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Computer Aided Docking Studies on Antiviral Drugs Against Hepatitis B Virus

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Abstract

Bioinformatics play an important role to identify and discover drugs against various diseases caused by microorganism. Hepatitis B Virus (HBV) causes liver disease such as Jaundice, Cancer in humans. Hepatitis B infection can be treated through medications including antiviral drugs and immune system modulators like interferon. Present study is an attempt to find out feasibility of HEX docking bioinformatics tool for designing drug against HB virus. The Protein- Ligand interaction plays a significant role in structural based drug designing. For our research work we have taken the Hepatitis B surface antigen as receptor and the commercially available synthetic drugs lamivudine, adefovir, telbivudine, entecavir, and natural compounds phyllanthin, hypophyllanthin against Jaundice. Analogs of the proteins were prepared by Marvin Sketch software. The receptor was docked to the above said drugs, compounds and the energy values are as follows: Adefovir (-239.1), Entecavir (-191.4), Lamivudine (-161.1), Telbivudine (-160.4), Phyllanthin (-241.8) and Hypophyllanthin(-245.7) against HBV. Comparative studies with Energy-values obtained from the natural compounds Phyllanthin and Hypophyllanthin has greater affinity towards the virus than the present synthetic drugs. Furthermore, the binding efficiency and steric compatibility of other drugs can be improved by several modifications made to the probable functional groups which were interacting with the receptor molecule to obtain a modified drug.

Key words: Phyllanthin, Hypophyllanthin, Energy-values, Marvin Sketch, HEX Docking.

Introduction

Hepatitis B virus (HBV) is a small, enveloped DNA virus that causes chronic hepatitis and often leads to cirrhosis and hepatocellular carcinoma^{1, 2, 3}. HB virus infects the liver of hominoidae, including humans. The acute illness causes liver inflammation, vomiting, jaundice and rarely death. Chronic hepatitis B may eventually cause liver cirrhosis and liver cancer⁴. The disease has caused epidemics in parts of Asia and Africa, and it is endemic in China⁵. About a third of the world's population, more than 2 billion people have been infected with the hepatitis B virus. This includes 350 million chronic carriers of the virus.

Transmission of hepatitis B virus results from exposure to infectious blood or body fluids containing blood⁶. Acute hepatitis B infection does not usually require treatment because most adults clear the infection spontaneously⁷. Early antiviral treatment may only be required in less than 1% of patients, whose infection takes a very aggressive course ("fulminant hepatitis") or who are immunocompromised. On the other hand, treatment of chronic infection may be necessary to reduce the risk of cirrhosis and liver cancer. Chronically infected individuals with persistently elevated serum alanine aminotransferase, a marker of liver damage, and HBV DNA levels are candidates for therapy⁸. Although none of the available drugs can

clear the infection, they can stop the virus from replicating, and minimize liver damage such as cirrhosis and liver cancer. Currently, the antiviral drugs licensed for treatment of hepatitis B infection in the United States include lamivudine (Epivir), adefovir (Hepsera), tenofovir (Viread), telbivudine (Tyzeka) and entecavir (Baraclude)⁹. However, prolonged therapy results in the emergence of drug-resistant mutants in 24% and 70% of patients after 1 and 4 years of therapy, respectively, followed by increase in viral load and re-elevation of transaminase levels¹⁰. Also, so far there is no consensus on an optimal regimen to a fatal disease with very poor response to current chemotherapy. To overcome these problems non conventional methods are discovered for drug designing using bio-informatics approaches.

