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# Docking-Based Screening of Cell-Penetrating Peptides with Antiviral Features and Ebola Virus Proteins as a Drug Discovery Approach to Develop a Treatment for Ebola Virus Disease

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## Abstract

Ebola drug discovery continues to be challenging as yet. Proteins of the virus should be targeted at the relevant biologically active site for drug or inhibitor binding to be effective. In this regard, by considering the important role of Ebola virus proteins in the viral mechanisms of this viral disease, the Ebola proteins are selected as our drug targets in this study. The discovery of novel therapeutic molecules or peptides will be highly expensive; therefore, we attempted to identify possible antigens of EBOV proteins by conducting docking-based screening of cell penetrating peptides (CPPs) that have antiviral potential features utilizing Hex software version 8.0.0. The E-value scores obtained in this research were very much higher than the previously reported docking studies. CPPs that possess suitable interaction with the targets would be specified as promising candidates for further in vitro and in vivo examination aimed at developing new drugs for Ebola infection treatment.

**Keywords:** bioinformatics, protein-peptide interactions, biological targets, drug development, HEX software, biological computation, drug design, CPP

## 1. Introduction

Ebola virus disease or EVD is a frequently fatal disease caused by a member of the *Filoviridae* family known as Ebola virus (EBOV) [1]. The pathogen was initially discovered in Africa in 1976 and then leaded to two serious outbreaks including the 2013–2016 outbreak of EVD in Western Africa that infected 28,652 people with

11,323 documented deaths; and 2018–2020 outbreak of EVD in the Democratic Republic of the Congo that affected 3481 people with 2299 documented deaths [2]. Ebola virus is transmitted to people from wild animals and spreads out in the mankind population by way of human-to-human transmission. The potential reservoirs of EBOV RNA are three species of African fruit bats [3]. The genome of this virus contains a negative-strand RNA that encodes six structural and one non-structural proteins, which can be employed as potential drug targets, including transmembrane glycoprotein (GP), nucleoprotein (NP), four viral protein (VP24, VP30, VP35, and VP40) and RNA polymerase (L) [4–6]. EBOV immediately suppresses the host's innate immune response and causes a severe febrile illness along with intense weakness, muscle pain, hypotension, coagulation disorders, sore throat, diarrhea, and vomiting [7–9].

Drug discovery and development for prevention of EBOV infections can be strikingly problematic due to the essential requirement of bio-safety level four (BSL-4) facilities that are needed for carrying out preclinical studies of Ebola virus [10, 11]. To date, there is only one approved vaccine for prevention of Ebola virus disease [12] and several recent FDA approved monoclonal antibody treatments for the patients [13–15]. The traditional drug discovery process remains time-consuming and faces rising costs, labors and challenges. Therefore, computational drug design assists to defeat these difficulties and is promising to meet the need for anti-Ebola medicines [16, 17]. As reported in many recent studies, docking based approaches have been effectively employed in drug development, for prediction of the potential ability of a given molecule to bind the other targets [18] and to provide productive results for accelerating identification and optimization of drug formulation [4].

Over the past decade, the pharmaceutical industry has come to appreciate the task of therapeutic peptides that can play in the improvement of medical needs and how this type of compounds can be either complement or preferable alternative to small molecules and other biological therapeutics [19]. Due to the particular features of protein-peptide interfaces (PPIs) the application of small molecules could be limited for target PPIs. Contact surfaces involved in PPIs are large in size and this resulted in small molecules not to be outstanding for modeling of new therapeutic drugs [20]. Adversely, peptide molecules are much more efficient to be developed for interaction with large and flat protein surfaces and appear to be better adaptive. In this regard natural or synthetic peptides that are capable of interfering with PPIs, termed interfering peptides (IPs), possess increasing application [21, 22]. Peptides have an extended history of avail in therapy and are recognized as being safe and well tolerated. Novel improvements in peptide administration, bio-delivery, safety and stability are also remarkable in the preference of peptidic drug design and formulation. IPs have the potential to modify various cellular processes and may affirm the idea that they would have a significant potential to become promptly valuable therapeutic instruments [22].

