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Docking study of Selected *Vinis vitifera* seeds constituents on Dengue viral proteins – An *In Silico* approach

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Abstract

Dengue is a mosquito-borne systemic viral infection caused by any of the four antigenically related dengue viruses (DENV).The dengue virus belongs to the Flaviviridae family of viruses that cause diseases in humans.A virtual screening analysis of phytochemical structures with dengue virus protein targets has been carried out using a molecular docking approach with *vins vinifera* seeds. Grapes (*Vinis vitifera*) are believed to have health benefits due to their antioxidant activity and polyphenols. In this study we examined the binding affinities of 14 ligands with seven non structural Dengu viral proteins through In Silico methods like virtual screening and docking process which showed that compound F and compound N had high binding efficiencies with these proteins along with the type of hydrogen bonds and their respective amino acid residues at their docked sites.

Introduction

Plants and their secondary metabolite constituents or herbal extracts have a long history of use in modern 'western' medicine and in certain systems of traditional medicine, and they act as drugs such as atropine, morphine, quinine and vincristine. *Herbs* generally refers to the leafy green of a plant (either fresh or dried), while *spices* are usually dried and produced from other parts of the plant, including seeds, bark, root and fruits. For instance, some types of herbal extract can be used for medical purposes to relieve depression and stress like St. John's-wort (*Hypericumperforatum*) [1].Grapes a natural product, organically a berry fruit, of the deciduous woody vines of the blooming plant family *Vitis*. *VitisVinifera* is an individual form of the *Vitaceae* family. Grapes are poly-phenolic mixes, such as catechin, gallic acid, and Anthocyanin. Grape seed extract is a rich source of antioxidants and oligomericproanthocyanidins which possess several health benefits [2].

The GCMS chromatogram of methanolic extract of seeds showed nearly 130 compounds. Triethylphosphine, Acetaldehyde Methyl hydrazone, (S)-(+)-2-amino-3-methyl-1-butanol, 2,3-Dihydro-3,5-dihydroxy-6-methyl-Pyran-4-one, 3,4-Difluoroanisole, L-Arabinitol, Xylitol, 5-Hydroxymethyl Furfural, 4-Mercaptophenol, 1,6-Anhydro-2,4-dideoxy-beta-D-ribo-hexopyranose,3-Butenoic acid,Chloroacetic acid,2,2 Dimethyl propylester,, Thymine, 9,12-Octadecadienoic acid compounds showed high peak areas with a wide variety of biological activities[2].

Dengue is a mosquito-borne systemic viral infection caused by any of the four antigenically related dengue viruses (DENV) [1]. 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) [3]. DENV is a positive-sense, single-stranded RNA virus with ~10.6kb genome [4]. 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 [5]. Envelop protein mediates virus entry into cells via interaction with a range of cell-surface receptor molecules [6]. NS1 protein attaches to plasma membrane of cells during infection [7]. 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 [8]. NS2B-NS3 protease is a crucial enzyme for the viral replication .This protein is heterodimeric protein of NS2B and NS3 protein [9]. NS3 helicase is also called as NS3 ATPase [10], a multi-domain dengue virus replication protein [11]. 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 [12].

Bioinformatics, the application of computational techniques to analyze the information associated with biomolecules [13]. There are number of applications of bioinformatics viz. sequence analysis and alignment, molecular modelling, docking, annotation etc[14].

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The aim of our study is to analyse the binding affinities of the selected 14 ligands of *Vitisvinifera* with seven dengue virus proteins which is given in the form of energy along with the type of hydrogen bonds and related amino acids.

Materials and Methodologies

Preparation of dengue 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 virus 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.

Preparation of ligands

Ligands selected were from the previous studies on GCMS analysis on *Vinisvitifera*[15]. 14 ligands were used for the study. Ligands were constructed using ChemSketch[16]. 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, G, H, I, J, L, M, and N respectively.

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 **[**16**].** 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.

