Docking Studies of HIV-1 Integrase using Phytochemicals from *Andrographispanniculata*

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Abstract—Human Immunodeficiency virus is an existing pathogen for which the development of drugs, vaccines, anti viral therapy has seen little success. The HIV-1 Integrase(HIV-1 IN) is a potential target for antiviral drugs since it plays a vital role in facilitating the integration of viral DNA into the host cell genome. Our present quest concentrates on discovering anti HIV compounds that are present in the ethanolic extract of Nilavembu (*Andrographis panniculata* Nees). It is an important medicinal herb belonging to the family Acanthaceae. The phytochemicals extracted from Andrographis panniculata were docked against the enzyme HIV-1 integrase. The results reveal that those compounds are active against HIV-1 integrase and will be effective for doing further research on plant *Andrographis panniculata* in drug designing against HIV.

Index Terms—*AIDS*, *Andrographis panniculata*, Docking, HIV-1 Integrase, pose energy, Phytochemicals, toxicity

1 INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is the end-stage disease of human immunodeficiency virus (HIV) infection[1]. The primary infection of HIV is characterised by a burst of viremia [2]. The role of Integrase in HIV is to transfer the viral DNA into the cell nucleus and facilitates its integration in the host cell genome [3-5]. Drugs which interfere with the key steps of viral replication can stop this fatal process. Thus by inhibiting the activity of integrase the virus can be stopped from infecting the host cell[6]. The work aims to produce inhibitor for HIV-1 Integrase , so that the growth of HIV can be stopped.

2 ANDROGRAPHIS PANNICULATA:

Andrographis panniculata, commonly known as "Nilavembu", belongs to the family Acanthaceae. It is a medicinal herb found widely in Tamilnadu, India. It grows mainly as a shrubin tropical, moist deciduous forest. The herb is hardy and erect.

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The plant has a number of medicinal uses. The phytochemicals of *Andrographis panniculata* are found to have anti-cancer, anti-HIV, hepatoprotective and anti-hyperglycemic properties. The compounds present mainly in the bark of the plant serves as a medicine[7].

Figure 1:*Andrographispanniculata*

3 OBJECTIVE:

Our main objective is to study the function of HIV-1 Integrase in causing AIDS disease and to perform docking studies using phytochemicals so as to obtain best docking results. Our protein target is HIV-1 IN (PDB ID: 1EX4) and the ligands are the phytochemicals obtained from A*ndrographis panniculata*- Bark (Table 1). The compounds from the plant were extracted by GC-MS chromatography and their respective ligands were downloaded from PUBCHEM database.

The protein structure was downloaded from Protein Data Bank database. Docking was

done with the compounds of *Andrographis panniculata* against HIV-1 Integrase using (chain A) ArgusLab 4.0.1 docking software[10].

TABLE1: PHYTOCHEMICALS PRESENT IN *ANDROGRAPHISPANNICULATA* –BARK OBTAINED FROM PUBCHEM DATABASE.

S.NO	COMPOUNDS	PUBCHEM ID
1.	3-O-Methyl-d-glucose	298225
2.	Acetic acid, 2-propenyl ester	11584
3.	2-Decene, 7-methyl-, (Z)-	5364557
4.	1,3-Propanediol, 2-(hydroxymethyl)-2-nitro-	31337
5.	p-Cresylglycidyl ether	16606
6.	Nitric acid, nonyl ester	88627
7.	4-((1E)-3-Hydroxy-1-propenyl)-2-methoxyphenol	1549095
8.	Dibutyl phthalate	3026
9.	1H-3a,7-Methanoazulene, octahydro-1,4,9,9-tetramethyl-	29408
10.	2,5-Octadecadiynoic acid, methyl ester	42151
11.	2H-Pyran, 2-(7-heptadecynyloxy)tetrahydro-	543312
12.	4H-1-Benzopyran-4-one, 5-hydroxy-6,7-dimethoxy-2-phenyl-	471722
13.	R(-)3,7-Dimethyl-1,6-octadiene	10997105
14.	Phytol	5280435
15.	1,2-Benzenedicarboxylic acid, diundecyl ester	19283

4 MATERIALS AND METHODS:

4.1 Preparations:

The three dimensional structure of the target HIV-1 IN was obtained from Protein data bank database. The compounds from *Andrographis panniculata* were made identified and separated by Gas Chromatography Mass Spectrometry (GC-MS Method). The .xml format was converted to .mol format using OPEN BABEL software[8]. The toxicity of the compounds was tested using TOXTREE software [9].

4.2 Docking

The ligands and water molecules were removed from the protein and the chemistry of the protein was corrected for the missing hydrogen followed by the energy minimization of the protein. Docking was done usingArgusLab molecular docking software.All the potential active sites were detected on HIV-1 integrase enzyme and docking was performed.

During docking at first the molecules were prepared and bonds, bond orders, explicit hydrogen's, charges, flexible torsions were assigned to both the protein and ligands. Ligands were selected from the docking wizard and ArgusLab score is used as a scoring function. The number of unlikely hydrogen bonds are reduced also internal hydrogen bond torsions; internal electrostatic interaction are calculated by enabling the ligand evaluation terms. The search algorithm is taken as ArgusLab and numbers of runs are taken 10 and max interactions were 2000 with population size 50 and with an energy threshold of 100 also at each step least 'min' torsions/translations/rotations are tested and the one giving lowest energy is chosen. If the energy is positive (i.e. because of a clash or an unfavorable electrostatic interaction) then additional 'max' positions will be tested.

