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Identification of Potential Novel Inhibitors for Nipah Virus – An *in silico* Approach

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A B S T R A C T

NipahVirus (NiV) is a zoonotic Virus which infects several animals and humans worldwide. Currently, there is no specific drug or vaccine to treat or control NiV infections. The present study is aimed to identify novel inhibitors of NiV from Indian medicinal plants. Glycoprotein was taken as target protein. Around 600 phytocompounds were taken from 10 Indian medicinal plants and subjected to Virtual Screening by using Libdock module from Discovery Studio 4.0. From these, the best 20 compounds were screened and evaluated for their Pharmacokinetic properties by using ADMETSAR and pKCSM tools. Toxicity studies were also performed using TOPKAT- Discovery Studio 4.0. Evaluated compounds were taken for individual docking. Molecular Dynamics (MD) simulation study was done by using GROMACS 5.1.2 to find the stability of the best interacted protein and ligand complex. From the results of this study, Neoandrographolide (Libdock score: 146.79), Hexahydrocurcumin (Libdock score: 146.501) and Nirphyllin (Libdock score: 141.896) showed better interaction with target protein. Hence, the present study concludes that the Neoandrographolide from *Andrographis paniculata*, Hexahydrocurcumin from *Zingiber officinale* and Nirphyllin from *Phyllanthus amarus* are having the potential ability to act as the best inhibitor for the target protein of NiV.

Introduction

Nipah virus belong to the genus *Henipavirus* of the family *Paramyxoviridae* and Nipah virus infections are of zoonotic nature (WHO, 2019). Encephalitis caused by Nipah virus is of significant public health importance and, based on the diffusion patterns and mortality rates, two different strains of Nipah virus (NiV) namely, NiV Malaysia (NiVM) and NiV Bangladesh (NiVB) have been reported of which, NiVB is more pathogenic (Shimojima *et al.*, 2006) than the other. Humans and many vertebrate animals are affected by NiV (Eaton *et al.*, 2006) and NiV infections have significant economic importance in pig husbandry (WHO, 2019). The first outbreak of NiV was reported in the year 1998 in Kampung Sungai Nipah, Malaysia and subsequently in Bangladesh

(Hsu *et al.,* 2004). Neighbouring India reported two outbreaks in the year 2001 and 2007 in the state of West Bengal (Searo, 2019a). In South India, the first NiV outbreak was found in Kozhikode, Kerala during May 2018 with 17 human deaths (Searo, 2019b).

Though very few outbreaks of NiV have been reported in Asia, it resulted in human mortality (WHO, 2019). Though pigs play a role in the transmission of NiV, involvement of pigs was not confirmed in the 1998-1999 outbreak in Malaysia. There has also been a strong evidence of human-to-human transmission of NiV in few of the Indian and Bangladesh outbreaks. In Bangladesh, 161 people were reported to have been died by NiV infection (Searo, 2019a).

Fruit bats (Flying foxes) are reported to be the natural wildlife reservoir of NiV which transmit the virus to both humans and animals. The Indian Flying Fox (*Pteropus giganteus*) and short-nosed Indian fruit bat (*Cynopterus sphinx*) are the mostly prevalent species in South Asia which act as main carriers for NiV (Bishop *et al.,* 2008). NiV has been found in urine, kidney and uterus of infected wild bats and the virus has also been found in fruits or juice like date palm sap contaminated with the urine or saliva of bat. Polluted drinking water, abandoned bat foetuses or other fluids/tissues of parturition have been reported as other source of NiV infections (WOAH, 2009).

Consumption of fruits or fruit products like contaminated raw date palm sap are the main causes for NiV outbreaks in India and Bangladesh (Luby *et al.,* 2012) apart from those working in trees (Montgomery *et al.,* 2008). In humans, symptoms of NiV infection generally include headache, fever, sore throat, myalgia and vomiting followed by dizziness, altered consciousness, and neurological signs like acute encephalitis. Atypical pneumonia and respiratory problems are also noticed in few instances with seizures leading to coma (WHO, 2019).

In domestic animals, pigs may be symptomless, but other animals might show acute febrile illness, laboured breathing, and neurological signs like trembling, twitching and muscle spasms (Nor *et al.,* 2000).

Understanding the molecular structure of the pathogens is essential in designing treatment and implementing control strategies. NiV genome consists six coding regions and several non-coding regions. The six coding regions include, Nucleoprotein (N), Large (L) protein, Phosphoprotein (P), Matrix (M) protein, Fusion (F) protein and Glycoprotein (G) wherein, nucleoprotein is used to make nucleocapsid and acts as a model for replication and transcription of the virus.

