Molecular Docking Study of Bioactive Compound of Andrographolide against Ebola Virus

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Abstract : Ebola virus is a single-stranded, negative-sense RNA virus that causes severe hemorrhagic fever in humans and nonhuman primates. This virus is resistance to many antibiotics also there is no proper treatment for EBOLA viral infection. In worldwide,thus many people affected by this virus and there is no drug available for treatment of Ebola virus infection. Therefore new drugs are need for therapy and prevention for this life threatening infection. Hence the current study deals with the evaluation of the potent bioactive compound Andrographolide against the three receptors of Ebola virus receptor proteins. The protein receptors VP40, VP35 and VP24 were docked with the Andrographolide and evaluated on the basis of total energy and binding affinity scores byAutoDock. Andrographolide showed a high docking score against the VP40, VP35 and VP24. Theestimated binding free energy of VP40 is −3.57 kcal/mol, the VP35 binding free energy is −7.18 kcal/mol. The VP24 binding free energy is −8.5 kcal/mol. This study showed that Andrographolide have high binding affinity and exhibit better interactions with all the Ebola Virus Protein receptors. This study will help to identify the new drug development for the EBOLA virus.

Keywords : Ebola virus, Molecular Docking, Virtual-screening, Andrographolide.

Introduction:

Ebola Viral Disease (EVD) is an acute viral disease that is embarked by high mortality in human and nonhuman primates. Ebola hemorrhagic fever (Ebola HF) is one of the numerous Ebola Viral Diseases which was first encountered by the virus family Filoviridae when Marburg virus appeared in 1967. Hemorrhagic fever is the major infection caused by Ebola virus which takes place in two phases, incubation period and late phase. Incubation period shows symptoms like arthritis, fever, fatigue, nausea which can last for one week and late symptoms include depression, eye inflammation, and hemorrhagic rash over the entire body[1, 2].

The VP24, VP35, VP30, and VP40 proteins as the potential drug targets looking into protein VP40 occurs at the plasma membrane and requires lipid raft micro domains [3]. During its replication, it also plays an important role either in the RNA metabolism of viral or host cell[4]. The Ebola VP35 protein is a crucial protein which acts as component of the viral RNA polymerase complex, viral assembly factor. It hampers the host interferon (IFN) production hence is vital for virulence of EBOV. Similarly the structural protein VP24 of Ebola virus (EBOV) has proven to be antagonizing the host interferon function. It had also been established that in a mice model this role could depend on the ability of VP24 to counter the interferon system[5]. VP30 is crucial for the formation of the viral mRNAs even though it has been reported that EBOV transcription could occur solely if the Nucleoprotein (NP) get changed; triggering the incorporation of the transcription initiation site . It has been hence conjectured that VP30 may help to beat this obstruction for transcriptional enactment, steady with its proposed part at an early phase of interpretation. VP30 due to its role in homo-oligomerization is considered as a potential target for antiviral treatment [6,7].

Andrographispaniculata(Acanthaceae) isone of the most valuable medicinal plant and bio-factory of diterpronidlactons which have immense value like immune stimulating, anti – inflammatory, anti- fertility,liver protection,anti – HIV and bilesecretion stimulating agent[8]. A number of active components are reported in this plant which mainly includes diterpone lactones, flavonoides and polyphenols [9].However, the most pharmacological properties present in active principle of Andrographolide. But no reports are available for antiviral property for ebola virus.Hence in current research we have analyzed the inhibitory property of bioactive compound of Andrographolide against Ebola virus protein receptors and hypothesized mode of action of few compounds. Virtual screening approach and molecular docking in bioinformatics study makes it easy to identify the inhibitory property of several compounds against many dreadful and chronic diseases and their significant proteins or signaling pathways. This is because of it reduces the efforts for clinical trial studies or in vivo studies. Here the computational study of bioactive compound of Andrographolide against Ebola virus protein receptors has been carried out and filtered some of the previously known drugs which has been approved by FDA for several diseases.

Materials and Method:

Selection of Protein Structure:

As per the literature review structure of the matrix VP40 at 1.60 ^{o}A resolution PDB ID 1H2D.VP35 at 1.40 ^{o}A resolution PDB ID 3FKE. VP24 at 1.92 ^{o}A resolution PDB ID 4M0Q were retrieved from Protein Data Bank.The structures were analyzed using DS Visualizer 4.0 and the water molecules were removed. The Energy minimization of protein structures were carried out using Swiss PDB viewer.

Screening of Lead Molecules:

After choosing the target protein the inhibitory drug compounds were chosen from pubchem and virtual screening was done by creating database of these compounds in CHIMERA. These databases were fed to ARGUSLAB for screening the best ligands with the target protein. The best ligands were chosen with low energy values, and virtual screening was done using ZINC DATABASE, from which class of similar compounds were obtained, and again were fed to ARGUSLAB and best compounds obtained were passed for docking studies.