Results and Discussion

Total Binding Energy (kcal/mol) profile for Dengue viruses protein with 14 ligands

Ligand	Compound name	Envelope protein	NS1 protein	Trans membrane domain of NS2A	NS2B / NS3 protease	NS3 helicase	NS5 protein	Capsid protein
A	Trimethyl Phosphine	-25.3	-31.4	-20.9	-23.5	-29.7	-28.3	-31.6
B	Acetaldehyde, Methylhydrazone	-50.3	-46.5	-39.5	-43.4	-48.1	-47.5	-47.4
C	(s) – (+) -2-Amino- 3- methyl- 1- butanol	-53.5	-63.3	-44.3	-53.7	-60.3	-60.5	-50.8
D	2,3 –Dihydro- 3,5-Dihyroxy-6-methyl-4H-Pyran-4-One	-67.8	-82.1	-56.9	-59.3	-72.7	-71.4	-64.6
E	3,4- Difluoroanisole	-54.8	-70.6	-53.0	-53.7	-59.8	-59.6	-64.4
F	L-Arabiniol	-77.6	-96.7	-61.1	-72.3	-81.5	-84.9	-73.4
G	Xylitol	-82.6	-87.3	-60.2	-78.8	-79.9	-83.1	-73.5
H	5-Hydroxymethyl Furfural	-65.5	-70.1	-54.0	-62.1	-64.5	-69.5	-69.9
I	4- Mercaptophenol	-55.4	-64.2	-47.3	-50.4	-58.3	-56.5	-53.7
J	1,6-Anhydro-2,4-Dideoxy-Beta-D-Ribo-Hexopyronose	-57.3	-72	-45.8	-51.0	-65.1	-63.1	-55.8
K	3-Butenoic Acid	-47.9	-50.7	-40.1	-48.9	-60.3	-56.1	-52.8
L	ChloroAcetic Acid, 2,2-Dimethyl Propyl Ester	-53.8	-69.4	-50.2	-53.6	-68.2	-62.6	-62
M	Thymine	-65.2	-73.4	-54.4	-64.2	-64.8	-66.2	-59.3
N	9,12-Octadecadienoic Acid	-83.7	-89.3	-86.2	-89.9	-79.7	-82.7	-87.7

Table – 1: The Total Binding Energy (kcal/mol) profile for Dengue viruses protein with 14 ligands

H – Bond profile for Dengue viruses protein with 14 ligands

Ligand	Compound name	Envelope protein	NS1 protein	Trans membrane domain of NS2A	NS2B/NS3 protease	NS3 helicase	NS5 protein	Capsid protein
A	Trimethyl Phosphine	-	-	-	-	-	-	-
B	Acetaldehyde, Methylhydrazone	H-S H-M	H-M	H-M	H-M H-S	H-M	-	H-M
C	(s) – (+) -2-Amino- 3- methyl- 1-butanol	H-S H-M	H-M H-S	H-M	H-M H-S	-	H-M	H-M
D	2,3 –Dihydro- 3,5-Dihyroxy-6-methyl-4H-Pyran-4-One	H-M	H-M H-S	H-M H-S	H-M H-S	H-M H-S	H-M	H-M H-S
E	3,4- Difluoroanisole	H-S	H-M	H-M	H-S	-	-	H-S
F	L-Arabiniol	H-M	-	H-M	H-M H-S	H-M H-S	H-M	H-M H-S
G	Xylitol	H-M	H-M	H-M H-S	H-M H-S	-	H-M H-S	H-M H-S
H	5-Hydroxymethyl Furfural	H-M H-S	H-M H-S	H-M H-S	H-M H-S	H-M H-S	H-M H-S	H-M H-S
I	4- Mercaptophenol	H-M H-S	H-M	H-M H-S	H-M	H-M H-S	H-M	H-S
J	1,6-Anhydro-2,4-Dideoxy-Beta-D-Ribo-Hexopyronose	H-M H-S	H-M H-S	H-M H-S	H-M H-S	H-M H-S	H-M H-S	H-M H-S
K	3-Butenoic Acid	H-M	H-M H-S	H-M H-S	H-M H-S	H-M H-S	-	H-M H-S
L	ChloroAcetic Acid, 2,2-Dimethyl Propyl Ester	-	-	-	-	-	-	-
M	Thymine	H-M	H-M H-S	H-M H-S	H-M H-S	H-M H-S	H-M H-S	H-M H-S
N	9,12-Octadecadienoic Acid	H-M	-	-	H-M H-S	H-M H-S	H-M H-S	H-S

