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Dr. Siva Nageswara Rao Mekala
Department of Clinical Pharmacology, The State University of Zanzibar, Tanzania

Dr. Ali Said Yussuf
Department of Surgery, The State University of Zanzibar, Tanzania

Dr. Saravanan R
Department of Pharmacology, RVS Dental College and Hospital, The Tamil Nadu Dr. M.G.R. Medical University, Coimbatore, Tamilnadu, India

Dr. Anand Paramasivam
Department of Physiology, RVS Dental College and Hospital, The Tamil Nadu Dr. M.G.R. Medical University, Coimbatore, Tamilnadu, India

Dr. Arul Amuthan
Department of Basic Medical Sciences, Manipal Academy of Higher Education, Manipal University, Manipal, Karnataka, India

Dr. Murugesan Annamalai
Department of Biochemistry, RVS Dental College and Hospital, The Tamil Nadu Dr. M.G.R. Medical University, Coimbatore, Tamilnadu, India

Corresponding Author:
Dr. Siva Nageswara Rao Mekala
Department of Clinical Pharmacology, The State University of Zanzibar, Tanzania

Molecular docking study of phyllanthus Amarus Metabolites: A potential alternative therapy for Hepatitis B

Siva Nageswara Rao Mekala, Ali Said Yussuf, Saravanan R, Anand Paramasivam, Arul Amuthan and Murugesan Annamalai

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Abstract
Hepatitis B (HB) is a major viral infection that endangers millions of people worldwide and traditional interventions such as Tenofovir have proven to be restrictive. Phytomedicine The traditional plant Phytanthus amarus is a wellknown antiviral (especially anti-HBV). It is a molecular docking study that assesses Phyllanthin, a bioactive product obtained in Phyllanthus Marus and tenofovir in the determination of their binding affinities to the core protein of Hepatitis B virus (PDB ID: 5WRE). The findings revealed that Phyllanthin has a MolDock score of -101.92, which is much lower than -86.87 that of Tenofovir, which means that it has a higher binding affinity. The hydrogen bond analysis demonstrated that the weaker bonds of Phyllanthin were compensated with the greater specificity and stability and it is a good candidate to be experimentally validated. These results indicate that Phyllanthin may be a successful alternative/ adjunct to traditional antiviral management of Hepatitis B.

Keywords: Hepatitis B, Phyllanthus amarus, Phyllanthin, molecular docking, Tenofovir

Introduction
Hepatitis B (HB) is a viral infection caused by the Hepatitis B virus (HBV) which mostly attacks the liver resulting in both acute and chronic diseases such as cirrhosis and liver cancer. It is a significant health issue in the world and there are more than 250 million individuals in the world living with the chronic HBV infection. Even with the antiviral treatments available, such as nucleoside analogs (e.g., tenofovir, entecavir) and interferon-based therapy, all these treatments are prone to side effects, reduced effectiveness and there is a risk of drug resistance. Thus, it is urgently required to find new and more efficient treatment agents to fight HBV infection and its consequences [1-5].

Natural products have become one of the potential sources of new antiviral agents in recent years, as they exhibit a wide array of chemical structures, as well as biological activities. A traditional plant such as Phyllanthus amarus which is a commonly used herb in medicine has shown strong antiviral action especially to HBV. Phyllanthus amarus plants are also known to possess numerous bioactive metabolites which have been demonstrated to have a variety of significant pharmacological effects that include hepatoprotective, anti-inflammatory and anti-viral activities. Specifically, it has been proven that Phytophytic compounds obtained by isolation of Phyllanthus amarus (phytanthin, hypophyllanthin) are capable of inhibiting replication of HBV as well as liver damage, thus the plant is a prospective source of antiviral drugs [6-11].

Molecular docking is a computer-based methodology which has proved to be an effective tool in the process of drug discovery as it enables a researcher to model interactions between small molecules (ligands) and target proteins. In silico technology offers information about the binding affinity, modes of interaction and modes of action of the prospective drug candidates and this information can help to hasten the drug discovery process. By examining docking models, one can determine certain molecular targets that are part of the viral life cycle, which include the HBV polymerase, surface antigen and capsid proteins, which are useful when developing more efficient and targeted therapies [12-16].

