Molecular Docking Study of Novel Anti-Hepatitis B Virus Agents Isolated from Talaromyces Species

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Abstract

Hepatitis B virus is the leading source of liver disorders and is a global health problem and needs advancements in its treatment against increasing problems. Recently five vanitaracin derivatives were isolated from the fungus Talaromyces species which have anti-Hepatitis B virus activity. Hence, in the present study, molecular docking was carried out with five vanitaracin derivatives isolated from Talaromyces species and three known inhibitors. The objective of this work is to study the interaction of newly isolated compounds and compare its interaction with known inhibitors. The docking results revealed that vanitaracin derivatives have good interactions and has better docking score with the Hepatitis B virus and suggest SER2, SER4 and ASP30 are important residues involved in interaction with the inhibitors. These result authenticates vanitaracin derivatives contributes to inhibitory activity of Hepatitis B virus to treat liver disorders.

Keywords: Hepatitis B Virus; Talaromyces Species; Molecular Docking.

1. Introduction

Hepatitis B virus (HBV) causes both acute and chronic infections of the liver and is a serious health problem worldwide which may lead to liver diseases such as cirrhosis and hepatocellular carcinoma[1-3]. WHO estimated that over 350-400 million people are chronically infected with HBV worldwide of which 100 million eventually will die with the HBV[4-8]. The goal of hepatitis B treatment is to prevent the serious infections like cirrhosis, liver decompensation and hepatocellular carcinoma whereas the treatment response is determined by suppression of serum HBV DNA levels, hepatitis B e antigen (HBeAg) seroconversion to hepatitis B antibody, hepatitis B surface antigen (HBsAg) loss, normalization of alanine aminotransferase levels and improvement in liver histology[9]. Current therapies to combat chronic HBV infection including immuno-modulator, interferons and nucleos(t)ide analogs (Entecavir, Telbivudine and Tenofovir) can deliver significant clinical improvement but they are still unsatisfactory, due to high recurrence, drug resistance and inevitable side effects[10-14]. Prolonged use of these drugs may lead to liver failure, acute infections and also associated with a high rate of resistance to the drug[2]. Although HBV infection can be largely prevented by use of effective vaccine, not everyone is vaccinated and there is no vaccine for the people who are already chronically infected. Therefore, there is continuous need for antiviral drugs to suppress viral replication or eliminate infection[15] and antiviral resistance is considered to be one of the most important factors associated with HBV treatment failure[16] and it determines the success of long-term therapy for chronic hepatitis B. Consequently, there is an urgent need to explore novel classes of drugs with different antiviral targets containing anti-HBV agents.

Molecular docking plays an important role in drug designing by placing a ligand molecule into the binding site of the target molecule[17] and is demonstrated in the following studies[18-20]. The present work aimed at the in silico docking of an anti-hepatitis B virus (HBV) drug called vanitaracin derivatives against a protein. The main purpose was to compare the interaction of vanitaracin derivatives with known inhibitors and suggest vanitaracin derivatives as anti-Hepatitis B inhibitors on the basis of binding interactions by using molecular docking studies. Docking program implemented in SYBYL called Surflex dock[21] was used to predict favorable receptor–ligand complex with reasonable
accuracy and speed. The docked complex is then visualized using pymol software\cite{22}.

2. Materials and Methods

2.1. Protein Preparation

In the present study, the X-ray crystal structure of HLA A*02:03 Bound to HBV core 18-27 was downloaded from PDB database (3OX8) and the protein structure was prepared using protein preparation tool in biopolymer module of SYBYL. During protein preparation, chain A were retained for docking, water molecules present in the crystal structure were removed and subsequently hydrogen atoms and charges such as Gasteiger Huckel charges were added to the protein structure. Finally, energy minimization of protein was performed for 100 steps utilizing Powell method, Gasteiger Huckel charge and Tripos force field.

