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Research article

In-silico studies for design and development of inhibitor against Covid-19

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Keywords: Computer Aided Drug Design, Covid-19, Peptides, ACE 2, Spike Protein.

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Abstract

Aim: The Covid-19 pandemic as declared by WHO, reported its first case in Wuhan, Hunei province, China. The infections have now been widespread and as of 30th March 2020, 6,93,224 infection cases and 33,106 deaths have been reported worldwide. This is an international concern related to public health. Several research studies are being carried on around the world to amid the crises. Various treatment and prevention hypothesis regarding vaccine development, repurposing of drugs along with development of new chemical entities are under investigation. Covid-19 is a virus from the coronavirus family of viruses of beta genus. It has similarity with the SARS-CoV which was reported earlier. We plan to propose a scaffold for designing peptide derived specific inhibitor against Covid-19.**Method:** Our strategy involves designing a peptide inhibitor that will interact with RBM of the SARS-CoV-2 and inhibit its entry inside the cell. We utilised online peptide designing platform called rosetta, Autodock Vena a computer aided drug designing software and Schrodinger's Drug Discovery Suite **Result:** We propose a peptide based on the sequence of human ACE2 which interacts strongly with RBM of the SARS-CoV-2. Interested readers can utilise the sequence for further modification of the peptide sequence to convert it into a peptidomimetic.**Conclusion:** Receptor binding motif of SARS-CoV-2 has stronger affinity towards the derived peptide so as to terminate the infection cascade. The proposed peptide can surely be used as scaffold for designing more active agents.

Introduction

Coronavirus disease 2019 (Covid-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first identified in 2019 in Wuhan, the capital of Hubei China, and has since spread globally, resulting in the 2019–20 coronavirus pandemic [1,2]. Common symptoms include fever, cough, and shortness of breath. Muscle pain, sputum production, diarrhoea, and sore throat are less common. While the majority of cases result in mild symptoms, some progress to pneumonia and multi-organ failure [3-5].

The World Health Organisation (WHO) declared the 2019–20 coronavirus outbreaks a Public Health Emergency of International Concern (PHEIC) on 30th, January 2020 and a pandemic on 11th, March 2020. Evidence of local transmission of the disease has been found in many countries across all six WHO regions [6, 7].

The Covid-19 virus is said to have acquired a mutation which allows it to have increased affinity towards human ACE2 receptor [8]. It also has similar binding affinity for

ACE2 receptor of those animals such as cats, ferrets, etc., which share sequence homology with human ACE2 [9]. It is this mutation that is allowing the virus to be more contagious (Human to human transmission) [10]. It has also been observed that even though there is sequence similarity between SARS-CoV and SARS-CoV-2, the antibodies for SARS-Cov are not active against SARS-CoV-2. This suggest the need of a designed inhibitor which will be structure and conformation specific to bind SARS-CoV-2. Protein-protein interaction inhibitors can be designed by taking into consideration the protein epitopes, the actual sequence that interacts and binds. Whole structure of SARS-CoV-2 can be described as a sequence that has namely two regions, the core region and the spike. The spike region is divided into two further subunits, S1 (Subunit1) which has the active site and the RBD (Receptor Binding Domain) domain, which flanks RBM (Receptor Binding Motif) [11,12]. It is the RBM that interacts with human ACE2 enzyme. S2 (Subunit2) has the poly basic furin cleavage site and O-linked glycans [8]. This site is responsible for its resistance against furin based proteases. It is reported that the O-linked glycans may be responsible for production of a mucin like substance that protects the virus epitopes [8,13-15]. This suggest that an Anti-Biofilm agent/antibiotic active against bacterias that produce capsule in combination with the effective drug could be a promising treatment therapy. Although more studies in this matter would be confirmatory [16,17]. The nine conservative amino acids essential for the interaction were determined from the sequence homology of SARS-CoV and SARS-CoV-2. We have utilised a RCSB deposited PDBid 6M17 as input after preprocessing and minimising the crystal structure for designing a peptide based on human ACE2 sequence. PDBid 6M17 is the crystal structure of SARS-CoV-2 RMD bound to the of ACE2.