In addition, RNA dependent RNA polymerase accelerates this protein (Wang *et al.,* 2001). Fusion protein is responsible for membrane fusion (Horvath *et al.,* 1992) and Glycoprotein is involved in fusion and attachment (Moller-Tank and Maury, 2015, Mehmood *et al.,* 2014, Moll *et al.,* 2004). In the present study, Glycoprotein was taken as target protein.

As of now, there are no specific drugs and vaccines available for the treatment and control of NiV infections, necessitating the need for focused research in developing vaccines and identifying possible therapeutic molecules. Use of medicinal plants is one of the priority areas in combating viral diseases and hence, the present study is designed to identify potential novel inhibitors of NiV from Indian medicinal plants through Structure based virtual screening, Pharmacokinetic, Docking and Simulation studies.

Materials and Methods

Selection and retrieval of 3D structures of target protein

In the present study, Glycoprotein (PDB ID: 3D11) was selected as target protein. The 3D structure of this protein was downloaded from the PDB database.

Selection and retrieval of 3D structures of ligands

Around 600 compounds were selected from ten medicinal plants namely, *Zingiber officinale, Punica granatum, Phyllanthus amarus, Ocimum basilicum, Momordica charantia, Hypericum perforatum, Curcuma longa, Centella asiatica, Azadirachta indica* and *Andrographis paniculata* using IMPPAT database (Mohanraj *et al.,* 2018), of which 250 compounds were shortlisted based on the Lipinski Rule of Five. Further, 3D structures of ligands were retrieved from PubChem database.

Virtual screening and docking

The 250 phytocompounds selected were subjected to virtual screening with target protein and the results were analyzed. Based on the analysis, the best compound was subjected to docking with target protein using LibDock module of Discovery studio 4.0 wherein higher LibDock scores indicated better affinity.

Pharmacokinetic and Toxicity studies

Compounds having the best LibDock score were evaluated for pharmacokinetic properties using ADMETSAR and pKCSM tools. Toxicity studies were also performed for the best compounds using TOPKAT- Discovery Studio 4.0 and the results were analyzed.

Simulation studies

Molecular Dynamics (MD) simulation was employed to investigate the stability of protein-ligand complex generated from the Discovery Studio 4.0 docking procedures. Gromacs 5.1.2 package was employed to perform MD simulation. Before MD simulation, Gromos 9643a1 force field was used for the protein coordinate parameters and topology. The ligand topology and initial geometries of the ligand were taken from PRODRG web server (Schuttelkopf and Van Aalten, 2004). The systems were designed after merging the coordinates and topology parameters of both the protein and ligand. TIP3P water model was used to solvate the system in a dodecahedron box and counter ions were used to neutralize the system. Steepest descent algorithm was used for energy minimization for 1000 steps. When the upper limit of the force was lower than 1000 kJ/mol, bad contacts and steric clashes of protein–ligand complexes were removed. Subsequently, protein–ligand and solvent-ions groups were formed in each minimized system for avoiding subside and it was taken for equilibration. Two components were involved in the equilibration of each system. With the help of Berendsen thermostat algorithm, the first equilibration was done at constant volume (NVT) for 100ps at constant temperature of 300 K. According to the algorithm of Parrinello– Rahmanbarostat and LINCS, the second equilibration was performed for 100 ps at constant pressure (NPT) of 1 bar. Electrostatic interactions were examined by Particle Mesh Ewald method (Essmann *et al.,* 1995). Thus, after completing all the optimization procedures, the simulation was done for 10 ns (10000 ps) to evaluate the stability. Finally, Root Mean Square Deviation (RMSD), Root Mean Square Fluctuations (RMSF) and Radius of Gyration (Rg) were analyzed using the GROMACS comments g_rmsd, g_rmsf and

g_gyrate, respectively (Van Der Spoel *et al.*, 2005).

Results and Discussion

Selection and retrieval of 3D structures of target protein and ligands

As there are no specific treatment or vaccines for NiV infection, increasing the public awareness about NiV infections, and identifying the therapeutic and vaccine candidates could be the possible solutions to prevent future NiV infections. Ribavirin, the drug used during NiV infections will be useful only in alleviating nausea, vomiting and convulsions (Chong *et al.*, 2001). Hence, in this study, we tried to identify potential inhibitors of NiV from Indian medicinal plants using *in silico* methods.

