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# DOCKING STUDIES ON SELECTED DENGUE AND RABIES VIRAL STRUCTURAL PROTEINS WITH *CORIANDRUM SATIVUM* L FLOWER CONSTITUENTS – AN *IN SILICO* APPROACH

**[1]Nisha R., [1]Rameen Taj S., [1]Sheetal. V. Rao, [1]Tulasi D. P., [1]Pavithra K. and *[2]Dr. Balasubramanian Sathyamurthy**

[1]Department of Biochemistry, Ramaiah College of Arts, Science and Commerce, Bangalore – 560054.
[2]Professor, Department of Biochemistry, Ramaiah College of Arts, Science and Commerce, Bangalore – 560054.

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

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## ABSTRACT

Dengue virus contains two structural proteins and five non-structural proteins and Rabies virus contains three proteins structural and one non-structural protein, which are considered to be the most effective for drug designing. Recent studies have shown that these proteins can effectively cause the inactivation of dengue and rabies infection in humans. The entire parts of the plant *Coriandrum sativum* L like seeds, leaves, flower, fruits are found to have anti-oxidant and anti-mutagenic and anti-microbial properties. In this particular study, the binding efficiency of 7 compounds that are present in the *Coriandrum sativum* L with the selected structural proteins of Dengue virus and rabies virus were performed through Insilico methods. By our molecular docking result found that the hexadecanoic acid,methyl ester have highest binding affinity with the proteins.

**KEYWORDS:** Coriandrum *sativum* L, structural proteins, molecular docking, amino acids.

## 1. INTRODUCTION

From many years human are using different parts of plants for medicinal purposes, as a source of food and feed. Humans are highly dependent on natural resources since years ago for their survival as these plants have been used to treat many illnesses, served as food and shelter too. Medicinal plants are the backbone of the traditional medicine.[1] Higher number of plant species has the ability to inhibit the various tumours. Plants are an important element of indigenous medical systems in all over the world. The ethno botany provides a rich resource for research and development of natural drug.[2] Coriandrum *sativum* L is one of the medicinal plants which belong to the family Apiaceae, species Umbelliferae. Its seeds are great source of secondary plant metabolites such as polyphenols, like phenolic acids and flavanoids. This Coriandrum is a popular ingredient in the preparation of the Ayurvedic Medicines.[3] It is used as Stomachic, Spasmolytic, Carminative and thus having a great bioactive property. Seeds, leaves, flower; fruit the entire parts of the plant possess antioxidant, anti-mutagenic, anti-microbial activity.[4] The modern research on the seeds of the Coriandrum plant have shown to decrease the blood sugar and reduce insulin resistance, this is likely due to flavonoids and polyphenols present. The leaves of the plant are shown to reduce the symptoms in arthritis. The leaves phenolic content specifically ethanolic extract shown to protect against the liver damages in rats.[5,6,7,8]

GC-MS chromatogram of the methanolic extract of *Coriandrum* L reveals the presence of benzofuran,2,3-dihydro, hexadecanoic acid, methyl ester (10.32 %), 2,4a-epioxy-3,4,5,6,7,8,-hexahydro-2,5,5,8a-tetramethyl-2H-1-benzofuran (9.35%), 2- methyoxy-4-vinylphenol (8.8%), 2,3,5,6-tetrafluroanisole (8.62%), 2,6-dimethyl-3- aminobenzoquinone (6.81%) and dodecanoic acid (5.00%). Benzofuran, 2, 3-dihydro having antiangiogenic property. Hexadecanoic acid, methyl ester used as cosmetics, antipsychotic medication, antioxidant, hypocholesterolemic nematicide, pesticide, anti-androgenic flavor, haemolytic and 5- Alpha reductase inhibitor. 2,4a-epioxy-3,4,5,6,7,8,-hexahydro-2,5,5,8a-tetramethyl-2H-1-benzofuran shows anti-malarial activity. 2- methyoxy-4-vinylphenol used as aroma flavour. 2, 3, 5, 6-tetrafluroanisole act as Fungicide. 2, 6-dimethyl-3- aminobenzoquinone and dodecanoic acid possess anti-microbial activity.[9]