In the present study, we aimed to design a scaffold peptide sequence which can be used by interested readers for developing new derivatives. We utilised a complex of SARS-CoV-2 RMD bound to the of ACE2 crystal structure PDBid 6M17 as an input, after processing (processing was performed using Schrodinger's Drug Discovery Suite Software), for rosetta online web server. Rosetta server inspects the interacting sequence residues of the complex (The two interacting domains i.e. of SARS-CoV-2 RMD and ACE2) and based on the epitope sequence complementarity, conformation it gives a short peptide sequence that will have similar or stronger interaction with chain/protein of interest. The output peptide sequence is claimed to interact and modify the native protein-protein interaction. Thus, can serve as the initiation point of further development. The sequence obtained was modified on the basis of binding site analysis of target i.e. SARS-CoV-2 RMD, receptor grid cavity and interacting sequence residues. Modification was such, to examine the effect of increase in chain length and increase in aromatic amino acid residues for higher interaction and bond formation. For increasing the interaction further and binding to a specific residue of SARS-CoV-2 RMD sequence, aromatic amino acids were incorporated, modifying the sequence. The output peptide sequence was 10 residue long, which was increased up to 12 aa residue longer. Derived peptide along with the newly modified were docked to check the binding interaction. Docking studies were performed using Autodock Vena Software. The modifications made showed positive result and higher interaction. Thus, further modifications can be made so as to improve the pharmacokinetic and pharmacodynamic profile of the scaffold peptide to make that drug-able candidate.

The basic idea is that SARS-CoV-2 should have more affinity and thus bind with more interaction energy to these derived peptides. Though this study is an overview, it will surely help researchers in the field with a basic scaffold to proceed with for designing specific peptidomimetics.

Material and methods

Rosetta online web server was accessed online by Ms. Pritam Bagwe from MacBook Air. Autodock Vena modification and docking operations were performed by Mr. Nikhil Pahelkar on Windows 10 pro platform of Dell laptop-l4JGKR3, Intel core i3 processor and 4GB RAM. Software License was available on the workstations setup in the ICT, Mumbai CADD lab. Workstations have linux CentOS platform, 4 processor speed and 8GB internal with additional external storage capacity.

Protein preparation

Protein preparation was performed by using Protein Preparation Wizard of Maestro interface, Schrödinger software. The PDB Id-6M17 was downloaded and treated to add missing hydrogen, assign proper bond orders, treat metal (breaking bonds to metal and correct the formal charge on metal and neighbouring atoms), and to delete water molecules that are more than 5Å from the heterogeneous groups. The H bonds were displayed. Finally, the protein structures were minimised to the default root-mean-square deviation value of 0.30 Å. The inhibitor structure was minimised using OPLS_3e force field. Minimisation was carried out at pH 7.4. 6Ml7 is a complex of SARS-CoV-2's receptor binding domain and ACE2 and the sodium-dependent neutral amino acid transporter B(O)AT1 in association with ACE2. This complex is present as double homo-mer units, so only one individual chain of the RBD of SARS-CoV-2 binding that of ACE2 was retained. Later the complex was optimised and minimized. The complex PDB downloaded from RCSB is shown in the Figure 1 for reference.

Obtaining peptide based scaffold from Rosseta Web server

The minimised complex was used as input on another software website; Rosetta Online Server. We entered the

PDB complex as input and mentioned the description of the job and expected number of amino acid residue peptide the software should predict for us. The software PeptiDerive [18] identifies a linear peptide segment for a given protein-protein interaction. A sequence segment that contributes the most to binding of the proteins to each other is analysed and can serve as inhibitor for the complex interaction. The peptides that are derived from this sequence can be modulators of the protein-protein interaction. In current case, the peptides can modulate the Viral Spike and ACE2 interaction and terminate the infection cascade. A list of derived peptides is obtained as output. This is the list of the peptides that contribute most to the interaction of the complex. The present situation generated only one peptide sequence. The software also provides quantitative and visual data about the binding mode and energetics. From the many sequence segments that the software considers, the fragment which constitute a significant portion of the binding energy are considered to be potential candidates for competing with the existing Viral spike and ACE2 complex interaction. This could be the starting sequence for designing and developing peptide-based inhibitors against SARS-CoV-2. Utilising the software derived sequence as scaffold we designed more five peptide sequences for analysing binding energy. The modifications were made based on the knowledge of binding site/receptor grid analysis and the major interacting residues. Basically, the aim was to engage those residues of SARS-CoV-2 RBM which interacted with ACE2.