Docking Studies:

In docking studies, the interaction between target and ligand was studied. The best ligands screened were loaded in to auto dock and docking studies were carried out. Based on the binding energies and details from the histogram, the drug lead compounds were determined.

Result and Discussion:

The overall objective of this work was to select the bioactive compound which can get docked with selected EBOLA virus receptor protein .The docked pose of EBOLA virus involved protein VP24, VP35, VP40 protein with Andrographolide ligands clearly demonstrated the binding positions of the ligand with protein. Analysis of the receptor/ligand complex models generated after successful docking of the Andrographolide it was based on the parameters such as, hydrogen bonds distance, amino acids interactions, binding energy and orientation of the docked bioactive compound with the active site (table1&Fig1-3). As a general rule, in most of the potent both hydrogen bond and hydrophobic interactions between the compound and the active sited of the receptor have been found to be responsible for mediating the biological activity.it is important to keep the predicted ligand-binding site as small as possible without compromising accuracy for a range of applications such as molecular docking. De novo drug design and structural identification and comparison of functional sites.

Table 1: Predicted binding free energies (docking scores) and detailed interactions observed between Bioactive compound the target proteins

S.NO	Selected compound	Target protein	Binding energy kcal/mol	Interaction with amino acids residues
1	Andrographolide	VP24	-3.57	Thr166, Lys163
2		VP35	-7.18	Val294, Pro292, Lys319, Ala291
3		VP40	-8.5	Ala144, Asn200, Gln279

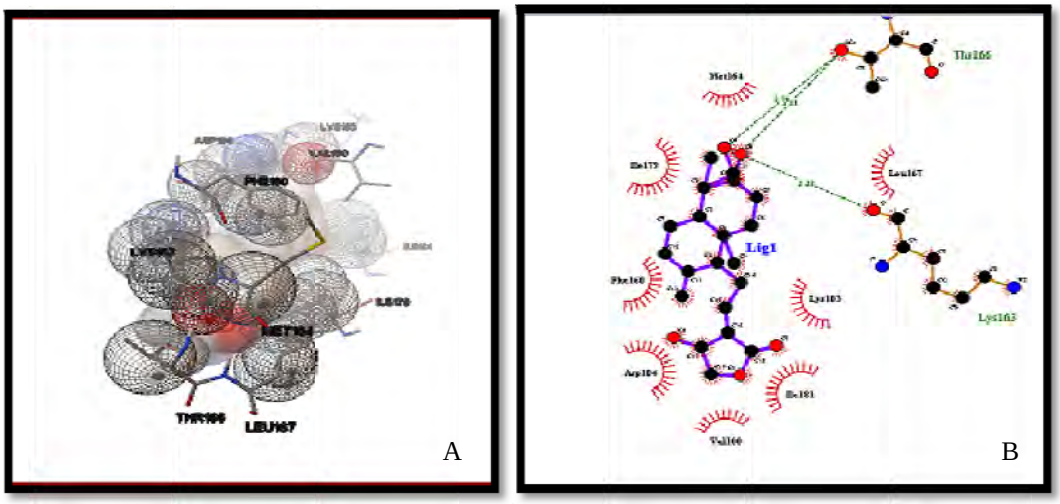

Fig. 1 Molecular interactions between bioactive compound (A) Docked with VP24 protein. The amino acid residues which interact with bioactive compound are marked . (B) Interactions between bioactive compound and VP24 with the H-bond distances generated by PyMOL. Dashed lines represent the H-bonds.