The causative agent for Dengue is Dengue virus (DENV), which is a mosquito-borne flavivirus. This virus is a single stranded RNA positive-strand virus of the family Flaviviridae, genus Flavivirus. This includes also the West Nile virus, Tick-borne Encephalitis Virus,

Yellow Fever Virus, and several other viruses which may cause encephalitis. DENV causes a range of diseases in humans, from a self limited Dengue Fever (DF) to a life-threatening syndrome called Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS).[10] There are four antigenically different serotypes of the virus. Dengue disease is an emerging arboviral, arthropodborne. The viral infection with 1 of 4 serotyes produces ranging clinical illness from an asymptomatic mild illness to severe forms of illness Dengue hemorrhagic fever (DHF) which is transmitted within humans through Aedes Female mosquitoes subgenus *Stegomyia. Ae. aegypti* which is the most epidemic vector. Dengue vaccine development has become a challenging due to the four serotypes each capable of eliciting cross-reactive and disease enhancing antibody response against the three remaining serotypes. The viral genome consists of positive sense of RNA which encoding for three structural proteins Capsid (c), premembrane (prM), envelop (E), and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5).[11] NS2B-NS3 protease is a hetero dimeric protein of NS2B and NS3 protein, which play an important role in the viral replication process.[12] The N-terminal of the NS3 protein in association with the NS2B cofactor forms crucial for the viral replication. NS2B/ NS3 protease enzyme has a role in the viral life cycle [13]. Envelope protein (structural protein) which has a major role in the assembly of virus. The protein which is utilised for this 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.[14] The capsid protein (structural proteins), having the major function in the viral genome encapsidation. The capsid protein used for this study was from dengue virus type 2 (strain Puerto Rico/PR159-S1/1969).[15] The protein used for this study was the trans-membrane domain of the NS2A of dengue virus type 2. NS2A which is a non structural protein 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.[16] NS3 helicase belongs to the non-structural and a multi-domain dengue virus replication protein.[17] The protein used for this study is the non-structural 5 (NS5) protein from the dengue virus type 3 (strain Sri Lanka / 1266 / 2000). This protein is classified under the transferases. The RNA dependent RNA polymerase (RdRp) domain of the NS5 protein plays a crucial part in the replication of the viral genome. RNA is synthesized via “de novo” by NS5 protein.[18]