Docking Study of peptides

We used the smina docking protocol [19], a fork of AutoDock Vina (v1.1.2) [20], on the selected compounds to quantify their interaction with each of the representative's structures from the generated ensemble. The ligand PDBQT files for docking were generated using the prepared lig.pdbqt script that comes with AutoDock Vina Tools (v1.5.4) [21]. Docking was performed at an exhaustiveness of 8, the search space was defined using the automatic method with smina, and a random seed of 1412428560 was selected. The active site residues mentioned for grid generation were residue number 442, 455, 472, 479, 480, 485, 487, 505 of receptor binding motif of SARS-CoV-2. Hits with a binding free energy below -7.0 kcal/mol. Likewise, the interaction with all five ensemble structures was quantified. Compounds with a free binding energy below -6.5 kcal/mol were then subjected to clustering based on the Tanimoto comparison of per-atom molecular fingerprints. For each of the 8 resulting clusters, the best two compounds (one compound in the case of a single structure per cluster) according to the binding energy were selected. The residues present at the interface of the complex are shown in the Figure 2. Majority of the active site residues of both the proteins lie within the complex interface as shown.

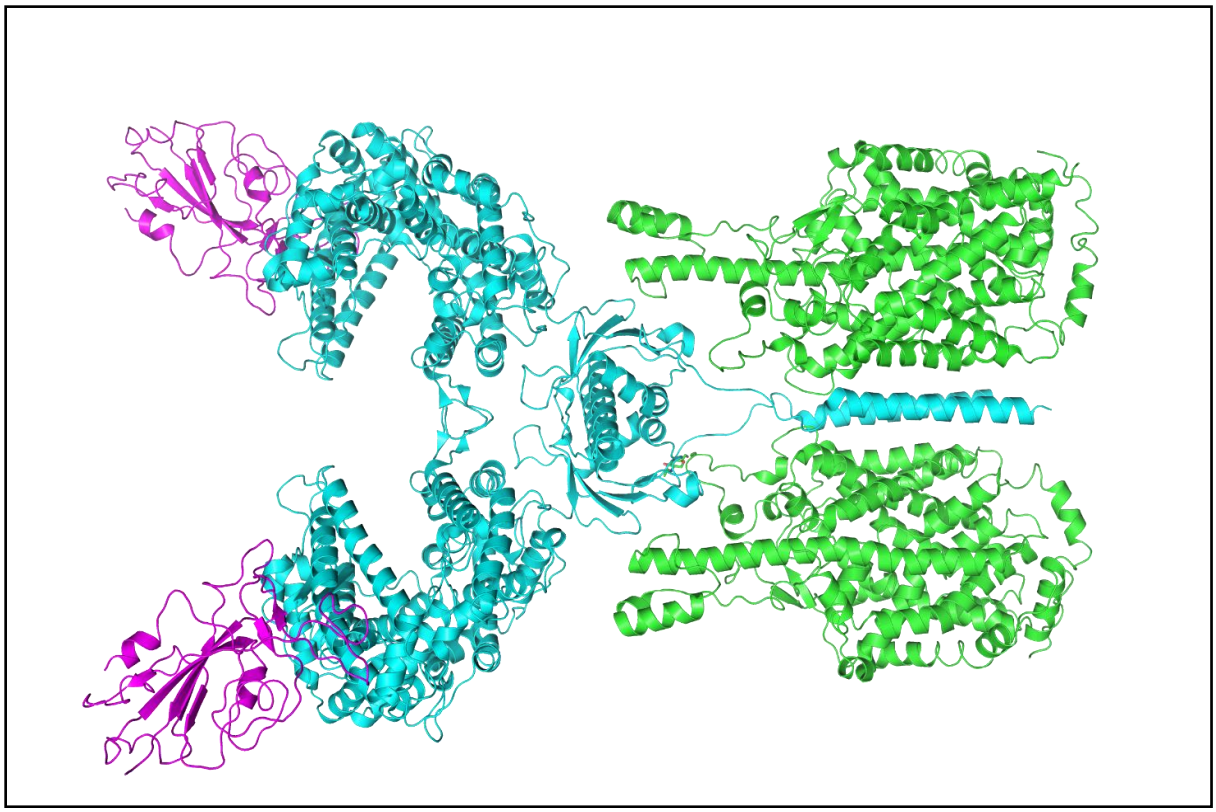


Figure 1. The complex PDBid 6M17 imported from RCSB. (Where, spike protein shown in pink colour, ACE2 shown in sky blue in colour and sodium-dependent neutral amino acid transporter shown in green colour).