The 3D structure of Glycoprotein (PDB ID: 3D11) was retrieved from PDB database and the 3D structures of all the ligands were taken from PubChem database and their CID numbers were noted.

Virtual screening and docking studies

In our study, the target protein (glycoprotein) of NiV was subjected to virtual screening and docking with phytocompounds of ten Indian medicinal plants and the best results obtained are shown in Table 1. Further, the 2D and 3D interaction of target protein with the best ligands are shown in Fig. (1-6).

NiV Glycoprotein was docked with phytocompounds of Indian medicinal plants (Table 1 and Fig. (1-6). 10 compounds were identified as good inhibitor of which, Neoandrographolide from *Andrographis paniculata* showed the best LibDock score of 146.79 and formed 14 hydrogen bonds with ASP 219, PRO 220, HIS 281, CYS 282, GLY 352, GLU 505 and GLY 506. Here the nitrogen atom in the amino acid residues of GLY 506 and GLY 352, spared one hydrogen atom to the oxygen atom of the ligand to form hydrogen bond between ligand and amino acid residues of the target protein. In addition, oxygen atom of CYS 282, GLY 352, PRO 220 and ASP 219 residues accepted hydrogen from the ligand Neoandrographolide to form hydrogen bond. Further, carbon atom in the GLU 505 spared hydrogen to the oxygen atom of the ligand to form hydrogen bond.

Similarly, nitrogen atom of the HIS 281 accepted hydrogen from carbon and oxygen atom of the ligand to form 2 hydrogen bonds. Thus, NiV glycoprotein interacted with neoandrographolide to form hydrogen bonds.

In addition, the interaction of glycoprotein with hexahydrocurcumin from *Zingiber officinale* gave the best LibDock score of 146.5 and formed 7 hydrogen bonds with CYS 282, LYS 560 and ASP 219, where CYS 282 and LYS 560 released hydrogen atom to make hydrogen bonds. ASP 219 received hydrogen atom to make hydrogen bonds. Nirphyllin from *Phyllanthus amarus* also showed better LibDock score (141.9) with 15 hydrogen bonds, where GLN 559, LYS 560, HIS 281, PRO 353, GLU 579 spared hydrogen atom to form hydrogen bonds and TYR 351, ASP 302, PRO 220, CYS 282, GLU 579 accepted hydrogen atom to form hydrogen bonds with ligands. Besides, among the ten inhibitors, Nimbidic acid from *Azadirachta indica* showed lowest Libdock score of 131.505 with 5 hydrogen bonds.

Though some of the earlier attempts have shortlisted around five compounds from fewer proteins (Ali *et al.*, 2018, Archana *et al.*, 2018), we targeted Glycoprotein. Our results identified Neoandrographolide from *Andrographis paniculata*, Hexahydrocurcumin from *Zingiber officinale* and Nirphyllin from *Phyllanthus amarus* as potential inhibitor of NiV.

Pharmacokinetic properties

Phytocompounds having good LibDock score with the target protein of NiV were evaluated for pharmacokinetic properties using ADMETSAR and pKCSM and the results are compiled and presented in Table 2. In the absorption parameters, all the molecules were found to have human intestinal absorption properties in ADMETSAR software. This is supported by the CaCo2 permeability prediction values as well. However, only one molecule, Niranthin was found positive for oral bioavailability but the other molecules showed negativity in bioavailability parameter which could be due to the first pass metabolism. This prediction could be weighed with caution since the degree of first pass metabolism is not predicted.