Table – 2: H – Bond profile for Dengue viruses protein with 14 ligands

Aminoacid position profile for Dengue viruses protein with 14 ligands

Ligand	Compound name	Envelope protein	NS1 protein	Trans membrane domain of NS2A	NS2B/NS3 protease	NS3 helicase	NS5 protein	Capsid protein
A	Trimethyl Phosphine	-		-	-	-	-	-
B	Acetaldehyde, Methylhydrazone	Pro(611)	Gly(249)	Ala(14)	Leu(128)	Val(406)	-	Val(51)
C	(s) – (+) -2-Amino- 3-methyl- 1- butanol	Lys(625)	Thr(262)	Leu(27)	Ala(56) Asp(58) Leu(74)	-	Glu(138) Cys(140)	Leu(29) Phe(47)

D	2,3 –Dihydro- 3,5-Dihyroxy-6-methyl-4H-Pyran-4-One	Vla(626)	Pro(250) Thr(262)	Asp(1)	Phe(130) Tyr(150) Gly(151)	His(194)	Ala(41)	Phe(47)
E	3,4- Difluoroanisole	Trp(670)	Lys(245)	Thr(7)	Trp(83)	-	-	Arg(41)
F	L-Arabiniol	Ile(616)	-	Thr(20) Leu(27)	Ala(57)	Asp(192)	Tyr(89) Tyr(119)	Phe(47)
G	Xylitol	Ile(616)	Gly(249)	Asp(1)	Ala(57)	-	Trp(87)	Phe(33)
H	5-Hydroxymethyl Furfural	Ser(582)	Pro(250)	Asp(1)	Asp(58)	Thr(200)	Gly(106)	Thr(25)
I	4- Mercaptophenol	Vla(626)	Pro(250)	Asp(1)	Glu(86)	Asn(329)	Pro(73)	Arg(41)
J	1,6-Anhydro-2,4-Dideoxy-Beta-D-Ribo-Hexopyronose	Ile(616) Val(626)	Leu(237) Ile(243) Gly(249) Pro(250)	Ile(2)	Ala(56)	Gly(196) Ala(197)	Cys(82)	Phe(33)
K	3-Butenoic Acid	Arg(629) Ile(630)	Thr(262)	Asp(1)	Arg(60)	Gly(196)	-	Thr(25)
L	ChloroAcetic Acid, 2,2-Dimethyl Propyl Ester	-	-	-	-	-	-	-
M	Thymine	Ile(616) Ile(618) Val(626) Gly(628) Arg(629) Ile(630)	Ile(242) Lys(245)	Asp(1)	Arg(55) Asp(58) Leu(74)	Thr(389)	Cys(82)	Leu(29) Arg(68)
N	9,12-Octadecadienoic Acid	Ile(630)	-	-	Asn(152)	Ser(386) Thr(389)	Thr(51)	Arg(68)

Table – 3: Amino acid position profile for Dengue virus protein with 14 ligands

Discussion

From the Table – 1, Table – 2 and Table – 3, the 3D structure coordinates of seven non structural proteins of dengue virus is optimized and 14 compounds from *Vinisvitifera* extract are identified. Their total binding energy was calculated using iGEMDOCK. Evaluations of binding conformation of 14 compounds with seven non structural dengue viral proteins are performed using iGEMDOCK. From docking study, we listed binding affinity of 14 compounds based on ligand binding energy (Table.1). The binding pose for each ligand molecule into the non structural dengue viral protein is 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. Among the 14 analogs, compound "N" is found to have lower ligand binding energy (binding energy value= -83.7 kcal/mol), than other analogs for Envelope protein. Compound "F" has least binding energy score with NS1 protein (binding energy value= -96.7 kcal/mol), Trans membrane domain of NS2A (binding energy value= -86.2 kcal/mol), NS2B / NS3 protease (binding energy value= -89.9 kcal/mol), NS3 helicase (binding energy value= -81.5 kcal/mol), NS5 protein (binding energy value= -84.9 kcal/mol) and Capsid protein (binding energy value = -87.7 kcal/mol). We further analyzed the docked pose for finding the binding mode of compound "N" and compound "F" in to seven non structural dengue proteins to validate the reasonable binding conformations.