Cell-penetrating peptides or CPPs (also known as protein transduction domains) are short-length peptides, generally made up of 5–30 amino acids, which are able to pass drugs or CPP/cargo complexes across plasma membrane into the cells [23]. CPPs have tremendous potential for mimicking PPI and can be great options to be used as drugs. Several studies on CPPs are presently undergoing pre-clinical and clinical trials that will offer new treatment options in the near future [24]. For further information, examples of which studies are available on references [25–27].

In this in silico study we identified 25 cell penetrating peptides (CPPs) that have antiviral potentials. Using them, we deployed series of peptide-docking screening against Ebola virus proteins as a drug discovery approach to develop a potential treatment for Ebola virus disease.

## 2. Methods

### 2.1 Ligand CPPs collection

CPPsite2.0 is a simple-to-use updated database that presents miscellaneous information about CPPs and includes 1855 entries [28]. In this study, CPPsite2.0 database was used for selection and extraction of the cell-penetrating peptide sequences. By using AVPpred web server, which is the first antiviral peptides prediction algorithm [29], CPPs that had antiviral properties were chosen (**Table 1** lists the selected CPPs). Default machine learning technique was SVM. Threshold 50 was used for screening. Four parameters used in AVPpred server for prediction of the viral features including:

1. Motif search using MEME/MAST (Bailey and Elkan 1994; Bailey, Boden et al. 2009)

2. Amino acid composition

| Peptide | Peptide Sequence | Length |
|---|---|---|
| MPGNLS | GALFLGFLGAAGSTMGAWSQPKSKRKV | 27 |
| Melittin | CIGAVLKVLTTGLPALISWIKRKRQQ | 26 |
| MPG-NLS | GALFLGWLGAAGSTMGAPKSKRKVGGC | 27 |
| hLFWT | KCFQWQRNMRKVRGPPVSCIKR | 22 |
| EGFP-MPG | GALFLGWLGAAGSTMGAPKKKRKV | 24 |
| Transportan10 | AGYLLGKINLKALAALAKKIL | 21 |
| b-WT1-pTj | CGGKDCERRFSRSDQLKRHQRRHTGVKPFQ | 30 |
| TatLK15 | RKKRRQRRRGGGKLLKLLLKLLLKLLK | 27 |
| MPGα | GALFLAFLAAALSLMGLWSQPKKKRKV | 27 |
| MPGβ | GALFLGFLGAAGSTMGAWSQPKKKRKV | 27 |
| pepM | KLFMALVAFLRFLTIPPTAGILKRWGTI | 28 |
| MPG-EGFP | GALFLGWLGAAGSTMGAPKKKRKV | 24 |
| A6 | KLLKLLLKLWKKLLKLLKGGGRRRRRRR | 28 |
| Res1 | KLIKGRTPIKFGKADCDRPPKHSQNGMGK | 29 |
| MPG | GALFLGFLGAAGSTMGAWSQPKKKRKV | 27 |
| DermaseptinS4 | ALWMTLLKKVLKAAAKAALNAVLVGANA | 28 |
| MousePrp(1–28) | MANLGYWLLALFVTMWTDVGLCKKRPKP | 28 |
| MG2d | GIGKFLHSAKKWGKAFVGQIMNC | 23 |
| P(beta) | GALFLGFLGAAGSTMGAWSQPKKKRKV | 27 |
| SN50 | AAVALLPAVLLALLAPVQRKRQKLMP | 26 |
| Peptide1 | MGLGLHLLVLAAALQGAWSQPKKKRKV | 27 |
| MCoTI-II | GGVCPKILKKCRRDSDCPGACICRGNGYCGSGSD | 34 |
| CL22 | KKKKKKGGFLGFWRGENGRKTRSAYERMCILKGK | 34 |
| Camptide | RKLTTIFPLNWKYRKALSLG | 20 |
| MAP | KLALKLALKALKAALKLAGC | 20 |

**Table 1.**
*List of selected CPPs, their sequences and lengths.*

3. Sequence alignment using BLAST

4. Physico-chemical parameters including secondary structure, charge, size, hydrophobicity and amphiphilic character as these yielded an appreciable accuracy using machine learning technique. The values of physico-chemical properties were retrieved from AA index database (Kawashima and Kanehisa 2000)

The three-dimensional model of the peptides was fabricated by Chimera 1.8.1 software.