Table.1 Interaction of glycoprotein with phytocompounds

Glycoprotein							
S. No.	**PubChem (CID)**	**Compound Name**	**Plant Name**	**LibDock Score**	**Number of H-bond**	**Interacting residues (D-H…A)**	**Bond Length (Å)**
1	9848024	Neoandrographolide	*Andrographis paniculata*	146.79	14	GLY 352 (N-H…O) GLY 506 (N-H…O) HIS 281 (N…H-O) CYS 282 (O…H-O) GLY 352 (O…H-O) CYS 282 (O…H-O) GLY 352 (O…H-O) GLU 505 (C-H…O) HIS 281 (N…H-C) PRO 220 (O…H-C) CYS 282 (O…H-C) ASP 219 (O…H-C) ASP 219 (O…H-C) PRO 220 (O…H-C)	2.08 2.10 2.01 1.95 2.69 1.70 2.75 2.18 2.58 2.63 2.44 2.95 2.22 2.44
2	5318039	Hexahydrocurcumin	*Zingiber officinale*	146.501	7	CYS 282 (N-H…O) LYS 560 (N-H…O) LYS 560 (N-H…O) ASP 219 (O…H-O) ASP 219 (O…H-O) LYS 560 (C-H…O) ASP 219 (O…H-C)	1.95 2.14 1.87 2.03 1.82 2.94 2.30
3	5491556	Nirphyllin	*Phyllanthus amarus*	141.896	15	GLN 559 (N-H…O) GLN 559 (N-H…O) LYS 560 (N-H…O) HIS 281 (C-H…O) PRO 353 (C-H…O) TYR 351 (O…H-C) ASP 302 (O…H-C) TYR 351 (O…H-C) ASP 302 (O…H-C) ASP 302 (O…H-C) PRO 220 (O…H-C) CYS 282 (O…H-C) GLU 579 (O…H-C) GLU 579 (O…H-C) GLU 579 (C-H…O)	2.15 1.67 2.89 2.73 2.70 2.54 2.96 2.58 2.51 2.56 2.67 2.53 2.55 2.63 2.96

4	9796792	Tetrahydrobisdemethoxycurcumin	*Curcuma longa*	136.915	6	LYS 560 (N-H…O) LYS 560 (N-H…O) GLY 506 (O…H-O) ASP 219 (O…H-O) ASP 219 (C-H…O) LYS 560 (C-H…O)	1.66 1.72 1.74 1.80 2.46 2.41
5	5318568	Isogingerenone B	*Zingiber officinale*	136.275	7	GLY 352 (N-H…O) TYR 508 (N-H…O) GLN 490 (O…H-O) CYS 282 (O…H-O) GLU 505 (C-H…O) VAL 507 (C-H…O) ASP 219 (O…H-C)	2.03 1.98 2.32 1.78 2.74 2.88 3.00
6	5281775	Gingerenone A	*Zingiber officinale*	135.903	11	GLY 352 (N-H…O) TYR 508 (N-H…O) TRP 504 (O…H-O) CYS 282 (O…H-O) GLY 352(O…H-O) HIS 281 (C-H…O) GLU 505 (C-H…O) VAL 507 (C-H…O) GLY 506 (O…H-C) GLN 490 (O…H-C) PRO 220 (O…H-C)	2.18 2.07 2.68 1.85 2.76 2.92 2.40 2.68 2.55 2.35 2.51
7	13989915	Niranthin	*Phyllanthus amarus*	133.595	6	THR 218 (C-H…O) HIS 281 (C-H…O) ASP 219 (O…H-C) CYS 282 (O…H-C) CYS 240 (O…H-C) CYS 240 (O…H-C)	2.47 2.43 2.98 2.42 2.49 2.36
8	5317593	Gingerenone C	*Zingiber officinale*	132.865	4	LYS 560 (N-H…O) GLY 506 (O…H-O) ASP 219 (O…H-O) LYS 560 (C-H…O)	2.33 1.99 1.78 2.26
9	5469424	Demethoxycurcumin	*Curcuma longa*	132.799	4	GLN 559 (N-H…O) LYS 560 (N-H…O) SER 232 (O…H-O) HIS 281 (C-H…O)	2.45 1.67 2.32 2.42
10	29803-85-8	Nimbidic Acid	*Azadirachta indica*	131.505	5	ASP 219 (N-H…O) ARG 248 (N-H…O) ASP 219 (C-H…O) ASP 219 (O…H-C) ASP 219 (O…H-C)	2.74 2.63 2.75 2.62 2.78

Table.2 Pharmacokinetic properties of phytocompounds

S. No.	Name of the Phytocompound	Absorption[1,2]			Distribution[1,2]					Metabolism - CYP inhibition (-/+) or substrate (S)[1,2]					Excretion[2]	
		HIA	HOB	Cc2	PPB	PgpI	PgpS	BBB	VD	1A2	2D6	2C9	2C19	3A4	TC	Renal OCT2
1	Neoandrographolide	+	-	-	0.83	-	-	-	-1.08	-	-	-	-	-/S	0.94	No
2	Hexahydrocurcumin	+	-	-	0.73	-	-	-	0.32	+	-/S	-	+	-/S	0.31	No
3	Nirphyllin	+	-	+	1.10	+	-	+	-0.18	-	-/S	+	+	+/S	0.63	No
4	Tetrahydrobisdemethoxy curcumin	+	-	-	0.55	-	-	-	0.32	-	-	+	-	+	0.22	No
5	Isogingerenone B	+	-	-	0.92	+	-	+	0.04	+	-	-	+	-/S	0.27	No
6	Gingerenone A	+	-	-	0.85	+	-	+	0.02	+	-	+	+	-	0.23	No
7	Niranthin	+	+	+	0.97	+	-	+	-0.10	-	+/S	+	+	+/S	0.47	No
8	Gingerenone C	+	-	-	0.80	-	-	+	0.23	+	-	+	+	-/S	0.21	No
9	Demethoxycurcumin	+	-	-	0.72	-	-	-	0.10	+	-	+	+	-	0.04	No
10	Nimbidic acid	+	-	-	0.81	-	+	+	-0.26	-	-	-	-	-/S	0.32	No

