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Molecular Docking of HIV-1 env gp120 Using Diterpene Lactones from *Andrographis paniculata*

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Abstract

The search for effective drugs to treat HIV/AIDS has been the major task of most researchers since several years of its discovery. Most synthetic drugs such as Efavirenz, Tenofovir, Emtricibatine among others are employed in the antiretroviral treatment which have dangerous effects on patients. Thus, herbal medicine can be used as an alternative source of treatment for HIV positive patients as they exhibit little or no side effects when compared to synthetic drugs. This research work sought to examine whether plant diterpene lactones isolated from *Andrographis paniculata* exhibit anti-HIV activity using molecular docking studies. The HIV-1 env gp120 was docked by two diterpene lactones namely; andrographolide and neoandrographolide using docking tool (igemdock v2.1) after retrieving protein structure from Protein Data Bank (PDB). The result indicates that neoandrographolide is a more promising drug against HIV-1 than andrographolide due to its low interaction energy for the formation of ligand-receptor complex.

Keywords: Andrographolide; Env gp120; HIV-1; Docking; PDB

Introduction

Plants serve as a source of new drugs for treating different kinds of ailments including HIV/AIDS. Reported that 25% of the drugs prescribed worldwide originate from plant, one hundred and twenty one such active compounds being in current use. Of the two hundred and fifty two drugs considered as basic and essential by World Health Organization (WHO), 11% are exclusively of plant origin and a significant number are synthetic drugs obtained from natural precursors. Plant based drugs are formulated to produce varieties of effective pharmaceutical formulations to enhance anti-HIV activities. Human Immunodeficiency Virus (HIV) is an endemic virus characterized by attacking the human immune system which makes the immune cells weak and unable to fight against it, thus leading to illness. The final stage in the life cycle of HIV is known as Acquired Immunodeficiency Syndrome (AIDS), a set of symptoms and infections resulting from the damage of the human immune system caused by the human immunodeficiency virus (HIV) [1]. The actual cause of virus is through sexual intercourse, exposure to infected body fluids or tissues, and from vertical transmission during pregnancy, delivery or breast feeding among others. According to WHO, 70 million people have been infected with HIV and 35 million people have died of AIDS since the inception of the epidemic. At the end of 2011, approximately 36 million people were HIV positive and 1.7 million people died of AIDS-related diseases. Recent research works show that HIV/AIDS is the leading cause of death in Sub-Saharan Africa and the fourth leading cause of death worldwide. To prevent more death and widespread of the virus, clinical trial by researchers is ongoing worldwide for novel anti-HIV drugs. The "King of bitters" (*Andrographis paniculata*), family Acanthaceae, is a small endangered medicinal plant native to India, China and Sri Lanka (Figure 1). It is widely cultivated in southern Asia, where the roots and leaves are used in traditional medicine and pharmaceutical industries [2]. Andrographolide, a bicyclic diterpenoid lactone, the main constituent of *Andrographis paniculata* is known for its pharmacological activities. Andrographolide is known to possess antihepatotoxic [3], antibiotic [4], anti-inflammatory [5], anti-snake venom [6], anticancerous [7] and anti-HIV [8] properties. Besides all it is generally used as immunostimulant [9] agent. Andrographolide content varies with plant parts and with the geographical distribution. Leaves of *A. paniculata* are reported to contain maximum andrographolide [10]. The "env" gene in HIV encodes a single protein, gp160. Cellular enzymes attack it when it travels to the cell surface, then protein gp 160 is chopping into two pieces gp120 and gp41. If and when new virus particles bud off from the host cell, these two pieces lie on opposite sides of the virus membrane. gp 120 sits on the outside of the virus particle, forming the virus's spikes, while gp41 sits just on the inside of the membrane – each protein is being anchored to each other through the membrane [11,12]. There is no report to the best of our knowledge as regards the availability of any plant-derived drug in clinical use in the treatment of HIV/AIDS and in fact, screening these large numbers of secondary metabolites of plant origin using computational tools will help in drug design and in a very short time compared to the conventional methods. In the present study, andrographolide and neoandrographolide was checked for inhibition against env gp120 using iGemdock.



Figure 1: *Andrographis paniculata*.