The Total Binding Energy for Dengue virus envelope protein with 14 ligands

From Table – 1, Table – 2 and Table – 3, the docking simulation of 14 ligands were performed for Dengue virus envelope protein. From the docking study, we observed that compound –N has best binding affinity with the target envelope protein with the binding energy value of -83.7 kcal/mol. Interaction analysis of binding mode of compound – N in dengue virus envelope protein reveals that it forms one hydrogen bonds with low energy, with Ile (630) residues. A close-up view of the Total Binding Energy (kcal/mol) profile for Dengue virus envelope protein with 14 ligands: is shown in Fig.1.

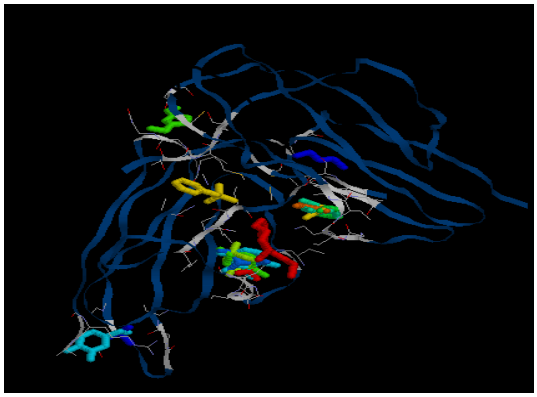

Fig.1: The Total Binding Energy for Dengue virus envelope protein with 14 ligands

The Total Binding Energy for Dengue virus NS1 protein with 14 ligands

From Table – 1, Table – 2 and Table – 3, the docking simulation of 14 ligands were performed for Dengue virus NS1 protein. From the docking study, we observed that compound – F has best binding affinity with the target NS1 protein with the binding energy value of -96.7 kcal/mol . Interaction analysis of binding mode of compound –F in dengue virus NS1 protein reveals that it forms no hydrogen bond with low energy, without any amino acid residue. A close-up view of the Total Binding Energy (kcal/mol) profile for Dengue virus NS1 protein with 14 ligands: is shown in Fig.2.

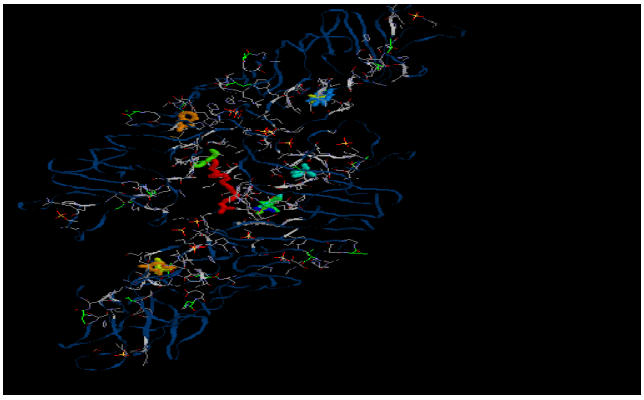

Fig.2: The Total Binding Energy for Dengue virus NS1 protein with 14 ligands

The Total Binding Energy for Dengue virus Trans-membrane domain of NS2A with 14 ligands:

From Table – 1, Table – 2 and Table – 3, the docking simulation of 14 ligands were performed for Dengue virus Trans-membranedomain of NS2A. From the docking study, we observed that compound – N has best binding affinity with the target Transmembrane domain of NS2A with the binding energy value of -86.2 kcal/mol- . Interaction analysis of binding mode of compound –N in dengue virus Trans-membrane domain of NS2Areveals that it does not form any hydrogen bond with low energy, without any amino acid residue. A close-up view of the Total Binding Energy (kcal/mol) profile for Dengue virus Trans-membrane domain of NS2A with 14 ligands: is shown in Fig.3.

