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Research Article

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Docking based modeling of VPU Protein from HIV-1 virus and CD4 receptor Protein from humans to predict and analyze the protein-protein complex for the studies of potential VPU Protein inhibitors using natural compounds.

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Abstract

HIV infects fundamental cells in the Human Immune system specifically CD4+ T-cells, macrophages and dendritic cells, HIV infection downregulates the levels of CD4+ T-cells through the various mechanisms, including pyroptosis and apoptosis. When CD4+ T cells number decreases below a critical level, cell-mediated immunity is lost resulting in the development of AIDS. The present study revealed that CD4 is more likely to be the cell receptor through which the Hiv-1 virus interacts with the host rough endoplasmic reticulum using the Vpu Protein and causes the downregulation of CD4 receptor. This may cause host more susceptible for HIV disease. The template structure of the HIV-1's vpu Protein and the humans CD4 receptor protein were docked using Hawkdock server to identify the interacting Domains of the said Proteins. Our aim in this study was to overcome the degradation of CD4 receptor caused by vpu protein. In the current study we selected 880 natural compounds from the ZINC Database for the molecular docking studies. Furthermore, we employed molecular docking studies of the 880 natural compounds with the vpu protein in order to evaluate the binding affinities and identify the potent anti-HIV compound against the HIV-1 disease. Among all the selected compounds Rheidin A (ZINC000085594516) had the Highest binding affinities with vpu protein with minimum energy levels of -8.1 kcal/mol respectively. This study could be implemented to design lead/inhibitor molecule against the HIV type-1 disease.

Keywords: HIV-1, Structure Prediction, STRING Database, KEGG Database, Protein-Protein Docking, Molecular Docking analysis

1. Introduction

The Human Immunodeficiency virus belongs to the genus Lentivirus within the family of Retroviridae, subfamily Orthoretrovirinae [1]. HIV infects fundamental cells in the human immune system specifically CD4+ T-cells, macrophages and dendritic cells HIV infection downregulates the levels of CD4+ T-cells through the various mechanisms, including pyroptosis of abortively infected T cells and apoptosis of uninfected bystander cells [1]. When CD4+ T cells number decreases below a critical level, cell-mediated immunity is lost resulting in the development of AIDS [2]. In the current Studies, we Provide an three dimensional protein Structure by calculating it's Q-mean score and also provides the details about the interaction, Biological Pathway, Protein network and Protein-Protein Complex between the Vpu Protein from Hiv-1 Virus and CD4 receptor from human for the further analysis of the CD4 downregulation caused by Viroporin U Protein [2][3][4]. An in depth we were docked the 880 compounds selected from the ZINC Database with vpu protein to find the efficient ligand molecule, it was observed that among all the selected compounds Rheidin A (ZINC000085594516), had the the Highest binding affinities with vpu protein with global minimum energy levels of -8.1 kcal/mol respectively This information is very useful to identify novel pathways to gain basic knowledge of Acquired Immunodeficiency Syndrome caused by Human immunodeficiency virus type-1.

2. Materials and Methods

2.1 sequences and data retrieval:

Programs: Bioinformatics Provides the various resources, Biological Databases by which the target sequences are obtained in specific fasta file format (developed by W. Pearson) using the biological database NCBI. Corresponding to the following accession numbers: QDC22486.1. (CD4 receptor human), QBK58201.1. (Vpu protein HIV-1) for further analysis.

2.2 Structure Prediction and Q-Mean score calculation: Structure Prediction is fundamental area in Structural Bioinformatics for the 3-dimensional Structure Prediction we took the amino acid Sequences of CD4 receptor protein from human and vpu Protein from Hiv-1 virus [1][3][4]. obtained sequences are processed to predict the structure of the sequence for homology modeling using the Swiss model server [4]. The Q-Mean & Z- score provides the structural features of the model, the Q-Mean & Z-score around zero (0) indicates good Quality of structure [3][4] [Table:1].

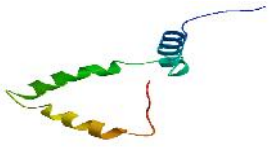
2.3 Protein-protein docking and binding energy scores estimation: The protein structure of the vpu protein of Hiv-1 virus complexed to human CD4 receptor. We used this structure as a template to build the complex of vpu protein from HIV-1 virus with the human CD4 receptor protein. The template structure of the ligand (vpu) and the receptor (CD4) was then used to predict the complex model of vpu protein with the CD4 receptor using the HawkDock server. For selection of model, we generated ten conformers from which we selected the model with the best DOPE score [6]. To calculate the binding energy scores we used, MM-GBSA method present in the HawkDock server. The contribution of each amino acid in protein partners was calculated with the help of HawkDock server [7].