ToxinPred tool was run with default parameters to calculate toxicity prediction of the determined peptides. All 25 peptides were non-toxic [30].
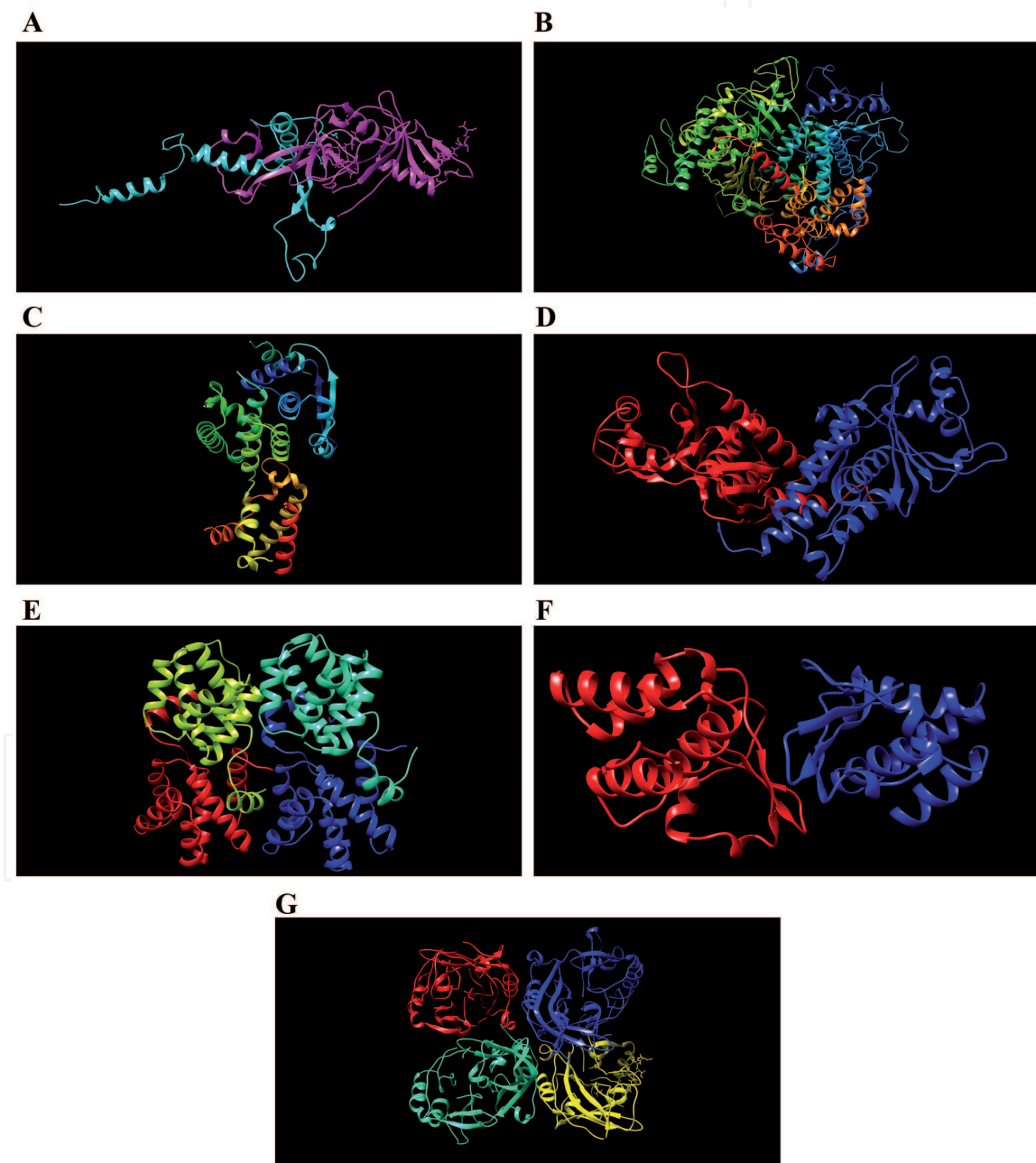