The objective of the proposed study is to employ the method of molecular docking-based screening to investigate the relationship between bioactive metabolites of the Phyllanthus amarus and the main proteins in the multiplication of HBV.

Through analyzing the binding affinities and interaction profiles of these compounds with the targets of interest in HBV, we aim at selecting possible candidates to be further validated by experiment. This method of computation may offer important data on the mechanisms of the antiviral action of the Phyllanthus amarus metabolites and help to develop the new, plant-based therapeutic options to combat hepatitis B.

Materials and Methods

Protein Preparation

The docking experiment was triggered by the establishment of the target protein structures in Molegro Virtual Docker (MVD). In order to obtain the 3D crystal structure of the Hepatitis B virus core protein (PDB ID: 5WRE), which is chosen due to its high-resolution data (less than 2.5 A) and, thus, the accuracy and integrity of the structure are guaranteed, the search of the Protein Data Bank (PDB) was performed. It was the protein structure that was imported into the MVD workspace with the help of the functionality of importing Molecule Protein File and optimized and refined [17-19].

Unless the ligand was to be stabilized, molecules of water were removed and unnecessary heteroatoms were eliminated to prevent interference during docking. Repair Add Missing Hydrogens tool was used to add polar hydrogen, which was necessary to have the correct charge distribution and geometry. MVD simply gave the correct atom types and bond orders automatically so that the molecular structure was consistent. Detect Cavities option was applied to determine any potential binding sites on the protein. The best volume and lowest energy were used to select the active binding pocket on which further simulations would be performed [20-22].

Ligand Preparation

In the case of the molecular docking simulations, Phyllanthin, which is a bioactive compound of Phyllanthus amarus was used as a ligand. Also Tenofovir, a proven antiviral medication, which is applied in treating Hepatitis B was compared. The chemical structure of Phyllanthin was accessed by the PubChem database either as a 2D or 3D structure and then saved in a regular file format [23-25].

The energy minimization of the ligands was done on Chem3D software in which MM2 force field or MMFF94 force field was applied to stabilize geometry and a good structure of the ligand. This was done to reduce steric strain; maximize the angles of the bonds as well as to have the ligands of the cells in their lowest energy state. The reduced structures were next exported in 3D either as .mol2 or.sdf files to be compatible with MVD. The "File Import Molecule Ligand" option was used to import ligands into MVD and any missing hydrogen atom was included in order to satisfy the valence requirement. MVD automatically fixed and resolved types of atoms and orders of bonds to prepare the ligands to docking simulation [26-29].

Molecular Import and Preparation

Phosphophytin and Tenofovir were added as ligands into the MVD workspace and the target protein (Hepatitis B virus core protein, PDB ID: 5WRE) was imported into the MVD workspace to be simulated by docking. To keep the protein and the ligands in their protonated states, the physiological pH (approximately 7.4) was used to maintain the correct electrostatic potential and the hydrogen-bonding pattern, which is important in ensuring effective docking results [30-33].

The binding site was determined by the application of the tool of Docking Wizard in MVD. Active binding pocket was chosen manually and the center coordinates (X, Y, Z), radius (8-12 A) of the binding pocket had to be typed in to direct the docking algorithm to the biologically important parts of the protein [34-36].

Docking Setup

A docking project was developed in MVD through the menu of docking, Docking > Start Docking Wizard > Create New Docking Job. MolDock SE (Simplex Evolution) algorithm was chosen because it is a good method to search through ligand conformational space. Scoring functions were employed to define the binding affinity wherein MolDock Score or Re-Rank Score in temperatures of non-bonded and steric complementarity were used [37-39].

The docking simulation parameters were as follows: number of runs = 10-30, maximum iterations = 1500-2000 and population size = 50-100. The option of Docking Constrain was also brought on to allow selective interactions between the Hepatitis B viral core protein residues and the ligands. An energy threshold of 100 was established and 10-20 saved in the analysis. Once the parameters had been established, the docking simulation was elicited and the software was used to conduct iterative conformational search until the best binding poses with minimum energy scores were identified [40-43].

