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In silico Analysis of a Novel Peptide Vaccine against Hepatitis B Virus (HBV)

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background : Hepatitis B is a potentially life-threatening liver infection caused by the Hepatitis B virus (HBV). It is a major global health problem and the most serious type of viral hepatitis. It can cause chronic liver disease and puts people at high risk of death from cirrhosis of the liver and liver cancer. HBV is found in highest concentrations in blood and in lower concentrations in other body fluids.
Methods: Target protein was retrieved from the swissprot database. Epitopes were predicted using the BCEPRED server. After running the BLAST algorithm for the target protein, the template with the best identity was selected. After modeling, target protein is verified by using the swiss model workspace and after this process the obtained target protein is allowed to interact with the MHC which is studied by using patchdock**,** finally these results were viewed by using the deepview tool.
Results: The target protein for vaccine development was downloaded from the SwissProt database. Its SwissProt ID was p29178. The protein was isolated from hepatitis B virus genotype G. The virus was isolated from the United States of America. The length of the target protein was found to be 195 amino acids. To confirm that the target protein could be used for vaccine development, the Presence of epitopes in the protein was confirmed using the BCEPRED tool. Results from the SAVS server showed 95.80 of the residues of the protein had an average 3D-1D score greater than 0.2. The protein attained a pass with an ERRAT value of 90.299.

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Conclusion: The present investigation recognized the promising complex formed between the HBV peptide and MHC molecules. All the downloaded MHC molecules were found to interact with the target protein through the formation of hydrogen bonds. Since these interactions are necessary during an immune response to invading pathogens, the target protein would ultimately trigger an immune response if it is administered as a vaccine for Hepatitis B virus genotype G.

Keywords: In silico study; HEPATITIS-B; peptive vaccine; swissport; environment.

1. INTRODUCTION

Hepatitis-B virus (HBV) is a serious liver infection which is caused due to HBV. HBVs are vaccine preventable and this type of virus is spread through exposure of infected body fluids such as saliva and blood semen [1] etc. The symptoms of hepatitis-B are yellowing of the eyes, abdominal pain and dark urine. The children are not affected by this virus often. The chronic condition of hepatitis B virus is liver cancer which ultimately leads to liver failure [2]. In the chronic condition liver transplantation is the final choice for the patients to help them to increase their lifespan [3]. In the present world the treatment for Hepatitis-B is conventional and pegylated interferon alfa and at same time most advanced treatment done for hepatitis-B is done with the Nucleotide analogues [4]. Hepatitis-B was a major public health issue in the world by which 250 million people are affected by this virus and more than 686,000 people are dead due to complications such as liver cirrhosis [5].

The life cycle of hepatitis-B virus gets started when the virus attaches to the cell membrane of the host by envelope proteins [6]. Then, the fusion between the viral membrane and host cell membrane occurs after the genetic material of the virus is newly introduced into the host cell in order to help the virus for their replication [7]. The replication of Hepatitis-B (HBV) will be more effective in the hepatocytes cells and at same time other types of cells that are found in the human body wouldn't be helpful for the replication of Hepatitis-B virus (HBV). For this replication process the virion first recognizes the suitable cell surface receptor and then enters the DNA of the host cell nucleus, IF the viral mRNA is shot it would be more convenient for the translocation by ribosome which attaches to the endoplasmic reticulum. The pregenome RNA is translocated to produce a polymerase protein P and then this binds to the specific site at 3' end of the strand [8].

The vaccine development for Hepatitis-B plays a major role in preventing infections and diseases and at same time it contributes a major part in biomedical science [9]. This helps to come out with the development of a new generation vaccine for the viral infection. For the development of the vaccine two factors are more important. First is to understand the microbial factors required for virulence and the nature of the immune response of the infection. Even though the vaccine against hepatitis B (HBV) is highly successful, more than 5% of individuals don't experience a response with a sufficient amount of antibody level to hepatitis B surface antigen [10]. In recent years, the studies have found that blood from hepatitis B virus carriers revealed the presence of smaller 22 nm particles consisting of a viral envelope as a surface protein of the virus. These nanoparticles are highly immunogenic and at same time it has been used for designing the vaccines for hepatitis B by using the yeast. By seeing the expression of protein in the yeast, these particular proteins are separated from the viruses that can be used for preparing the parenteral immunization [11].