Note:1 – ADMETSAR online tool, 2 – pkCSM online tool | HIA – Human Intestinal absorption; + is >30%, - is <30% | HOB- Human oral bioavailability – logK (%F) > 0 is + / < 0 is - | Cc2 – CaCo2 permeability + permeable/- not permeable
PPB – Plasma protein binding (x100%) | PgpI – P-glycoprotein inhibitor/PgpS – substrate| BBB – Blood brain barrier – does not cross (-)/cross (+) | VD – volume of distribution at steady state – log L/Kg (Low if <-0.15 and high if >0.45)
CYP- Cytochrome P450 inhibitor (+ yes/ - no) or Substrate
TC – Total clearance (log ml/min/kg); higher the value higher is the clearance and vice versa | Renal OCT2- organic cationic transporter 2 – NO (not a substrate) /Sub (substrate)

Table.3 Toxicity prediction of phytocompounds

S. No.	Phyto compounds & PubChem CID	TOPKAT Rat Female NTP Prediction	TOPKAT Rat Male NTP Prediction	TOPKAT Mouse Female FDA None vs Carcinogen Prediction	TOPKAT Mouse Male FDA None vs Carcinogen Prediction	TOPKAT Ames Prediction	TOPKAT Skin Irritancy	TOPKAT Skin Sensitization	TOPKAT Ocular Irritancy	TOPKAT Aerobic Bio degradability Prediction
1	Neoandrographolide (9848024)	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Mutagen	Moderate	None	None	Degradable
2	Hexahydrocurcumin (5318039)	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Mutagen	None	Strong	Moderate	Non-Degradable
3	Nirphyllin (5491556)	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Mutagen	Mild	Strong	Mild	Degradable
4	Tetrahydrobisdemethoxycurcumin (9796792)	Non-Carcinogen	Non-Carcinogen	Carcinogen	Non-Carcinogen	Non-Mutagen	None	Strong	Severe	Non-Degradable
5	Isogingerenone B (5318568)	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Mutagen	Mild	Strong	Severe	Non-Degradable
6	Gingerenone A (5281775)	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Mutagen	Mild	Strong	Severe	Non-Degradable
7	Niranthin (13989915)	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Mutagen	Moderate	Strong	Mild	Degradable
8	Gingerenone C (5317593)	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Mutagen	Mild	Strong	Severe	Non-Degradable
9	Demethoxycurcumin (5469424)	Carcinogen	Non-Carcinogen	Non-Carcinogen	Carcinogen	Non-Mutagen	Mild	Strong	Mild	Degradable
10	Nimbidic Acid (29803-85-8)	Non-Carcinogen	Non-Carcinogen	Carcinogen	Non-Carcinogen	Non-Mutagen	Mild	None	Moderate	Degradable

