World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 5.088

IN SILICO DRUG DESIGNING STUDIES ON DENGUE CAPSID 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.

***Corresponding Author: Dr. Balasubramanian Sathyamurthy**
Professor, Department of Biochemistry, Ramaiah College of Arts, Science and Commerce, Bangalore.

Article Received on 11/07/2018 **Article Revised on 02/08/2018** **Article Accepted on 23/08/2018**

ABSTRACT

The key proteins involved in causing dengue are the seven major proteins, which are considered as major therapeutic targets for dengue drug development. Recent studies have reported positively for capsid 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 binding efficiency of 11 compounds that are present in the dragon fruit seeds with capsid protein through Insilico methods. By our virtual screening and docking result, we found that the Compound C has the highest binding affinity with the Capsid Protein and also we predicted the binding site amino acid residues and the nature of hydrogen bonding. However more invivo experimental validation of our results with animal models will enlighten the development of more potent drugs from these compounds for treatment of dengue.

KEYWORDS: Capsid protein, Binding interaction, molecular docking, dengue.

INTRODUCTION

Pitaya belonging to the family of cactaceae is a tropical fruit which is fealy in appearance. It is a epiphytic cacti having the genus name *Hylocereus* and *Selenicereus*.[1] Pitaya is rich in nutrients like vitamin, calcium, potassium and phosphorous. It is also a source of high carbohydrate and fiber content.[2] The pulp of the fruit was shown to have antioxidants and oligosaccharides which have prebiotic properties.[3] Has compared to the pulp, peel of the fruit was reported to contain high amounts of antioxidants.[4] Some of the carbohydrates present in the fruit are cellulose, hemicellulose, lignin, arabinose, galactose, glucose, rhamnose [5]. The seeds of the fruit were found to contain high amounts of essential fatty acids such as linoleic and linolenic acid.[6] The nitrogen-containing pigment betacyanin, is the most responsible for the antioxidant property of the fruit and also for the red coloration of it.[7] The fruit was found to contain compounds such as β-amyrin, γ -sitosterol, octadecane, heptacosane, campesterol, nonacosane, trichloroacetic acid and hexadecyl. The steroids and triterpenoids have been reported to have anti-cancerous and anti-HIV activities.[8] A recent study on the methanolic extract of the seeds of pitaya (*Hylocereus undatus*) was found to possibly contain tetradecanoic acid, phytol, 9,12,15-octadecatrienoic acid, 9,12-octadecadienoic acid, 9,17-ocatdecadienal, 7,10,13-hexadecatrienoic acid, methyl-8,11,14-heptadecatrienoate, n-hexadecanoic acid, nonanoic acid and S-(-)-butanetriol.[9]

The predominant and major outbreak in India has of now has been the dengue fever which is a hemorrhagic fever.[10] Four main serotypes of dengue virus are involved in the dengue infection. All these four serotypes differ antigenically but are similar genetically.[11] The virus structure consists of seven main proteins which include both structural and non structural proteins.[12] The capsid protein is one of the structural proteins, which is involved in the encapsidation of the viral genome. The capsid protein used for this study was from dengue virus type 2 (strain Puerto Rico/PR159-S1/ 1969).[13]

Bioinformatics is an interdisciplinary.[14] and a multidisciplinary branch of science which is a combination of computer science, statistics, mathematics and biology. It uses computational method to analyse the vast biological data.[15] PDB (Protein Data Bank) is one of the bioinformatic tools which have a large storage of the 3-D structures of the proteins, ligands and other macromolecules.[16] PDB has a history of 27-years.[17] Docking analysis is an important aspect for getting the information on the interaction profile and the fitness of the protein with the ligand. The interaction of the protein with the ligands is given by the binding energy. The information on the bonds formed is also determined in

this analysis. This analysis gives a pharmaceutical basis for the drug production.[18]

MATERIALS AND METHODOLOGIES

Preparation of macromolecule Dengue Capsid 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. Dengue capsid 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 Chem Sketch.[17] 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 [17]. 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

Table 1: The fitness and the interaction profile of the dengue virus capsid protein with the ligands.

