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IN SILICO STUDIES ON DENGUE AND HANTAAN VIRAL STRUCTURAL PROTEINS WITH SELECTED *CORIANDER SATIVUM* L CONSTITUENTS

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ABSTRACT

Coriander sativum L belongs to family *Umballiferae/Apiaceae*. The constituents of *Coriander sativum* L are used as herbs in Ayurvedic medicine. They are believed to possess anti-diabetic, anti microbial, anti inflammatory properties. The GCMS results showed the presence of 7 compounds in *Coriander sativum* L with a wide variety of biological activities. The comparative study of Dengue and Hantaan viruses with their structural protein for dengue were carried out through In Silico methods. In this study we examined the binding affinities of 7 ligands with 4 proteins of both dengue and Hantaan viruses. By our virtual screening and molecular docking result, we found that the Compound Hexadecanoicacid, methyl ester had the highest binding affinity with these proteins

KEYWORDS: Molecular docking, Dengue virus, Hantaan virus, Hydrogen bond.

1. INTRODUCTION

Plants are very useful source of various bioactive compounds and the use of plants and their parts as an ethno-medicine for the treatment of various diseases is a common practice since time immemorial. There were number of plants documented in the Ayurveda and Unani system of medicines for the treatment of asthma in India.[1] *Zatariamultiflora* is a plant consists of small ovate or nearly round dotted, leathery leaves mixed with numerous minute flowers. *Cassia angustifolia* (syn*Cassia senna*) is a well know traditional medicinal plant belonging to family *Leguminosae. Cassia angustifoliais* a valuable plant used for the treatment of constipation.[2] The genus *Coriandrum* L. has two species, *C sativum* L is coriander, approximately 30–100 cm in height, with strong-smelling leaves. The odour and flavour of mature seed, fresh herbage and flower are completely different.[3] The mature fruits have a fresh and pleasant flavor and are largely used all over the world. The plant is used as a flavoring agent in food products, perfumes, cosmetics and soaps. It is widely used in India in food.[4]

GC-MS chromatogram of the methanolic extract of *Coriander sativum* L showed seven major peaks, 2,3,5,6-tetrafluroanisole; 2,6-dimethyl-3-aminobenzoquinone; 2-methyoxy-4-venylphenol; benzofuran,2,3-dihydro; dodecanoic acid; hexadeconoicacid, methyl ester and 2,4a-epioxy-3,4,5,6,7,8,-hexahydro-2,5,5,8a-tetramethyl-2H-1-benzofuran. These compounds showed anti–oxidative, antimicrobial, anti ulcer, and cholesterol reducing activities.[5]

Dengue is a mosquito-borne systemic viral infection caused by any of the four antigenically related dengue viruses (DENV).[6] There are two well defined manifestations of dengue virus infection in humans, dengue fever and severe dengue (dengue hemorrhagic fever / dengue shock syndrome, DHF/DSS).[7] DENV is a positive-sense, single-stranded RNA virus with ~10.6kb genome.[8] There are seven non-structural proteins. Capsid protein which is responsible for gathering the viral RNA into a nucleocapsid that forms the core of a mature virus particle.[9] Envelop protein mediates virus entry into cells via interaction with a range of cell-surface receptor molecules.[10] NS1 protein attaches to plasma membrane of cells during infection.[11] NS2A is a component of viral replication complex which is functionally active in the assembly of the virion and also it acts as an antagonist to the host immune response.[12] NS2B-NS3 protease is a crucial enzyme for the viral replication. This protein is heterodimeric protein

of NS2B and NS3 protein.[13] NS3 helicase is also called as NS3 ATPase,[14] a multi-domain dengue virus replication protein.[15] NS5 protein consists of Methyl Transferase [MTase] and RNA-dependent RNA polymerase [RdRp] domains, which catalyzes 5' –RNA capping/methylation and RNA synthesis, respectively, during viral genome replication.[16]

Hantaan virus is the prototypic of the *Hantavirus* genus within the family *Bunyaviridae* and is a causative agent of the potentially fatal hemorrhagic fever with renal syndrome. This is a negative-sense RNA virus with three-part segmented genomes. Virions are enveloped and decorated with spikes derived from a pair of glycoproteins (Gn and Gc).[17] Hantaviruses have a tripartite genome that encodes an RNA-dependent RNA polymerase (L segment), the nucleocapsid (N) protein (S segment), and the G1 and G2 glycoproteins (M segment). The N protein encapsidates genomic and antigenomic vRNAs.[18] The two glycoproteins of Hantaan virus (HTV), G1 and G2, are encoded as a continuous single open reading frame in the M segment of the virionRNA.[19] This virus contain square-shaped surface spikes of four-fold symmetry and that each spike protrudes ~12 nm (TULV) and ~10 nm (HTNV) from the viral membrane. Hantavirus Gn and Gc Envelope Glycoproteins are Key Structural Units for Virus Cell Entry and Virus Assembly.[20]