The energy penalty was set to 100, RMSD threshold was 2.00 and RMSD calculation by atom ID (fast) were set. Docking was conducted between Protein and Inhibitor which results binding affinities in kcal/mol and docking run time. The Phytochemical which gives lowest binding energy is chosen as best inhibitor. ArgusLab showed better overall performance in docking simulations when compared with other software.

5 TOXICITY PREDICTION:

Toxicity of the compounds were predicted using TOXTREE software and the compounds having toxic effect over human beingswere not taken into account even as they produced best docking results.

6 RESULTS:

Physiochemical properties of the compounds of *Andrographis panniculata* were examined and the results of docking were tabulated. On docking against HIV-1 IN, the compound of *Andrographis panniculata* (1,2-BENZENEDICARBOXYLIC ACID, DIUNDECYL ESTER) showed greater binding affinity towards the enzyme and got a best ligand pose energy of -13.7605 with low toxicity. The former compound is thus an effective inhibitor that can stop the function of integrase and could render the virus non infectious. Further research on the plant *Andrographis panniculata* will be useful in designing drug for inhibiting HIV-1 IN.

TABLE 3:PHYSIOCHEMICAL PROPERTIES OF COMPOUNDS FROM *ANDROGRAPHISPANNICULATA*

S.NO	COMPOUNDS	MOLECULAR FORMULA	MOLECULAR WEIGHT(g/mol)	XLOGP3	H-BOND DONAR	H-BOND ACCEPTOR
1.	3-O-Methyl-d-glucose	$C_7H_{14}O_6$	194	-2.9	4	6
2.	Acetic acid, 2-propenyl ester	$C_5H_8O_2$	100	1	0	2
3.	2-Decene, 7-methyl-, (Z)-	$C_{11}H_{22}$	154	5.1	0	0
4.	1,3-Propanediol, 2-(hydroxymethyl)-2-nitro-	$C_4H_9NO_5$	151	-2.2	3	5
5.	p-Cresylglycidyl ether	$C_{10}H_{12}O_2$	164	2	0	2
6.	Nitric acid, nonyl ester	$C_9H_{19}NO_3$	189	4.5	0	3
7.	4-((1E)-3-Hydroxy-1-propenyl)-2-methoxyphenol	$C_{10}H_{12}O_3$	180	1.4	2	3
8.	Dibutyl phthalate	$C_{16}H_{22}O_4$	278	4.7	0	4
9.	1H-3a,7-Methanoazulene, octahydro-1,4,9,9-tetramethyl-	$C_{15}H_{26}$	206	5.7	0	0
10.	2,5-Octadecadiynoic acid, methyl ester	$C_{19}H_{30}O_2$	290	7.0	0	2
11.	2H-Pyran, 2-(7-heptadecynyloxy)tetrahydro-	$C_{22}H_{38}O_2$	334	8	0	2
12.	4H-1-Benzopyran-4-one, 5-hydroxy-6,7-dimethoxy-2-phenyl-	$C_{19}H_{18}O_5$	298	3.3	1	5
13.	R(-)3,7-Dimethyl-1,6-octadiene	$C_{10}H_{18}$	138	2	0	0
14.	Phytol	$C_{20}H_{40}O$	296	8.2	1	1
15.	1,2-Benzenedicarboxylic acid, diundecyl ester	$C_{30}H_{50}O_4$	474	12.3	0	4

TABLE 4: DOCKING AND TOXICITY RESULTS

S.NO	COMPOUNDS	Pose Energy (K cal/mol)	TOXICITY
1.	3-O-Methyl-d-glucose	-7.34747	High
2.	Acetic acid, 2-propenyl ester	-7.0955	Inter-mediate
3.	2-Decene, 7-methyl-, (Z)-	-8.17568	Low
4.	1,3-Propanediol, 2-(hydroxymethyl)-2-nitro-	-6.8103	High
5.	p-Cresylglycidyl ether	-7.71809	High
6.	Nitric acid, nonyl ester	-9.09406	High
7.	4-((1E)-3-Hydroxy-1-propenyl)-2-methoxyphenol	-8.30269	Low
8.	Dibutyl phthalate	-10.281	Low
9	1H-3a,7-Methanoazulene, octahydro-1,4,9,9-tetramethyl-	-9.8514	Low
10.	2,5-Octadecadiynoic acid, methyl ester	-10.5536	Low
11.	2H-Pyran, 2-(7-heptadecynyloxy)tetrahydro-	-9.7507	High
12.	4H-1-Benzopyran-4-one, 5-hydroxy-6,7-dimethoxy-2-phenyl-	-8.6639	High
13.	R(-)3,7-Dimethyl-1,6-octadiene	-8.31392	Low
14.	Phytol	-10.8585	Low
15.	1,2-Benzenedicarboxylic acid, diundecyl ester	-13.7605	Low

7 CONCLUSION:

1. Phytochemicals of Andrographispanniculata with best binding energies were obtained in docking studies with HIV-1 integrase (1EX4).

2.The mechanism of action of Phytochemicals against diseases were clearly understood.

3.Further investigations can be done on our in silico approach to produce more effective and potential HIV-1 integrase inhibitors through ligand based drug designing approaches.

4. Finally, from this analysis it was found that1,2-BENZENEDICARBOXYLIC ACID, DIUNDECYL ESTEReffectively inhibit HIV-1 integrase (1EX4) and the phytochemicals of *Andrographispanniculata* can act as HIV-1 Integrase inhibitors.

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