**Figure 1.**
*Structures of EBVO proteins obtained from PDB; (A) GP; (B) L, (C) NP, (D) VP24, (E) VP30, (F) VP35, (G) VP40.*

## 2.2 Target proteins collection

All the seven proteins of Ebola virus were chosen as targets. The structures of GP (PDBID: 5JQB), VP35 (PDBID: 3FKE), VP24 (PDBID: 4M0Q), VP30 (PDBID: 5DVW), VP40 (PDBID: 4LDB) and NP (PDBID: 4Z9P) proteins of EBOV were collected from Protein Data Bank which is an open access online database for the 3D structural data of biological macromolecules [31]. The retrieved structure of GP protein had one mutation at position no 42. The mutation was returned to the reference state through the utility of Spdbv software (Alanine nucleotide was converted to Threonine nucleotide). There was no structure of EBOV L protein in the PBD. The sequence of L protein was taken from UniPort and modeling was performed by Swiss-model [32–34]. All water molecules and hetero-molecules that attached to the protein structures were eliminated. The drawn structures of Ebola proteins are shown below in **Figure 1**.

## 2.3 Energy minimization

Energy minimization was carried out for the selected peptides by making use of Chimera software and for all of the target proteins by using Spdbv software. The aim of energy minimization is to discover a set of coordinates indicating the least energy conformation for the given structure.

## 2.4 Peptide – Protein docking of viral targets with ligands

Hex software is a tool for calculating and representing possible docking modes of pair of protein and peptide molecules [35]. Docking screening of the target proteins and antiviral CPPs was done by HEX software version 8.0.0 and finally, the free energy of binding between receptor-peptide was obtained that is shown in **Figure 2**. The parameters used in the docking process were:

1. Correlation type: shape only

2. FFT mode: 3D

3. Grid Dimension: 0.6

4. Receptor Range: 180

5. Ligand Range: 180

6. Twist Range: 360

7. Distance Range: 40

## 2.5 Results

The binding energies obtained from the docking method are publicized in **Figure 2**. The docking pose of the best peptide in protein cavity of each of the target proteins are well shown from the below docked **Figures 3–9**.

| Peptide/Target | GP | L | NP | VP24 | VP30 | VP35 | VP40 |
|---|---|---|---|---|---|---|---|
| A6 | -496.17 | -683.74 | -663.4 | -594.04 | -721.91 | -563.78 | -404.14 |
| b-WT1-pTj | -358.98 | -550.85 | -573.37 | -612.75 | -626.5 | -580.08 | -420.93 |
| Camptide | -378.94 | -615.77 | -485.78 | -582.82 | -620.38 | -390.66 | -494.4 |
| CL22 | -511.08 | -577.85 | -605.75 | -650.13 | -636.09 | -560.84 | -535.43 |
| DermaseptinS4 | -390.85 | -531.73 | -575.27 | -614.92 | -638.04 | -625.71 | -400.38 |
| EGFP-MPG | -358.35 | -562.85 | -552.36 | -529.89 | -574.69 | -502.78 | -338.7 |
| hLFWT | -354.97 | -568.18 | -552.13 | -560.74 | -540.04 | -562.43 | -333.88 |
| MAP | -294.94 | -543.51 | -463.39 | -613.29 | -580.94 | -357.94 | -443.75 |
| MCoTI-II | -370.08 | -564.92 | -545.8 | -678.08 | -588.13 | -466.23 | -491.89 |
| Melittin | -378.63 | -557.77 | -572.52 | -584.93 | -617.02 | -601.16 | -334.3 |
| MG2d | -358.28 | -544.1 | -497.29 | -528.38 | -587.99 | -472.31 | -387.07 |
| MousePrp(1-28) | -396.81 | -562.25 | -592.58 | -617.27 | -611.68 | -497.34 | -407.69 |
| MPG | -388.73 | -605.78 | -610.68 | -568.28 | -664.07 | -554.02 | -429.42 |
| MPG-EGFP | -326.52 | -554.77 | -567.43 | -538.48 | -566.99 | -566.18 | -343.57 |
| MPGNLS | -341.62 | -602.47 | -590.88 | -562.08 | -644.37 | -570.6 | -311.24 |
| MPG-NLS | -327.33 | -559.61 | -556.75 | -543.95 | -593.77 | -543.51 | -409.1 |
| MPGα | -317.08 | -618.87 | -557.53 | -538.5 | -668.5 | -582.29 | -332.87 |
| MPGβ | -335.57 | -581.02 | -558.2 | -533.64 | -712.66 | -574.42 | -313.42 |
| P(beta) | -390.33 | -607.33 | -541.65 | -671.07 | -667.55 | -545.77 | -491.08 |
| pepM | -391.46 | -601.41 | -577.31 | -593.6 | -658.94 | -644.36 | -365.71 |
| Peptide1 | -381.54 | -577.24 | -608.68 | -647.26 | -618.47 | -479.81 | -481.43 |
| Res1 | -456.89 | -557.41 | -611.73 | -635.45 | -677.4 | -531.16 | -440.27 |
| SN50 | -386.69 | -553.81 | -548.98 | -570.48 | -609.27 | -471.95 | -443.61 |
| TatLK15 | -364.67 | -569.16 | -579.49 | -614.37 | -609.66 | -580.46 | -455.45 |
| Transportan10 | -305.62 | -543.68 | -520.11 | -547.36 | -592.08 | -497.26 | -290.36 |