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Materials and Methods

iGemDock

The tool was developed by Jinn-Moon Yang, a Professor of the Institute of Bioinformatics, National Chiao Tung University. It is a Generic Evolutionary Method for molecular docking. iGEMDOCK is a program for computing a ligand conformation and orientation relative to the active site of target protein. It is a graphical-automatic drug discovery system used for integrating docking, screening, post-analysis, and visualization of various ligands. The main features of iGemdock are scoring function and evolutionary algorithm. In scoring function, the complicated AMBER-based energy function is replaced by local minima. The new rotamer based mutations operator is used to reduce search space in the ligand structure which is an advantage over the Gaussian and Cauchy mutation effects [13]. The core idea in it is Generic algorithm, scoring function.

PUBCHEM and PDB SUM

PUBCHEM is used to obtain the database of the protein like primary, 2D; 3D and other literature survive of researchers. The ligand and analogues andrographolide of *Andrographis paniculata* is derived from PUBCHEM. PDB SUM is used for finding the active site, number of chains, the number of amino acids present in the each chain and motif details. Figure 2 shows the structure of HIV env gp120 obtained from PUBCHEM.

Preparation of target protein

Protein Data Bank (PDB) is a repository of 3-D structural data of bio macromolecules [14]. In the present study, the structure of env gp120 was procured from PDB as given below.

1G9M: It is viral envelope glycoprotein (gp) 120 structure of strain HIV-1 hxbc2 complicated with the CD4 and induced neutralizing antibody 17b.

Preparation of Ligand

With the numerous use of natural products in clinical research due to their medicinal and therapeutic values without any side effects as compared to the drugs. We have taken plant diterpene lactones from the *Andrograhis paniculata* into consideration since some of the phytochemicals extracted from the plant showed anti-HIV activity [8]. The ligands which were taken into consideration are andrographolide and neoandrographolide. The ligands for the study were analyzed for their hydrophobicity. The hydrophobic activity is usually calculated by Lipinski filter tool by DruLito tool. The distribution of the Log P shows the hydrophobic activity of the drug. The structures of the ligands were taken from ChemSketch and were docked by iGEMDOCK tool. Finally all the results were compared and discussed.

Results and Discussion

Lipinski rule of five analysis

The drug-likeness is necessary to be evaluated at the primary stage as this reduces the chances of selecting the false positive results. Various basic physicochemical properties such as log P, H-bond acceptor, H-bond donor, molecular weight ad molar refractivity were calculated to evaluate a molecule to act as drug. The value of log P should be ≤ 5; this is the distribution coefficient important for finding the solubility of the drug that is lipophilicity. Molecular weight of the compound should not exceed 500Da as most of the drugs are small molecules [15,16] (Figures 3 and 4).

1. Andrographolide	2. Neoandrographolide
Molecular Weight: 350.4492	Molecular Weight: 480.598
Hydrogen bond donor: 3	Hydrogen bond donor: 4
Hydrogen bond acceptor: 5	Hydrogen bond acceptor: 8
Log P=2.9	Log P=1.17
Molar refractivity: 94.1	Molar refractivity: 124.83

It is evident from Table 1 that neoandrographolide has a lower Log P value than andrographolide which indicates that the former has higher hydrophobic activity than the latter. The best ligand for docking studies is determined by evaluating the interaction energy for the specific ligand-receptor complex under study (Table 2). It is evident from the above result that neoandrographolide is a more promising drug against HIV-1 than andrographolide because of its lower interaction energy (-108.61 kcal), However, none of the two ligands has violated Lipinski rule (Figures 5-7).

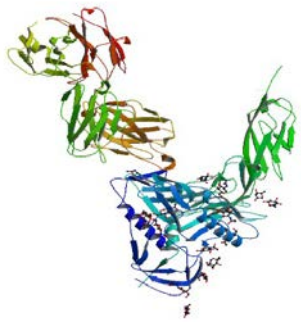


Figure 2: HIV env gp120, PDB id: 1G9M.

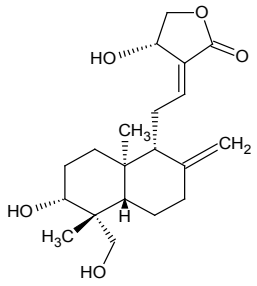


Figure 3: Andrographolide.

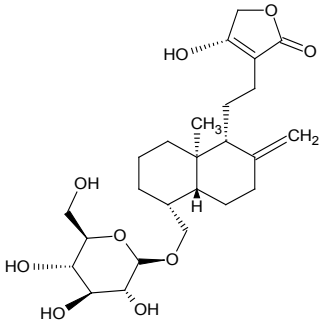


Figure 4: Neoandrographolide.

