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Review Article

Review on molecular docking analysis of herbal compounds and their activity against SARS and JEV using *In-silico* and *In vitro* approaches

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ABSTRACT

In-silico or computational methods play key role to design and develop new drugs and target proteins in the fields of pharmaceutics and biotechnology. Various methods like Homology modelling, Molecular docking, Monte Carlo simulation etc. are used in *In-silico* drug designing. In this review, we describe the different medicinal compounds which were screened by using computational methods and *In vitro*. Many of the natural herbal compounds have been found to be effective against in SARS CoV infection by inhibiting viral replication and nucleo-capsid protein. Similarly, compounds like Chemdiv-3, kaempferol, etc. have been studied for their action against JEV. In order to screen the thousands of compounds in library the *in-silico* predictions are the best tools to select the compound which has potential affinity to inhibit the JE infection. However, the experimental data also must require determining the activity of compound against specific target and the data obtained in the *in-silico* may not be reliable as compared to in-vitro or in-vivo. Variations are found between Computational and experimental data.

1. Introduction

To bring out a new drug from the laboratory to the market, it takes approximately 10-12 years with an average cost US $1.2 to $1.4 billion or more per drug.[1] Thus, there is a need for some fast processes and methods for the designing, discovery and development of a new chemical entity (NCE). There are many computational and *Insilico* tools such as genomics, proteomics, bioinformatics, and excellent technologies like, combinatorial chemistry, high throughput screening (HTS), virtual screening *in vitro*, in silico ADMET screening, *de novo* and structure-based drug design that plays an important role to speed up the modern era drug discovery and development process.[2] Computational drug design approaches are mainly concentrating on the design of ligands/molecules for active or target sites with identified three-dimensional structure. Computational methods are also helpful to check the Drug-likeness properties of the molecule, after that molecule is docked with the target, selected according to their binding affinities. These molecules are further optimized to enhance binding characteristics and the toxicity is predicted by using different online web servers. Computational techniques integrate biological, mathematical and computer-based models to predict the most favourable binding conformation of ligands in the active site of the particular receptor. The prediction power of these techniques is increasing day by day due to advancement in the field of Molecular Biology, Biotechnology, Bioinformatics, Mathematics, and Chemistry.[3] The *insilico* drug discovery process is described in figure below-

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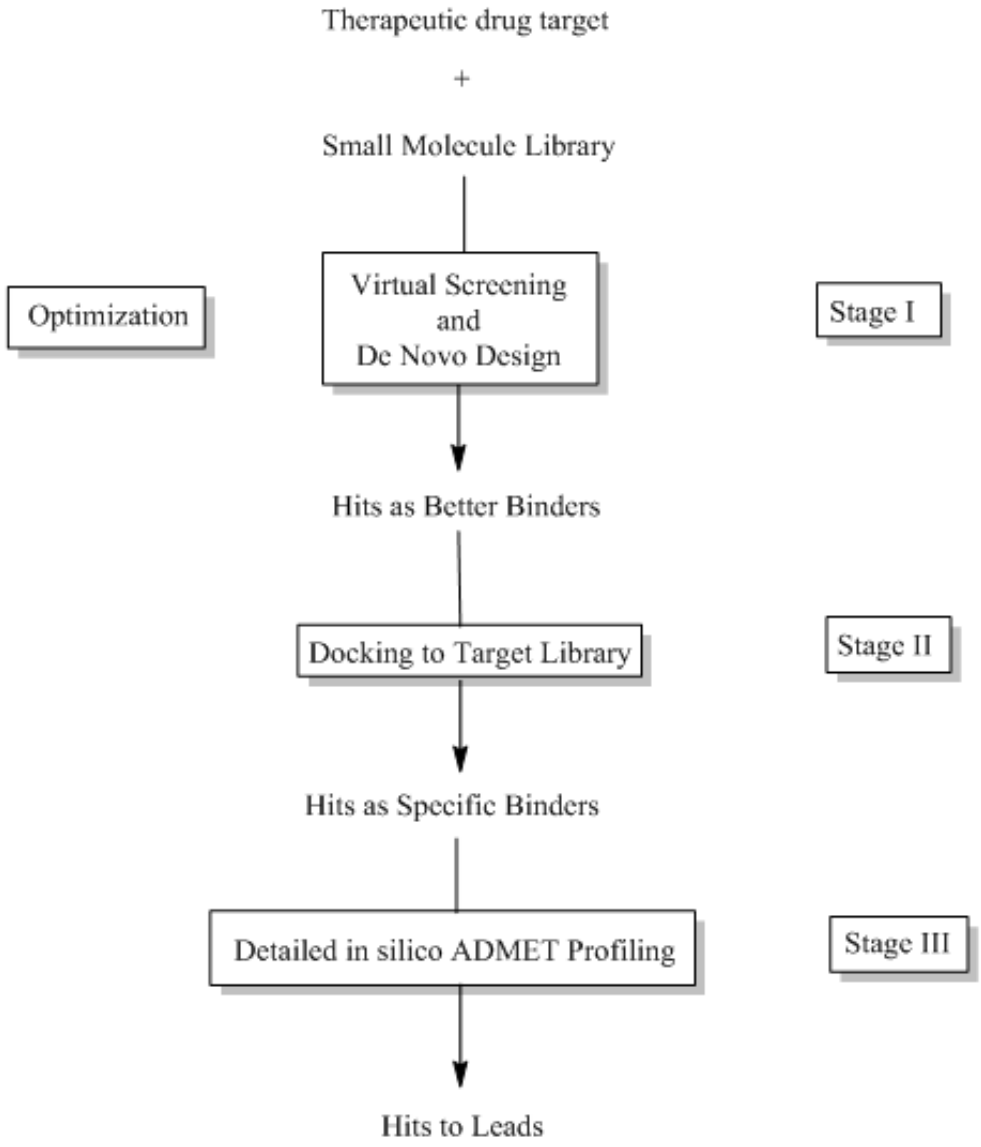

