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IN SILICO DRUG LIBRARY SEARCH AND DOCKING STUDIES WITH THE TARGET ORF 61 GENE PRODUCT RESPONSIBLE FOR CHICKEN POX

[1]SHAKYA D, [2]TIWARI A, [3]ROY M, [4]PAL PK, [5]GANGWAR P AND [6*]MOHAN A

1, 2, 4: Mangalayatan University, Aligarh-Mathura Highway, U.P.

3, 5, 6: Bio-EGICORE, Department of Life Sciences, Lucknow, U.P.

***Correspondence E Mail: bioegicore@gmail.com**

ABSTRACT

Chicken Pox (Varicella) is highly infectious, most common among viral disease, caused by the infection of Varicella Zoster Virus (VZV). It occurs both in temperate and tropical climate of various countries including India. Open Reading Frame (ORF) 61 gene of VZV encodes ORF 61 protein that transactivates viral and cellular promoters. This protein has been targeted for in silico drug designing in this work. The 3-dimensional structure of the query protein, obtained from online bioinformatics databases, was allowed for docking studies against various ligand molecules. These ligands were isolated from online drug database Drug Bank. Molecular docking has been performed using AutoDock software, which has given a best suitable molecule, 4AYC_CPQ_A_1489, having minimum free energy of -12.5kcal/mol.

Keywords: Chicken Pox, Dog Site Scorer, Auto Dock, Drug Bank, Varicella, ORF 61, in silico, Open Bable

INTRODUCTION

Varicella, commonly known as chicken pox, is an acute infectious, highly contagious, self limited, universal viral disease, usually mild in immunocompetent children but can be fatal in immune-deficient individuals (1, 2). As it is highly contagious, it can easily spread from person to person during viral shedding from nasopharynx by the way of droplets and aerosols and with the fluid from the blisters of infected person (skin lesions). (7, 6, 5) This disease appears with a mild fever (a body temperature of 38^0 C, 100 F), tiredness, and

slight body discomfort usually comes with an itchy rash which is first appears as small, reddish spots or pimples and then converted into skin lesions or blisters. (4)(2)(9) The contagious period of Varicella begins1-2 days before the appearance of the rashes and ends still all the vesicles have crusted, generally within 5-7 days. In temperate regions, 13-16 cases per 1000 people per year has been found, having highest frequency in children aged 1-9 years old (8). Besides it, an increased incidence has been observed in the children aged more than 5 years due to attendance at child care centres. On the other hand, in tropical countries, in India, the frequency of occurrence of Varicella is higher in adults (5) (3). In most of the regions of temperate and tropical countries, the occurrence of Varicella shows pronounced seasonality, with higher frequency of occurrence during winter springs and in temperate climates, epidemiologic studies of Varicella showed the occurrence in every 2- 5 y ears. The overall case fatality rate in developed countries like United States is estimated at 2- 4 per 100,000 cases, with the highest death risk at the extremes of age. The hospital admission rate for all ages is 2- 6 per 100,000 of population in which most of the admitted patients are children. (5, 6)

Varicella Zoster Virus (VZV) is a neutrotropic, alphaherpes virus, a member of the herpesvirus group, whose genetic information is stored in DNA (deoxyribonucleic acid) (12). Like other herpesviruses, it has the capacity to retain in the body after the latent (primary) infection. VZV is able to retain stubbornly inside sensory nerve ganglia by the way of respiratory tract and conjunctiva (site of entry); the replication sites are nasopharynx and regional lymph nodes. Primary infection with VZV results in chickenpox whereas recurrent infection causes Herpes Zoster (shingles). It has believed that the survival time of virus is short in the environment. After 4 to 6 days of infection, primary viremia occurs during which VZV invades liver, spleen, and sensory ganglia. Secondary viremia occurs after the further replication process in viscera, with skin infection. (6)

Varicella-zoster virus (VZV) open reading frame 61 (ORF61) gene encodes transactivates viral and cellular promoters in transient-transfection assays which is the orthologue of herpes simplex virus ICP0 (12, 13). This work is an approach for in silico drug designing against the protein encoded by ORF61 gene of the Varicella Zoster Virus. A suitable protein structure has modeled using

modeling biological software (14), which was then used for docking studies against the various ligand molecules isolated from drug databases (Drug Bank). The best molecule having minimum free energy has been subjected to bioavailability and toxicity prediction, using freely available online servers.

MATERIALS AND METHODS

Drug Library Search

The Drug Bank database is a unique bioinformatics and chemoinformatics resource that combines detailed drug (i.e. chemical, pharmacological and pharmaceutical) data with comprehensive drug target (i.e. sequence, structure, and pathway) information. In this work, ligand molecules were extracted out using this database and the downloaded file was converted into PDB format from SDF format, by using Open Babel software, which is a free biological tool used for converting chemical file formats. The converted PDB formats of the ligand molecules were then allowed to dock with respect to the targeted protein.

Docking Studies

Docking of the molecules were performed by using an automatic docking tool, Auto Dock, a graphical user interface, designed to predict the binding behavior of the small molecules such as substrates, with their receptors of known 3D structures. Various ligands molecules were chosen from the drug databases, but only fifteen molecules were selected for docking analysis, performed by Auto Dock 4.6.

RESULTS AND DISCUSSION

With the help of this research, we have been successful in docking studies against ORF61 gene product. Docking with different possible ligands has resulted in finding the most probable ligand, having minimum free energy. The resultant molecule, 4AYC_CPQ_A_1489, with a free energy of -12.5 has chosen for further de novo synthesis of drug against Varicella (Chickenpox) **(Figure 1, 2 and Table 1)**.

CONCLUSION

In this work, chicken pox has been chosen as a target disease which is caused by Varicella-zoster virus (VZV). By following the appropriate bioinformatics tool for molecular docking, various possible ligands were docked with the query protein structure. Therefore, the present studies have concluded that the resultant selected docked molecule, having lowest free energy can be used as a drug for further treatment against Chicken pox, keeping other factors ideal.

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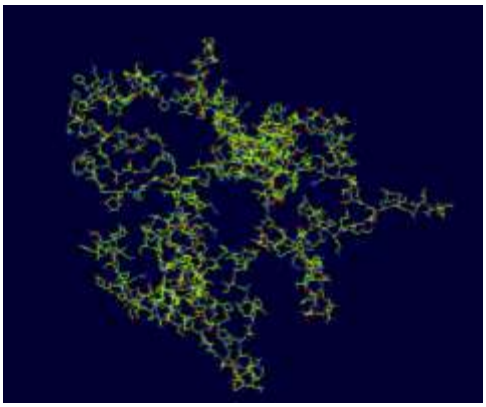

Fig. 1: 3-dimensional structure of ORF 61

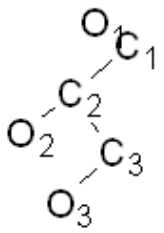

Fig. 2: Structure of best ligand 4AYC_CPQ_A_1489

Table 1: Docking Result of the eight molecules (drug)

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
2BCN_HEM_109 2HOD_NDG_E_470	-11.0	0	0
	-5.8	0	0
4AYC_CPQ_A_1489	-12.5	0	0
4AYC_GOL_B_1488	-3.6	0	0
3W5M_CA_A_1201	-1.8	0	0
2BCN_ZNH_A_295	-10.7	0	0
3U92_KAI_A_258	-6.4	0	0
3W5M_TRS_A_1202	-4.0	0	0