S No	Ligand Name	MW (g/mol)	Log P	H-bond donor	H-bond acceptor	Molar refractivity
1	Andrographolide	350.4492	2.9	3	5	94.1
2	Neoandrographolide	480.598	1.17	4	8	124.83

Table 1: Characteristics of Ligands. *MW: Molecular weight.

S No	Ligand-receptor complex	Energy (kcal)
1	cav4HHB-HEM-zinc_andrographolide	-91.42
2	cav4HHB-HEM-zinc_neoandrographolide	-108.61

Table 2: Bond Energy Interaction for specific ligand-receptor complex.

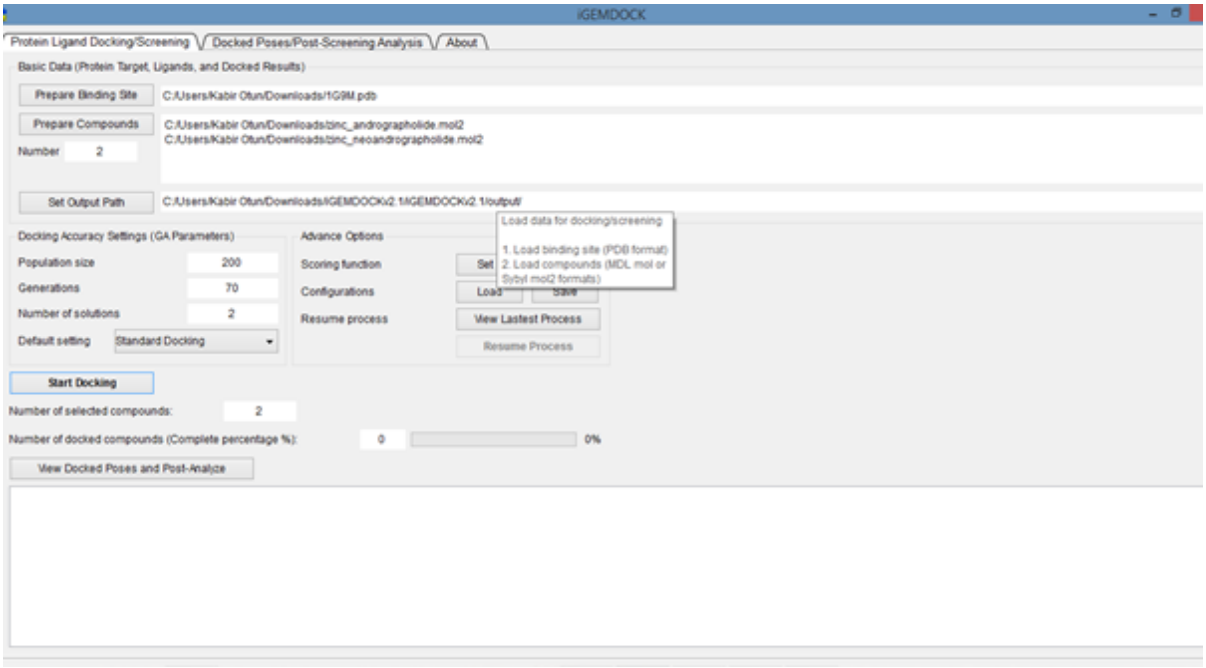


Figure 5: Screenshot of Preparing Binding site and Ligand in iGEMDOCK.