Ligand	Compound name	Total Binding Energy (kcal/mol)	Vander Waal's Force (kcal/mol)	E(pharma)	V-S ARG 41	V-S ILE 72	H -Bond Energy (kcal/mol)	Electrostatic Force (kcal/mol)	Aver Con Pair
				Z-score=>	2.00	2.22			
				W (pharma) =>	0.90	1.00			
A	7,10,13-hexadecatrienoic acid	- 99.52	- 58.35	- 110.6	-6.9	- 1.7	- 33.94	- 7.23	22.56
B	9,12,15-octadecatrienoic acid	- 92.75	- 82.23	- 92.7	0	0	- 10.5	0	20.04
C	9,12- ctadecadienoic acid	- 106.59	- 79.97	- 89.4	0	- 4.3	- 20.29	- 6.34	25.29
D	9,17-octadecadienal	- 73.96	- 73.96	- 57.4	0	- 6.2	0	0	24.95
E	methyl-8,11,14-heptadecatrienoate	- 74.39	- 70.50	- 99.5	0	0	- 3.88	0	21.15
F	n-hexadecanoic acid	- 76.57	- 55.28	- 74	0	0	- 21.30	0	25.94
G	Nonanoic acid	- 75.98	- 63.91	- 77.2	- 5.9	- 0.3	- 10.5	- 1.57	37.64
H	Octadecanoic acid	- 87.03	- 83.53	- 87.6	0	- 7.4	- 3.5	0	30.55
I	Phytol	- 87.21	- 84.43	- 76.6	0	0	- 2.79	0	28.19
J	S-(-)-1,2,4-Butanetriol	- 54.30	- 38.57	- 78	- 4.6	0	- 15.73	0	36.71
K	Tetradecanoic acid	- 83.95	- 74.44	- 94.8	- 5.2	- 10.8	- 9.50	0	35.625

Table 2: The cluster interaction table for the dengue virus capsid protein with the ligands.

Ligand	Compound name	H - Bond	Amino acid position	H - Bond Energy (kcal/mol)
A	7,10,13-hexadecatrienoic acid	H – M	Leu (46)	- 6.2
		H – S	Arg (32)	- 16.5
B	9,12,15-octadecatrienoic acid	H – M	Gly (42)	- 3.5
		H – S	Arg (41)	- 7.0
C	9,12-octadecadienoic acid	H – S	Arg (68)	- 16.6
D	9,17-octadecadienal	-	-	-
E	methyl-8,11,14-heptadecatrienoate	H – S	Asn (93)	- 3.5
F	n-hexadecanoic acid	H – M	Arg (22)	- 7.0
		H – S	Thr (25)	- 2.5

G	Nonanoic acid	H – M	Leu (44)	- 3.5
		H – S	Arg (41)	- 7.0
H	Octadecanoic acid	H – M	Gly (64)	- 3.5
I	Phytol	H – M	Gly (64)	- 2.8
J	S-(-)-1,2,4-Butanetriol	H – M	Phe (47)	- 3.5
		H – S	Arg (41)	- 10.5
K	Tetradecanoic acid	H – M	Ala (77)	- 3.5