Fig.1 3D interaction of Glycoprotein with Neoandrographolide

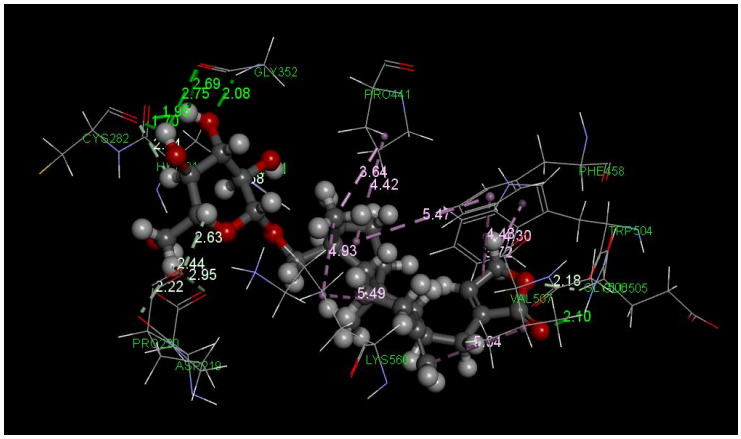


Fig.2 2D interaction of Glycoprotein with Neoandrographolide

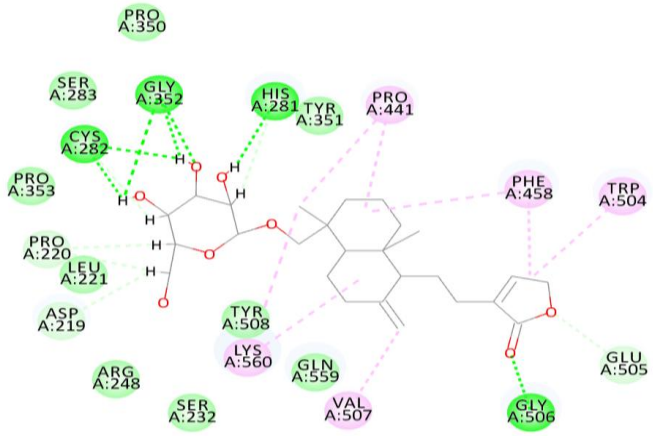


Fig.3 3D interaction of Glycoprotein with Hexahydrocurcumin

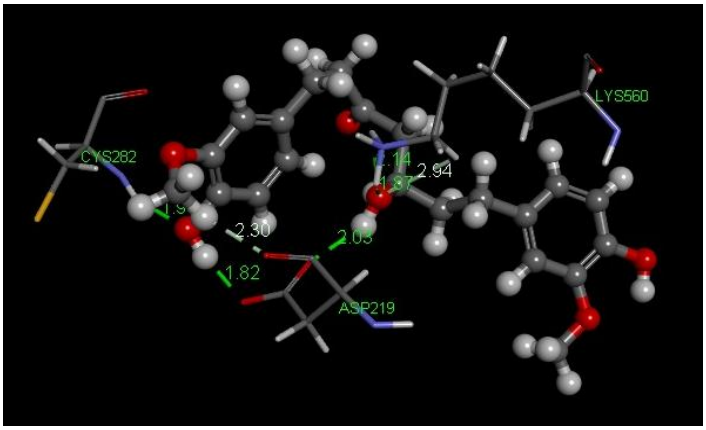


Fig.4 2D interaction of Glycoprotein with Hexahydrocurcumin

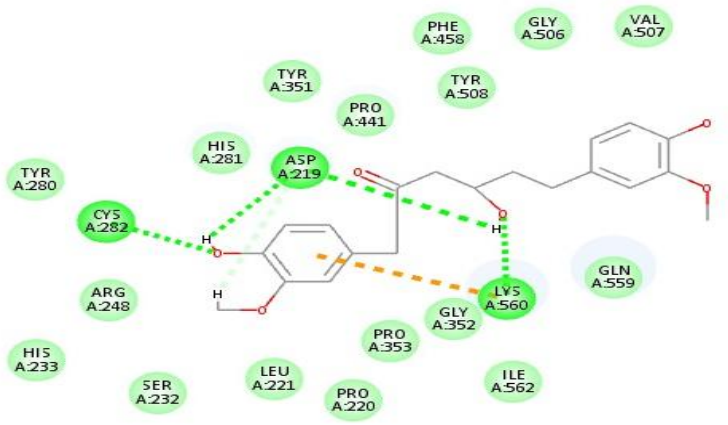