Rabies Virus (RABV) is a deadly zoonotic disease of public health importance caused by lyssa viruses, belonging to Rhabdoviridae family and is a neuro invasive human and animal pathogen. RABV is a negative-sense; non-segmented, single-stranded RNA virus measures approximately 60 nm × 180 nm. The Rabies virus is composed of an internal protein core or nucleocapsid, which contains the nucleic acid, and an outer envelope, a lipid-containing bilayer covered with transmembrane glycoprotein spikes. The viral genome encodes five proteins either associated with the complex ribonucleoprotein or the viral envelope. The proteins includes nucleoprotein (N), Phosphoprotein (P), matrix protein (M), glycoprotein (G) and polymerase (L).The two major structural components includes a helical ribonucleoprotein core (RNP) and a surrounding envelope. Two other viral proteins, the phosphoprotein and the large protein (L-protein or polymerase) are associated with the RNP. Only the encapsidated genomic RNA will be a template for replication of the viral genome and transcription of the viral mRNAs by the RNA-dependent RNA polymerase, L protein. The P protein functions as a cofactor of the viral RNA polymerase binding to both N and L proteins. During virus assembly, the RNP is wrapped into an envelope containing an inner layer of the M protein and the transmembrane spike protein, G protein.[19] The principal host cell response for the viral infection activation is type –I interferon (IFN alpha/Beta) mediated immune response. Due to the capacity of P protein binding to STATs via CTD, these P proteins are major IFN antagonists of these viruses.[20] P-proteins can thereby inhibit activation of IFN-dependent reporter genes in protein expression studies. The M protein has the ability to bud from the cell surface in the form of lipid-enveloped virus-like particles, even in the absence of any other viral components; this information provides strong evidence that M protein plays a major role in the late budding step of the virus life-cycle.[21] G Protein-attaches the virus to the host cellular receptor, induces the endocytosis of the virion. L protein which is RNA dependent RNA polymerase has the potential to be therapeutic target for rabies as this protein is essential for the production of all viral proteins. It also conducts the replication of viral genomic RNA through its replicase activity. To act as a viral RdRp, the L protein needs to bind with its essential cofactor, P protein, existing in a viral ribonucleoprotein (RNP) complex which is formed by encapsidation of viral genomic RNA by N proteins.[22] Zoonotic infection begins with the bite of an infected animal into a muscle, followed by spread of virus particles through peripheral nervous system (PNS) somatic motor neurons and into the central nervous system (CNS). Spread of the infection from the CNS to salivary glands facilitates transmission to other hosts.[23] RABV initially infects peripheral tissues, followed by invasion of the innervating axon termini. Virus particles must undergo long distance retrograde axonal transport to reach the neuron cell bodies in the peripheral or central nervous system (PNS/CNS). In most cases, RABV in mammals reaches the brain causing the fatal encephalitis.[24] RABV infection which is a mitochondrial disorder initiated by interaction of the RABV P and Complex I. It is reported that mitochondrial dysfunction produces oxidative stress in neurons causing acute degenerative changes affecting neuronal processes resulting in severe clinical disease. This information

could be an important for the future development of novel therapies for rabies.[25]

Bioinformatics in its broad sense involves computer application for solving biological problems. It is a computational tools needed to effectively and efficiently process large amounts of data which are generated as a result of recent innovations in biology and medicines like wide variety of clustering and classification algorithms, including self-organized maps (SOM), artificial neural networks (ANN), support vector machines (SVM), and hyphenated techniques as neuro-fuzzy networks. These bioinformatics tools are being evaluated and applied in various medical areas including early detection, risk assessment, classification, and prognosis of cancer.[26] It is an interdisciplinary branch of science which utilizes statistics, computer and mathematics to analyse biological data.[27] Bioinformatics has been used now for many researches 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.[28] Docking analysis is conducted for the protein and the ligand for analyzing 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.[29]

The aim of our study is to compare the best docking fit for the selected *Coriandrum sativum* L flower constituents with the selected Dengue and Rabies 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 rabies virus were used for this study. The 3D structure of all the fourteen proteins were downloaded from PDB and saved in PDB format. The downloaded proteins were viewed in Py-Mol viewer.[30]

### 2.2. Preparation of ligands

Ligands selected were from the previous studies on GCMS analysis on *Coriandrum sativum* L flower extract.[9] 7 ligands were used for the study. Ligands were constructed using ChemSketch.[31] 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 and C 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.[32] 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.[33]

## 3. RESULTS

### 3.1. Total Binding Energy (kcal/mol) profile for Dengue and Rabies viruses proteins with 7 ligands.

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

| Ligand | Compound name | Dengue Virus | Rabies Virus | | |
|---|---|---|---|---|---|
| | | Envelope protein | Glyco protein | Polymerase L. | Phospho protein |
| A | Benzofuran,2,3-dihydro | -54.47 | -55.16 | -57.86 | -54.07 |
| B | 2-Methyoxy-4-vinylphenol | -68.32 | -63.87 | -66.6 | -70.57 |
| C | 2,6-Dimethyl-3-aminobenzoquinone | -67.56 | -67.72 | -71.15 | -68.61 |
| D | 2,3,5,6-Tetrafluroanisole | -64.06 | -70.38 | -64.21 | -61.29 |
| E | Dodecanoic acid | -71.92 | -65.62 | -63.36 | -81.06 |
| F | 2,4a-Epioxy-3,4,5,6,7,8,-hexahydro-2,5,5,8a-tetramethyl-2H-1-benzofuran | -57.81 | -57.54 | -54.63 | -55.31 |
| G | Hexadecanoic acid,methyl ester | -74.21 | -76.08 | -91.81 | -81.99 |