2.4 Molecular Docking analysis: The natural compounds were Docked with Viroporin U protein from Hiv-1 Virus [8]. Docking is often used to evaluate the atomic interaction association of drug candidates against protein targets to predict the binding affinity and activity of the drug using The Autodock Vina tool [8].

3. Results and Discussion

3.1 Structure prediction: the main problem in structural Bioinformatics is to work out with the three-dimensional protein structure (3d) when only a sequence of amino acid residues is given [4]. Several Procedure, methodologies and algorithms are projected as an answer to the 3-d Protein Structure Prediction Problem [5]. These methodologies are often divided into the three main classes: (a) comparative modeling (homology modeling) (b) Threading (fold recognition) (c) ab initio [4]. Protein tertiary structure prediction is a fundamental area in Bioinformatics which aims to create 3-dimensional models from the amino acid sequence. Protein Structure Prediction is one of the main Problem in Structural Bioinformatics today because the biological function of the Protein is determined by it's three dimensional Structure, because the Protein 3-dimensional Structure Prediction is fundamental area in Structural Bioinformatics [5]. for the 3-dimensional Structure Prediction we took the amino acid Sequence of Vpu protein and CD4 receptor. The Q-Mean & Z- score provides the structural features of the model, the Q-Mean & Z-score around zero (0) indicates good Quality of structure [4][5] [Table:1].

Table 1: Shows the Protein structure and it's Q-Mean score

sr.no	Name	NCBI Accession	Protein structure	Q-Mean
1	VPU Protein Human immunodefficiency virus-1	QBK58201.1		-2. 31
2	CD4 receptor human	QDC22486.1.		-3. 82

3.2. STRING Database: STRING Database: the STRING (search tool for the retrieval of interacting genes/proteins), it is freely accessible database, contains information from many sources including computational prediction methods and public text collections [9].The STRING Database was used to predict the protein-protein interaction network associated with the experimentally confirmed sequences [9]. In this work we predict the protein-protein interaction network associated with Vpu protein from Hiv-1 Virus and CD4 receptor from humans [1][9].