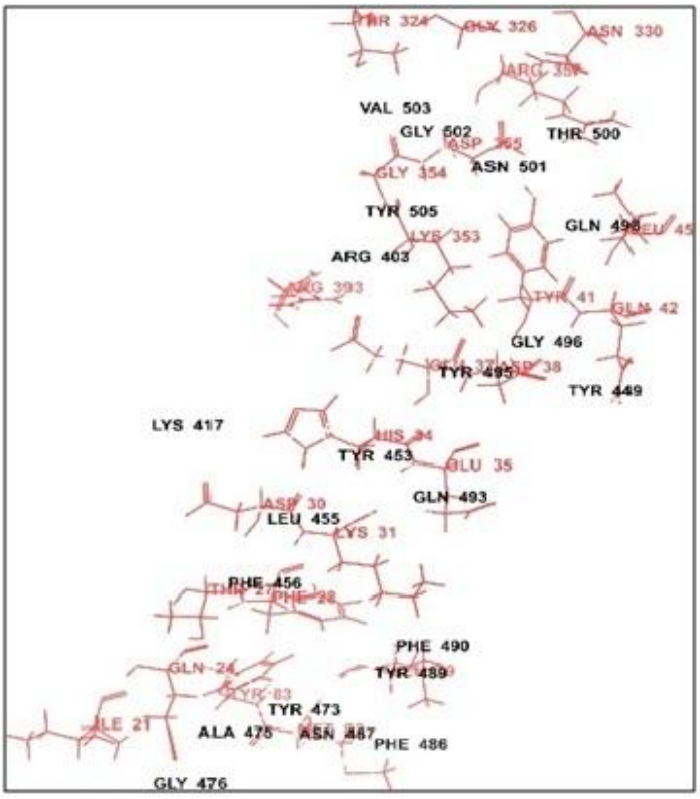


Figure 2. Residues at complex interface. (Protein-protein interaction interfaces).

Result and Discussion

Preprocessed, optimised and minimised SARS-CoV-2 RBD and ACE2 complex

The PDBid 6M17 after minimisation has a complex of SARS-CoV-2 RBD and ACE2. The sodium-dependent neutral amino acid transporter B(O)AT1 in the complex is retained since it was found in the bound form to the ACE2 and may have some inherent function. The minimisation was carried out successfully. The Ramachandran plot was checked for accuracy of minimisation. The prepared PDB complex which was used as input for rosetta software is shown in the Figure 3.

Rosetta derived 10 amino acid sequence peptides

The software gives the output information of the peptide derived from a particular chain pair and of a certain length. The Receptor E (RBD of SARS-CoV-2), and Partner B (10aa derived peptide residue) in PDB format is the output. The Partner B is derived from that sequence of ACE2 which interacts the most with RBD of SARS-CoV-2. Peptide derived is from position 9-18 i.e. residues 29-38 of ACE2, which perfectly match with the active site residues of human ACE2 reported in the literature. The peptide derived is shown in the Figure 4. This is indicated in the Peptide score vs. window position diagram in Figure 5. The best linear peptide obtained was LDKFNHEAED, with interface score -6.740 and relative interface score percentage to be 35.17. The total interface score was found to be -19.16 REU (Residue units).