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

**Table 2: H – bond profile for Dengue and Rabies virus structural proteins with 7 ligands.**

| Ligand | Compound name | Dengue Virus | Rabies Virus | | |
|---|---|---|---|---|---|
| | | Envelope protein | Glyco protein | Polymerase L | Phospho protein |
| A | Benzofuran,2,3-dihydro | H-M | H-S | H-M | H-M<br>H-S |
| B | 2-Methyoxy-4-vinylphenol | H-M | H-S<br>H-M | H-S | H-S<br>H-M |
| C | 2,6-Dimethyl-3-aminobenzoquinone | H-M<br>H-S | H-M | H-M<br>H-S | H-M<br>H-S |
| D | 2,3,5,6-Tetrafluroanisole | H-M | H-S | H-S | H-M |
| E | Dodecanoic acid | H-M<br>H-S | H-M | H-M | H-S<br>H-M |
| F | 2,4a-Epioxy-3,4,5,6,7,8,-hexahydro-2,5,5,8a-tetramethyl-2H-1-benzofuran | H-S | H-M | - | - |
| G | Hexadecanoic acid, methyl ester | H-S<br>H-M | H-S<br>H-M | H-M | H-M |

### 3.3. Amino acid position profile for Dengue and Rabies viruses protein with 7 ligands

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

| Ligand | Compound name | Dengue Virus | Rabies Virus | | |
|---|---|---|---|---|---|
| | | Envelope protein | Glyco protein | Polymerase L | Phospho protein |
| A | Benzofuran,2,3-dihydro | Arg (629) | Gln(565) | Thr(248) | Leu(259), Tyr(294) |
| B | 2-Methyoxy-4-vinylphenol | Arg (629) | Gln(565), Val(566) | Gln(288) | Asp(289), Ser(220), Gly(221) |
| C | 2,6-Dimethyl-3-aminobenzoquinone | Lys(625), Val(626), Arg(629), Ile(630) | Tyr(536), Gln(565), Val(566) | Thr(248), Lys(242), Val(244), Gly(246), Arg(249), Thr(248) | Leu(257), Arg(260) |
| D | 2,3,5,6-Tetrafluroanisole | Gly(628), Arg(629), Ile(630) | Gln(565) | Gln(288) | Leu(259), Arg(260) |
| E | Dodecanoic acid | Arg(619), Lys(625) | Met(540) | Gly(246) | Lys(214), Arg(260) |
| F | 2,4a-Epioxy-3,4,5,6,7,8,-hexahydro-2,5,5,8a-tetramethyl-2H-1-benzofuran | Lys(625) | Trp(2), Glu(3) | - | - |
| G | Hexadecanoic acid,methyl ester | Ser(582), Asn(663) | Trp(2) | Arg(249) | Lys(214) |

## 4. DISCUSSION

Considering all the tables from Table – 1, to Table - 3, the 3D structure coordinates of one protein of dengue virus and three proteins of Rabies virus are optimized and 7 compounds from *Coriandrum sativum* L *flower* extract are identified. The total binding energy of the compounds with all the four proteins was calculated using iGEMDOCK. Evaluations of binding conformation of these 7 compounds with one dengue as well as three Rabies viral 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 rabies 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 structural proteins of Dengue virus, the, compound "G" is found to have lower ligand binding energy (binding energy value -74.21 kcal/mol), than other analogs for Envelope protein. The structural proteins of rabies virus had following binding energies, Glycoprotein ('G' binding energy value -76.08kcal/mol),

Polymerase ('G' binding energy value -91.81 kcal/mol), Phosphoprotein('G', binding energy value -81.99 kcal/mol). We further analyzed the docked pose for finding the binding mode of compound "G" in to one dengue and three rabies viral proteins to validate the reasonable binding conformations.

