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IN SILICO MOLECULAR DOCKING OF ANTIVIRAL DRUGS AGAINST NS3 PROTEIN OF ZIKA VIRUS

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ABSTRACT

Zika virus (ZIKV) is a mosquito borne pathogen currently causing large epidemics in Brazil. Its infection can cause microcephaly, a serious birth defect during pregnancy. The recent outbreak of ZIKV in february 2016 in Brazil realized it as a major health risk, demands an enhanced surveillance and a need to develop novel drugs against ZIKV. In this study, we performed molecular docking analysis of four known antiviral drugs such as Quinacrine, Amodiaquine, Berberine and Prochlorperazine against nonstructural 3 (NS3) protein of ZIKV using Autodock 4.2 tool. The protease activity of NS3 is necessary for viral replication and its prohibition could be considered as a strategy for treatment of ZIKV infection. Amongst these four drugs, Berberine has shown lowest binding affinity of -8.03 kcal/mol with NS3 protein. Other drugs Quinacrine, Amodiaquine and Prochlorperazine have -7.32 kcal/mol, -7.31 and -7.17 kcal/mol with NS3 protein, respectively. Further the docked complexes were analyzed through Python Molecular Viewer software for their interaction studies. Thus from the Complex scoring and binding ability it is deciphered that Berberine is more potent drug for NS3 protein of ZIKV as drug target. Observations made in this study will be useful in designing noble potent inhibitors against ZIKV infection.

***Keywords*:** Docking; NS3-protein; AutoDock4.2; Antiviral drugs; Dengue virus

INTRODUCTION

Zika virus is a mosquito-borne flavivirus that was initially recognized in Ugand, Africa (Faye et al., 2014) in 1947 in monkeys through a method that observed yellow fever. It was later distinguished in people in 1952 in Uganda and the United Republic of Tanzania. Congenital ZIKV syndrome includes microcephaly, spasticity, craniofacial disproportion, irritability, seizures and other brainstem dysfunctions (Costello et al., 2016) has caused a public health emergency of international concern (WHO, 2016). Brazil without immunity in the population saw large numbers infected immediately as the virus was amplified in the population, resulting in thousands of pregnant women infected at once. The Brazilian ZIKV strain has been shown to cause birth defects in experimental models by targeting cortical progenitor cells, inducing cell death and impairing neurodevelopment (Cugola et al., 2016). Initially the Brazilian Ministry of Health advised reporting diagnosed cases of Zika as dengue, since the symptoms were in most of the cases similar to a mild case of the latter. The first baby in the USA born with ZIKV occurred on January 16th, 2016 (McNeil, 2016). Amodiaquine (Boonyasuppayakorn et al., 2014), prochlorperazine (Simanjuntak et al., 2015), quinacrine (Shum et al., 2010), and Berberine (Shum et al., 2010) are promising drugs approved by Food and Drug Administration against dengue virus which also belong to Flaviviridae family (Tian et al., 2016). The WHO Director-General declared on February 1st, 2016 that the cluster of microcephaly cases and other neurological disorders reported in Brazil constitutes a Public Health Emergency of International Concern (Anon et al., 2016), it has therefore been identified as a problem for the entire world to deal with NS3 protein of ZIKV (Bollati et al., 2010). Due to the absence of any relevant treatment, this is especially important for the rapid discovery of a drug against ZIKV. Special priority should be given to the antivirals that were shown to be active against other flaviviruses such as dengue virus, yellow fever, Japanese encephalitis, etc., and

to a lesser degree, against other members of the *flaviviridae* family like Hepatitis C. There are many things that dengue and Zika have in common like they both are mosquito borne viruses spread especially by the *Aedes* mosquito. ZIKV consist of a single stranded, positive sense, 5'-capped RNA with genome size of around 11 kb which immediately released into the cytoplasm following by cell entry (Bollati et al., 2010). There are 59 and 39 un-translated regions along with only one open reading frame which codes a polyprotein that further cleaved into three structural proteins and seven nonstructural proteins i.e., NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 (Baronti et al., 2014). Among them the NS3 and NS5 proteins play a central role, together they harbor most of the catalytic activities needed for capping and replication (Bollati et al., 2010). In this study, we have taken four FDA approved drugs as Quinacrine, Amodiaquine, Berberine and Prochlorperazine against DENV as ligands and performed molecular docking analysis against NS3 protein of ZIKV in order to observe the binding affinity of these drugs. Among these four drugs, the drug showing minimum binding energy has been considered as the lead drug for further analysis.