AutoDock Vina results

We intended to modify the sequence of peptide output from Rosetta with the view of increasing the binding interaction and find the docking score using AutoDock Vina software for designing and development of potential peptide inhibitors for SARS-CoV-2. The list of peptides can be seen in Table 1 and structure of best fit peptide shown in figure 6.

Preprocessed and minimised PDBid 6M17 of the SARS-CoV-2 and ACE2 complex was modified to remove ACE2 and sodium ion channel and used to dock 10 amino acid long peptide using AutoDock Vina software. Extended confirmation of LDKFNHEAED binds to the RBD site of SARS-CoV-2 but binding energy was found to be -4.7 kcal/mol. Therefore, to increase binding energy as well as for more interaction between peptide and spike protein of SARS-CoV-2 we modified peptide sequence (knowledge based binding site amino acid analysis). QLRWEHYMQD, WQLREHMQDF, YQLREHMQDF are the new designed peptides containing 2 aromatic amino acids. These peptides were docked against modified spike protein PDBid (6M17) using AutoDock Vina software. Among them YQLREHMQDF showed best fit in RBD pocket of SARS-CoV-2 with binding good energy. Interaction diagram of peptide YQLREHMQDF with RBD site of SARS-CoV-2 is shown in the Figure 7.

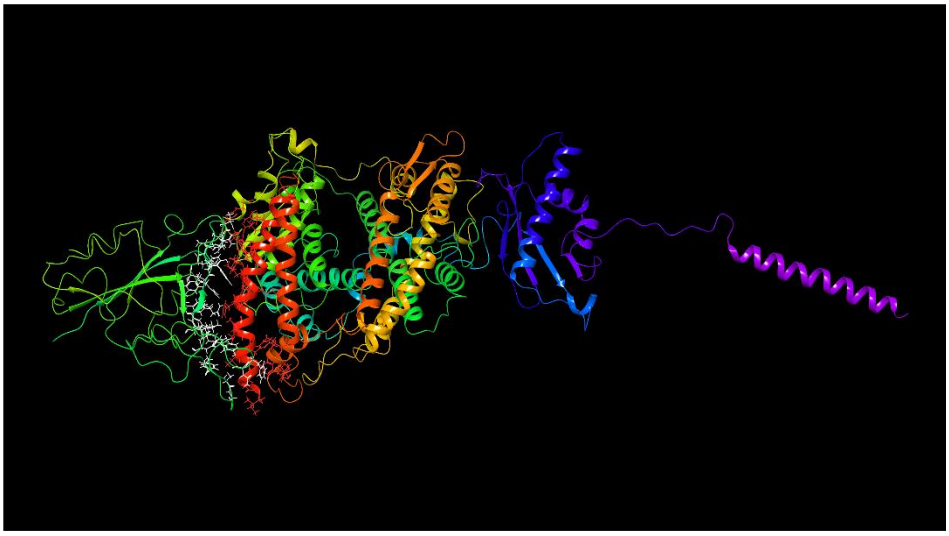


Figure 3. Completely preprocessed and minimised complex structure which was used as input for Rosetta.

