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Research Article

Molecular Docking of HIV-1 Protease using Alkaloids from Tinospora cordifolia

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ABSTRACT

Since three decades of the AIDS pandemic and HIV discovery, the search for the cure has been the major theme and is still on. New advances and setbacks offer important clues in the search for A HIV cure ranging from novel treatment methods to gene therapy. The search for the cure has been extended to natural compounds as they don't have any side effects compared to the drugs. The aim of this work was to find out whether plant alkaloids from Tinospora cordifolia exhibits anti-HIV activity using molecular docking studies. The HIV-1 protease was docked by three alkaloids namely; jatrorrhizine, magnoflorine and tinosporide using Igemdock v2.1 software after retrieving the protein structure from the protein data bank. The result shows that all the selected alkaloids had bound to the protease inhibiting its activity. Among them the most promising alkaloid which can be used as a drug was jatrorrhizine due to its low iteraction energy for formation ligand-receptor complex.

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LIFE SCIENCES RESEARCH ARTICLE

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ABSTRACT

Since three decades of the AIDS pandemic and HIV discovery, the search for the cure has been the major theme and is still on. New advances and setbacks offer important clues in the search for A HIV cure ranging from novel treatment methods to gene therapy. The search for the cure has been extended to natural compounds as they don't have any side effects compared to the drugs. The aim of this work was to find out whether plant alkaloids from Tinospora cordifolia exhibits anti-HIV activity using molecular docking studies. The HIV-1 protease was docked by three alkaloids namely; jatrorrhizine, magnoflorine and tinosporide using Igemdock v2.1 software after retrieving the protein structure from the protein data bank. The result shows that all the selected alkaloids had bound to the protease inhibiting its activity. Among them the most promising alkaloid which can be used as a drug was jatrorrhizine due to its low iteraction energy for formation ligand-receptor complex.

1. INTRODUCTION

AIDS is one of the most devastating pandemic diseases of the human immune system across the globe caused by infection with human immunodeficiency virus (HIV) [1]. It continues to be a major global public health issue, having claimed more than 36 million lives so far. Till date, it is estimated that approximately 35.3 [32.2–38.8] million people living with HIV. There is no cure for HIV infection. However, effective treatment with antiretroviral drugs can control the virus so that people with HIV can enjoy healthy and productive lives [2]. Around 31 drugs have been licensed by the United States Food and Drug Administration serving as antiretroviral drugs, still around 1.7 million AIDS related deaths has occurred in 2011. This epidemic disease caused by HIV infection has created an urgent need for vaccines or new classes of antiretroviral agents. Many drugs have been designed to deactivate the HIV by administering the drugs that acts as inhibitors at various stages. Most of the drugs designed and licensed have been classified as Nucleoside Reverse Transcriptase inhibitors (NRTI's), Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI's), Protease Inhibitors (PI's), Fusion Inhibitors, HIV integrase strand transfer inhibitors and Inhibitors – CCR5 co-receptor antagonist [3]. There are around 11 approved PI's which inhibits the activity of HIV protease which plays a crucial role in the life cycle of HIV. HIV protease cleaves the newly synthesized polyproteins at the appropriate places to create the mature protein components of an infectious HIV virion [4].

Drug design also referred to as rational drug design, is the inventive process of finding novel medications based on the knowledge of the biological target. The drug is most commonly an organic small molecule which inhibits or activates the function of a biomolecule such as protein which in turn results in a therapeutic benefit to the patient. This type of modeling is often referred to as computer aided drug design. In computational drug discovery various computational tools and software (freely available) are used to simulate drug receptor interactions. Using these computational tools help us to understand large insight to the drug receptor

interactions along with helping in reducing the time and cost. It is also able to predict whether the molecule will be success or fail in the market. There are two major types of drug design. The first is the ligand-based drug design and the second, structure-based drug design.

Three basic tasks must be accomplished in any docking procedure:

1. Characterization of the binding site in the targeted protein
2. Positioning of the ligand into the binding site and
3. Evaluation of the interaction strength for a specific ligand-receptor complex.

Nature has always been a rich repository of drugs for various ailments. Over the past decade, substantial progress has been made in research on the natural products possessing anti-HIV activity. A variety of secondary metabolites extracted in the crude form have been reported to have anti-HIV activity [5, 6]. Many of them have potential to interfere with the particular viral target. Although none of plant originated drug is currently in clinical use to cure AIDS. Screening these large numbers of secondary metabolites of plant origin using computational tools will help in drug designing in a very short time compared to the conventional methods.