Fig. 1: A flowchart outlining a generalized structure-based *insilico* drug discovery strategy

To select a novel drug candidate, *in-silico* or computational methods play key role to design and develop new drugs and target proteins in the fields of pharmaceutics and biotechnology. These methods are used to investigate molecular modeling of gene, gene sequence, gene analysis and 3D structure of proteins which play a great role in target identification and prediction of new chemical entity.

2. Methods used in *in-silico* drug designing

Some important *in-silico* techniques which are helpful in drug design are follows.

2.1. Homology modelling

Homology modelling allows making an unidentified model of a target protein according to its amino acid arrangement and experimental three-dimensional structure of a related homologous protein and displays similarity with the sample sequence.[4]

2.2. Molecular docking

Molecular docking includes the interaction of two or more molecules to form a stable complex. Stability of the complex depends upon the binding properties of ligand and target protein.[5] The most appropriate complexes are selected on the basis of scoring function in the software. The molecules are docked against the active site and then scored to identify

the one which binds more tightly to the target protein.[6]

2.3. Virtual screening

Virtual screening allows testing of large libraries of molecules and compounds for their potential to interact with specific site of target protein which can screen more than thousands of possible molecules to a practicable number that can be easily synthesized, purchased and tested in the laboratory.[7]

2.4. Quantitative structure-activity relationship

Quantitative structure-activity relationship is widely used to demonstrate the relationship between the structural properties of molecules with their biological activities.[8]

2.5. Comparative molecular field analysis

Comparative molecular field analysis is a well-recognized 3D QSAR method which gives the values of ClogP which shows the solvent repellent constraints of the ligands and also describes the steric and electrostatic values of the ligands.[9]

2.6. Comparative molecular similarity indices analysis

Comparative Molecular Similarity Indices Analysis is used in the drug discovery process to recognize the common properties, which are important for the suitable biological receptor binding with ligands.[10]

2.7. 3D Pharmacophore mapping

3D Pharmacophore mapping quickly predicts lead compounds along with a preferred target which has been used to make it most powerful and successful *insilico* and computational method.[11]

2.8. Conformational analysis

Conformations of molecules play a key role in the prediction of the physio-chemical properties but also helpful in prediction of biological activity of the compound.[12]

2.9. Monte carlo simulation

Monte Carlo simulation helps in the generation of suitable conformations of a system by using computer simulation to allow thermodynamic, structural, and numerical properties to be calculated as a weighted average of these properties over these conformations.[13]

In this review we describe the different medicinal compounds which can be screened by the use of computational methods.