The development of the peptide vaccine is prepared by using the amino acid sequence of the protein antigen [12]. These peptide vaccines have highly purified peptides which are made up of large quantities and simple antigenic composition may afford protection to the host individual with less side effects [13]. Generalized approach towards the peptide vaccine development is to identify the potential epitope in a protective protein antigen [14]. Our team has extensive knowledge and research experience that has translate into high quality publications [15–19]

There is no proper survey or research carried out previously on peptide vaccine against the Hepatitis B virus. The main aim of this survey is to know that the novel peptide vaccines are useful to prevent theHepatitis B virus.

2. MATERIALS AND METHODS

2.1 Target Protein for Vaccine Development

2.1.1 Template selection for modeling

The fasta sequence of the target protein was entered in the *BLAST* algorithm. Protein data bank was selected for the database section. The algorithm *BLASTP* was selected. The program was then run to search for a template from the database. After running the *BLAST* algorithm for the target protein, the template with the best identity was selected.

2.1.2 Viewing the structure of the template protein

The atom file of the template protein was obtained from the *PDB* database. After saving the file, the structure of the modeling the target was viewed using the *deepview* tool. In the *deepview* tool, the file containing the pdb file of the template protein was located and opened. File menu >open PDB File.

2.1.3 Modeling of the target protein

Homology modeling was adopted to build the three-dimensional structure of the target protein. The methodology builds the 3D structure of a protein of unknown structure. The template protein was loaded onto the *Swiss PDB Viewer*. The raw sequence of the target protein was loaded by the command Swiss model > load raw sequence to model. Target protein sequences was aligned with respect to template structure with the help of command fit>fit raw sequence. The target was superimposed onto the template by the command fit>magic The raw sequence was then fit onto the template using the command fit This was then followed by an iterative magic fit and improve fit .The superimposed structure was then saved with a pdb extension and submitted to the *Swissmodel* server as a modeling request

2.1.4 Verification of the structure of the modeled protein

The three dimensional structure of the modeled target protein was verified using SAVS (Structural Analysis and Verification Server. The pdb file of the modeled protein was uploaded on the *SAVS* server. After uploading the pdb file, the programs verify 3D, errat and prove were selected. By clicking on the RUN ALL PROGRAMS button, the structure verification was started by the server. The server takes a few minutes to return the results of the verification. The atom file of the modeled protein was downloaded from the *Swiss model* workspace. The saved file was opened using the *deepview* tool to visualize the structure of the modeled protein. The structure obtained was given a coloring by the following operations .In the windows menu, the control panel was selected. In the control panel, all the residues of the protein were selected. From within the control panel, the color option was opened and the modeled protein was given coloration.

2.1.5 Energy minimization

Energy minimization is done on the protein once it is found to be unstable. Instability is indicated by the presence of some residues of the protein outside the allowed region of the Ramachandran plot.

2.1.6 Downloading the Structure of MHC molecule

The MHC molecule that was used to test for interaction with residues of the target protein was identified from the swissprot database and structure was downloaded from PDB database. The atom file of the MHC molecule was obtained from the PDB database. After saving the file, the structure of the MHC molecule can be viewed using the deepview tool. Ten structures of MHC molecules (numbered from serial no.1-10) were downloaded from the pdb database.

2.1.7 Viewing the Structure of MHC molecule

The structure of the MHC molecule was viewed using the *deepview* tool. After opening the atom file of the MHC molecule, the command window > control panel was given. From the control panel that appeared, all the residues of the MHC were selected. The MHC molecule was given coloration by selecting the color option within the control panel. The interaction between the target protein and the MHC molecule was studied by using the patchdock tool. The request for docking is then sent to the server. The email of the user is also provided since the results of the docking from the server are sent to the email address of the user.

2.1.8 Viewing the interaction between MHC with the target protein

The results that were obtained in *patchdock* were downloaded and saved with pdb extension. The

location of the PDB file containing the structure was located and the file opened. The view of the structure formed between the target protein and the MHC molecule was then viewed using the *deepview* tool. The structure that was displayed was then colored using different colors to distinguish the two molecules.

- The residues of the MHC were selected from the control panel of the deepview tool. They were given one color by selecting the color option in the control panel.

- Similarly the residues of the target protein were selected from the control panel and were then given one color from the color option in the control panel. The structure formed was analyzed to further verify the interaction.

