RESEARCH ARTICLE

In-silico Docking and ADME Studies of Natural Phytoconstituents from Different Medicinal Plants as Potential HIV Reverse Transcriptase Inhibitors

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ABSTRACT

Human immunodeficiency virus (HIV) is a serious global public health concern, having claimed more than 35 million lives to date. Human immunodeficiency virus-1 reverse transcriptase is an essential enzyme for viral replication. If the enzyme is blocked, viral replication may be dramatically reduced. Several human immunodeficiency virus medicines are available, though better effective treatments are always needed due to the drug confrontation and negative outcomes. According to prior research, several natural substances have a high affinity for the human immunodeficiency virus-1 reverse transcriptase enzyme. Flavonoid glycosides are some of these chemicals. This work aimed to get more ideas about phytocompounds with human immunodeficiency virus-1 reverse transcriptase inhibitory effects utilising docking. From the results, the most suggested phytocompounds, those with the highest negative free energy to make complex were menthoside, morindin and sesaminol glucosides. This was due to the interactions of all three phytocompounds with key amino acid residues: Leu 100, Val 179, Tyr 318, Tyr 188, Val 106, Lys 101, Gly 190, His 235. Flavonoid glycoside (Menthoside) showed lowest binding energy with a docking score -10.6 kcal/mol.

Keywords: Human immunodeficiency virus, Molecular docking, Reverse transcriptase, Adsorption, Distribution, Metabolism, Excretion, Toxicity, Flavonoid, Glycosides, Terpenoids.

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INTRODUCTION

The human immunodeficiency virus (HIV) is a virus that destroys and inhibits immune cell function[1]. To live, it, like all viruses, must multiply. When HIV replicates in the host cell, it uses critical manufacturing enzymes such as reverse transcriptase, protease, and integrase to produce mature virions. HIV has genomic RNA in its virion, which is transformed by reverse transcriptase within the host cell to cDNA (complementary DNA), which is then integrated into the host cell to make the necessary protein for fresh viral development. Reverse transcriptase has been identified as a significant anti-HIV-1 therapeutic target.[2] As HIV replicates in the body, it occasionally mutates and develops variants. HIV variants that emerge when a person is receiving HIV medications can result in drug-resistant strains of HIV. There are already several HIV medicines available, however more effective treatments are always needed due to the likelihood of drug resistance and long-term negative effects.[3] Plant metabolites have shown to be the most effective pathway of prospective therapeutic leads.[4]

A computational technique is dependable for identifying active phytocompounds from multiple databases. This method is being used in drug discovery research right now. Using a computational method, one of the most important jobs in the drug development process is the assortment of structural proteins.

Glycoside is a chemical formed by the glycosidic link between a simple sugar (glycone) and another molecule (aglycone). Glycosylation in flavonoids has a variety of biological effects, which are difficult to generalize.[5,6] *In-silico* approaches have been widely used in creating and testing pharmacological hypotheses. An *in-silico* analysis might reduce failure chances toward *in-vivo/in-vitro* testing by anticipating failure promises such as the collaboration of a substance with receptors. As a result, the *in-silico* approach was used.

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In the present study, I have selected seven medicinal plants: *Terminalia chebula, Mentha piperita, Morinda citrifolia, Momordica charantia, Ricinus communis, Sesamum indicum, Azadirachta indica* based on their different biological applications.

From the plants, from all phytocompounds, 35 compounds were screened against HIV reverse transcriptase as target. Among them, the compounds were evaluated further utilizing ADME and drug similarity characteristics. The focus of this study was to propose compounds that have remarkable HIV-1 reverse transcriptase inhibitory activity.

MATERIALS AND METHODS

Softwares

PyMOL, Auto-Dock tools, PyRx.

3D Structure of Phytocompounds

The seven selected Indian medicinal plants (*Terminalia chebula, Mentha piperita, Morinda citrifolia, Momordica charantia, Ricinus communis, Sesamum indicum, Azadirachta indica*) contain many more phytocompounds, which were salvaged from the database like PubChem and also downloaded positive control compounds nevirapine and efavirenz in SDF format.