### 4.1. Structural proteins of Dengue Virus

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

From Table – 1, Table – 2 and Table – 3, the docking simulation of 7 ligands were performed for Dengue virus Envelop 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 -74.21 kcal/mol. Interaction analysis of binding mode of compound –G in dengue virus Envelope protein reveals that it forms two hydrogen bond with low energy, with Ser(582), Asn(663) 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.

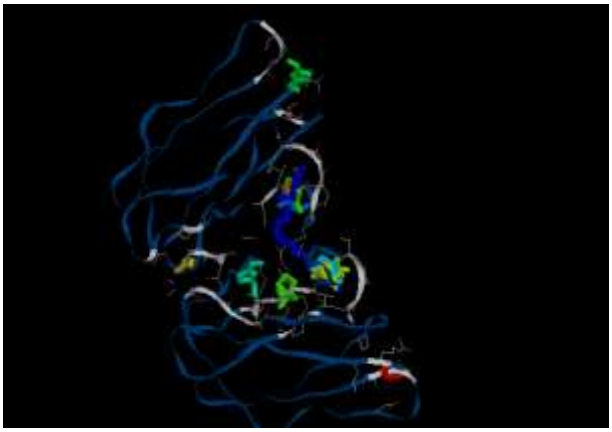

**Fig. 1: The Total Binding Energy for Dengue virus Envelope protein with 7 ligands.**

### 4.2. Structural proteins of Rabies virus

#### 4.2.1. The Total Binding Energy for Rabies virus Glyco protein with 7 ligands

From Table –1, Table – 2 and Table – 3, the docking simulation of 7 ligands were performed for Rabies virus Glycoprotein. From the docking study, we observed that compound – G has best binding affinity with the target Glycoprotein with the binding energy value of -76.08 kcal/mol. Interaction analysis of binding mode of compound –G in dengue virus Glycoprotein reveals that it forms two hydrogen bond with low energy, both with Trp(2) residue. A close-up view of the Total Binding Energy (kcal/mol) profile for Rabies virus Glycoprotein with 7 ligands: is shown in Fig.2.

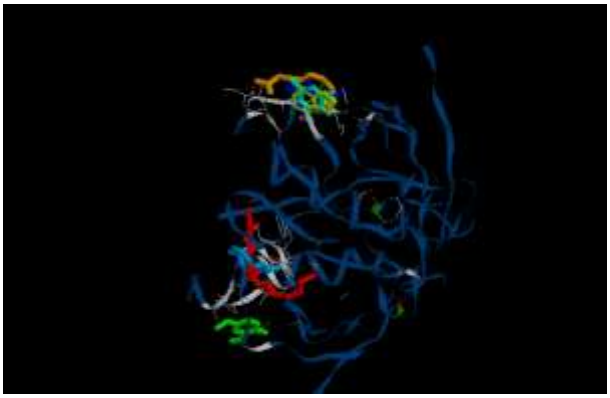

**Fig. 2: The Total Binding Energy for Rabies virus glycoprotein with 7 ligands.**

#### 4.2.2. The Total Binding Energy for Rabies virus Polymerase L protein with 7 ligands

From Table – 1, Table – 2 and Table – 3, the docking simulation of 7 ligands were performed for Rabies virus Polymerase L protein. From the docking study, we observed that compound – G has best binding affinity with the target polymerase L protein with the binding energy value of -91.81 kcal/mol. Interaction analysis of binding mode of compound –G in dengue virus polymerase L protein reveals that it forms one hydrogen bonds with low energy, with Arg(249) residue. A close-up view of the Total Binding Energy (kcal/mol) profile for Rabies virus polymerase L protein with 7 ligands: is shown in Fig.3.