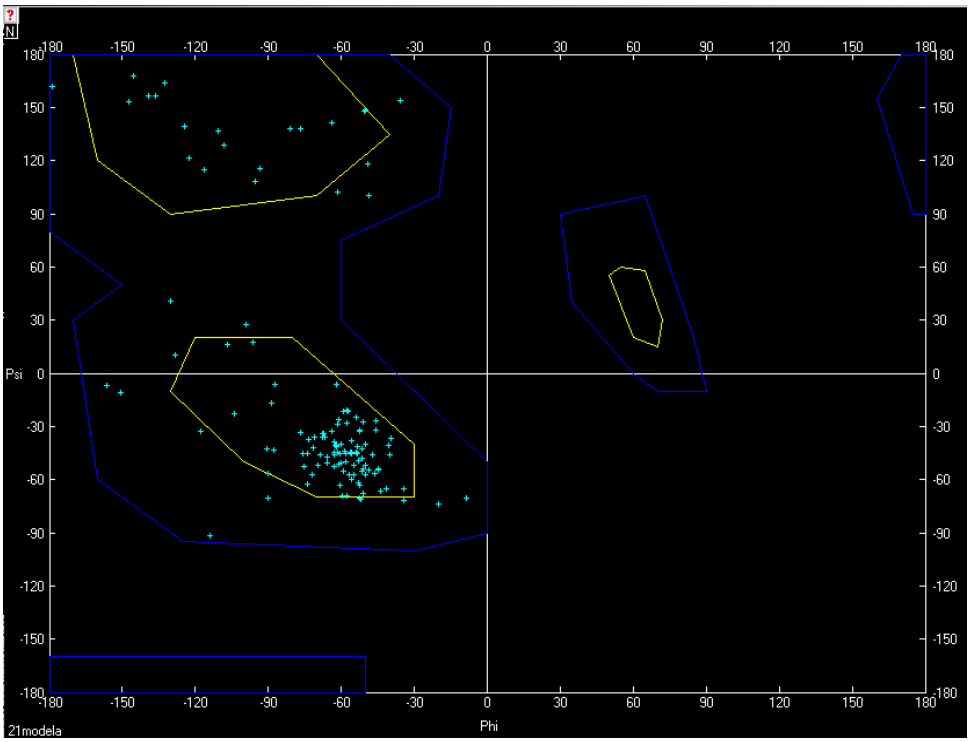

Fig. 1. Energy minimization

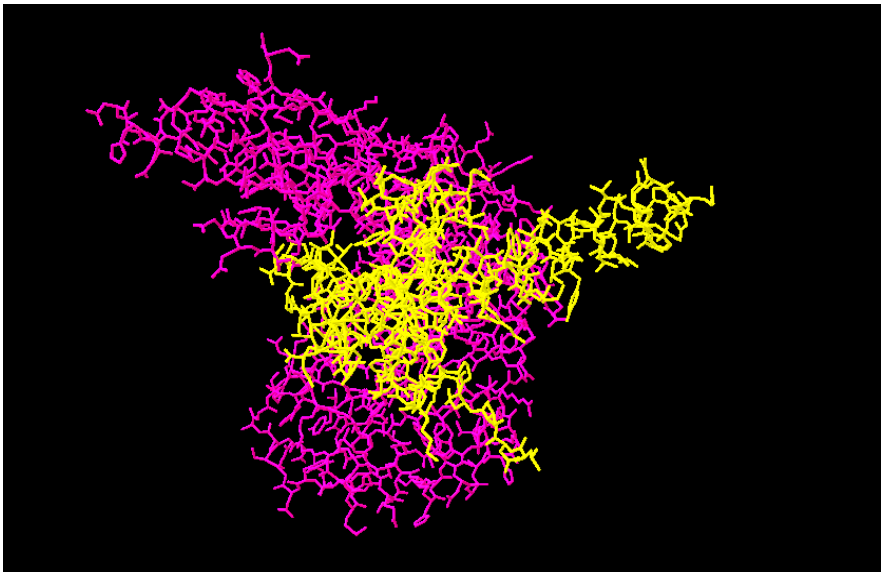

Fig. 2. Viewing the interaction between MHC with the target protein

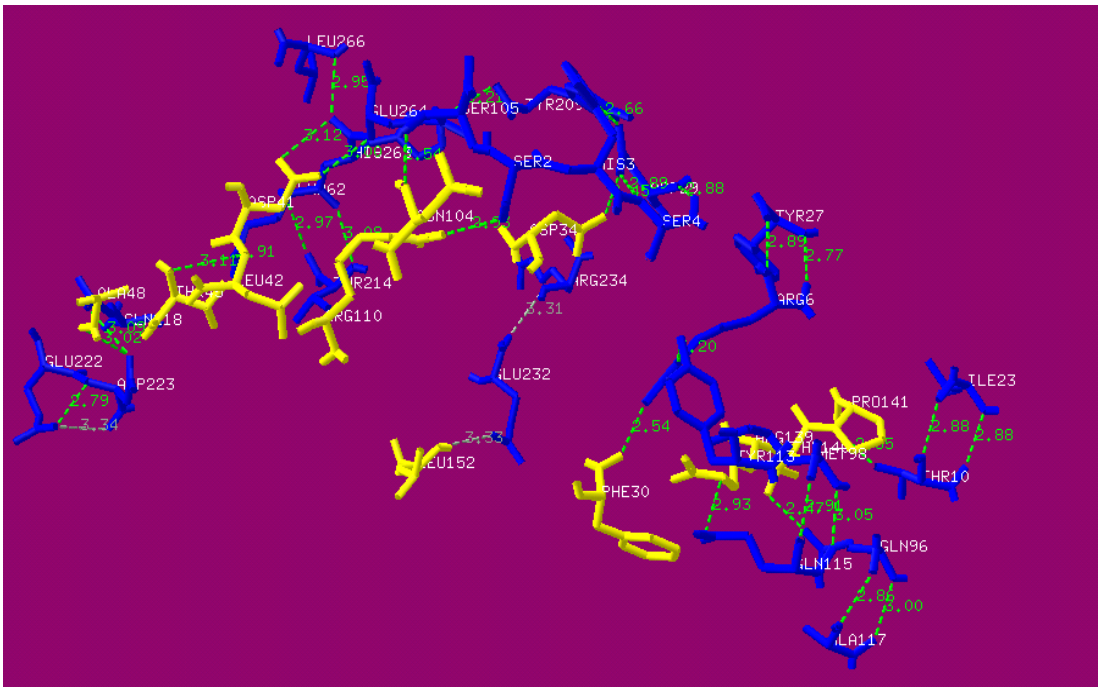

Fig. 3. Verification of interactions

2.1.9 Verification of interactions

In the tools menu of the main deepview program, the command compute H bonds was given. In the display menu of the program, the command shows H bond distances and the distances between the bonds. In the display menu still, only H bonds from selection and finally only groups with visible H bonds were shown.

3. RESULTS AND DISCUSSION

3.1 Target Protein for Vaccine Development

The target protein for vaccine development was downloaded from the SwissProt database. Its SwissProt ID was p29178. The protein was isolated from hepatitis B virus genotype G. The virus was isolated from the United States of America. The length of the target protein was found to be 195 amino acids. To confirm that the target protein could be used for vaccine development, the Presence of epitopes in the protein was confirmed using the BCEPRED tool. The FASTA sequence of the target protein was downloaded from the swissprot database and is as shown below >Sp|P29178|CAPSD_HBVG1 Capsid protein OF=Hepatitis B virus genotype G subtype adw2 (isolate United States of America/sf/1990) GN=C PE=3 SV=1

3.2 Epitopes in the Target Protein

Epitopes in the target protein were checked using the BCEPRED tool.

The tool returned results in graphical format and in tabular form. Both were viewed and the amino acid residues that formed the epitopes in the target protein were analysed. The peak of the amino acid residue segment above the threshold value(default is 2.38) is considered as a predicted B-cell epitope.

3.2.1 Epitopes of target protein in linear sequence

The predicted B cell epitopes are shown in blue color and underlined.

3.2.2 Template for modeling

The template for modeling was obtained from the **PDB** server. The hit with the highest identity was selected as the template for modelling the target protein. Its PDB ID was 1QGT/C . It had an identity of 96% with the target proteins. A high identity between the template and the target protein ensures that the 3D structure developed from modelling is highly similar to the template protein. This verifies the 3D structure of the selected target protein.