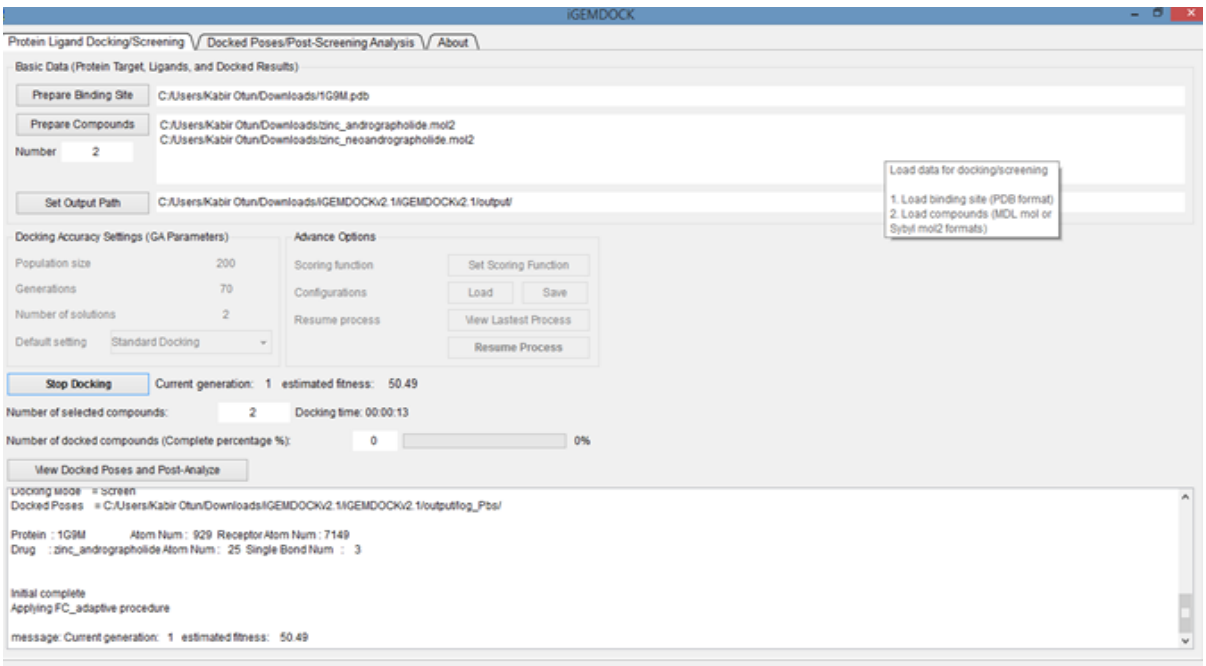


Figure 6: Screenshot of docking process in iGEMDOCK.

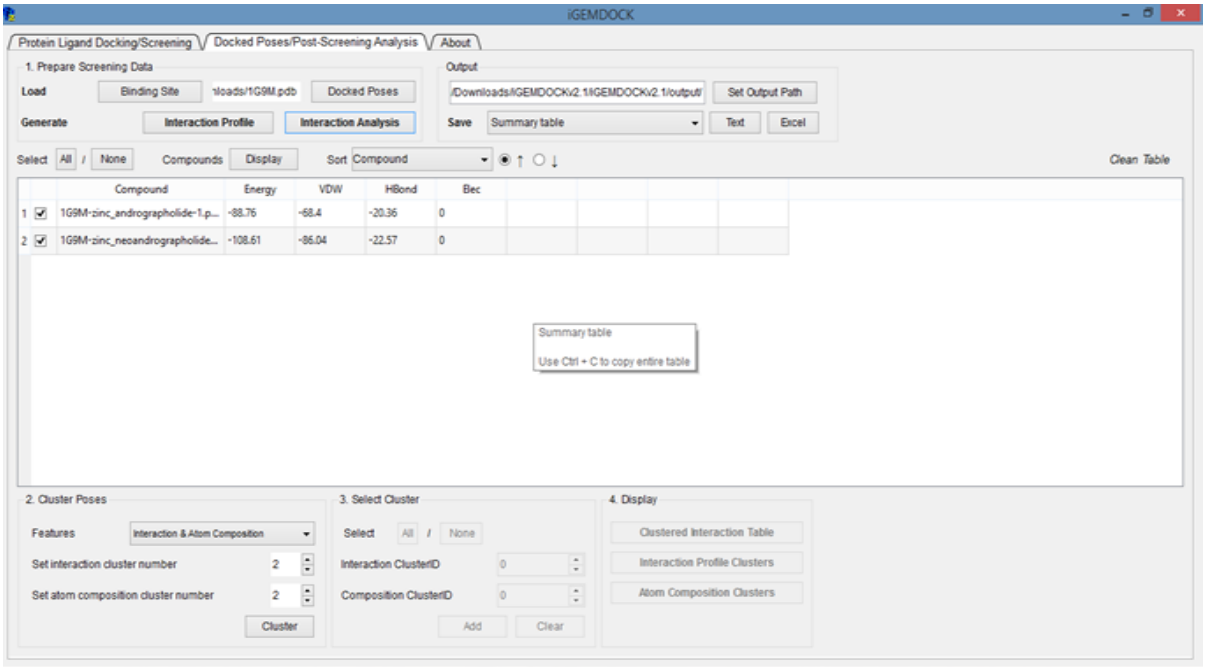


Figure 7: Final output of docking in iGEMDOCK.

Conclusion

The molecular docking helps in drug design and provide a good understanding of the mechanism of interaction of the drug and target protein. From this study, we conclude that the ligand neoandrographolide, the active compound of *Andrographis paniculata* is more effective in inhibiting HIV env gp120 than andrographolide. Hence, neoandrgrapholide can be subjected to further analysis and preceding preclinical trials.

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