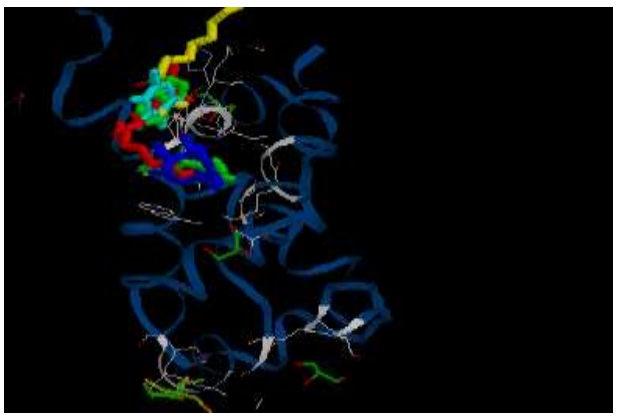

**Fig. 3: The Total Binding Energy for Rabies virus Polymerase L protein with 7 ligands.**

#### 4.2.3. The Total Binding Energy for Rabies virus Phosho protein with 7 ligands

From Table – 1, Table – 2 and Table – 3, the docking simulation of 7 ligands were performed for Rabies virus Phosphoprotein. From the docking study, we observed that compound – G has best binding affinity with the target Phosphoprotein with the binding energy value of -81.99 kcal/mol. Interaction analysis of binding mode of compound –G in dengue virus Phosphoprotein reveals that it forms one hydrogen bond with low energy, with Lys(214) residue. A close-up view of the Total Binding Energy (kcal/mol) profile for Rabies virus Phosphoprotein with 7 ligands: is shown in Fig.4.

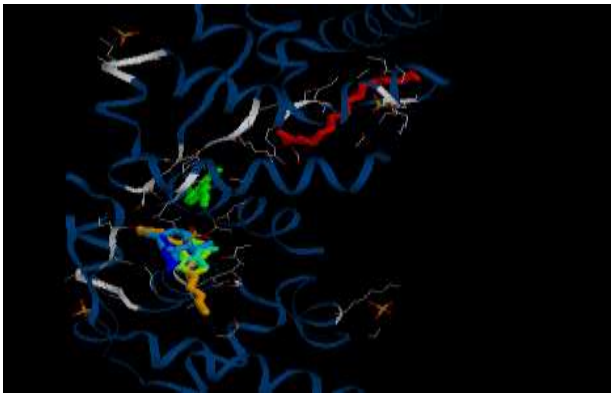

**Fig. 4: The Total Binding Energy for Rabies virus Phosphoprotein with 7 ligands.**

## 5. CONCLUSION

Our molecular docking studies explored the possible binding modes of 7 compounds that are present in *Coriandrum sativum* L *flower extract* with one envelope proteins of Dengue virus and three proteins of Rabies virus. Dengue virus consists of envelope protein; Rabies virus consists of Glycoprotein, Phosphoprotein and Polymerase L protein. It revealed that all the 7 compounds show minimum affinity with all the proteins. The compound G (hexadecanoic acid, methyl ester) shows 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 most of the selected structural proteins of Dengue virus as well as Rabies virus. Therefore it can be used as an effective drug target for Dengue virus as well as Rabies virus. 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 Rabies.