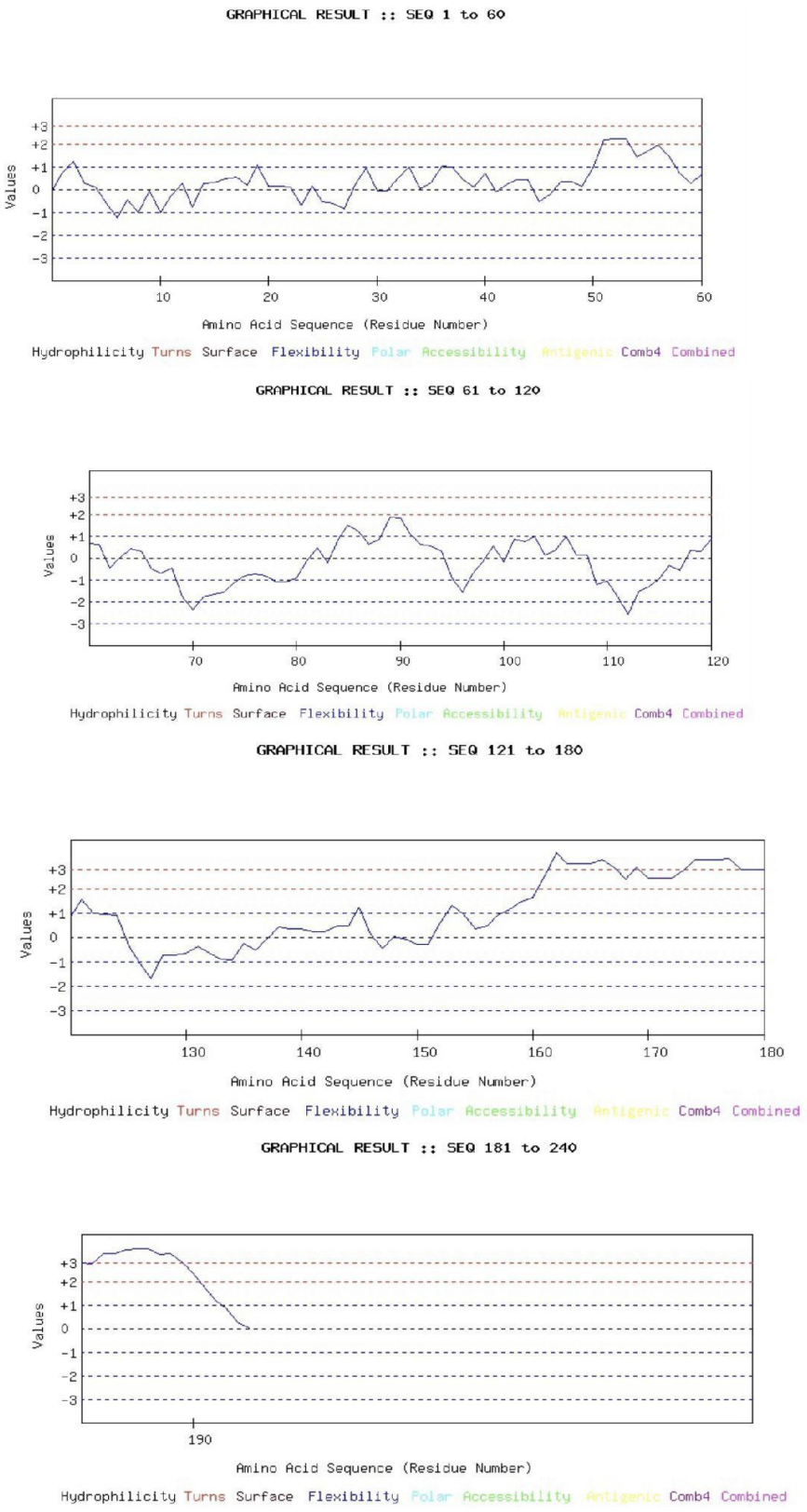

Fig. 4. Epitopes in the protein for residues 1-60, Epitopes in the protein for residues 61-120, Epitopes in the protein for residues 121-180 and Epitopes in the protein for residues 181-195

3.3 Structure of the Modeled Protein

3.3.1 Results from SAVS server

95.80 of the residues of the protein had an average 3D-1D score greater than 0.2

The protein attained a pass with an ERRAT value of 90.299.

3.3.2 Structure of MHC molecule (serial no 7)

The structure of the mhc molecules that were downloaded from the pdb database were viewed using the deepview tool.

3.3.3 Structure of MHC molecule (serial no 8)

Hydrogen bonds formed between MHC with target protein and Hydrogen bonds formed between MHC with target protein. All MHC molecules that were tested for interaction with the target protein were found to form hydrogen bonds with the target proteins. The number of the target protein residues that formed bonds varied from one MHC molecule to another.The above two figure represents the H-bond interaction between target protein and MHC with serial number 7and8 .Thus similar interaction studies were carried out for all other MHC molecules.