Bioinformatics is seen as an emerging field with the potential to significantly improve how drugs are found, brought to the clinical trials and eventually released to the market. Bio-informatics can be thought of as a central hub that unites several disciplines and methodologies. Computer aided drug design (CADD) is a specialized discipline that uses computational methods to stimulate drug receptor interactions. Computer aided drug designing methods are heavily dependent on bio-informatics tools, applications and databases. As such, there is considerable overlap in CADD research and bioinformatics. Methods developed to facilitate and speedup the drug designing process are rational drug design (RDD). These processes are used in bio-pharmaceutical industry to discover and develop new drugs. RDD uses a variety of computational methods to identify novel compounds. One of those methods is docking of drug molecules with receptors to the site of drug action, which is ultimately responsible for the pharmaceutical affect. In this research paper we demonstrate the application of the rational drug designing methods to dock Hepatitis B surface antigen receptor against the commercially available synthetic drugs lamivudine, adefovir, telbivudine, entecavir and natural compounds phyllanthin, hypophyllanthin using HEX docking bioinformatics tool for designing efficient drug against HB virus.

Tools and materials used

Bioinformatics online databases and software used are as follows- Marvin Sketch, HEX docking, BLAST (Basic Local Alignment Search Tool), FASTA (FAST Alignment), RASMOL (Raster

Display of Molecules), GTOP, PDB (Protein Data Bank), Prosite, Genbank, and NCBI (National Center for Biotechnology Information)

Experimental

1. The Structure of HBV was downloaded from protein data bank (PDB) which has the DNA polymerase integrated with its core protein. PDB is a repository for the processing and distribution of 3D-structure data of large molecules of proteins and nucleic acids. Most were determined by X-ray crystallography and some are NMR. The retrieved structure of HBV was analyzed by using RasMol. RasMol is a molecular graphics program intended for the structural visualization of proteins and nucleic acids and small biomolecules.
2. The structural analogs of synthetically available drugs and the structures of Phyllanthin and Hypophyllanthin were created by using Marvin sketch software. Marvin Sketch is a Java based chemical drawing tool which allows creating and editing of molecules in various file formats.
3. Molecular docking was carried out with each of the drugs using HEX Docking software. The docking analysis of analogs Adefovir, Entecavir, Lamivudine, Telbivudine, Phyllanthin and Hypophyllanthin with HBV was carried by HEX Docking software. Docking is the process of fitting together of two molecules in 3-dimensional space. Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and an enzyme receptor HBV fit together and dock to each other well, like pieces of a three-dimensional jigsaw puzzle. The molecules binding to a receptor, inhibit its function, and thus act as drug. The collection of Adefovir, Entecavir, Lamivudine, Telbivudine, Phyllanthin and Hypophyllanthin and HBV receptor complexes was identified via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations.

The total Energy-Values (E-Values) of each docking was calculated and compared all the drugs with the structure of HBV.

Results and Discussion

Docking was carried out with each synthetic [Adefovir (-239.1), Entecavir (-191.4), Lamivudine

(-161.1) and Telbivudine (-160.4)] and naturally occurring [Phyllanthin (-241.8) and Hypophyllanthin (-245.7)] drugs (Table 1);

Table 1. Docking results of HBV with synthetic and natural occurring drugs

Drug docked	E-value
HBV v/s Adefovir	-239.1
HBV v/s Entecavir	-191.4
HBV v/s Lamivudine	-161.1
HBV v/s Telbivudine	-160.4
HBV v/s Phyllanthin	-241.8
HBV v/s Hypophyllanthin	-245.7

a comparative study with the E-values (if the E-values are more, the protein-ligand interaction between the compounds is low, and vice-versa) reveals that the natural compounds Phyllanthin and Hypophyllanthin has greater affinity towards the Hepatitis B virus than the present synthetic drugs. Hence this information would prove to be important in designing of drug Phyllanthin and Hypophyllanthin against a fatal disease Hepatitis B.

Conclusion

The present study shows the efficiency or effectiveness of the natural compounds obtained from *Phyllanthus* sps viz., Phyllanthin and Hypophyllanthin in treating Hepatitis-B. Further studies regarding protein-ligand interaction would give way to use natural compounds as a substitute for the presently used synthetic drugs like lamivudine, adefovir, telbivudine, entecavir for treating hepatitis B.

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