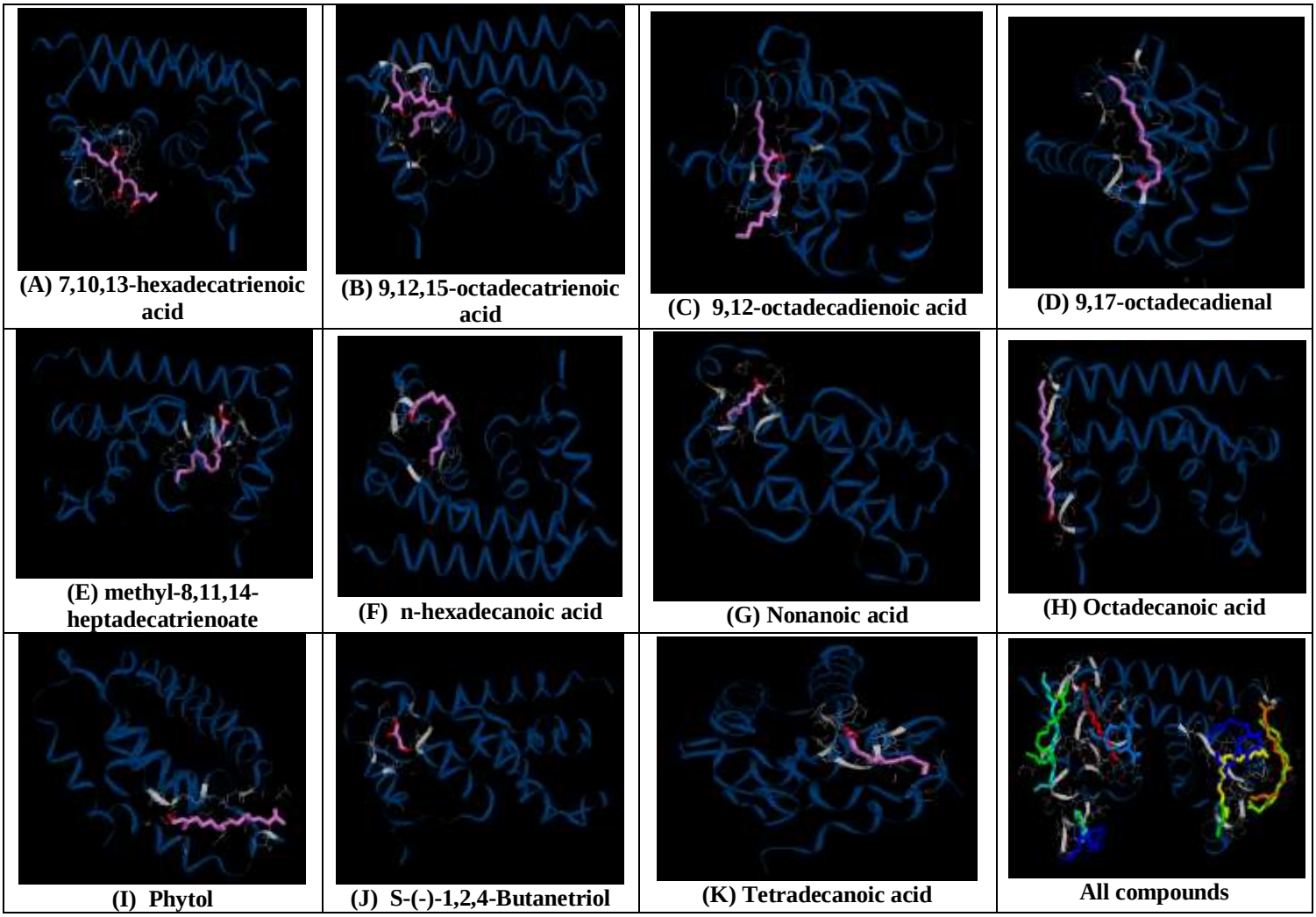

Fig. 1: Interaction of compounds with capsid protein.

From the Table – 1, the 3D structure coordinates of capsid protein is optimized and 11 compounds from dragon fruits seeds are identified. Their total binding energy were calculated using iGEMDOCK. Evaluation of binding conformation of 11 compounds with capsid 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 capsid protein is analyzed and the one having lowest ligand binding energy with capsid 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 C are found to have lower ligand binding energy value than other analogs. Compound "C" has least binding energy score with capsid protein (binding energy value = - 106.59 kcal/mol). We further analyzed the docked pose for finding the binding mode of compound "C" in to capsid protein to validate the reasonable binding conformations.

Docking of compound – C into capsid protein

From Table – 2 and Figure – 1, the docking simulation of compound - C is performed for capsid protein. From the docking study, we observed that compound – C has best binding affinity with the target protein. Interaction analysis of binding mode of compound –C in capsid protein reveals that it forms one strong hydrogen bonds, one with branched chain residue Arg 68 having - 16.6 kcal/mol as its bond energy. A close-up view of binding

mode of compound – C with capsid protein is shown in Fig.2.

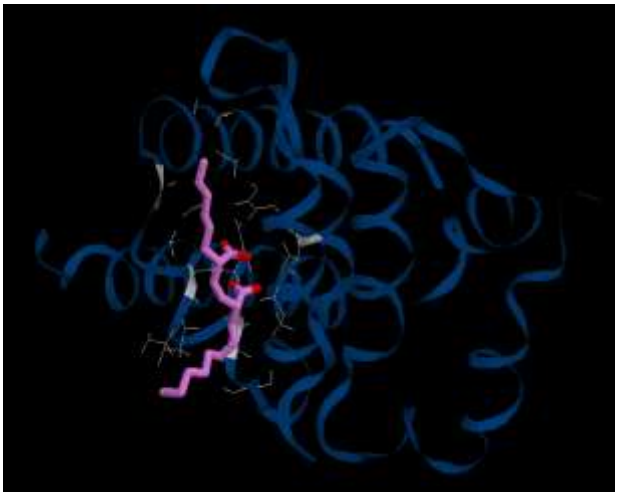

Fig. 2: A close-up view of binding mode of compound – C with capsid protein.

CONCLUSION

Our molecular docking studies explored the possible binding modes of 11 compounds that are present in dragon fruit seed with capsid protein. It revealed that all the 11 compounds show minimum affinity with target protein. Especially the 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 C has the highest binding affinity with the capsid 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 capsid protein. Our study is probably the first such attempt to predict the binding site, However validation of our results through invivo and invitro experiments and also with animal models will enlighten hope for the future development of more potent drugs for the treating Dengue.