MATERIALS AND METHODS

Protein preparation

The 3D coordinates of the Crystal Structures of Unlinked NS2B-NS3 Protease from Zika Virus and its Complex with a Reverse Peptide Inhibitor (PDB Id: 5GPI) was retrieved from Protein Databank (http://www.rcsb.org/).

Inhibitors dataset

Chemical structures of Quinacrine, Amodiaquine, Berberine and Prochlorperazine were downloaded in .sdf format from pubchem compound database (Kim et al., 2016). They were later converted in .pdb format with the help of open babel (O'Boyle et al., 2011) tool. All the drugs were subjected to energy minimization using the HyperChem software (HyperChem (TM) Release 7.5).

Molecular docking

Docking of Quinacrine, Amodiaquine, Berberine and Prochlorperazine with NS3-protein were done using molecular docking program AutoDock (Morris et al., 1998). Gasteiger charges are added to the ligand and maximum 6 numbers of active torsions are given to the lead compounds using AutoDock tool (http://autodock.scripps.edu/resources/adt). Kollman charges and the solvation term were added to the protein structure. The Lamarckian genetic algorithm implemented in Autodock was used for docking.

RESULTS & DISCUSSION

Zika virus infection in humans is usually mild or asymptomatic. However, some babies born to women infected with Zika virus have severe neurological sequelae. An unusual cluster of cases of congenital microcephaly and other neurological disorders in the WHO Region of the Americas, led to the declaration of a public health emergency of international concern by the World Health Organization. In docking studies of known antiviral drugs with NS3-protein, best autodock score was used as criteria to interpret the best conformation among the 10 conformations, generated by AutoDock 4.2 program. The docking result of these drugs with NS3-protein was shown in Table 1.

Table 1: Docking results of known antiviral drugs with NS3 Protein of Zika Virus.

Compound Name	PubChem CID	BE	IME	IE	TorE	VdwE	EE
Quinacrine	237	-7.32	-10.01	-1.29	2.68	-10.06	0.05
Amodiaquine	2165	-7.31	-9.4	-0.99	2.09	-9.36	-0.04
Berberine	2353	-8.03	-8.62	-0.3	0.6	-8.64	0.01
Prochlorperazine	4917	-7.17	-8.37	-1.27	1.19	-8.24	-0.12

BE= Binding Energy; IME: Intermolecular Energy; IE= Internal Energy; TorE= Torsional; Energy; VdwE= vdW + Hbond + desolv Energy; EE= Electrostatic energy.

Further, the docked complexes were analyzed through Python Molecular Viewer software for their interaction studies. Docked complex of Berberine with NS3-protein is shown in Fig.1.

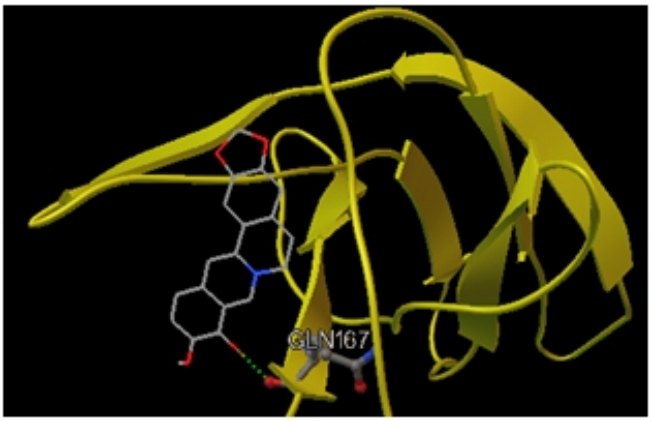

Fig.1: Docked complex of Berberine with NS3-protein.