3. Materials and Methods

3.1. Selection and refinement of various targets of JEV protein

The reported three-dimensional (3D) crystal structures of different microbial proteins were retrieved from Protein Data Bank (PDB) available at (http://www.rcsb.org/pdb/home/home.do). Retrieved structures were downloaded in PDB format and exported into the Maestro software (Schrodinger, LLC, Cambridge, USA) and refined by mediating insertion of processing, optimization, and minimization steps indicated in protein preparation wizard.

3.2. Binding site detection

Site map tool from Schrodinger was used to find the active sites in protein which have not internal ligand in their structure. The site score and draggability scores were used to select potential binding sites. The sites having the draggability score near to 1 were considered for docking study.[14]

3.3. Preparation of ligands

Chemical structures of the herbal compound were obtained from the PubChem chemistry database, and the structures drawn and optimized in ChemDraw (Perkin Elmer Informatics, Waltham, MA, USA). The low energy 3D conformation of ligand was executed with the support of LigPrep OPLS3e force field. The ionization states were also adjusted prior to docking simulations.

3.4. Molecular docking

Maestro suites (Schrodinger, LLC, Cambridge, USA) was used to dock herbal compounds against the target proteins of microbes. The receptor grid was generated by specifying the internal ligand and by doing the site mapping for the proteins which have not internal ligand in their structure.[15]

3.5. Molecular dynamics simulations were performed for herbal compounds towards the target proteins by using Desmond module of Schrödinger with 100ns simulation time. The root mean square deviation (RMSD) for the protein backbone and root mean square fluctuation (RMSF) of the protein residues were plotted to examine the convergence of the ligands to equilibrium.

4. Review of Literature

4.1. In-silico study or computational screening of compounds against SARS

Shen et al.[16] have screened 290 compounds against HCoV-OC43 strain and found 27 compounds to be effective against SARS.

Table 1: In- vitro study of herbals used against SARS

Herbal extract	Active Constituent	Family	Cells	Strain	Conc.	IC 50 value/EC 50 value	Mechanism	
-	Lycorine	Amaryllidaceae	Vero E6, BHK-21, DBT, 293 FT, LLC-MK2, 17-Cl-1, and DPP4 expressing Huh 7.5 cells	HCoV-OC43	-	EC 50 value 0.15 μM	Inhibition of viral replication	[16]
Pectolinarin	α-L-rhamnopyranosyl, L- mannopyranosyl, β-D-glucopyranoside and β-D-glucopyranoside	-	E. Coli BL 21(DE3)	-	2-320 μM	IC 50 value 37.78 μM	-	[17]
Tetraandrine	-	Menispermaceae	MRC-5	HCOV-OC 43	0.2 μM	IC 50 value 0.33± 0.03 μM	By inhibiting the nucleocapsid protein and HCoV-OC43 spike expression	[18]
Juglanin (arabinose residue)	Kaempferol, kaempferol glycoside, acylated kaempferol glucoside	*Polygonaceae*	Xenopus oocytes	-	10 μM, 20 μM	IC 50 value 2.3 μM	Inhibit 3a ion channel of coronavirus	[19]
(ethanolic extract)	Phlorotannin	-	Vero cells (African green monkey cell line)	PEDV SM 98 strain	30 μM	IC 50 value 12.4 ±2.2 μg/ml	By inhibiting viral haemagglutination binding to SA receptor in host cells	[20]

Continued on next page

Table 1 continued

-	Scutellarein	Lamiaceae	-	-	2 μm	IC50 value 0.86± 0.48μM	Inhibition of SARS CoV helicase and nsP13 by affecting the ATPase activity	[21]
Salvia miltiorrhiza (dried roots) (ethanol extract)	-	Laminaceae	E. Coli BL21 (DE3) Codon Plus RIL cells	-	30, 15, 7.5 μM	IC 50 value 0.7 μM	Inhibits cysteine protease	[22]
-	Gallocatechin gallate	-	-	-	-	IC 50 value 47 μM	By blocking the enzymatic activity of SARS CoV 3CL ^{pro}	[23]
Euphorbia neriifolia (ethanolic extract)	3-β-friedelanol, 3-β-acetoxyfriedelane, friedelin actinomycin D, epitaraxerol,	Euphorbiaceae	MRC-5 cells	Strain 229 E	-	-	-	[24]
Pelargonium sidoicks (aqueous extract)	Eps 7630	Geraniaceae	MDCK, Vero, Caco-2, Mel-Ho, Human foreskin fibroblast	Influenza virus strain H1N1, H3N2, H5N1	100 μg/ml	-	-	[25]
Sinomenium acutum	-	Menispermaceae	Mouse Spleenic lymphocytes	-	0-400 μg/ml	IC 50 value 198.6 μg/ml	By inhibiting SARS CoV RdRp and 3CL pro	[26]
Coriolus versicolor	-	Polyporaceae	Mouse Spleenic lymphocytes	-	0-400 μg/ml	IC 50 value 108.4 μg/ml	By inhibiting SARS CoV RdRp and 3CL pro	[27]