2. MATERIALS AND METHODS

Retrieval of Protein Sequence:

The protein sequence of the HIV-1 protease was retrieved from NCBI. HIV-1 protease has 99 amino acids and 2 hits in the sequence. The structure of the protein was retrieved from the protein data bank and binding site of the receptor was calculated by PROSITE tool. A lot of small molecule databases in public domain such as ZINC, ChemDB, ChemSpider, Pubchem, KEGG ligand databases are used for virtual screening and selection of the drug. These drugs also have to be designed in such a way that these should not affect any other similar molecules in appearance to the targeted molecule.

Then the ligands for the study were selected and 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 highest hydrophobic activity of the drug. The structures of the ligands were taken from ChemDB and were docked by iGEMDOCK tool. Finally all the results were compared and discussed.

Selection of Ligand:

As various natural products are gradually gaining much importance in clinical research due to their medicinal and therapeutic values without any side effects as compared to the drugs. We have taken plant alkaloids from the *Tinospora cordifolia* into consideration since some of the phytochemicals extracted from the plant showed anti-HIV activity [7, 8]. The ligands which are taken into consideration are Jatrorrhizine, Magnoflorine and Tinosporide.

3. RESULTS AND DISCUSSION

Prosite Analysis:

It shows the domain for presence of the binding site in HIV-1 protease at (20-89) for inhibition. The active site is present at 25 for protease activity (by similarity).

Table 1: Result of PROSITE Analysis

HITS in HIV-1 protease	**2**
Position of HITS in protein	20-89, 25
Domain	20-89
Active site	25 for protease activity(by similarity)
Patterns	1
Profiles	1
Aspartyl-protease domain	PS50175
Aspartyl-protease active site	PS00141

Lipinski Rule of Five Analyses:
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 physico-chemical 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 [9].

1. **Magnoflorine**

Molecular Weight = 342.17
Hydrogen Bond Acceptor = 4
Hydrogen Bond Donor = 2
LogP = 0.924
Molar Refractivity = 101.13

2. **Tinosporide**

Molecular Weight = 374.14
Log P = 1.251
Molar Refractivity = 90.01
Hydrogen Bond Acceptor = 7

3. **Jatrorrhizine**

Molecular Weight = 338.14
Hydrogen Bond Acceptor = 4
Hydrogen Bond Donor = 1
Log P = 2.631
Molar Refractivity = 102.04

Table 2: Log P Values

S.No	Ligand Name	Log P
1.	Magnoflorine	0.924
2.	Tinosporide	1.251
3.	Jatrorrhizine	2.631

Table 3: Bond Energy of interaction for Specific ligand-receptor complex

S.No	Ligand-Receptor Complex	Energy
1	1A8G_2Z4-Jatrorrhizine_4922454	-99.79
2	1A8G_2Z4-Magnoflorine_3967334	-99.36
3	1A8G_2Z4-Tinosporide_6918635	-98.67