REFERENCES

1. Mello F R, Bernardo C, Dias C O, Züge L C B, Silveira J L M, Amante E R, Candido L M B, Evaluation of the Chemical Characteristics and Rheological Behaviour of Pitaya (*Hylocereus undatus*) Peel; Fruits, 2014; 69: 381-390
2. Zainoldin KH, Baba AS, The effect of *Hylocereus polyrhizus* and *Hylocereus undatus* on Physiochemcial, Proteolysis and Antioxidant Activity in Yogurt, World Acad. Sci. Eng. Technol, 2009; 60: 361-366.
3. Wichienchot S, Jatupornpipat M, Rastall RA, Oligosaccharides of Pitaya (Dragon Fruit) Flesh and Their Prebitoic Properties, Food Chem., 2010; 120: 850-857.
4. Li-Chen W, Hsiu-Wen H, Yun-Chen C, Chih-Chung C, Yu-In L, Ja-An AH, Antioxidant and Antiproliferative Activities of Red Pitaya, Food Chem., 2006; 95: 319-327.
5. Montoya-Arroyo A, Schweiggert RM, Pineda-Castro M, Sramek m, Kohlus R, Carle R, Esquivel P, Characterization of Cell Wall Polysaccharides of Purple Pitaya (*Hylocereus* sp.) Pericarp, Food Hydrocoll, 2014; 35: 557-564.
6. Ariffin AA, Bakar J, Tan CP, Rahman RA, Karim R, Loi CC, Essential Fatty Acids of Pitaya (Dragon Fruit) Seed Oil, Food Chem., 2009; 114: 561-564.
7. Wybraniec S, Platzner I, Geresh S, Gottlieb HE, Haimberg M, Mogilnitzki M, Mizrahi Y, Betacyanins from Vine Cactus *Hylocereus polyrhizus*, Phytochemistry, 2001; 58: 1209-1212.
8. Luo H, Cai Y, Liu Tao, Yang S, Chemical Composition and *in-vitro* Evaluation of the Cytotoxic And Antioxidant Activities of Supercritical Carbon dioxide Extracts of Pitaya (Dragon Fruit) Peel; Chemistry Central Journal, 2014; 8: 1.
9. Sushmitha HS, Roy CL, Gogoi D, Velagala RD, Nagarathna A, Balasubramanian S, Rajadurai M, Phytochemical and Pharmacological Studies on *Hylocereus undatus* Seeds: An *In Vitro* Approach; World Journal of Pharmacological Research, 2018; 7(14): 986-1006.
10. Mishra B, Sharma M, Pujhari SK, Ratho RK, Gopal DS, Kumar CN, Sarangi G, Chayani N, Varma SC, Utility of Multiplex Reverse Transcriptase-polymerase Chain Reaction for Diagnosis and Serotypic Characterization of Dengue and Chikungunya Viruses in Clinical Samples, Diagnostic Microbiology and infectious Diseases, 2011; 71(2): 118-125.
11. Yung CF, Lee KS, Thein TL, Tan LK, Gan VC, Wong JGX, Lye DC, Ng LC, Leo YS, Dengue Serotype-Specific Differences in Clinical Manifestation, Laboratory Parameters and Risk of Severe Disease in Adults, Singapore. Am. J. Trop. Med. Hyg., 2015; 92(5): 999-1005.
12. Perera R, Kuhn RJ, Structural Proteomics of Dengue Virus, Curr Opin Microbiol, 2008; 11(4): 369-377.
13. Ma L, Jones CT, Groesch TD, Kuhn RJ, Post CB, Solution Structure of Dengue Virus Capsid Protein Reveals Another Fold, Proc. Natl. Acad. Sci. USA, 2004; 101: 3414-3419.
14. Mehmood MA, Sehar U, Ahmad N, Use of Bioinformatic Tools in Different Spheres of Life Sciences, Journal of Data Mining in Genomics & Proteomics, 2014; 5(2): 1000158.
15. Chowdhary M, Rani A, Parkash J, Shahnaz M, Dev D, Bioinformatics: An Overview for Cancer Research, Journal of Drug Delivery and Therapeutics, 2016; 6(4): 69-72.
16. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN, Bourne PE,

The Protein Data Bank, Nucleic Acids Research, 2000; 28(1): 235-242.
17. Ferreira LG, Ricardo N, Oliva G, Andricopulo AD, Molecular Docking and Structure-Based Drug Design Strategies, Molecules, 2015; 20: 13384-13421.
18. Al-Khaboori SA, Balasubramanian S, Kumar KM, In Silico Drug Designing on Human Protein Kinases Inhibitors, Int. J. Rec. Biotech., 2015; 3(4): 10-17.