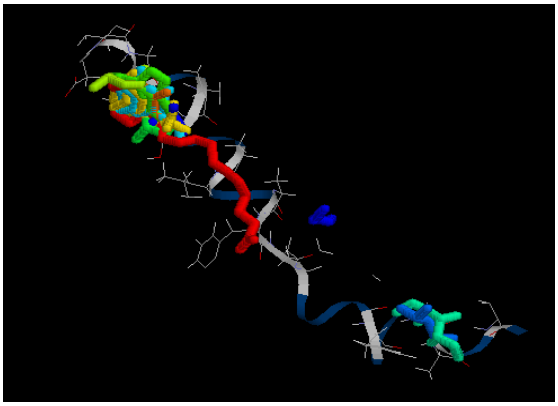

Fig.3: The Total Binding Energy for Dengue virus Trans membrane domain of NS2A with 14 ligands

The Total Binding Energy for Dengue virus NS2B / NS3 protease with 14 ligands:

From Table – 1, Table – 2, Table – 3 and Figure – 4, the docking simulation of 14 ligands were performed for Dengue virus NS2B / NS3protease. From the docking study, we observed that compound – N has best binding affinity with the target NS2B / NS3protease with the binding energy value of -89.9 kcal/mol. Interaction analysis of binding mode of compound –N in dengue virus NS2B / NS3protease reveals that it forms two hydrogen bond with low energy, with Asn (152) residue. A close-up view of the Total Binding Energy (kcal/mol) profile for Dengue virus NS2B / NS3protease with 14 ligands: is shown in Fig.4.

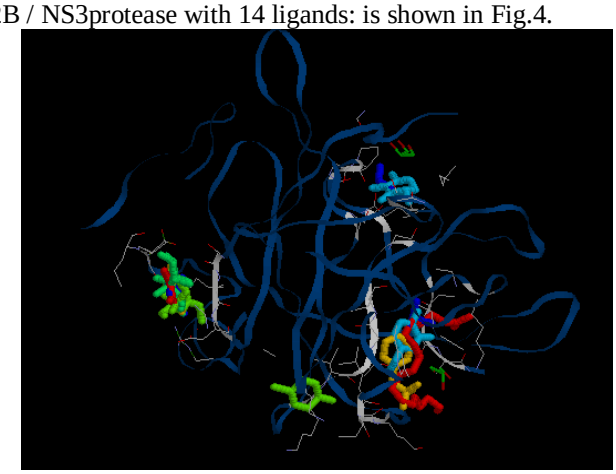

Fig.4: The Total Binding Energy for Dengue virus NS2B / NS3 protease with 14 ligands

The Total Binding Energy for Dengue virus NS3 helicase with 14 ligands

From Table – 1, Table – 2, Table – 3 and Figure – 4, the docking simulation of 14 ligands were performed for Dengue virus NS3helicase. From the docking study, we observed that compound – F has best binding affinity with the target NS3helicase with the binding energy value of -81.5 kcal/mol. Interaction analysis of binding mode of compound –F in dengue virus NS3 helicase reveals that it forms two hydrogen bond with low energy, with Asp (192) residue. A close-up view of the Total Binding Energy (kcal/mol) profile for Dengue virus NS3helicase with 14 ligands: is shown in Fig.5.