Bioinformatics is an interdisciplinary branch of science which utilizes statistics, computer and mathematics to analyse biological data.[21] Bioinformatics is now utilized to identify many aspects such as evolution. Protein Data Bank (PDB) is a protein storage bioinformatics tool. It contains the structures of large numbers of proteins, ligands and other macromolecules.[22] Docking analysis are conducted for the protein and the ligand to analyse the fitness and the interaction with each other in the form of energy. This interaction could be used as the pharmaceutical approach for drug production.[23]

The aim of our study is to compare the best docking fit for the selected *Coriander sativum* L constituents with the Dengue and Hantaan viral structural proteins.

2. MATERIALS AND METHODOLOGIES

2.1. Preparation of viral proteins

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. Proteins of dengue and hantaanvirus were used for this study. The 3D structure of all the seven proteins were downloaded from PDB and saved in PDB format. The downloaded proteins were viewed in Py-Mol viewer.[24]

2.2. Preparation of ligands

Ligands selected were from the previous studies on GCMS analysis on *Coriander sativum* L extract.[25] Seven ligands were used for the study. Ligands were constructed using ChemSketch.[26] The constructed ligands were optimized to add the hydrogen bonds and the obtained structures were saved in mol for docking analysis and named as A, B, C, D, E, F and G respectively.

2.3. 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.[27] The proteins and the ligands were loaded and the out path was set. Standard docking parameters were used for docking (population size=200, generations =70 and Number of solutions =2). The docking process was initiated. After the docking process, the best docking pose for the individual ligands can be obtained for all the seven dengue viral proteins. 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.[28]

3. RESULTS

3.1. Total Binding Energy (kcal/mol) profile for Dengue and Hantaan virus proteins with 7 ligands.

Table 1: The Total Binding Energy (kcal/mol) profile for Dengue and Hantaan virus structural proteins with 7 ligands.

Ligand	Compound name	Dengue Virus	Hantaan Virus		
		Envelope protein	Glycoprotien [G_N]	Glycoprotien [G_C]	Nucleoprotien
A	2,3,5,6-tetrafluroanisole	-64.0	-62.6	-66.8	61.9
B	2,4a-epioxy-3,4,5,6,7,8,-hexahydro-2,5,5,8a-tetramethyl-2H-1-benzofuran	-62.1	-61.4	-66.1	-66.2
C	2,6-dimethyl-3-aminobenzoquinone	-67.6	-64.3	-73.4	-68.6

D	2 – methyoxy – 4 – vinylphenol	-66.5	-66.0	-69.1	-68.5
E	Benzofuran,2,3 – dihydro	-54.3	-53.3	-57.3	-60.5
F	Dodecanoic acid	-71.1	-72.2	-77.7	-72.9
G	Hexadecanoicacid,methyl ester	-73.7	-83.2	-83.4	-79.3

3.2. H – Bond profile for Dengue and Hantaan viruses protein with 7 ligands.

Table 2: H – Bond profile for Dengue and Hantaan virus structural proteins with 7 ligands.

Ligand	Compound name	Dengue Virus	Hantaan Virus		
		Envelope protein	Glycoprotien [G_N]	Glycoprotien [G_C]	Nucleoprotien
A	2,3,5,6-tetrafluroanisole	H – M	H – S H – M	-	-
B	2,4a-epioxy-3,4,5,6,7,8,-hexahydro-2,5,5,8a-tetramethyl-2H-1-benzofuran	H – M	-	H – M	H – S
C	2,6-dimethyl-3-aminobenzoquinone	H – M H – S	H – M	H – M H – S	H – M H – S
D	2 – methyoxy – 4 – vinylphenol	H – M	H – M	H – S H – M	H – M
E	Benzofuran,2,3 – dihydro	H – M	-	H – S	H – S
F	Dodecanoic acid	H – M	H – M H – S	H – S H – M	H – S H – M
G	Hexadecanoicacid,methyl ester	H – S	-	H – M H – S	H – M H – S

3.3. Amino acid profile for Dengue andHantaan virus structural proteins with 7 ligands

Table 3: Amino acid profile for Dengue and Hantaan virus structural proteins with 7 ligands.