FGRETVLEYLVSFGVWIRTPPAYRPPNAPILSTLPETTVVRRRGRSPRRRTPSPRRRRSPSPRRRRSQSRESQC 195

FGRETVLEYLVSFGVWIRTPPAYRPPNAPILSTLPETTVVRRRGRSPRRRTPSPRRRRSPSPRRRRSQSRESQC 195

Fig. 5. Epitopes of target protein in linear sequence

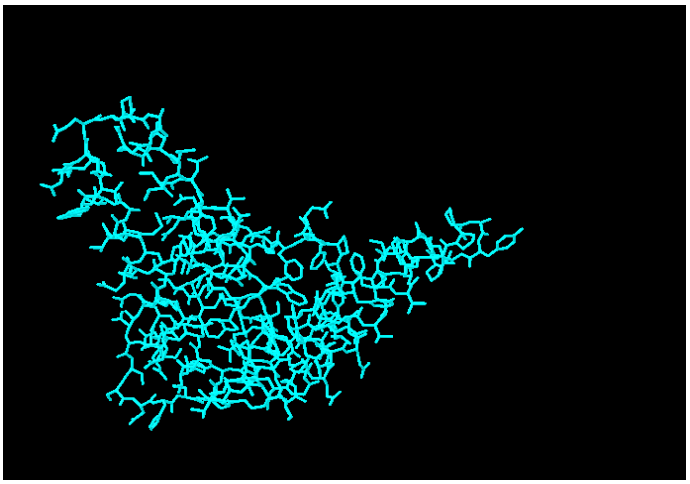

Fig. 6. Structure of the modeled protein