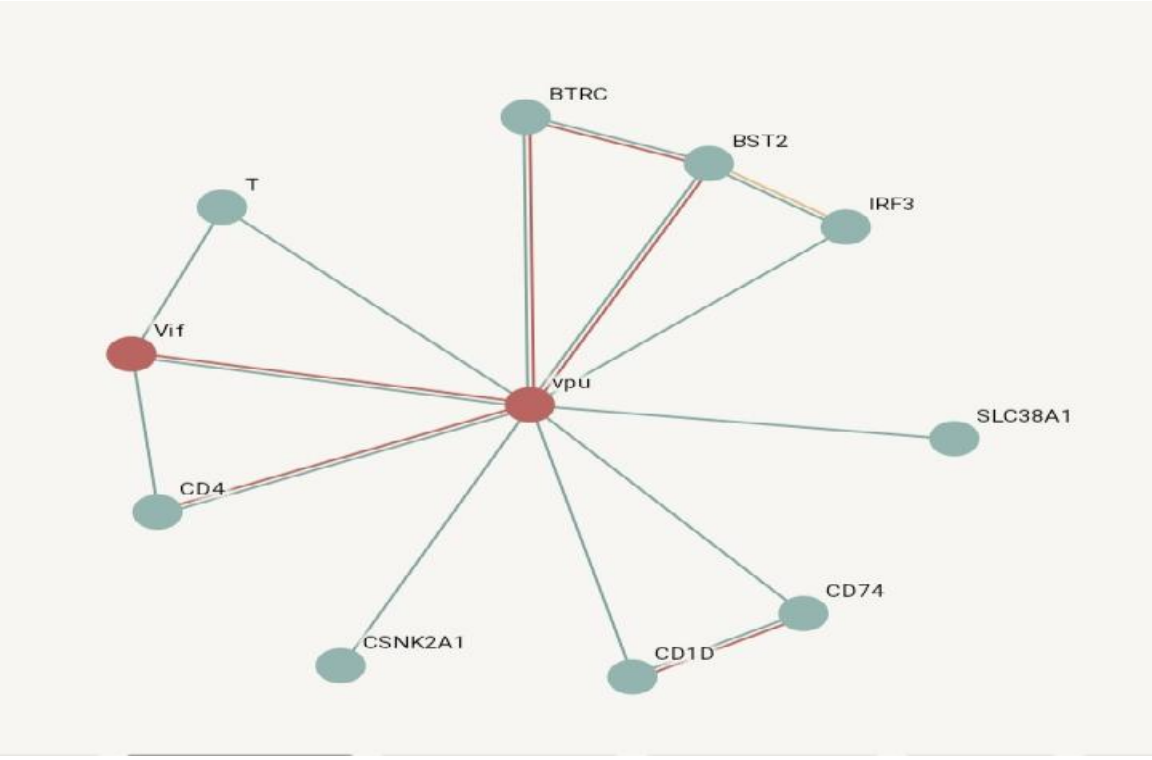


Fig 1: Shows the Vpu Protein associated networks

3.3. KEGG Database: KEGG (Kyoto Encyclopedia of Genes and Genomes) is a collection of various databases contains the information about the genomes, biological Pathways, diseases, drugs and chemical substances KEGG Database is used in various Studies including metagenomics, genomics, metabolomics, modelling and simulation and translational research in drug development. In this work we studied the Biological Pathway for the Hiv-1 Virus (Fig: 2) [1][10].

