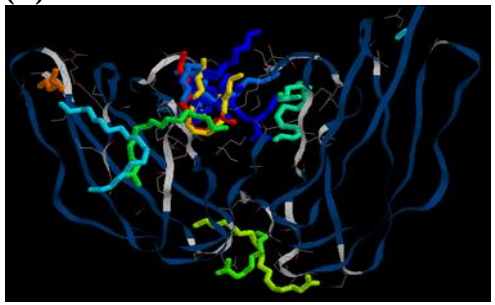
(I) Phytol



(J) S-(-)-1,2,4-Butanetriol



(K) Tetradecanoic acid



All compounds

Fig. 1: Interaction of compounds with Envelope Protein

From the Table – 1, the 3D structure coordinates of envelope protein is optimized and 11 compounds from dragon fruits seeds are identified. Their total binding energy was calculated using iGEMDOCK. Evaluation of binding conformation of 11 compounds with envelope protein is performed using iGEMDOCK. From docking study, we listed binding affinity of 11 compounds based on ligand binding energy (Table.1).The binding pose for each ligand molecule into the envelope protein is analyzed and the one having lowest ligand binding energy with envelope protein among the different poses are generated. The lower energy scores represent better target protein-ligand binding affinity compared to higher energy score. Among the 11 analogs, compound A and C are found to have lower ligand binding energy value than other analogs. Compound "A" has least binding energy score with envelope protein (binding energy value = - 103.4 kcal/mol) and compound "C" has ligand binding energy value of -101.6 kcal/mol. We further analyzed the docked pose for finding the binding mode of compound "A" and compound "C" in to envelope protein to validate the reasonable binding conformations.

Docking of compound – A into envelope protein:
From Table – 2 and Figure – 1, the docking simulation of compound - A is performed for envelope protein. From the docking study, we observed that compound – A has best binding affinity with the target envelope protein. Interaction analysis of binding mode of compound –A in envelope protein reveals that it forms three hydrogen bonds, one with branched chain residue Ile 630 having - 6.9 kcal/mol as its bond energy, one hydrogen bond is observed at Arg 619 and one at Lys 625, both of which have – 7.0 kcal/mol as bond energy. A close-up view of binding mode of compound – A with envelope protein is shown in Fig.2.

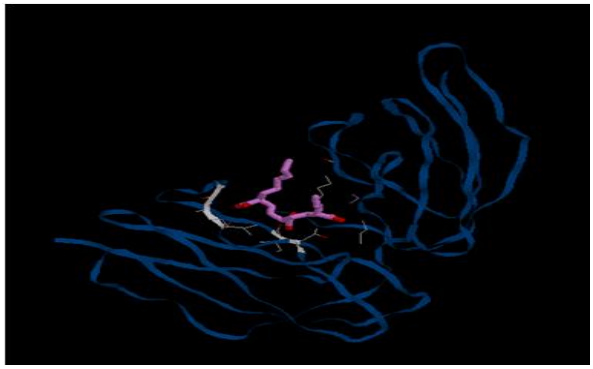


Fig. 2: A close-up view of binding mode of compound – A with envelope protein

Docking of compound - C into envelope protein:
From Table – 2 and Figure – 1, the docking studies of 11 compounds are performed for the target envelope protein. In our results on the binding conformation modes of compounds with envelope protein, compound - C shows higher affinity with the envelope protein. In examining the binding interaction and position of the compound C with envelope protein ligand binding site predicted by your docking procedure, it is found that three strong hydrogen bonds are formed, one with branched chain residue Ile 630 having - 6.7 kcal/mol as its bond energy and other two at Arg 619 and Lys 625 with – 3.5 kcal/mol as bond energy. A close-up view of binding mode of compound – A with envelope protein is shown in Fig.3.

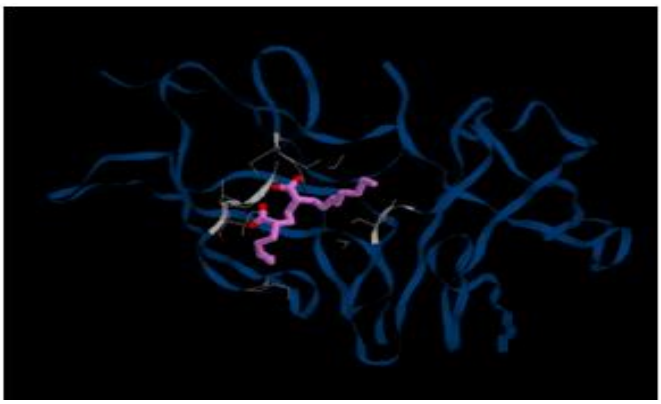


Fig. 3: A close-up view of binding mode of compound – C with envelope protein

CONCLUSION

Our molecular docking studies explored the possible binding modes of 11 compounds that are present in dragon fruit seed with envelope protein. It revealed that all the 11 compounds show minimum affinity with envelope protein. Especially the compound A (7,10,13-hexadecatrienoic acid) and compound C (9,12-octadecadienoic acid) shows best result when compared with other compounds. On comparing the binding energy and the binding site residues, we found that all compounds differ either in their binding modes or with the binding site residues for hydrogen bond formation. The conclusion drawn from our virtual screening and docking result was that the Compound A and Compound C have highest binding affinity with the Envelope Protein. Though, there are many reports on the *in vitro* analysis of these compounds and its antioxidant properties, but there are no in silico studies that predict the binding and active regions especially with envelope protein. Our study is probably the first such attempt to predict the binding site. However, validation of our results through *in vivo* and *in vitro* experiments and also with animal models will enlighten hope for the future development of more potent drugs for the treating Dengue.

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