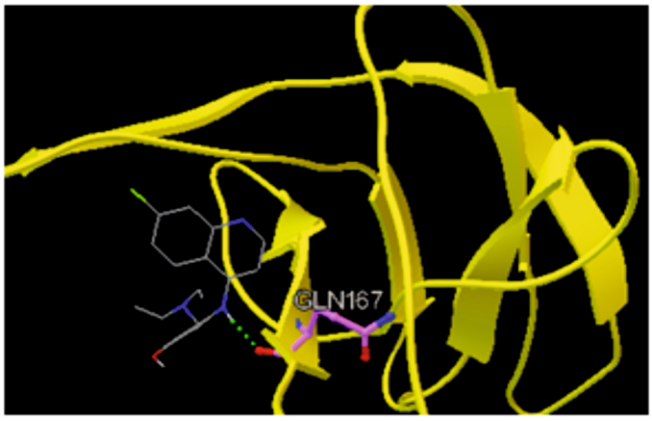

Fig.2: Docked complex of Amodiaquine with NS3-protein.

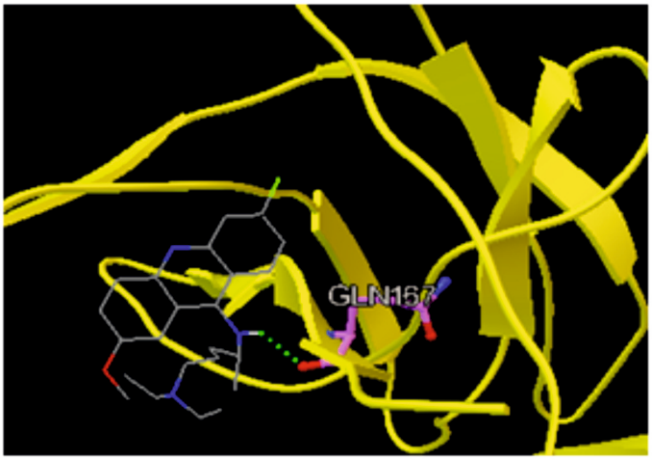

Fig.3: Docked complex of Quinacrine with NS3-protein.

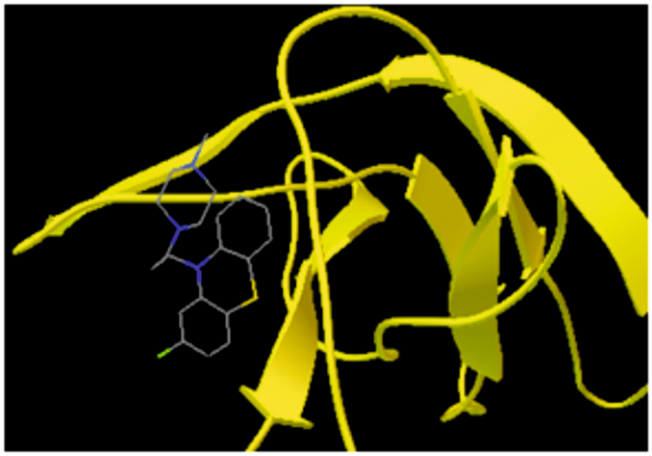

Fig.4: Docked complex of Prochlorperazine with NS3-protein.

In docked complexes, protein is represented as cartoon model with yellow color and lines presents drug molecule. Lines are color by atom type. In docked complex of Berberine with NS3-protein shows one H-bond between NS3-protein residue GLN167 and Berberine (Fig.1). Docked complex of Amodiaquine, Quinacrine and Prochlorperazine with NS3-protein were shown in Fig. 2, 3 & 4 respectively. One H-bond formed between NS3-protein residue GLN167 with Amodiaquine and Quinacrine, respectively (Fig.2 & Fig.3).