Preparation of Macromolecule Structure

The x-ray crystal structure of the receptor was salvaged from the Protein Data Bank with PDB ID: 1lwo. Chain A of the protein receptors was selected and relieved from het atoms. Optimization were done by adding polar hydrogens, deleting water molecules, fixation of charges and energy minimization.[7]

Docking of Positive Control and Phytocompounds

The Vina wizard in-built in PyRx tool was employed to screen the phytocompounds against the reverse transcriptase. Energy minimization of all the phytocompounds were done using MMFF94 force field with open babel. Over time the minimized structures were obtained as pdbqt file format.[8,9] The 3D grid maps were set onto the active site of the proteins. Amongst all phytocompounds, 35 phytocompounds were carefully chosen based on their top binding affinity against reverse transcriptase enzyme. The top three compounds were further validated with Auto-Dock 4.2 tool to compare the binding affinity.

Analysis of Protein-ligand Interaction

The visualization of interaction was performed using Discovery Studio software. The purpose was to scrutinize the existence of various bonds between phytocompounds and positive control compounds to the targeted enzymes.

ADME Prediction and Analysis

After the structural based virtual screening of the about 178 phytocompounds against target protein, the phytocompounds menthoside, morindin and sesaminol glycosides were chosen for ADME properties using the ADMET lab 2.0 to predict their ADME properties, the log P, logD and logS, were measured to evaluate the outcome.[10]

RESULT AND DISCUSSION

The standard with docking score -9.6 kcal/mol was nevirapine. Flavonoid glycoside (Menthoside) and, lignan glycoside (Sesaminol Glucoside) and anthraquinone (Morindin) indicated the lowest binding energy. The results are shown in Table 1. The targeted receptor with PDB ID:1lw0 has an active binding site, as shown in Figure 1**.** Active site amino acid residues are Leu 100, Val 179, Tyr 318, Tyr 188, Val 106, Lys 101, Gly 190, His 235. The interaction of phytocompounds with amino acid residues are shown in Figure 2.

Molecular Docking

From this research, flavonoid glycoside, menthoside indicated lower binding free energy than the other phytoconstituents. Docking score in Table 1 for all phytocompounds and four selected compounds had interactions with Tyr188 and Val 179 residues **(**Table 2**)** which were crucial amino acids in reverse transcriptase.

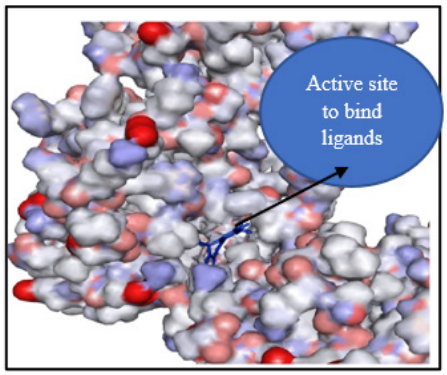

Figure 1: Schematic representation of reverse transcriptase receptor with its active binding sites, PDB: 1lw0.