## 6. REFERENCES


1. Maryam Ahvazi, Farahnaz Khalighi-Sigaroodi, Mohammed Mahdi Charkhchiyan, Faran Mojab, Vali-Allah Mozaffarian and Hamideh Zakeri; "Introduction of Medicinal Plants Species with the Most Traditional Usage in Alamut Region", *Iranian Journal of Pharmaceutical Research*, 2012 Winter; 11(1): 185-194.
2. Farnsworth, N.R. "The Role of Ethno Pharmacology in Drug Developmen". Ciba Foundation Symposium 154. Bioactive Compounds from Plants. John Wiley & Sons, Baffins Lane, Chichester (England), 1990; 2-21.
3. M.M.Sharma, R.K.Sharma; "Handbook of Herbs and Spices", 2004; 2.
4. Muhammad Nadeem, Faqir Muhammad Anjum, Muhammad Issa Khan, Saima Tehseen, Javed Iqbal Sultan, Ahmed El-Ghorab ; "Nutritional and medicinal aspects of Coriandrum (Coriandrum sativum L.) : A review", *British Food Journal*, 115(5): 743-755.
5. Blumenthal M, Goldberg A, Brinkmann J, eds. Herbal Medicine: Expanded Commission E Monographs. Austin, TX: American Botanical Council; Newton, MA: Integrative Medicine Communications, 2000.
6. Aissaoui A, Zizi S, Israili ZH, Lyoussi B; "Hypoglycemic and hypolipidemic effects of Coriandrum sativum L. in meriones shawi rats", *Journal of Ethnopharmacol*, 2011; 137: 652-661.
7. Gray AM, Flatt PR; "Insulin-releasing and insulin-like activity of the traditional anti-diabetic plant Coriandrum sativum (Coriandrum)", *British Journal of Nutrition (United Kingdom)*, 1999; 81(3): 203– 209.
8. Srinivasan K; "Plant foods in the management of diabetes mellitus: spices as beneficial antidiabetic food adjuncts", *International Journal of Food Science and Nutrition*, 2005; 56(6): 399-414.
9. R. Dharmalingam and P. Nazni; "Phytochemical Evaluation of *Coriandrum* L Flowers", *International Journal of Food And Nutritional Sciences*, 2013; 2(4): 34-39.
10. Fan X, Schäfer H, Reichling J, Wink M. "Antibacterial properties of the antimicrobial peptide Ib-AMP4 from Impatiens balsamina produced in E. coli", *Biotechnol. J*, 2013; 8: 1213–1220.
11. Perera R, Kuhn RJ. Structural Proteomics of Dengue Virus. *Curr Opin Microbiol*, 2008; 11(4): 369-377.
12. Parekh J, Chanda S; "Antibacterial and Phytochemical Studies on Twelve Species of Indian Medicinal Plants". *African Journal of Biomedical Research*, 2007; 10(2): 175-181.
13. Sarangi KM, Padhi S; "Dengue and its Phytotherapy A Review". *International Journal of Pharmaceutical and Phytopharmacological Research*, 2017; 4(1): 37–46.
14. Elahi M, Islam MM, Noguchi K, Yohda M, Toh H, Kuroda Y; "Computational Prediction and Experimental Characterization of a Size Switch Type Repacking during the Evolution of Dengue Envelope Protein Domain III (ED3)". *Biochem Biophys Acta*, 2014; 1844(3): 585–592.
15. 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.
16. Xie X, Gayen S, Kang C, Yuan Z, Shi PY; "Membrane Topology and Function of Dengue VirusNS2A Protein". *J. Virol*., 2013; 87: 4609 – 4622.
17. Perera R, Kuhn RJ; "Structural Proteomics of Dengue Virus". *Curr Opin Microbiol*, 2008; 11(4): 369–377.
18. Lim SP, Noble CG, Seh CC, Soh TS, El Sahili A, Chan GK, Lescar J, Arora R, BensonT, Nilar S, Manjunatha U, Wan KF, Dong H, Xie X, Shi PY,