Docking Analysis

Following docking simulations MVD produced a prioritized list of ligand-protein binding poses ranked by MolDock Scores (predicted binding energies). The most stable and energetically favorable complex, in terms of the lowest (negative) score indicated the pose of the greatest affinity between the ligand and the protein active site. In order to visualise the interactions among the molecules, MVD View Ligand Interactions function was employed. This gave comprehensive images of hydrogen bonding, hydrophobic interactions and electrostatic interactions between Phyllanthin or Tenofovir and the Hepatitis B virus core protein residues [18, 32, 44, 45].

The length of the bond (in A) and interacting amino acids were examined in order to determine the stability and specificity of the interaction. The poses of the binding were compared against the co- crystallized ligands to test the accuracy of the docking. The energy components such as hydrogen bonding, van der Waals forces, steric interactions, electrostatics and torsional penalties were also studied to better explain the binding mechanisms. The outcomes were either written in the format of.mol2, .pdb or images to be analyzed and visualized by creating 2D, 3D and secondary interaction maps that were used to prepare the figures in the publications [18, 44, 46, 47].

Results

The docking study of Phyllanthin, a bioactive compound of *Phyllanthus amarus* and Tenofovir, a commonly used antiviral drug to treat Hepatitis B, against the Hepatitis B virus core protein (PDB ID: 5WRE) provided some valuable information. As depicted in Table 1, the MolDock score of Phyllanthin was -101.92 as opposed to -86.87 of Tenofovir,

a much lower score (resulting in a higher binding affinity) of the former. This implies that the Phosphanthin has the potential of binding better with the core protein of the hepatitis B virus as compared to tenofovir. This conclusion is also supported by Rerank score, Phyllanthin -57.78 score is against -53.35 score of Tenofovir.

The higher value in the Rerank indicates that Phyllanthin is more stable and specific to interact with the protein which once again implies it would be more useful as a therapeutic candidate. This result is also supported by the hydrogen bond analysis, as Phyllanthin has a bond value of -0.32, which is significantly weaker than that of Tenofovir, -4.96. It indicates that although Phyllanthin has weaker hydrogen bonding energy than that of Tenofovir, it is able to interact well with the Hepatitis B virus core protein. These findings suggest that although Tenofovir might be more hydrogen bonding, the binding affinity and specificity of Phyllanthin in general with the target protein can provide a real benefit regarding therapeutic performance.

The visual representation of the binding interactions between the ligands and the Hepatitis B virus core protein is presented in figure 1 to figure 6. The 2D, 3D and second interaction diagrams show the way through which Phyllanthin and Tenofovir form hydrogen bonds and hydrophobic interactions with the protein, which underscores their ability to interfere with the process of virus replication. These results indicate that Phyllanthin has potential to be an alternative or supplement to traditional antiviral agents such as Tenofovir in treating Hepatitis B.

Table 1: Ranking of Ligands and Poses against Hepatitis B virus core protein Based on Moldock Score. Protein: 5WRE

Ligand	Species Name	MolDock	Rerank	H Bond
358901	Phyllanthin	-101.92	-57.78	-0.32
464205	Tenofovir (Standard Drug)	-86.87	-53.35	-4.96

Fig: 1-6: Interactions of Ligands with Protein (Hepatitis B virus core protein).