Fig.5 3D interaction of Glycoprotein with Nirphyllin

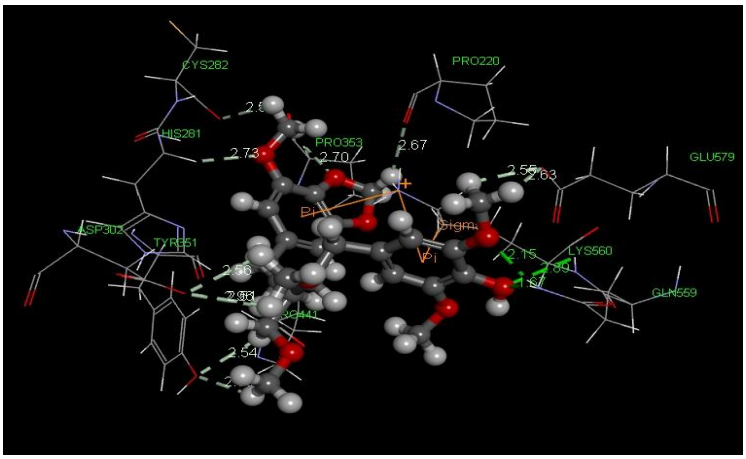


Fig.6 2D interaction of Glycoprotein with Nirphyllin

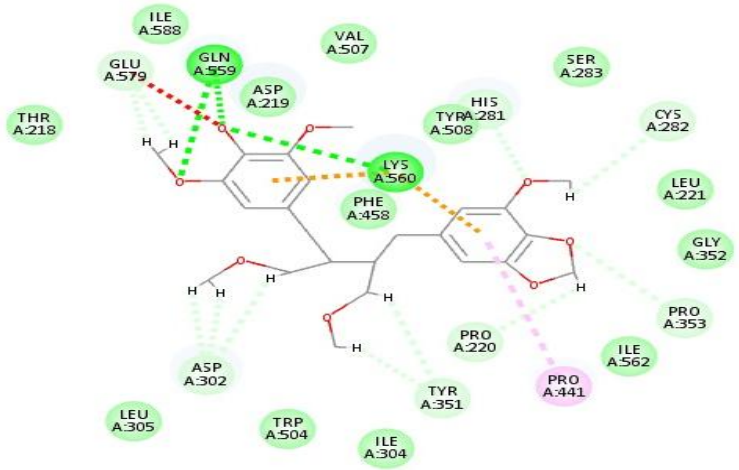


Fig.7 RMSD for the complex of Glycoprotein and Neoandrographolide

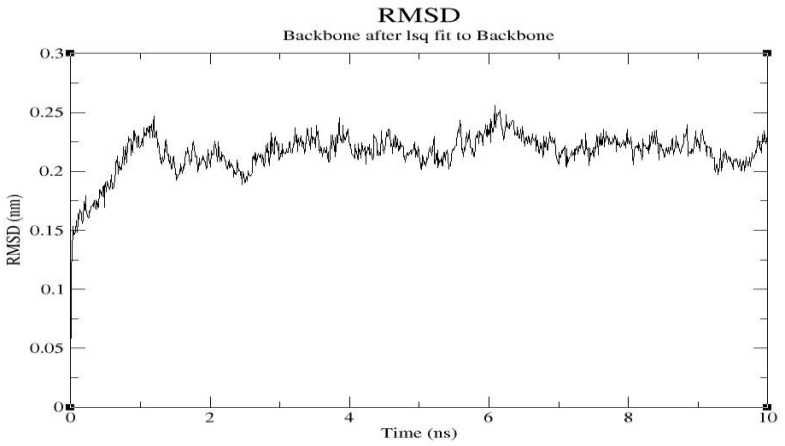


Fig.8 RMSF for the complex of Glycoprotein and Neoandrographolide

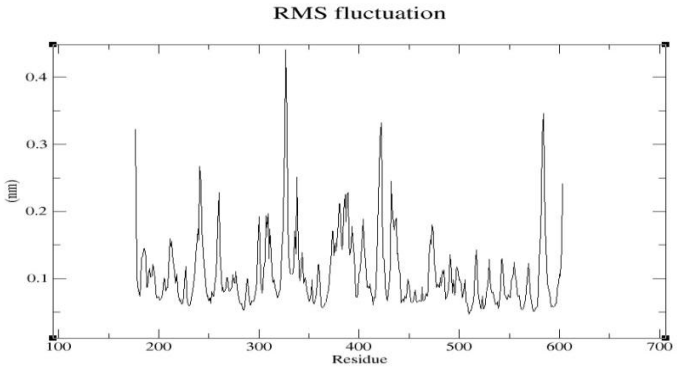
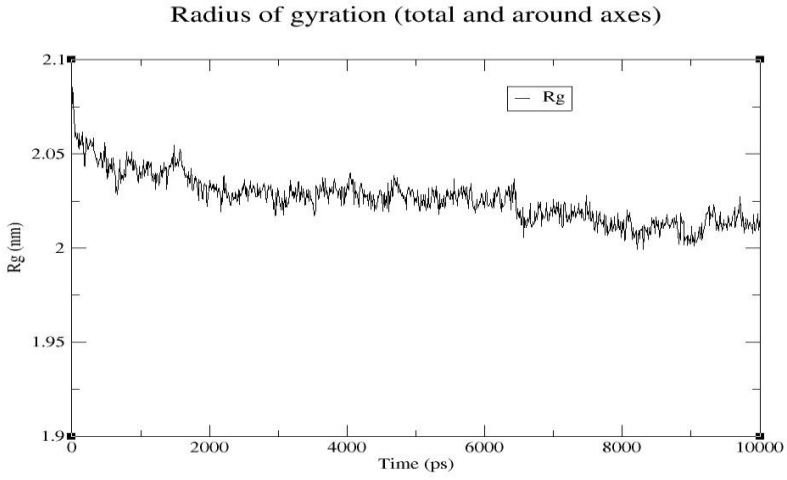