Ligand	Compound name	Dengue Virus	Hantaan Virus		
		Envelope protein	Glycoprotien [G_N]	Glycoprotien [G_C]	Nucleoprotien
A	2,3,5,6-tetrafluroanisole	Gly (628) Arg (629) Ile (630)	His (207) Gly (251)	-	-
B	2,4a-epioxy-3,4,5,6,7,8,-hexahydro-2,5,5,8a-tetramethyl-2H-1-benzofuran	Gly (628) Arg (629) Ile (630)	-	Arg (179)	Trp (119)
C	2,6-dimethyl-3-aminobenzoquinone	Lys (625) Val (626) Arg (629) Ile (630)	Ser (323) Thr (359)	Pro (97), Asn (89)	His (308)
D	2 – methyoxy – 4 – vinylphenol	Arg (629)	Ser (323)	Ser (30)	Thr (123)
E	Benzofuran,2,3 – dihydro	Gly (628) Arg (629) Ile (630)	-	Ser (178)	Arg (339)
F	Dodecanoic acid	Gly (628) Arg (629)	Thr (173)	Lys (102)	His (308)
G	Hexadecanoicacid,methyl ester	Arg (619)	-	Lys (212) His (213)	Leu (141)

4. DISCUSSION

Considering all the tables from Table – 1, Table – 2 and Table - 3, the 3D structure coordinates of one proteins of dengue and three proteins of Hantaan viruses are optimized and 7 compounds from *Coriander sativum* L extract are identified. The total binding energy of the compounds with all the three proteins was calculated using iGEMDOCK. Evaluations of binding conformation of these 7compounds with one dengue and 3Hantaanviral proteins are performed using iGEMDOCK. From docking study, we listed binding affinities of 7 compounds based on ligand binding energy (Table.1). The binding pose for each ligand molecule into the dengue and Hantaan viral proteins are analyzed and the one having lowest ligand binding energy with these proteins among the different poses are generated. The lower energy scores represent better protein-ligand target binding affinity compared to higher energy score. Considering the envelope protein of Dengue virus, among the 7 analogs, compound " G" is found to have lower ligand binding energy (binding energy value = -73.7kcal/mol). The structural proteins of Huntaan virus had following binding energies, Glycoprotein [G_N] ('G', binding energy value = -83.2 kcal/mol), Glycoprotien[G_C] ('G' binding energy value = -83.4kcal/mol), Nucleoprotien[N] ('G ' binding energy value = -79.3 kcal/mol), We found that the compound "G" was found to have the best binding affinity with envelope protein of dengue and three proteins of Hantaan virus.

4.1. Structural proteins of Dengue Virus

4.1.1. The Total Binding Energy for Dengue virus envelope protein with 7 ligands

From Table – 1, Table – 2, and Table – 3 and Figure – 1, the docking simulation of 7 ligands were performed for Dengue virus envelope protein. From the docking study, we observed that compound – G has best binding affinity with the target envelope protein with the binding energy value of -73.7kcal/mol .Interaction analysis of binding mode of compound –G in dengue virus envelope protein reveals that it forms one hydrogen bond with low energy with Arg (619) residue. A close-up view of the Total Binding Energy (kcal/mol) profile for Dengue virus envelope protein with 7 ligands: is shown in Fig.1.

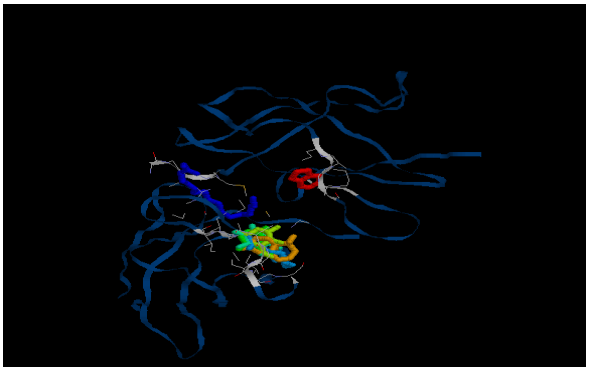

Fig. 1: The Total Binding Energy profile for Dengue virus envelope protein with 7 ligands.

4.2. Structural proteins of Hantaan Virus

4.2.1. The Total Binding Energy for Glycoprotien [G_N] with 7 ligands

From Table – 1, Table – 2, and Table – 3 and Figure – 2, the docking simulation of 7 ligands were performed for Hantaan glycoprotien[G_N]. From the docking study, we observed that compounds – G has best binding affinity with the target glycoprotien [G_N] with the binding energy values of -83.2kcal/mol. A close-up view of the Total Binding Energy (kcal/mol) profile for Hantaan virus glycoprotien [G_N] with 7 ligands: is shown in Fig.2.

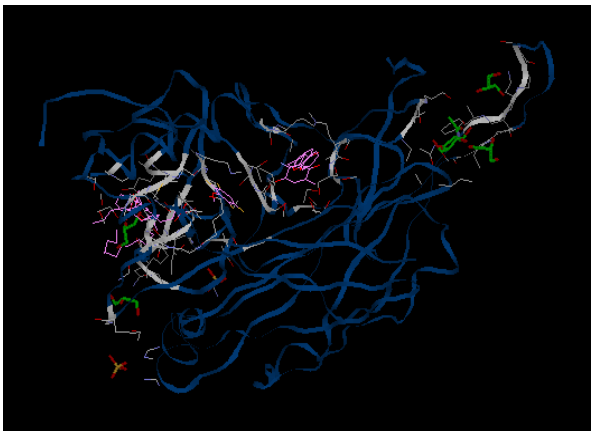

Fig. 2: The Total Binding Energy profile for Hantaan virus glycoprotien [G_N] with 7 ligands.