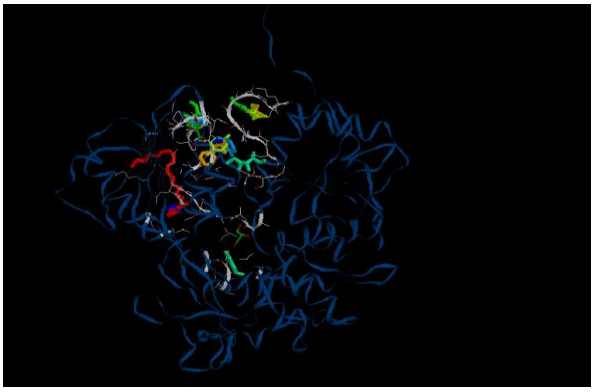

Fig.5: The Total Binding Energy for Dengue virus NS3 helicase with 14 ligands

The Total Binding Energy for Dengue virus NS5 protein with 14 ligands

From Table – 1, Table – 2, Table – 3 and Figure – 6, the docking simulation of 14 ligands were performed for Dengue virus NS5 protein From the docking study, we observed that compound – F has best binding affinity with the target NS5 protein with the binding energy value of -84.9 kcal/mol. Interaction analysis of binding mode of compound –F in dengue virus NS5 protein reveals that it forms one hydrogen bond with low energy, with Tyr(89) and Tyr (119) residues. A close-up view of the Total Binding Energy (kcal/mol) profile for Dengue virus NS5 protein with 14 ligands: is shown in Fig.6.

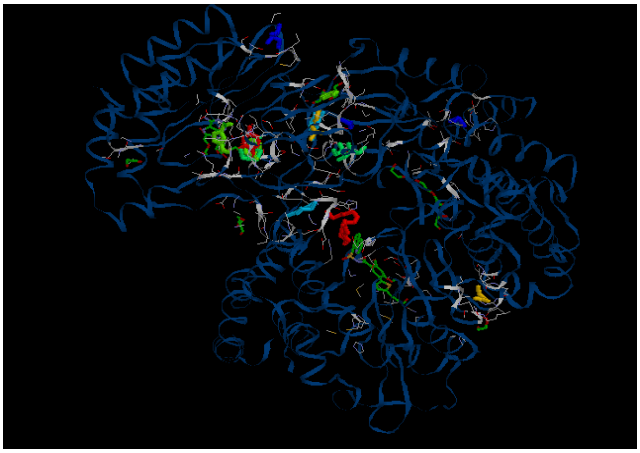

Fig.6: The Total Binding Energy for Dengue virus NS5 protein with 14 ligands

The Total Binding Energy for Dengue virus Capsid protein with 14 ligands:

From Table – 1, Table – 2, Table – 3 and Figure – 7, the docking simulation of 14 ligands were performed for Dengue virus Capsid protein. From the docking study, we observed that compound – N has best binding affinity with the target Capsid protein, with the binding energy value of -87.7 kcal/mol .Interaction analysis of binding mode of compound –N in dengue virus Capsid protein, reveals that it forms one hydrogen bond with low energy, with Arg(68) residues. A close-up view of the Total Binding Energy (kcal/mol) profile for Dengue virus Capsid protein, with 14 ligands: is shown in Fig.7.

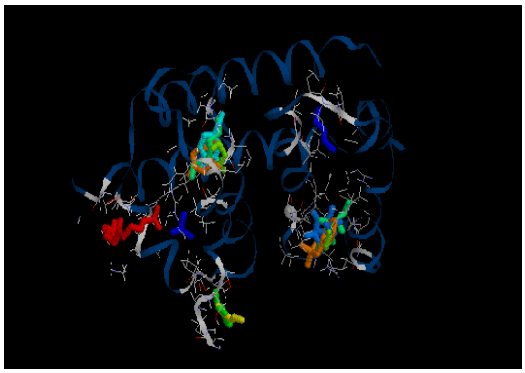

Fig.7: The Total Binding Energy for Dengue virus Capsid protein with 14 ligands

Conclusion

Our molecular docking studies explored the possible binding modes of 14 compounds that are present in *Vinis vitifera seed* extract with seven non structural proteins which are envelope protein, NS1 protein, Transmembrane doamin of NS2A, NS2B/NS3 protease, NS3 helicase, NS5 protein and capsid protein. . It revealed that all the 14 compounds show minimum affinity with all the proteins. Especially the compound F (L-Arabinitol) and compound N (9, 12-Octadecadienoic acid) shows best results compared to other compounds. On comparing the binding energy and the binding site residues, we found that all compounds differ either in their binding modes and the binding site residues for hydrogen bond formation. From our virtual screening and docking result the 9,12-Octadecadienoic Acid and L-Arabiniol has highest binding affinity with most of the proteins and it can be used as an effective drug target for Dengue virus. The validation of our results through *invivo* and *invitro* experiments along with animal models will enlighten further for the future development of more potent drugs for treating Dengue.

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