**E-value**

Lower

Higher
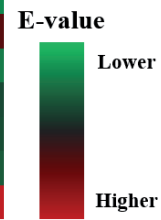
**Figure 2.**
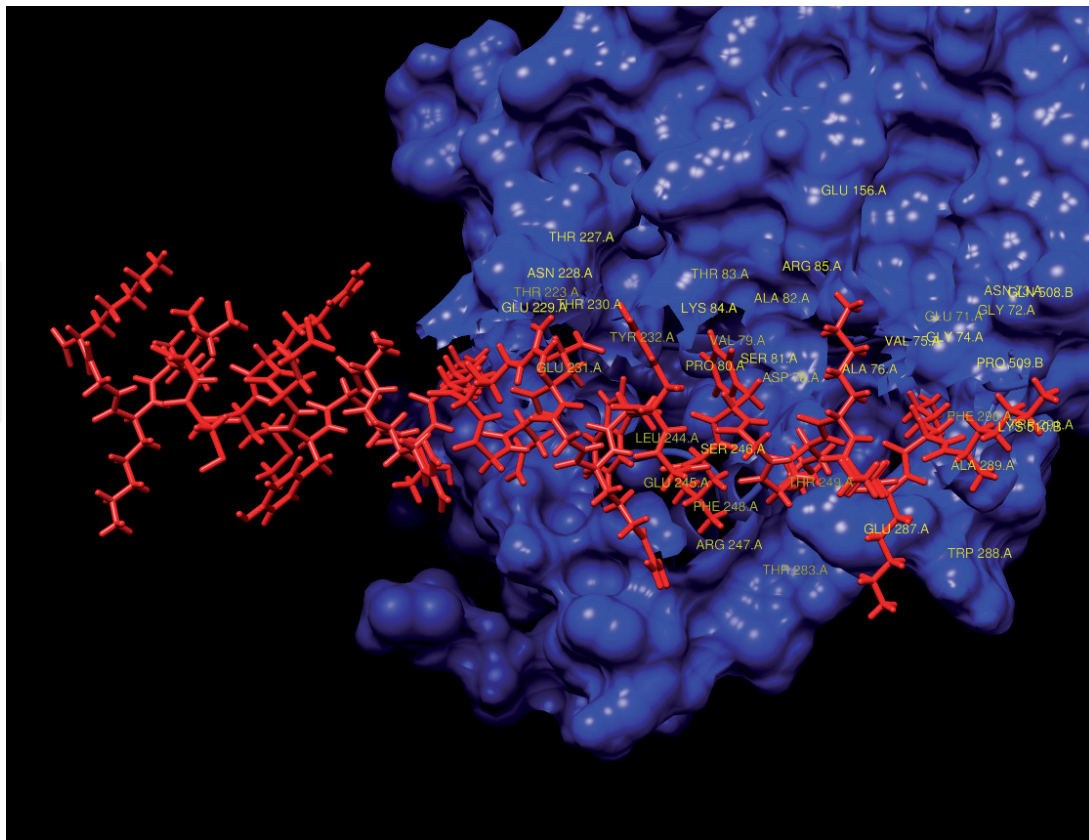*The binding energy scores obtained from Hex docking software.*