Continued on next page

Table 1 continued

Torreya nucifera (leaf) (ethanolic extract)	Amentoflavone	Taxaceae	–	-	100 μg/ml	IC 50 value 8.3 μM	By inhibiting SARS CoV 3CL protease activity	[28]
Tylophorine compounds (methanolic extract)	phenanthroindozolidine and phenanthroquinolizidine	Apocynaceae	Vero 76 cells	SARS CoV Urbani strain	5, 50, 500 nm	less than 5 to 40 nm		[29]
-	Procyanidin A2 Procyanidin B1	-	-	SARS CoV PUMC 01F5	-	i)IC50 value 29.9±3.3μM ii)IC50 value 41.3±3.4 μM	Interfering with endocytosis	[30]
Rheum palmatum L. (root and rhizomes) (ethanolic extract)	Anthraquinone	*Polygonaceae*	Vero E6 cells	SARS CoV and SARS CoV 3CL protease	100, 50, 25, 12.5, 6.25, 3.12 and 1.56 μg/ml	IC 50 value 13.76 ±0.03 μg/ml (96%)	Inhibits SARS-3CL pro activity	[31]
Toona sinensis (aqueous leaf extract)	-	Meliaceae	African green monkey kidney cell line Vero (CCL-81)	i) HCoV 229 E strain ii) Sar CoV strain FFM1	i)5-20 μg/ml ii)50-200 μg/ml	-	Inhibit the cellular entry of SARS CoV	[32]
Houttuyria cordata (aqueous extract)	-	Saururaceae	Mouse splenic lymphocytes	-	0-400μg/ml	IC50 value 50-1000 μg/ml	By inhibiting SARS CoV 3CL protease activity, viral polymerase and RdRp activity	[33]
Sophora subprostateradix (methanolic extract)	Matrine, oxymatrine, sophoranone, sophocarpine	Fabaceae	Vero cells	Plaque cloned A59 strain of MHV Mouse DBT cells	1, 10, 50, 100 μg/ml	EC 50 value 27.5 ±1.1 μg/ml	-	[34]

Continued on next page

Table 1 continued

Veronica linariifolia (ethanolic extract)	Luteolin	Plantaginaceae	Vero E6 cells	SARS CoV (BJ01 strain)	-	EC50 value 10.6 μm	By binding with the surface spike protein of the virus and interfering with the entry of the virus into the host cells	[35]
Boenninghausenia sessilicarpa (ethanolic extract)	Laptodactylone	-	Vero E6 cells	RPMI-1640	100, 20, 4 μg/ml	EC50 value 60%, 4% and 0% respectively	-	[36]
-	Saikosaponin B2		MRC-5, ATCC, CCL-171	HCoV 229E strain	6 μmol/L	IC50 value 1.7±0.1 μmol/L	By preventing viral attachment and penetration at the early stage of HCoV-229E infection	[37]
Glycyrrhiza	Glycyrrhizin, Glycyrrhizic acid derivative	Fabaceae	Vero E6 cells	SARS CoV strain FFM1	4000ug/ml	EC 50 value-40 μM (5- 50 μM)	Inhibition of viral replication, Induction of cellular NO -synthase and thus affecting viral adsorption and penetration	[38]
Lindera aggregate (root) (ethanolic extract)	-	Lauraceae	-	Viral Strain i) BJ001 ii) BJ006	–	EC50 value 88.2(±7.7) EC50 value 80.6(±5.2)	-	[39]
Isatis indigotica (root) (aqueous extract)	Indigo, indirubin, indicant, β-sitosterol γ-sitosterol and sinigrin	Cruciferae	Vero cells	-	-	IC50 value 90.1±4.2 (217 μM)	By inhibiting the 3CL protease enzyme	[40]