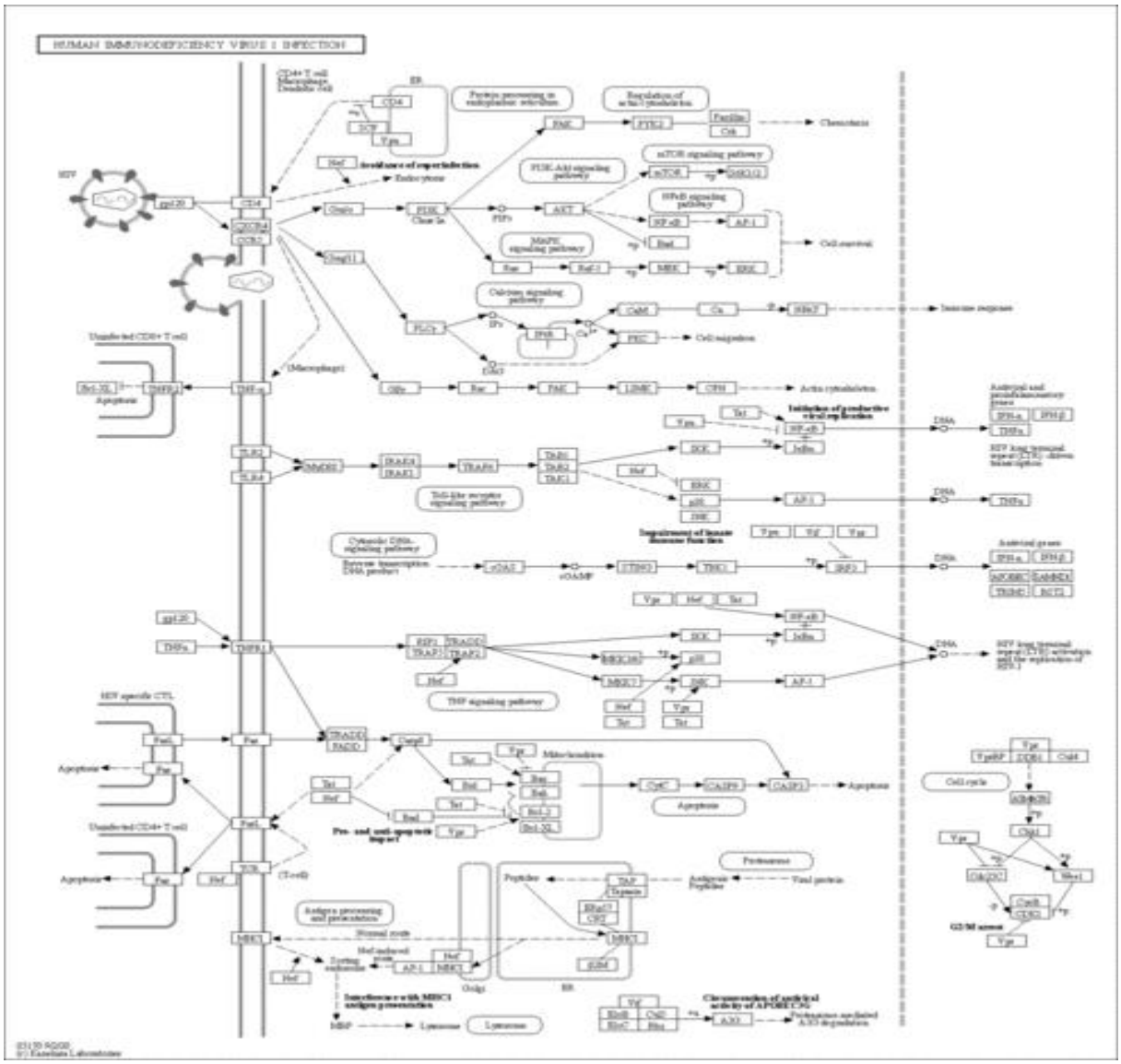


Fig 2: Biological pathway for HIV-1 Virus

3.4. Protein-Protein Docking: Macromolecular docking is the computational modelling of the two or more interacting biological macromolecules to form the complex, the role of macromolecular docking is the prediction of the three-dimensional structure of the macromolecular complex to understand the structural and functional role of the targeted protein [7][8]**.** in the current work we calculate the binding energy score between vpu protein from Hiv-1 virus and CD4 receptor from human and Provide the complex Structure between them (Table: 2)[7].These study could be implemented to design lead/inhibitor molecule against Acquired Immune Deficiency Syndrome caused by Human Immunodeficiency virus type-1 at molecular level [8].

Table 2: Protein-protein complex of vpu protein (ligand, pink color) and CD4 receptor (Blue color) and it's Binding score

Sr. no	Protein-protein complex structure	Binding Score
1		-4806. 72

3.5. MM/GBSA: The molecular mechanics energies combined with the generalized Born and surface area continuum solvation (MM/GBSA) method are a popular method which is commonly used in the estimation of the relative binding free energy of ligands to macromolecule this approach makes use of protein-ligand complexes obtained from molecular docking calculations [7]. In the present work we have successfully implemented this method In the macromolecular Structure of vpu protein from Hiv-1 virus and CD4 receptor from human to form the complex Structure between them.

Table 3: shows the top five amino acid residues and it's Binding free energy score from CD4 receptor and Vpu protein (ligand)

Rank	Residues (ligand)	Binding free energy	Residues (Receptor)	Binding free energy
1	B-VAL-21	-3.5	A-LYS-2	-5.18
2	B-SER-53	-3.41	A-THR-11	-4.87
3	B-VAL-22	-2.99	A-LYS-72	-4.49
4	B-ILE-25	-2.94	A-THR-156	-4.27
5	B-ASN-55	-2. 84	A-VAL-4	-2.65

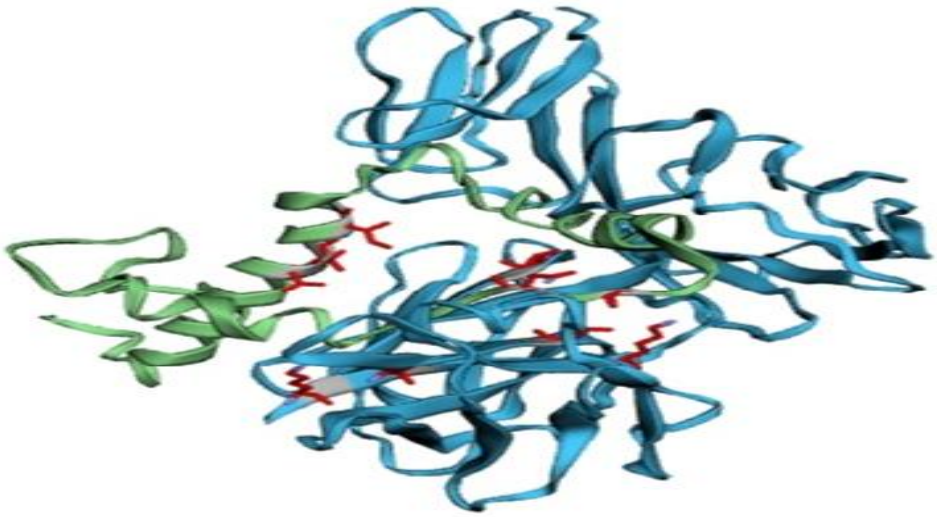
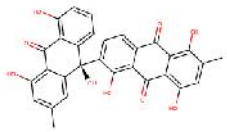
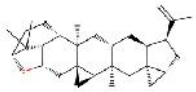
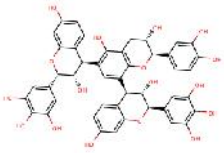
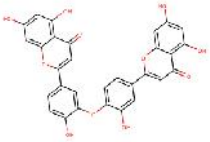