2.2. Ligand Preparation

The five vanitaracin derivatives obtained from *Talaromyces* species\cite{23} and three known inhibitors namely entecavir, telbivudine and tenofivir\cite{15} were drawn using sketch molecule function in SYBYLX2.0. The energy minimization of the molecules was performed using Tripos force field and Gasteiger Huckel charge. The structure of vanitaracin derivatives and known inhibitors used in this study are shown in Fig. 1(a) and (b) respectively.

2.3. Molecular Docking

Five vanitaracin derivatives which are proved to have anti-hepatitis B virus activity and three compounds which inhibit reverse transcriptase of HBV were taken for docking. Surflex dock module of SYBYL was utilized to perform molecular docking in this study. The docking algorithm in surflex dock uses an idealized

![Fig. 1. (a) Chemical structure of vanitaracin derivatives isolated from *Talaromyces* species (b) Chemical structure of known inhibitors against Hepatitis B virus.](image-url)
active site called protomol[24] which is the representation of intended binding site to which the ligand molecules were docked. The extent of a protomol was determined by two parameters, namely threshold and bloat. Since the active site of the protein was not determined previously, the automatic mode was used for generation of protomol. Surflex dock uses an empirical scoring function which takes into account several terms, including hydrophobic, polar, repulsive, entropic and solvation and the docking scores are expressed in terms of -log_{10}K_d units, where K_d represents a dissociation constant of a ligand[25].

3. Results and Discussion

To study the interaction of vanitaracin derivatives and the known inhibitors, molecular docking was performed using Surflex dock using crystal structure of HLA Bound to HBV core.

3.1. Molecular Docking

Molecular docking was performed for vanitaracin derivatives and the known inhibitors where 20 different conformations was generated for each inhibitor molecule and the best conformation was chosen based on surflex score and interaction with the residues. The docking score and H-bond forming residues for all the molecules are tabulated in Table 1. Here we found that the docking score of vanitaracin derivatives are somehow similar to known inhibitors entecavir, telbivudine and tenofovir. In addition to that it was observed that SER2, SER4 and ASP30 play a major role in interaction of these vanitaracin derivatives with the protein. The same was observed in known inhibitors were entecavir has interaction with SER2 and SER4, telbivudine has interaction with SER2 and ASP30 and tenofovir had interaction with SER4 and ASP30. The interaction of vanitaracin derivatives was depicted in Fig. 2, 3, 4, 5 and 6 and known inhibitors are represented in Fig. 7. These results authenticates that SER2, SER4 and ASP30 are important residues and vanitaracin deriva-

| Table 1. Docking scores and H-bond forming residues formed between HBV and inhibitors |
|----------------------------------|-----------------|-----------------|
| Compound                        | Surflex docking score | Interacting residues |
| Vanitaracin derivatives          |                 |                  |
| 1                               | 4.87            | SER2, ARG6, ASP102 |
| 2                               | 5.39            | GLU212, THR233   |
| 3                               | 4.76            | SER2, ASP30      |
| 4                               | 3.65            | GLN32, ALA236, GLY237, GLY239, THR240 |
| 5                               | 4.67            | SER4, ASP30      |
| Entecavir                       | 4.91            | SER2, SER4, ASP30 |
| Telbivudine                     | 4.65            | SER2, ASP30, GLU212 |
| Tenofovir                       | 4.82            | SER4, ASP29, ASP30 |
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Fig. 4. Interaction between HBV and vanitaracin derivative (compound 3).

Fig. 5. Interaction between HBV and vanitaracin derivative (compound 4).

Fig. 6. Interaction between HBV and vanitaracin derivative (compound 5).

Fig. 7. Interaction between HBV and known inhibitor [(a) entecavir, (b) telbivudine, (c) tenofovir].

4. Conclusion

In silico docking study of five vanitaracin derivatives isolated from *Talaromyces* species with HBV receptor demonstrates that these compounds docked well with the target HBV. This study also clearly indicated the binding site of these compounds were similar to the known inhibitors such as entecavir, telbivudine and tenofovir. This study offered valuable information on vanitaracin derivatives for seeking anti-Hepatitis B Virus drug candidates for chronic liver disorders.
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