Fig.9 Radius of gyration for the complex of Glycoprotein and Neoandrographolide



In case of distribution, all the compounds tested showed 50-100% plasma protein bindings, indicating the chances of longer duration action. Few compounds were found to be P-glycoprotein inhibitor which will not have any impact on its own intestinal absorption and only one compound, i.e., Nimbidic acid, showed as the substrate for P-gp which may have less intestinal absorption due to the possibility of efflux potential. All the compounds showed moderate to high volume of distribution.

In the metabolism profile, compounds showed both as CYP inhibitor and/or CYP susbstrate, hence the possibility of drug-drug interaction can happen with other drugs which requires the experimental studies to confirm the same.

In the excretion parameters, the total clearance was low (<0.35 log ml/min/kg) for 7 compounds and moderate to high (>0.35) for the rest of the compounds. But, there were no compounds found to be substrate for renal OCT2 transporter. Among the 10 compounds, Neoandrographolide had highest docking score for which the molecular dynamics properties were studied.

Among the 10 compounds, Gingerenone showed favourable pharmacokinetics properties such as good human intestinal absorption, blood brain barrier crossing, moderate distribution, good plasma protein binding and less total clearance, indicating the possibility of longer duration of action.

Though Neoandrographolide showed less favourable pharmacokinetic properties, the binding property against the target proteins of Nipah virus was high. If experimentally proved, the pharmacokinetic parameters could be modified by the lead optimization strategy without affecting the activity of the compound.

Toxicity prediction of phytocompounds

In the toxicological parameters predicted using TOPKAT, all the compounds were found to be non-genotoxic, non-carcinogenic and had no hepatotoxic potentials. However, though there were indications for the skin sensitization, skin irritancy and ocular irritancy predicted for Neoandrographolide, Gingerenone A and C, these compound could still be subjected for further studies considering the positive aspects of these compounds and the possibilities of overcoming the drawbacks by proper precautionary measures (Table 3).

Simulation studies

Molecular dynamics simulation studies were done for the best interacted molecule for 10 ns using GROMACS 5.1.2. In the docking analysis, when glycoprotein was interacted with phytocompounds of medicinal plants, neoandrographolide showed the best Libdock score. Hence, the simulation study was done for the complex of glycoprotein and neoandrographolide to find their stability. RMSD, RMSF and Radius of gyration were calculated Fig. (7-9) and the results of RMSD showed that the peak started at 0.125 nm and the RMSD was not deviated above 0.25 nm during 10 ns simulation time. This indicated that the complex was stable. However, the RMSD was highly stable at 3 to 4 ns and 7 to 9 ns during the entire simulation time. In the RMSF peak, most of the residues were not fluctuated above 0.2 nm. When the fluctuation of the active site residues and main chain atoms are low, conformational changes will be low and it results in a stable conformation (Priyadarshini *et al.*, 2014). In our study, the residues between 500 to 600 were not fluctuated above 0.15 nm and most of the other residues were also not fluctuated above 0.3 nm indicating that the complex is stable. Radius of gyration (Rg) was also used

to find the stability of docked complex based on shape and conformation (Singh *et al.*, 2018) and for our docked complex also the Rg was stable from 2 to 6 ns and 6.5 to 8.5 ns.

Hence, the present study concludes that Neoandrographolide from *Andrographis paniculata*, Hexahydrocurcumin from *Zingiber officinale* and Nirphyllin from *Phyllanthus amarus* are having the potential ability to act as inhibitors for the target protein Glycoprotein. Among these, Neoandrographolide from *Andrographis paniculata* is found to have the potential to act as the best inhibitor for Nipah Virus based on our preliminary studies. Nevertheless, further *in vitro* and *in vivo* studies are planned to be done to confirm the *in silico* findings of this study which might play a crucial role in the control of NiV infections in the days to come.

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