Yokokawa F. " Potent Allosteric Dengue Virus NS5 Polymerase Inhibitors: Mechanism of Action and Resistance Profiling". *PLoS Pathog,* 2016; 12(8): e1005737.
19. Tatsunori Masatani, Naoto Ito, Kenta Shimizu, Yuki Ito, Keisuke Nakagawa, Yoshiharu Sawaki, Hiroyuki Koyama, Makoto Sugiyama,; "Rabies Virus Nucleoprotein Functions To Evade Activation of the RIG-I-Mediated Antiviral Response", *Journal of Virology,* DOI: 10.1128/JVI.02220-09.
20. Linda Wiltzer Kazuma Okada Satoko Yamaoka Florence Larrous Henna Veera Kuusisto Makoto Sugiyama Danielle Blondel Hervé Bourhy David Andrew Jans Naoto Ito, Gregory William Moseley; "Interaction of Rabies Virus P-Protein With STAT Proteins is Critical to Lethal Rabies Disease", *The Journal of Infectious Diseases*, 2014; 209(11): 1744–1753.
21. Anastassia V. Komarova Eléonore Real Andrew M. Borman Michèle Brocard Patrick England Noël Tordo John W.B. Hershey Katherine M. Kean Yves Jacob; "Rabies virus matrix protein interplay with eIF3, new insights into rabies virus pathogenesis", *Nucleic Acids Research,* 35(5): 1522 – 1532.
22. Kento Nakagawa,a Yuki Kobayashi,b Naoto Ito,corresponding authora,c,d Yoshiyuki Suzuki,e Kazuma Okada,c Machiko Makino,c Hideo Goto,c Tatsuki Takahashi, a and Makoto Sugiyama; "Molecular Function Analysis of Rabies Virus RNA Polymerase L Protein by Using an L Gene-Deficient Virus", *Journal of Virology,* 2017; 91(20): e00826-17.
23. Davis BM, Rall GF, Schnell MJ. Everything You Always Wanted to Know about Rabies Virus (But Were Afraid to Ask). Annu Rev Virol., 2015; 2: 451–471.
24. Margaret A, Mac Gibeny, Orkide O, Koyuncu, Christoph Wirblich, Mathias J. Schnell, Lynn W. Enquist; "Retrograde axonal transport of rabies virus is unaffected by interferon treatment but blocked by emetine locally in axons", 2018; https://doi.org/10.1371/journal.ppat.1007188.
25. Alan Jackson, Wafa Kammouni, Heidi Wood, Paul Fernyhough; "Rabies Virus Causes Acute Neurological Disease by Inducing Mitochondrial Dysfunction and Oxidative Stress: Critical Role of the Rabies Virus Phosphoprotein (S41.003)", *American Academy of Neurology*, 2018; 90(15 supplement).
26. Izet M. Kapetanovic, Simon Rosenfeld, Grant Izmirlian; "Overview of Commonly Used Bioinformatics Methods and Their Applications", *Annals of the Newyork Academy of Sciences,* 2004; 1020: 10–21.
27. Mehmood MA, Sehar U, Ahmad N. "Use of Bioinformatic Tools in Different Spheres of Lifesciences". *Journal of Data Mining in Genomics &Proteomics*, 2014; 5(2): 1000158.
28. 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.
29. Ferreira LG, Ricardo N, Oliva G, Andricopulo AD. "Molecular Docking and Structure-Based Drug Design Strategies". *Molecules*, 2015; 20: 13384–13421.
30. Sushmitha H. S, Balasubramanian Sathyamurthy. "In Silico drug designing studies on Dengue Virus NS2BNS3 Protease", *Indo American Journal of Pharmaceutical Sciences*, 2018; 5(80: 7784 – 7790.
31. Sushmitha H. S, Balasubramanian Sathyamurthy. "In Silico drug designing studies on Dengue Virus Envelope Protein". *World Journal of Pharmaceutical sciences,* 2018; 6(9): 138–143.
32. Sushmitha H. S, Balasubramanian Sathyamurthy. "In Silico drug designing studies on Dengue Virus NS3 Helicase". *European Journal of Biomedical and Pharmaceutical sciences*, 2018; 5(9): 520–524.
33. Sushmitha H. S, Balasubramanian Sathyamurthy. "In Silico drug designing studies on Dengue Capsid Protein". *World Journal of Pharmaceutical and Life Sciences*, 2018; 4(9): 157–161.