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Table 1 continued

Calophyllum blancoi (acetone extract)	Blancoxanthone	Guttiferae	Human lung fibroblast (MRC-5)	HCOV-229 E strain	-	EC 50 value 3 μg/ml	–	[41]
Galla chinensis (ethanolic extract)	Tetra-O-galloyl-β-D glucose (TGG)	-	Vero E6 cells	SARS CoV (BJ01 strain)	-	EC50 value 4.5 μm	By binding with the surface spike protein of the virus and thus interfering entry of the virus into the host cells	[42]
Scutellaria baicalensis	Baicalin	Lamiaceae	i)frhK4 cell line ii) Vero E6 cells	i)SARS CoV ii)39849 strain	11 μg/ml	i)EC 50 value 12.5-25 (48 hr) 25-50 (72 hr) ii)EC 50 value 12.5(48 hr) 100 (72 hr)	Inhibit Angiotensin-converting enzyme (ACE)	[43]
Aescin (Horse chestnut)	-	Sapindaceae	Vero E6 cells	-	3 μM	EC 50 value 6.0 μM	-	[44]
Glycyrrhiza	Glycyrrhizin, Glycyrrhizic acid derivative	Fabaceae	Vero cells	SARS CoV	4000ug/ml	EC 50 value-300 mg/L (316-62.5 mg/L)	Inhibition of viral replication, Induction of cellular NO -synthase and thus affecting viral adsorption and penetration	[45]

Jo et al.[17] have screened various compounds through induced fit docking studies and proteolytic assay and found that compounds such as Herbacetin, rhoifolin pectolinarin were found to be effective against SARS CoV.

Nguyen et al.[23] have screened various flavonoids through molecular docking studies against 3CLpro of SARS CoV and found gallocatechin gallate (with binding energy -14kCal/mol) to be the best compound effective against SARS-CoV. Ryu et al.[28] reported flavones such as apigenin, luteolin and quercetin were able to inhibit 3CLpro activity with IC50 values of 280.8, 20.2, and 23.8 μM respectively.

Chen et al.[56] performed molecular docking studies and SPR/FRET-based bioassay on quercetin-3-β-galactoside which might be effective against SARS CoV through inhibition of 3CLproactivity. Ho et al.[35]have performed computational screening of 312 Chinese medicinal herbs and found 3 compounds belonging to the family *Polygonaceae* to be effective against SARS virus.

Wang et al.[57] screened 11 molecules from TCMD primarily based on template strain MDL 28170 and found MOL736 (derived from *Artemisia annua*) with the lowest binding energy and highest similarity reported to be effective against SARS CoV by inhibiting endosomal protease activity of SARS virus.

Toney et al.[58] have screened 14000 molecules and reported 1853 molecules to serve as 3CLpro inhibitors. Further molecular docking studies showed that the 10 compounds have the lowest docking energy (-11.6 kCal/mol) with desirable chemical properties as therapeutics.

4.2. Herbals used against SARS (in-vitro study)

Many of the natural compounds like lycorine, emetine, herbacetin, pectolinarin, rhoifolin, glycyrrhiza, lycoris radiata, aloe-emodin, baicalin and isatis indigotica are found to be effective against in SARS infection by inhibiting viral replication and nucleocapsid protein against SARS CoV strain. The relevant studies have been extracted from Pub Med and compiled in the below mentioned Table 1.

5. Correlation of *In-silico* data to Experimental Data

In order to screen the thousands of compounds in library the *in-silico* predictions are the best tools to select the compound which has potential affinity to inhibit the JE infection. However, the experimental data also must determine the activity of compound against specific target and the data obtained in the *in-silico* may not be reliable as compared to *in-vitro* or *in-vivo.*

The drugs show different activity *in-vivo* as compared to *in-silico* and in-vitro, this may be due to poor pharmacokinetic properties or physicochemical properties or inability to interact with the target at particular environment etc. So, in current review we have correlated the *in-silico* and experimental (in-vitro or in-vivo) activity of the molecule against JEV infection. However, we have found valid and similar results against JE infection under *in-silico* and also in-vitro and in-vivo except for some compounds.

