2nd International BioDesign Research Conference 2021

Applying Pharmacoinformatics, Virtual Screening, and Molecular Dynamics Simulation are being Used to Find Best Inhibitors for the Human Infectious Lujo Virus 6GH8 Target.

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ABSTRACT

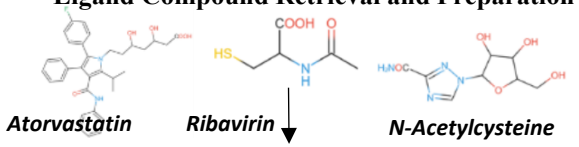
Lujo Hemorrhagic Fever Virus (LUHFV) has emerged as a human pathogenic viral infectious disease with a high mortality rate. Lujo is a single-stranded RNA virus that belongs to the Arenaviridae family and is a recognized human cause of viral hemorrhagic fever (VHF). This study aims to identify promising beat potential compounds for the treatment of viral hemorrhagic fever through molecular modelling against Lujo Hemorrhagic Fever Virus.

INTRODUCTION

Viral hemorrhagic fevers have been plaguing the African continent for centuries, claiming the lives of many. In terms of severity and fatality, the Lujo virus is the second most pathogenic Arenaviruses after Lassa. There is still no effective treatment like drugs or vaccines against Lujo fever, apart from supportive therapy along with the antiviral drug, Ribavirin. An in-depth study is difficult on Lujo Virus since it is endemic to remote and politically insecure regions of the continent. Our study aims to examine potential small molecule drugs for Lujo fever utilizing different in-silico tools. These drug targets will be screened using molecular docking and molecular dynamics simulation approaches and ADMET properties will reveal the efficacy and safety of these compounds. In this study, we used two other antiviral drug molecules such as Ribavirin, N- acetylcysteine along with Atorvastatin compounds for searching the potential small molecules.

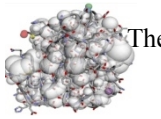
METHODS

Ligand Compound Retrieval and Preparation



Atorvastatin *Ribavirin* *N-Acetylcysteine*

Active Site Determination Analysis and Receptor Grid Ligand Interaction



The active site of 4AKL (Chain b) modeled through the CASTp Server.

Target Protein Retrieving and Preparation

Chain B of Lujo Hemorrhagic Fever viral protein 6GH8 (PDB ID: 6GH8)

Protein–Protein Interaction and Protein folding Determination analysis

STRING

CO

Pharmacokinetics and Toxicity (ADMET) Properties Prediction

Absorption,Distribution,Metabolism,Excretion,Toxicity

Molecular Docking Studies

Identification of the binding mode of desired protein with selected phytochemicals the molecular docking was carried out by **PyRx** tool **AutoDock Vina**.

Molecular Dynamic (MD) Simulation

GROMACS was used to perform MD simulation. Topology file of ligands Ribavirin, N- acetylcysteine & Atorvastatin with their best compounds & proteins Lujo refined 6gh8 protein were created with CgenFF & pdb2gmxscript with Charmm36 & Jul2020 force field.

RESULTS

- **Ligands Retrieval and Preparations**

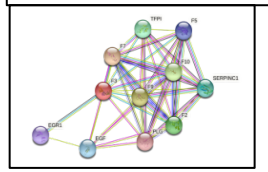
Ambinter database was searched for parameter: 80% of default similarity search compounds and a total of 276 compounds were identified for further analysis.

- **Active Site Determination Analysis**

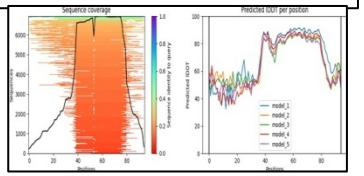
We found most area coverage in pocket ID 1: 5869.075 most vol 3769.615. The active site started SeqID 87 (GLN-N) to SeqID 196 (THRCG2) & we set grid box between 87 to 196 amino acid residue. Pocket 1 has large area coverage & high volume so it is selected for this study.

- **Protein-Protein Interaction (PPI)**

PPI network was very well visualized and the information regarding the major pathways involved, the function each of those genes entails, and major Pfam domains were all understood. All these helped to identify the key points in the regulation of disease-related cellular processes and in designing new potential candidates



STRING Visualization For F3 Gene



Local Distance Difference Test Result After ColabFold2 Deep Purpose Analysis.

- **ColabFold Analysis for Protein Structure Predict**

Using fasta files of Lujo virus proteins several models of input files were generated using **Google ColabFold.**

- **Molecular Docking & Dynamics Studies**

Based on the molecular docking analysis results, Ribavirin, N-acetylcysteine, & Atorvastatin with their top 3 binding affinity compound, a total of 12 compounds were selected for further analysis. MDsimulations have matured into a method that can be utilized to study macromolecular structure-to-function connections efficiently.

Serial number	Ligands	Binding Affinity Score (Kcal/mol)	RMSD/ub	RMSB/lb
1.	Amb. ID:33839414	-6.4	0	0
2.	Amb. ID:35793910	-6.3	0	0
3.	Amb. ID:17607406	-6.2	0	0
4.	Amb. ID:12035	-3.9	0	0

Figure: N-Acetylcysteine with their Top Three Molecular Binding Affinity Compounds.

Serial number	Ligands	Binding Affinity Score (Kcal/mol)	RMSD/ub	RMSD/lb
1.	Amb. ID:17608546	-8.3	0	0
2.	Amb. ID:17609209	-8.2	0	0
3.	Amb. ID:17608560	-8.0	0	0
4.	Amb. ID:60823	-6.5	0	0

Figure: Atorvastatin with their Top Three Molecular Binding Affinity Compounds.

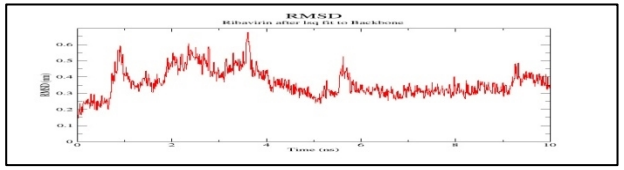


Fig: Ribavirin RMSD analysis graph

CONCLUSION

Lujo is a novel arenavirus, genetically different from other members of the family, including the Lassa virus, according to sequence research. The risk posed by this virus has necessitated the design and development of the associated viral inhibitor. The 12 identified compounds have the potential of being a target to this virus and thus should further be developed through wet laboratory studies.

REFERENCE

1. Cohen-Dvashi H, Kilimnik I, Diskin R. Structural basis for receptor recognition by Lujo virus. Nat Microbiol. 2018;3(10):1153-1160. doi:10.1038/s41564-018-0224-5