Fig 1. Screenshot of Preparing Binding Site and Ligands in iGEMDOCK

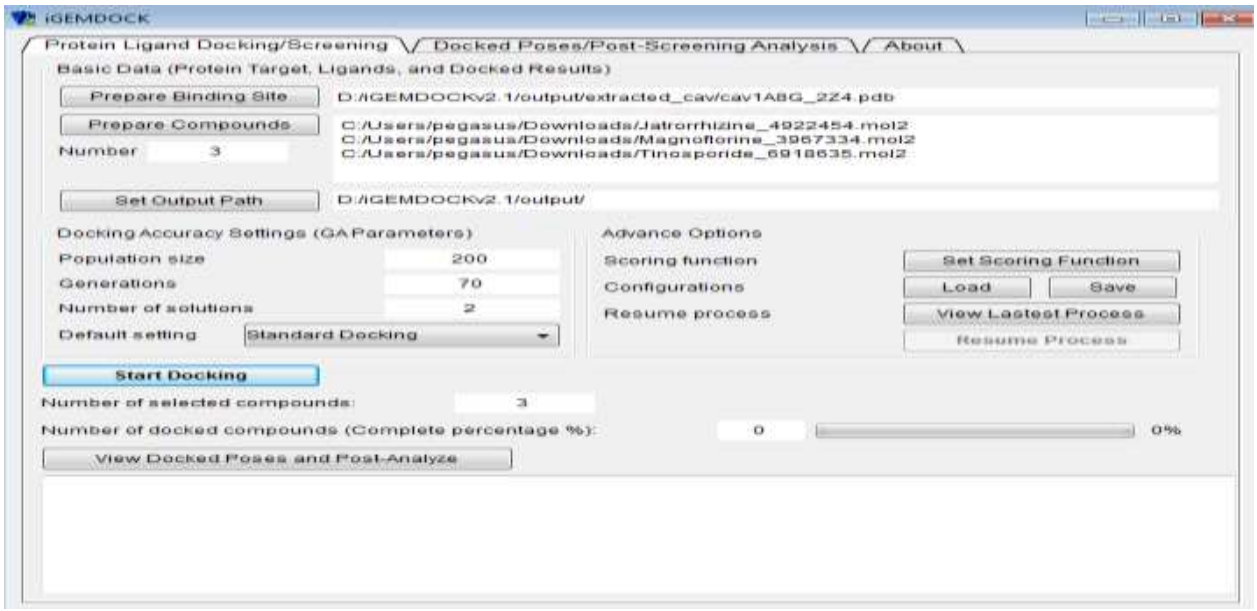


Fig 2: Screenshot of Docking Process in iGEMDOCK

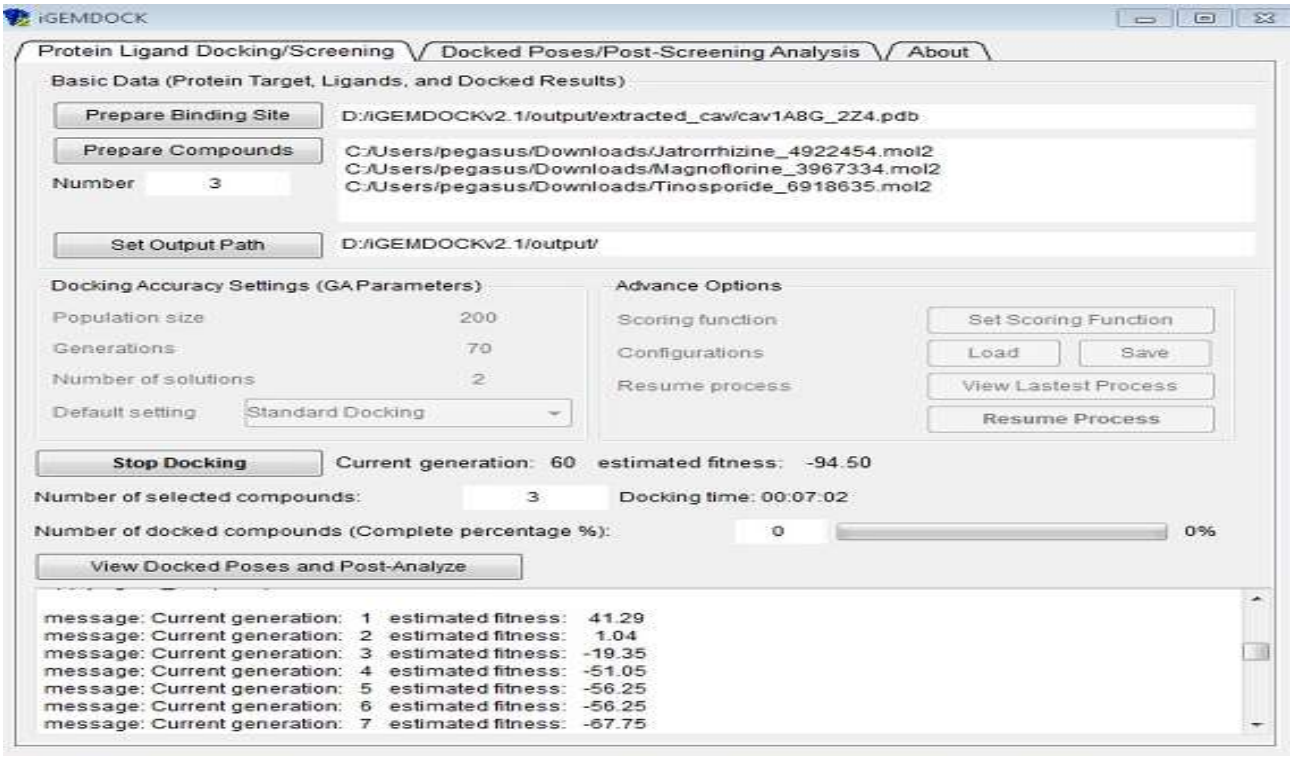
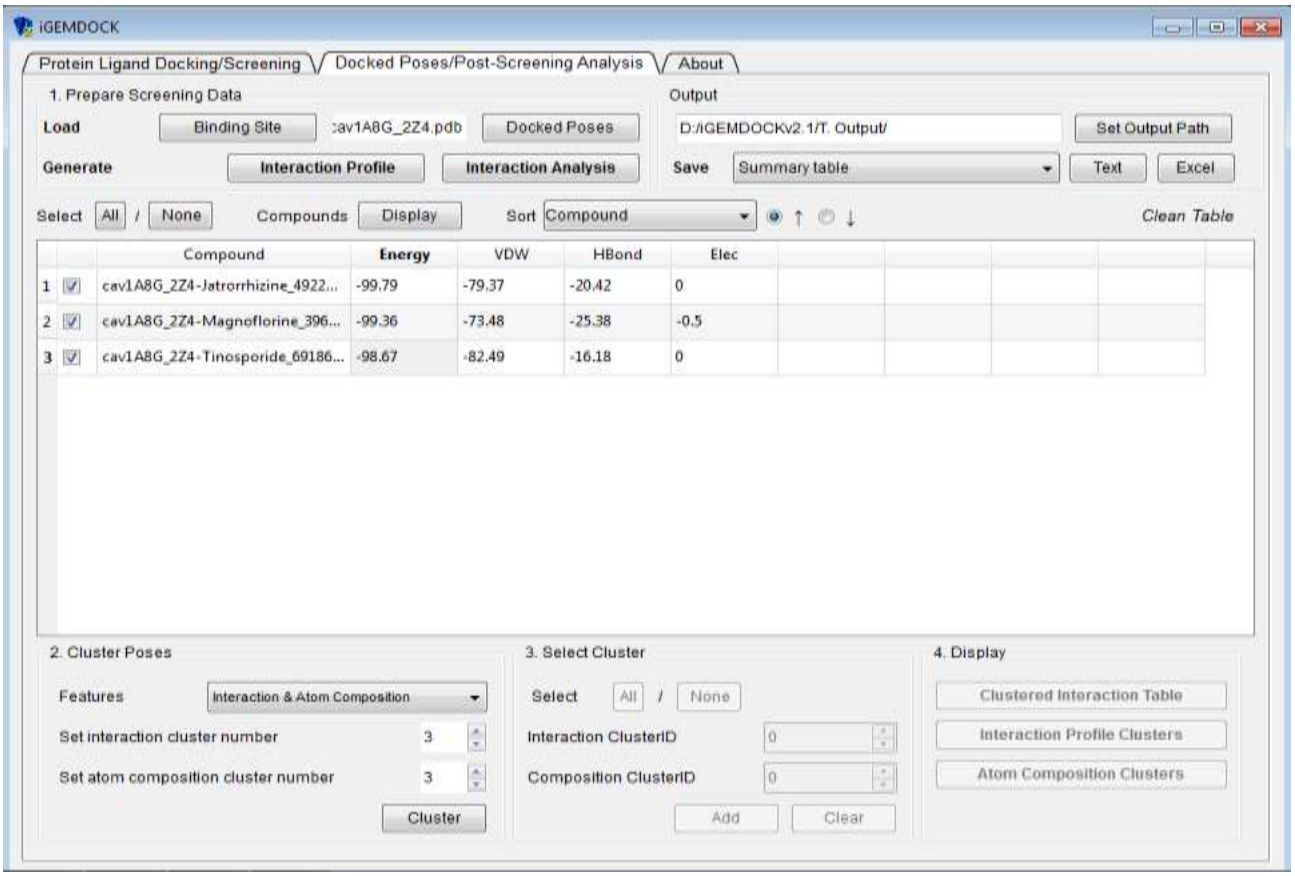


Fig 3: Final Output of docking in iGEMDOCK



4. CONCLUSIONS

The best ligand is usually identified by evaluating the interaction energy for the specific ligand-receptor complex under study. From the results it can be found that among the ligands studied the one which can be a promising drug is jatrorrhizine since it has very less interaction energy (-99.79. kcal) when compared to other ligands. Moreover, none of the ligands has violated Lipinski rule of five. It can also be observed that Log P values of the ligands increases from magnoflorine to jatrorrhizine indicating reduction in hydrophobic activity. It can be concluded that molecular docking helps in drug design and provides a good understanding of the mechanism of interaction of the drug and target protein.

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