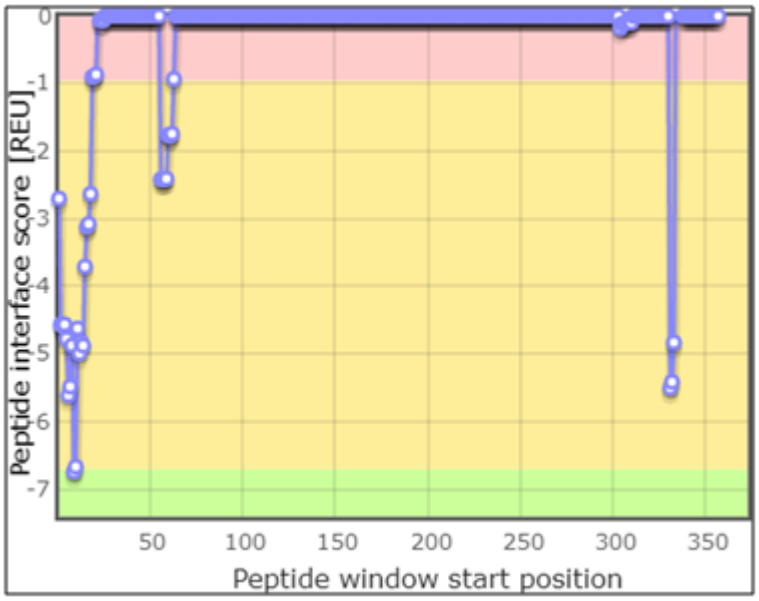


Figure 4. Peptide score vs. window position diagram.

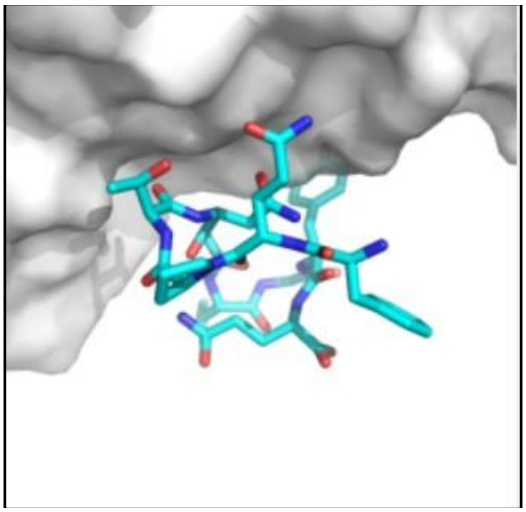


Figure 5. SARS-CoV-2 RBD used as receptor and ACE2 as template for deriving the new peptide. (Where, receptor is shown as a grey surface and the peptide shown in sky blue colour).

Table 1. Binding energy of docked peptides.

Sr. no	Sequence length	Peptide sequence	Binding energy in kcal/mol
1	10	LDKFNHEAED	-4.7
2	10	QLRWEHYMQD	-4.9
3	10	WQLREHMQDF	-5.1
4	10	YQLREHMQDF	-5.5
5	12	FSDMEHFKRLQW	-5.1
6	12	YSDMEHFKRLQW	-5.1