By computer simulations, Chemdiv-3 was found to be effective against JEV, and at a concentration of 20μM has potential to inhibit the viral growth in animal (Balb-2 strain mice), it has shown moderate activity against JE infection and the mice survived 3 more days compared to control mice (which JE infected mice).[46] In case of Phytolacca-mother tincture, excellent results were shown *in-silico* as well as in-vivo (in JE infected human), at the concentration of 26.5μM upon daily administration.[55]

Kaempferol and daidzein have also shown great activity by computational simulations. However, the experimental data has shown that moderate activity (in-vitro) towards JE infected BHK-21 cells which inhibitted 70% of viral replication at the concentration of 25.7 μM kaempferol and 29.7 μM for daidzein.[48] Doxycycline and kanamycin are capable of inhibiting JE infection and inflammation under in-vivo conditions similar to computational study. But, doxycycline has shown more activity than kanamycin intraperitoneally into Swiss albino mice.[59] CW-33 has shown similar interaction under *in-silico* and in-vitro by inhibiting the RNA replication against JEV.[50]

Niclosamide, Cilnidipine and FGIN-1-27 and Rosameric acid have shown very effective against JEV by computational simulation. However, Niclosamide, Clinidipine have shown poor activity in-vivo (mice) due to poor penetration into blood brain barrier, whereas Rosameric acid and FGIN-1-27 have shown similar activity as *in-silico* which prevented increasing of viral load in JE infected mice.[51,52] Fang et al.[53] have discovered 2 azole compounds which have shown similar interaction *in-silico* whereas, compound 1 has shown 71% inhibition and compound 2 has shown 95% inhibition in-vitro.

Other drugs like 4-hydroxypandurantin, Aminotetrahydroquinazoline derivative were tested only by *in-silico* approaches, further investigation is required for the exploration of those drugs for the treatment of JEV infection.[54]

6. Conclusion

Studies conducted on treatment of viruses like SARS CoV and Japanese Encephalitits Virus with various herbal compounds. The efficacy of the drugs or compounds was tested by different In silico and *In vitro* methods. The drugs have shown varied binding efficacy targeting different viral proteins and few of them interacting with viral RNA. The inhibitory action of the drug also varied with the concentration. However, the behavior of the drug is different In silico and *In vitro*.

Table 2: List of compounds analyzed against JEV by using *insilico* techniques

Drug	Binding interactions with different targets of JEV.	Binding affinity (ΔG) Kcal/Mol	Target	
Chemdiv-3	H-Bonding- ASN313, PRO314, ALA315, VAL323.		Envelope protein. (3P54)	46
4-hydroxypandurantin	H-Bonding- GLY80, ASP81, ILE60, VAL60, TRP62. Hydrophobic contact- ASP79, CYS101, LEU104, ALA105, THR108, ALA111, ILE112, ALA115, TYR119.	−9.95	NS3 helicase	47
kaempferol	Make complex with RNA by R1B, R2B, R3B.	R1b= -3.64 R2b= -3.70 R3b= -5.04	NS1 (5O36)	48
kanamycin	Vander waal force-LYS200, GLN457	-147.367	NS3 helicase/nucleoside triphosphatase (2z83)	49
CW-33	H-BOND- ASN152, GLU115. Π cation-ARG76.	Dock score= 42.021	NS2B‑NS3 protease (4R8T)	50
Rosameric acid	Hydrogen and weak vab der waal forces with LYS, TYR, PRO, ALA, PHE.	-126	Envelope Protein Domain III (3P54)	51
Niclosamide	H-BOND- LYS166: LYS166:123.	-5.43	Envelope protein (3P54)	52
Compound 1 and compound 2.	Compound-1- H-bond- HIS-288, THR451, ARG458. Compound-2- THR451, HIS288, ARG458, THR290.	_____	NS3 helicase (2z83)	53
Deoxynojirimycin	H-BOND- ASP10, ASN8, ASP10, CYS30, VAL24.	-6.55	envelope protein (3P54)	54
Phytolacca Americana L	ASP-542, CYS-82	NS3 (-655.1) NS5 (-782.7) envelope protein (633.4)	NS5 (4K6M) NS3 (2Z83) envelope protein(3p54)	55

7. Conflict of Interest

The authors declare no relevant conflicts of interest.

8. Source of Funding

None.

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