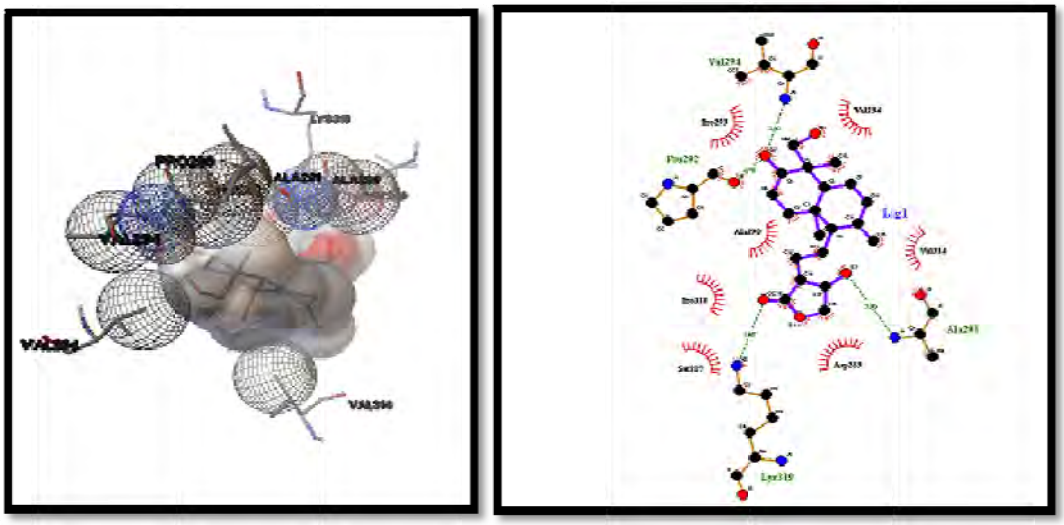

Fig. 2 Molecular interactions between bioactive compound (A) Docked with VP35 protein. The amino acid residues which interact with bioactive compound are marked. (B) Interactions between bioactive compound and VP35 with the H-bond distances generated by PyMOL. Dashed lines represent the H-bonds.

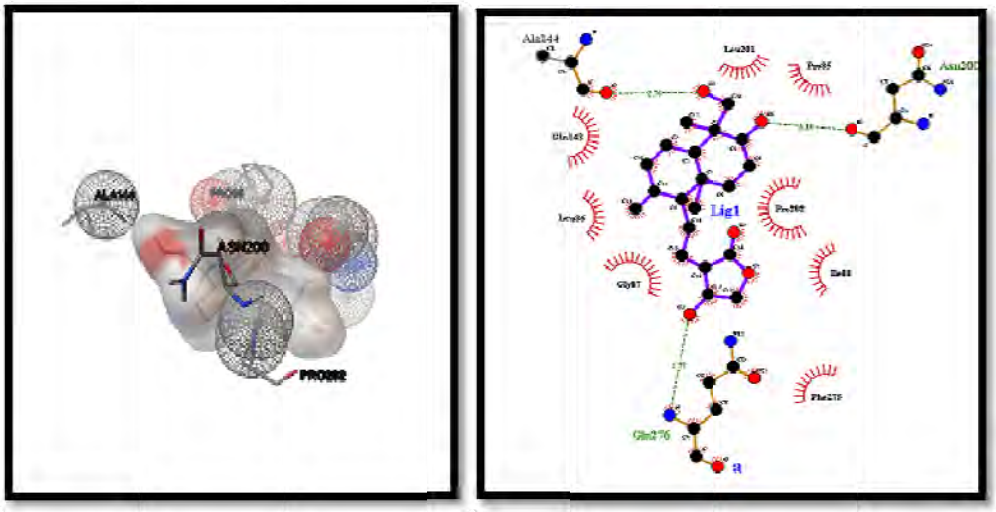

Fig. 3 Molecular interactions between bioactive compound (A) Docked with VP40 protein. The amino acid residues which interact with bioactive compound are marked. (B) Interactions between bioactive compound and VP40 with the H-bond distances generated by PyMOL. Dashed lines represent the H-bonds.

Andrographolide shown the better binding energy (-3.57 kcal/mol) for VP24 protein than other tested receptor proteins.wherever the binding energy of VP35 and VP40 is -7.18 kcal/mol, -8.5 kcal/mol. It indicatesthat bioactive compound of Andrographolide shows the higher binding energy for all target proteins.Moreover in Andrographolide exhibited good interactions withVP24(targeting residues are Thr166, Lys163 with hydrogen bonds distance 2.32 A^O, 2.70 A^O, 2.11 A^O). There were 4 interactions withandrographolide (namely Val294, Pro292, Lys319, Ala291 with hydrogen bonds distance is 2.03 A^O, 1.96 A^O, 1.63 A^O ,3.05A^O) for VP35 protein. Respectively for VP40, there were 3 interactions of amino acid namely Ala144, Asn200, Gln279, with hydrogen bonds distance is 2.76 A^O, 2.77 A^O, 3.35 A^O ..

Conclusion:

Now a day's molecular docking play a key role in understanding drug receptor interaction, which further help in designing novel, or potent inhibitors through drug receptor interaction mechanism. Ebola, have the dubious distinction of being associated with some of the highest case-fatality rates of any known infectious disease. Ebola cause severe hemorrhagic fever in humans and nonhuman primates, since it causes high mortality rate and currently no drugs are available, there is an urgent need for novel antiviral against Ebola virus infections. Knowledge on the molecular interactions of bioactive compound of Andrographolide with essential EBOLA targets is a potentially useful tool for the design and development of new anti-EBOLA drug. This in molecular docking study revealed that theplant-derived compound of Andrographolide had the potential to interact with selected proteins that were essential to EBOLA. Further work is required to gain a better insight into structure-active site relationships using a wider variety of structurally-related derivatives as well as to correlate the results of the docking study with in vitro experiments in the search for new anti-EBOLA drugs. The lead found out, could possibly inhibit the infection. However, these leads should undergo various preclinical analysis and optimization process before going into clinical trials.

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