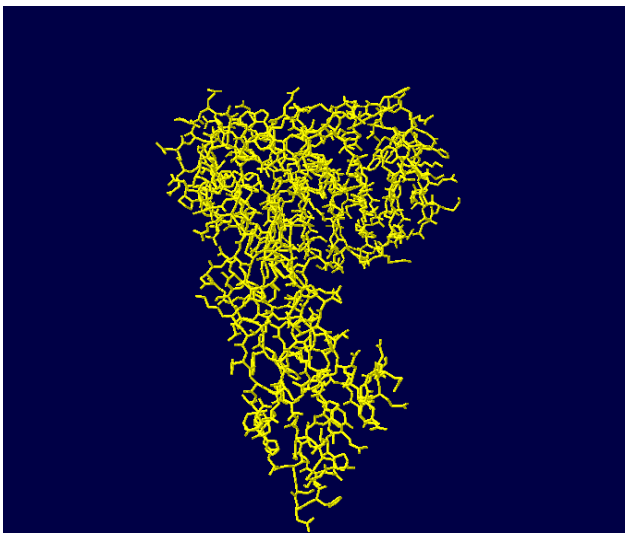

Fig. 7. Structure of MHC molecule

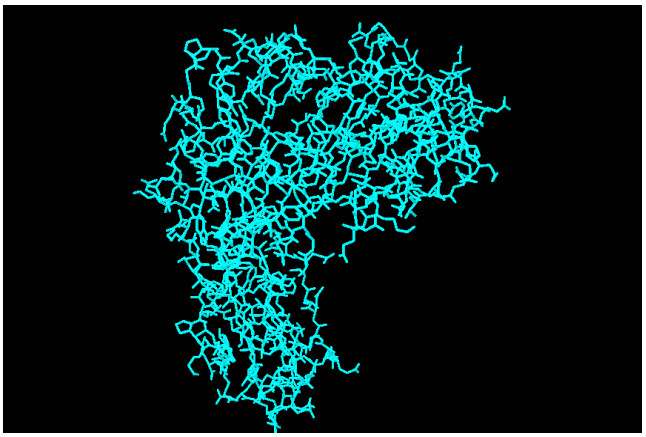

Fig. 8. Structure of MHC molecule

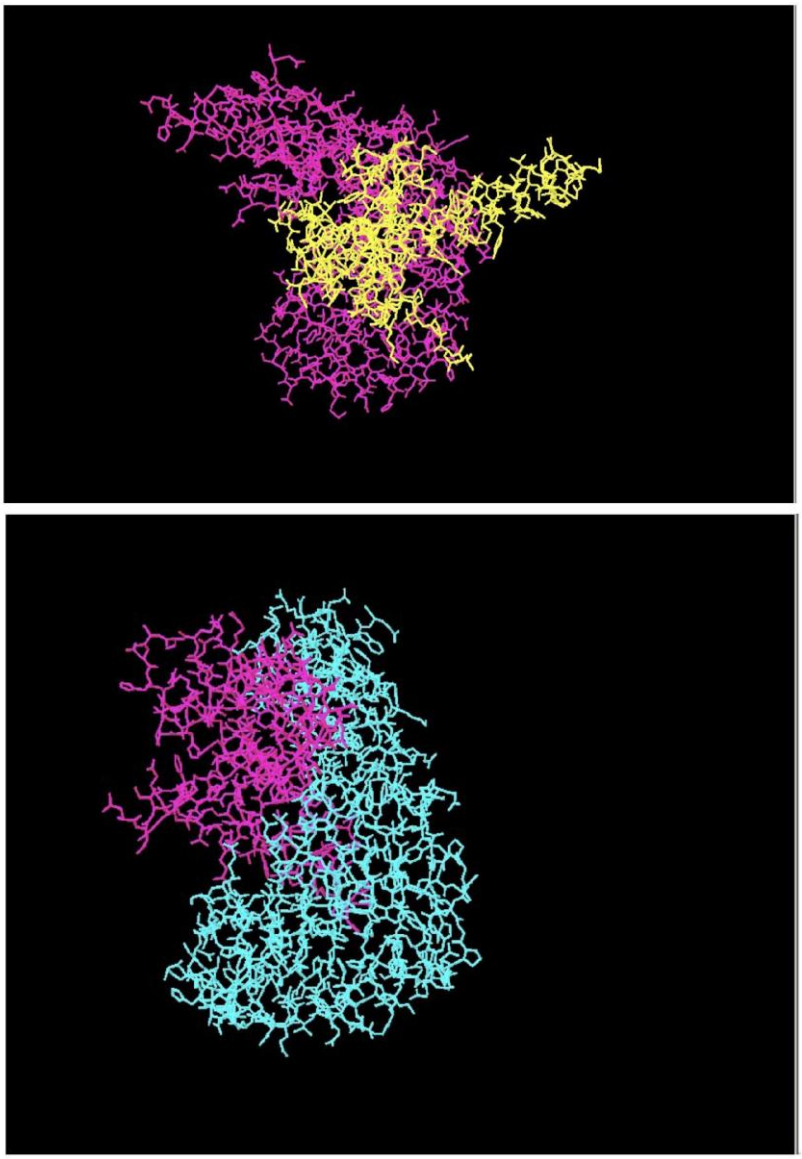

Fig. 9. MHC (serial no.7) docked with target protein and MHC (serial no.8) docked with target protein