4.2.2. The Total Binding Energy for Glycoprotien [G_C] with 7 ligands

From Table – 1, Table – 2 and Table – 3 and Figure – 3, the docking simulation of 7 ligands were performed for Hantaan glycoprotien [G_C]. From the docking study, we observed that compound – G has best binding affinity with the target glycoprotien [G_C] with the binding energy value of -83.4kcal/mol. Interaction analysis of binding mode of compound –G in Hantaan virus glycoprotein reveals that it forms two hydrogen bond with low energy one with Lys(212) and other with His(213) residue . A close-up view of the Total Binding Energy (kcal/mol) profile forHantaan glycoprotien [G_C] with 7 ligands: is shown in Fig.3.

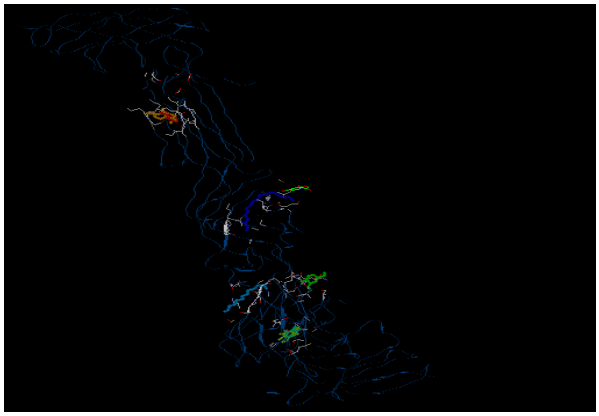

Fig. 3: The Total Binding Energy profile for Hantaan virus Glycoprotien [G_C] with 7 ligands.

4.2.3. The Total Binding Energy for Nucleoprotein [N] protein with 7 ligands

From Table – 1, Table – 2 and Table – 3 and Figure – 3, the docking simulation of 7 ligands were performed for Hantaan Nucleoprotien [N]. From the docking study, we observed that compound – G has best binding affinity with the target Nucleoprotien [N] with the binding energy value of -79.3kcal/mol. Interaction analysis of binding mode of compound –G in Hantaan virus nucleoprotein reveals that it forms two hydrogen bond with low energy one with Leu (141) residue. A close-up view of the Total Binding Energy (kcal/mol) profile for Hantaan Nucleoprotien [N] with 7 ligands: is shown in Fig.4.

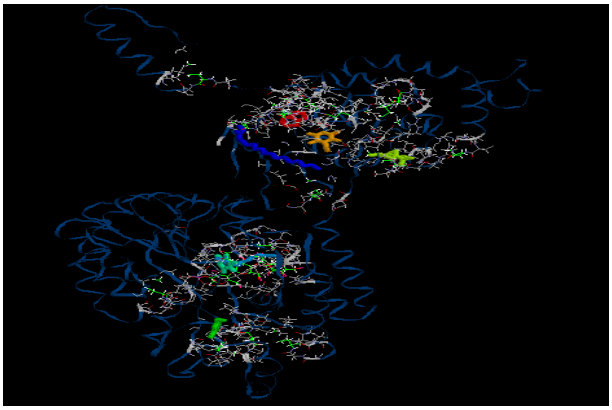

Fig. 4: The Total Binding Energy profile for Hantaan virus Nucleoprotien [N] with 7 ligands.

5. CONCLUSION

Our molecular docking studies explored the possible binding modes of 7 compounds that are present in *Coriander sativun* L with envelope protein of Dengue virus and 3 proteins of Hantaan virus which are structural protiens. It revealed that all the 7 compounds show minimum affinity with all the proteins. The compound 'G' (Hexadecanoic acid, methyl ester) showed the best results compared to other compounds. On comparing the binding energy and the binding site residues, we found that all the compounds will differ in either of them for hydrogen bond formation. The conclusion which is drawn from our virtual screening and docking result are that the Compound 'G' has highest binding affinity with the structural protein of Dengue virus and Hantaan virus. Hence, the Compound 'G' may be considered as the effective drug target for both dengue and Hantaan virus because it can effectively bind to most of the proteins of both the viruses. Though, there are many reports on the *in vitro* analysis of these compounds and its medicinal and toxic properties, there are no in silico studies that predict the binding and active regions especially with these proteins. Our study is probably the first such attempt to predict the binding site and the binding residues. 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 and Hantaan.

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