**Figure 3.**
*Docking pose of GP with CL22 peptide; amino acid residues within 5 Å distance of binding site are labeled.*
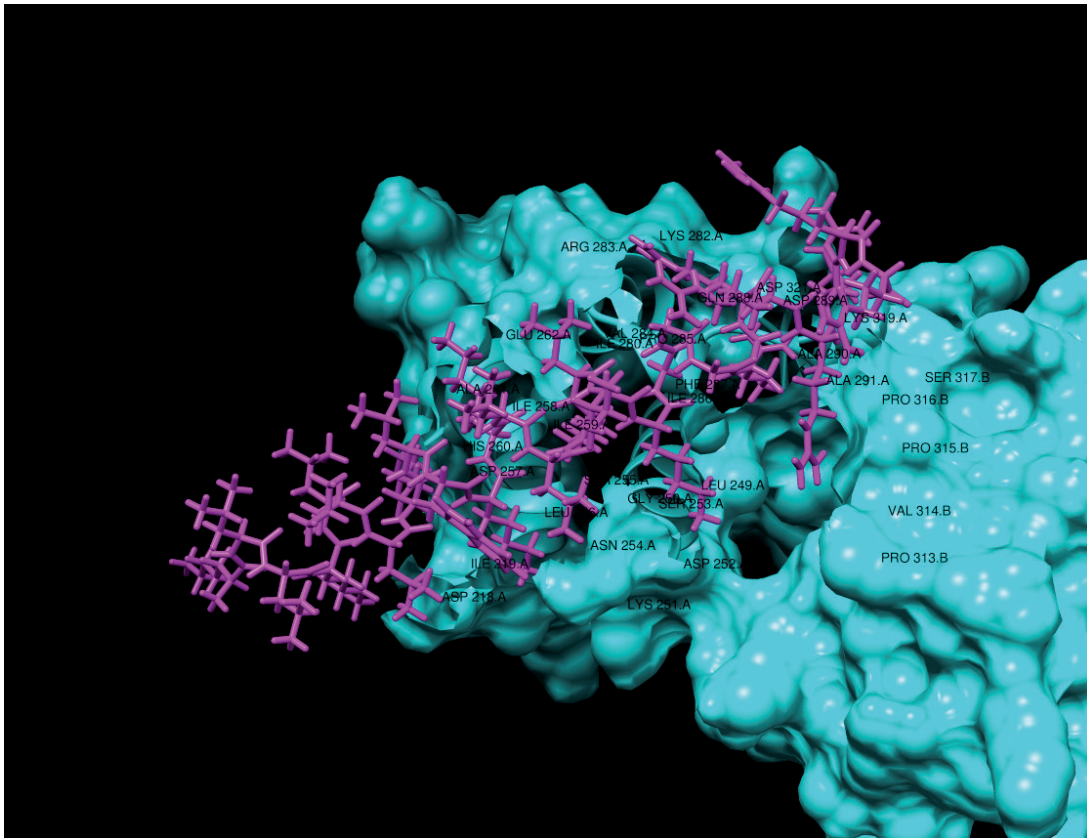
**Figure 4.**
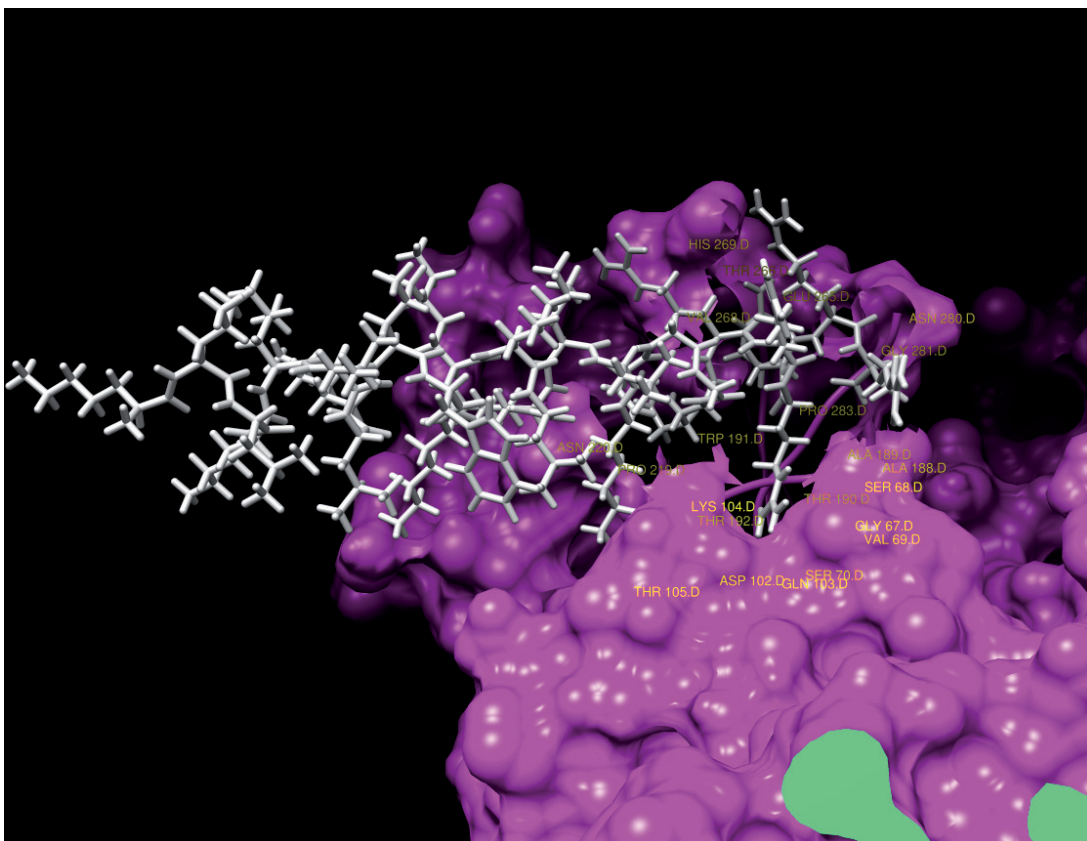*Docking pose of L with A6 peptide; amino acid residues within 5 Å distance of binding site are labeled.*