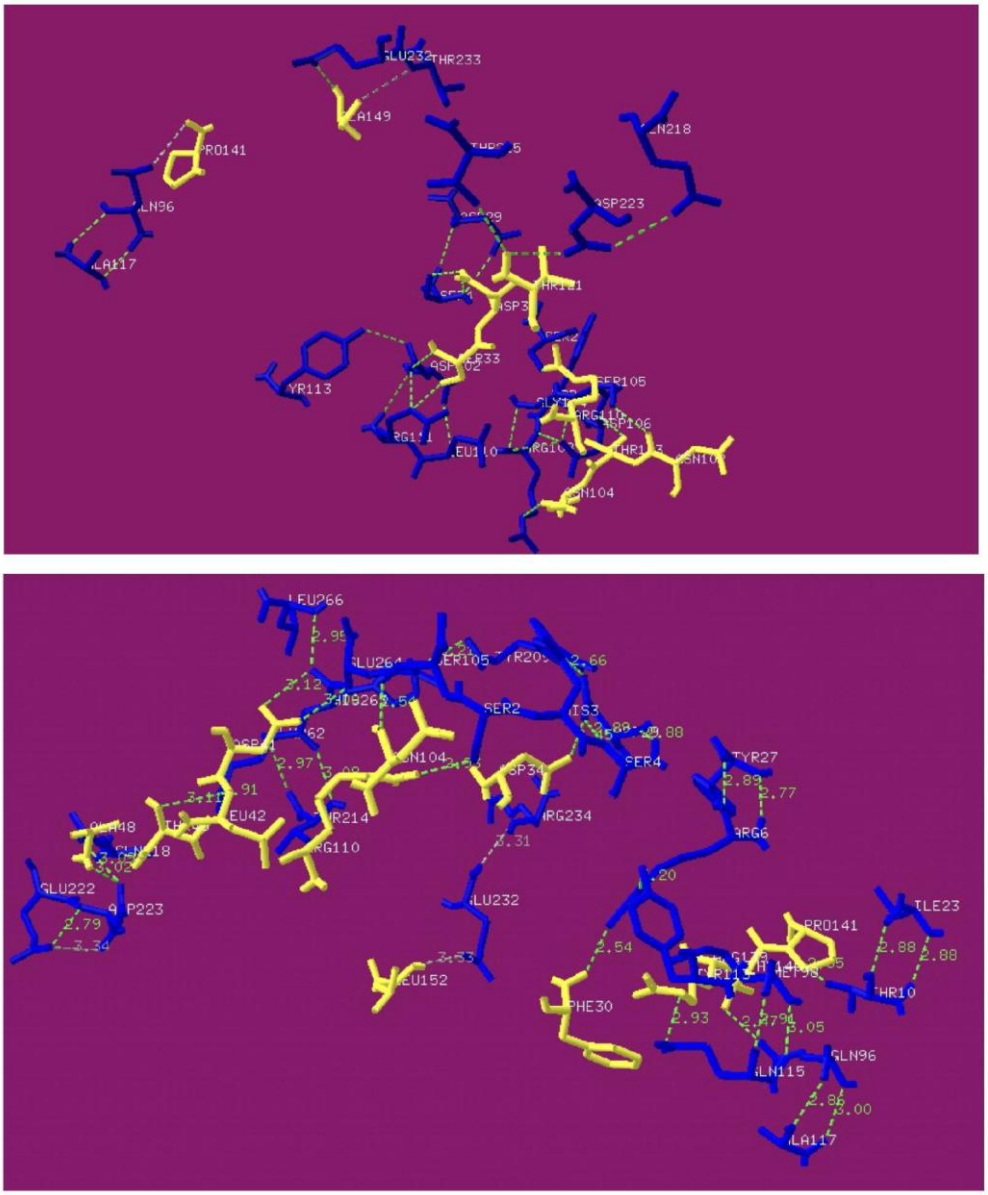

Fig. 10. Hydrogen bonds formed between MHC with target protein

Table 1. Target Protein residue that interacted with MHC

MHC molecule serial number	Number of target protein residues that interacted with the MHC.
1	8
2	10
3	5
4	5
5	10
6	8
7	12
8	12
9	7
10	10

Table 2. H bonds formed between target protein and MHC (serial no 7)

Target protein residue	MHC molecule residue	Bond length
Ser 2	Arg 110	2.24
Ser 4	Asp 34	3.19, 2.29
Gly 96	Pro 142	3.33
Asp 102	Ser 33	2.61
Ser 105	Asn 102	2.86
Asp 106	Thr 103	2.52
Arg 108	Asn 104	2.58
Arg 111	Ser 33	2.67
Asp 223	Thr 121	2.73
Thr 225	Phe 122	3.18
Glu 232	Ala 149	2.53
Thr 233	Ala 149	3.31

Table 3. H bonds formed between target protein and MHC (serial no 8)

Target protein residue	MHC molecule residue	Bond length
Ser 2	Arg 110	2.93
Arg 6	Phe 30	2.54
Thr 10	Pro 141	2.65
Asp 29	Asp 34	2.45
Gln 96	Thr 140	2.47
Ser 105	Asn 140	2.54
Gln 115	Arg 139	2.93
Asp 223	Leu 49	3.02
Glu 232	Leu 152	3.33
Gln 262	Leu 42	2.91
His 263	Asp 41	3.12
Glu 264	Asp 41	3.00

Our team has extensive knowledge and research experience that has translate into high quality publications[20–39]**.**

CONCLUSION

The present investigation recognized the promising complex formed between the HBV peptide and MHC molecules. All the downloaded MHC molecules were found to interact with the target protein through the formation of hydrogen bonds. Since these interactions are necessary during an immune response to invading pathogens, the target protein would ultimately trigger an immune response if it is administered as a vaccine for Hepatitis B virus genotype G. It can therefore be recommended that the target protein is a potential vaccine against the Hepatitis B virus genotype G. However further experimental validation must be done *in-vitro* for its immunological response and memory.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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