CONCLUSION

The results obtained from this study would be useful in understanding the inhibitory mode of Quinacrine, Amodiaquine, Berberine and Prochlorperazine with NS3-protein and accurately predicting the activities of drugs on the basis of docking scores. Here, we concluded that the Berberine be a novel inhibitor for NS3-protein preventing from Zika Virus.

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REFERENCES

1. Anon. WHO Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain-Barré syndrome.2016.
2. Baronti C., Piorkowski G., Charrel R.N., Boubis L., Leparc-Goffart I., de Lamballerie X. Complete coding sequence of Zika virus from a French Polynesia outbreak in 2013. Genome Announc 2014; 2:e00500-e00514.
3. Bollati M., Alvarez K., Assenberg R., Baronti C., Canard B., Cook S., et al. Structure and functionality in flavivirus NS-proteins: perspectives for drug design. Antiviral Res. 2010; 87:125-148.
4. Boonyasuppayakorn S, Reichert E.D., Manzano M, et al. Amodiaquine, an antimalarial drug, inhibits dengue virus type 2 replication and infectivity. Antiviral Res. 2014; 106: 125–34.
5. Costello A., Dua T., Dura P., Gülmezoglu M., Oladapo O.T., Perea W., Pires J., Ramon-Pardo P., Rollins N., Saxena S. Defining the syndrome associated with congenital Zika virus infection, Bull. World Health Organ. 2016, 94: 406–406A.
6. Cugola F.R., Fernandes I.R., Russo F.B., Freitas B.C., Dias J.L.M., Guimarães K.P. et al. The Brazilian Zika virus strain causes birth defects in experimental models, Nature. . 2016; 534: 267–271.
7. Faye O, Freire C.C., Iamarino A, et al. Molecular evolution of Zika virus during its emergence in the 20th century. PLoS Negl Trop Dis.; 2014; 8(1): e2636.
8. HyperChem (TM) Release 7.5, Hypercube, Inc., 1115 NW 4th Street, Gainesville, Florida 32601, USA.
9. Kim S, Thiessen P.A., Bolton E.E., Chen J, Fu G, Gindulyte A, Han L, He J, He S, Shoemaker B.A., Wang J, Yu B, Zhang J, Bryant S.H. PubChem Substance and Compound databases. Nucleic Acids Res. 2016; 44(D1):D1202-13.
10. McNeil D.G.J. Hawaii Baby With Brain Damage Is First U.S. Case Tied to Zika Virus. In The New York Times. 2016.
11. Morris G.M., Goodsell D.S., Halliday R.S., Huey R., Hart W.E., Belew R.K., Olson A.J. Automated Docking Using a Lamarckian Genetic Algorithm and Empirical Binding Free Energy Function. J Comput Chem.1998; 19:1639-1662.
12. O'Boyle N.M., Banck M., James C.A., Morley C., Vandermeersch T., Hutchison G.R. Open Babel: An open chemical toolbox. J Chemin form. 2011; 3: 33.
13. Shum D, Smith J.L., Hirsch A.J, et al. High-content assay to identify inhibitors of dengue virus infection. Assay Drug Dev Technol. 2010; 8(5): 553–70.
14. Simanjuntak Y., Liang J.J., Lee Y.L, et al. Repurposing of prochlorperazine for use against dengue virus infection. J Infect Dis. 2015; 211(3):394–404.
15. Tian H., Ji X., Yang X., Xie W., Yang K., Chen C., Wu C., Chi H., Mu Z., Wang Z., Yang H. The crystal structure of Zika virus helicase: basis for antiviral drug design, Protein Cell. 2016; 7:450–454.
16. WHO Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain-Barre Â syndrome http://who.int/mediacentre/news/statements/2016/emergency-committee-zika-icrocephaly/en/ 2016, 2016.