**Figure 5.**
*Docking pose of NP with A6 peptide; amino acid residues within 5 Å distance of binding site are labeled.*

**Figure 6.**
*Docking pose of VP24 with MCoTI-II peptide; amino acid residues within 5 Å distance of binding site are labeled.*



**Figure 7.**
*Docking pose of VP30 with A6 peptide; amino acid residues within 5 Å distance of binding site are labeled.*

**Figure 8.**
*Docking pose of VP35 with pepM peptide; amino acid residues within 5 Å distance of binding site are labeled.*



**Figure 9.**
*Docking pose of VP40 with CL22 peptide; amino acid residues within 5 Å distance of binding site are labeled.*

## 3. Conclusions

In our present study, protein – peptide docking technique were accomplished to assess the binding orientations of the seven viral targets from Ebola virus with the 25 selected cell penetrating peptide ligands. Each one of the targets was tightly bound to every 25 different types of CPPs with good score. The E-value scores were very much higher than the previously reported docking studies. Moreover, this research concluded that among all ligands, the CL22, A6 and Res1 peptides interacted efficiently with four of the Ebola proteins and would be considered as potent promising antiviral agents. It is anticipated that this study could pave a way for further in vitro and in vivo investigations to discover new approaches and candidates for Ebola drug design and formulation.

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