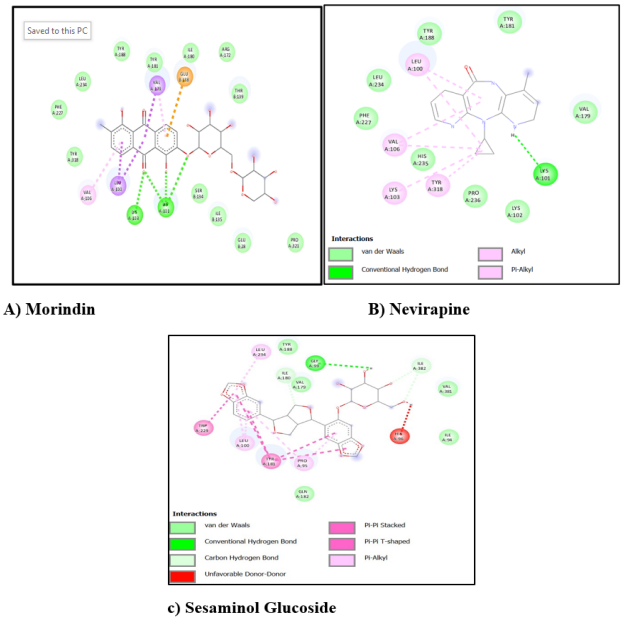

Figure 2: 2D Interaction schematic representation of phytocompounds with protein

Table 1: Selected plants and their phytoconstituents

S. No.	*Name of plant*	*Name of phytocompounds*	*Class of phytocompounds*	*Binding energy (kcal/mol)*
1	*Terminalia chebula*	Chebulagic acid	Phenolic acids	-9.9
		Arjunolic acid	Triterpenoids	-8.3
		Maslinic acid	Triterpenoids	-9
		Arjungenin	Triterpenoids	-8.3
2	*Mentha Piperita*	Menthoside	Flavonoid glycoside	-10.6
3	*Morinda citrifolia*	Morindin	Anthraquinones	-10.2
		Morindone	Anthraquinones	-8.7
		Asperuloside	Monoterpenoids	-7.8
		Rubiadin	Anthraquinones	-7.8
		Damnacanthal_	Anthraquinones	-7.7
		Primeveroside	carbohydrate conjugates	-8.5
		Scopoletin	Coumarins	-6.4
4	*Momordica charantia*	Urosolic acid	Triterpenoids	-8.7
		Diosgenin	Steroids	-8.8
		Momordicoside A	Triterpenoids	-8.3
		Momordicine	steroid derivatives	-8.2
		Momordicoside B	Triterpenoids	-8.2
		Vicenin-2	Flavonoid glycosides	-8
		Vicine	carbohydrate conjugates	-7
5	*Seasmum indicum*	Sesaminol glucoside	Lignan Gycosides	-9.6
		Episesaminone	Furanoid lignans	-8.6
		Sesamolinol	Furofuranoid lignans	-8.3
		Sesamose	Polysaccharides	-7.7
		Sesamol	Benzodioxoles	-5.9
6	*Azadirachta indica*	Nicotiflorin	Flavanoids	-8.6
		Myricetin	Flavonoids	-8.7
		Isoazadirolide	Triterpenoids	-8.6
		Vilasinin	Triterpenoids	-8.5
		Nimbinene	Triterpenoids	-7.5
		Azadirachtanin	Triterpenoids	-8
		6-Deacetylnimbin	Triterpenoids	-7.8
7	*Ricinus communis*	Corilagin	Ellagitannin	-8.8
		Isoquercitrin	Flavonoid	-7.9
		Rutin	Flavonoid	-8.2

Table 2: Phytocompounds and amino acid residues interaction.

Ligands	*Binding energy (kcal/mol)*	*Amino acid interactions*
Morindin	-10.2	Leu 100, Val 179, Tyr 318, Val 106, Lys 101, Gly 190, His 235
Menthoside	-10.6	Leu 100, Val 179, Tyr 318, Tyr 188, Val 106, Lys 101, His 235
Sesaminol glucoside	-9.6	Leu 100, Val 179, Tyr 188, Lys 101, TRP 229
Efavirenz (control)	-9.5	Leu 100, Val 179, Tyr 318, Tyr 188, Val 106, Lys 101, Gly 190, His 235
Nevirapine (control)	-9.6	Leu 100, Val 179, Tyr 318, Tyr 188, Val 106, Lys 101, Gly 190, His 235

Table 3: Physicochemical properties and toxicity assessment

Physicochemical properties	*Morindin*	*Menthoside*	*Sesaminol glycoside*
Molecular weight (MW)	564.2	740.2	532
Volume	517	695.033	488.2
Density	1.09	1.065	1.09
nHA	14	17	12
nHD	8	9	4
nRot	5	10	5
nRing	5	6	7
MaxRing	14	10	9
nHet	14	17	12
fChar	0	0	0
nRig	30	38	35
Flexibility	0.167	0.263	0.143
Stereo centers	9	10	9
TPSA	232	275.5	157.9
logS	-2.4	-4.372	-3
logP	0.18	1.835	0.09
logD	0.87	2.294	1.85
hERG blockers	No	No	No
Respiratory toxicity	No	No	No
Skin sensitization	No	No	No

ADMET Study

All intended compounds were checked for their ADME properties by ADMET lab 2.0. Among them, three compounds with decent docking scores related to standard substance (Nevirapine) are revealed in Table 3. Among them, menthoside and sesaminol glucoside have good solubility. Morindin, compared to other phytocompounds has less solubility.

CONCLUSION

Flavonoid glycoside (Menthoside) and anthraquinone (Morindin) lower binding free energy on HIV-1 reverse transcriptase than control ligand nevirapine and efavirenz. Sesaminol glucoside showed similar binding energy with nevirapine. Among three compounds menthoside and sesaminol glucoside have shown good drug-likeness properties. This result needs to be further explored by means of experimental study.

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