Fig 3: shows the Protein-protein interaction between Vpu protein (ligand, green color) and CD4 receptor (Blue color) and it's Binding residues (red color) from Table: 3

3.6. Molecular Docking Analysis: in the current studies we docked 880 Natural compounds selected from ZINC Database were docked with vpu protein to evaluate the binding affinities & activity of the drug, the scores of docking was observed that among all the selected compounds Rheidin A (ZINC000085594516) had the Highest binding affinities with vpu protein with minimum energy levels of -8.1 kcal/mol respectively.

Table: 4: Shows the binding affinities of the compound

ZINC ID	Compound name	Compound structure	affinity (kcal/mol)
ZINC000085594516	Rheidin A		-8.1
ZINC000095485933	(s) Terpinenol		-7.6
ZINC000095486142	Dioncophylline C and dionclactone A		-7.7
ZINC000150338900	3,4- dihydro-2H-chromene-3,5,7-triol		-7.5
ZINC000095486263	oxyskyrin		-7.8

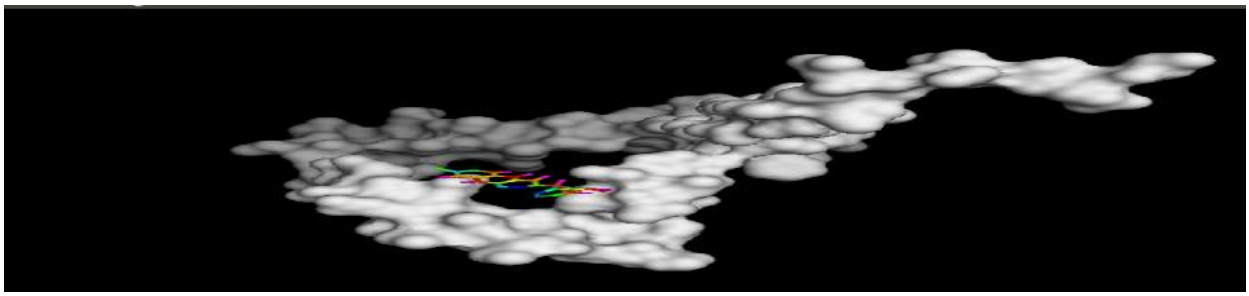


Fig 4.1: shows the interaction between VPU Protein and the Rheidin A compound with -8.1 kcal/mol binding energy

4. Conclusion

In the current Studies, we Provide an three dimensional protein Structure of the VPU Protein from HIV-1 Virus and CD4 receptor from human by calculating it's Q-mean score, the Q-Mean & Z- score provides the structural features of the model, the Q-Mean & Z- score around zero (0) indicates good quality of the Predicted Protein Structure [Table:1]. We used this structure as a template to build the complex of vpu protein from HIV-1 virus with the human CD4 receptor protein. The template structure of the ligand (vpu) and the receptor (CD4) was then used to predict the complex model of vpu protein with the CD4 receptor using the HawkDock server.For selection of model, we generated ten conformers from which we selected the model with the best DOPE score. To calculate the binding energy scores we used, MM-GBSA method, The contribution of each amino acid in protein partners was calculated with the help of HawkDock server. An in depth we were docked the 880 compounds selected from the ZINC Database with vpu protein to find the efficient ligand molecule, it was observed that among all the selected compounds Rheidin A (ZINC000085594516), had the the Highest binding affinities with vpu protein with global minimum energy levels of -8.1 kcal/mol respectively [Table: 4].

This study could be implemented to design lead/inhibitor molecule from the natural source against the HIV type-1 disease and also data of these interactions is vital for best management of the patients who have the Acquired Immunodeficiency Syndrome caused by Human Immunodeficiency virus type-1.

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