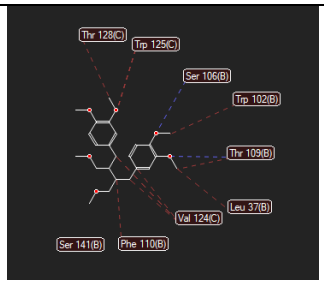

Fig 1: 2D Interaction

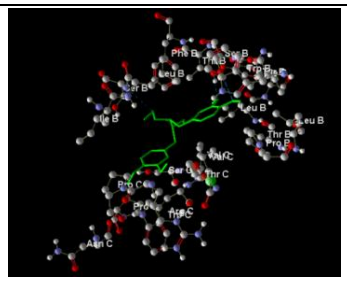

Fig 2: 3D Interaction

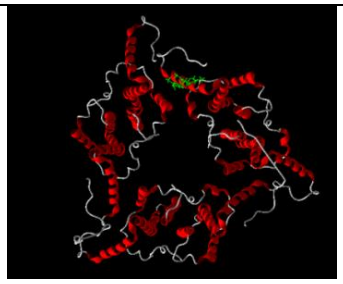

Fig 3: Secondary Interaction

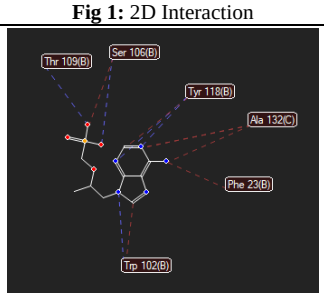

Fig 4: 2D Interaction

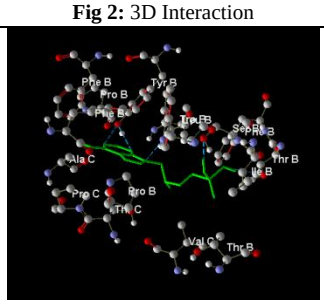

Fig 5: 3D Interaction

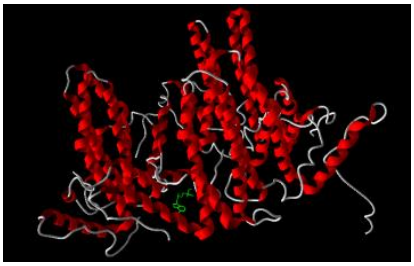

Fig 6: Secondary Interaction

Discussion

Hepatitis B virus (HBV) is one of the significant human health issues, caused by millions of people worldwide. Although there are useful medicines such as Tenofovir, they are limited by some factors such as side effects and resistance. To this end, natural products are becoming favorite sources of new therapeutic agents in the eyes of researchers. HBV replication was inhibited by a plant called Phyllanthusamarus that has been identified as a hepatoprotective plant and antiviral. Phyllanthin is one of the bioactive compounds of the plant that have attracted interest in its possible effectiveness against HBV. In this investigation, the molecular docking was used to model the interaction between Phyllanthin and Tenofovir and hepatitis B virus core protein (PDB ID: 5WRE), which is one of the products of HBV replication [9, 18, 48-50].

The docking analysis showed the MolDock score of Phyllanthin is -101.92, which is much smaller than the score of Tenofovir -86.87. This means that Phyllanthin has a higher binding affinity to the target protein implying that it will be able to interact better with the HBV core protein. As well, the Rerank score of Phyllanthin (-57.78) is much lower than that of Tenofovir (-53.35), thus again suggesting the possibility that the interaction of Phyllanthin with the protein is more stable and specific. These findings suggest that Phyllanthin has a high level of potential to be developed as an antiviral agent.

Although the hydrogen bond analysis revealed that Tenofovir established stronger relationships -4.96 with the protein than Phyllanthin -0.32, it does not make Phyllanthin any less effective as an antiviral agent. Although hydrogen bonding strengths are weaker, the total binding specificity and affinity of the Phyllanthin to Hepatitis B core protein virus imply that it can have great therapeutic advantages. Moreover, the images of the docking interactions (Figures 1 6) denote the importance of hydrogen bonds and

hydrophobic interactions and indicate the potential of both Phyllanthin and Tenofovir to inhibit HBV replication.

This is in line with earlier reports, which have revealed that Phyllanthus amarus and its extracts have anti-viral effects and have capability to cure a range of viral infections such as HBV. Phyltanthin antiviral activities would therefore serve as an alternative or supplement to the antiviral treatment available. Subsequent *in vitro* and *in vivo* research is required to confirm these in silico positive results and develop more on the potential of Phyllanthin as a treatment to Hepatitis B.

Conclusion

The molecular docking analysis presents Phyllanthin of Phyllanthus amarus as a prospective antiviral agent in the management of Hepatitis B. The findings indicate that Phyllanthin has a better binding affinity with the core protein of the Hepatitis B virus (PDB ID: 5WRE) than its antiviral counterpart Tenofovir. Phyllanthin has lower specificity and stability, but its stronger hydrogen bonding properties imply that it might make a good alternative or supplement to traditional antiviral therapy. This research forms a good basis towards enhancing experimental research on the effectiveness of Phyllanthin as a therapeutic agent against Hepatitis B.

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