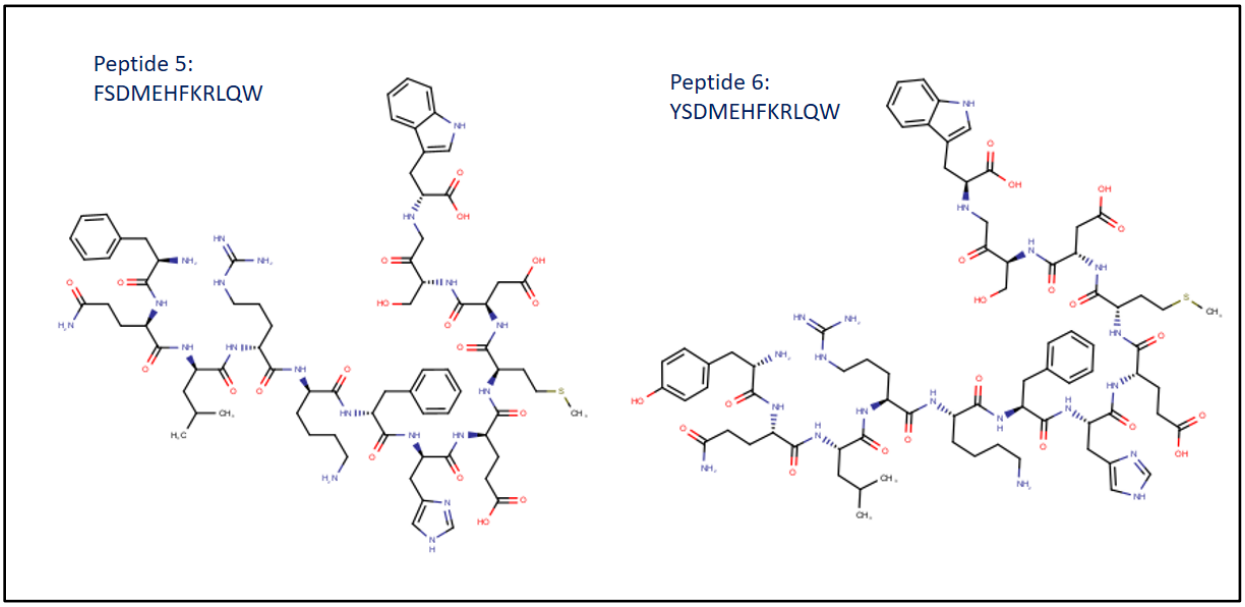


Figure 6. Chemical structure of peptide 5 and 6 respectively.

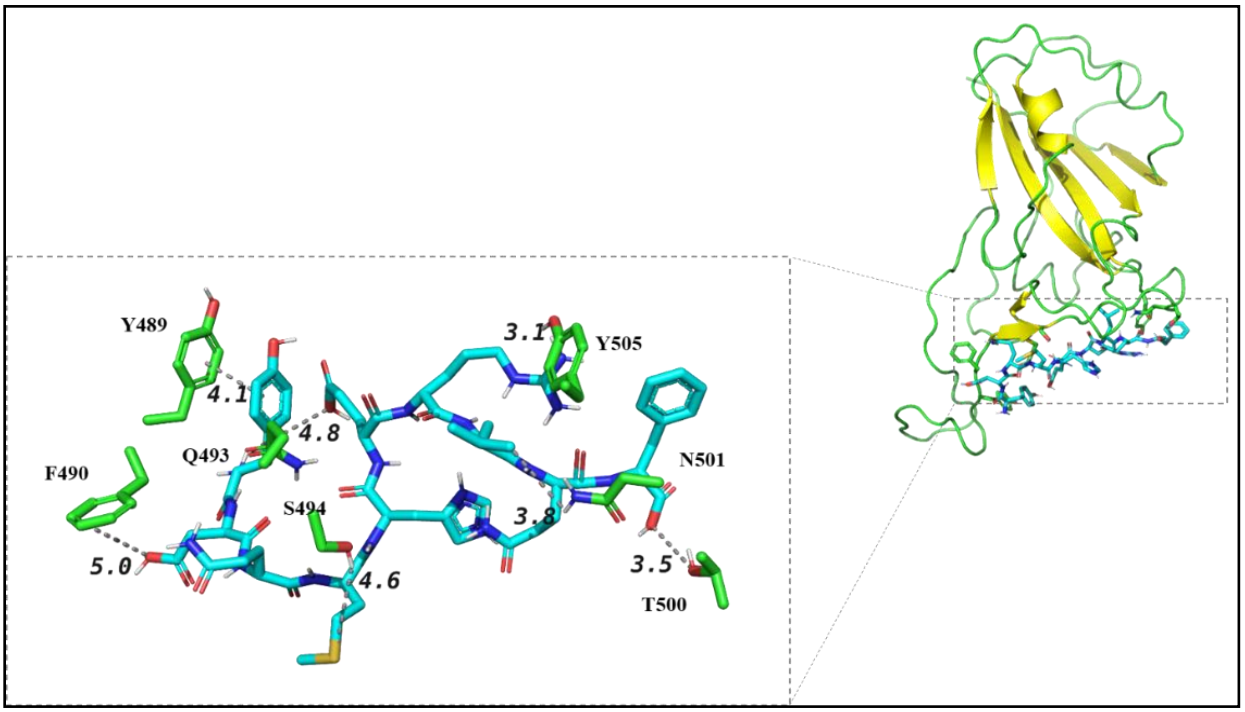


Figure 7. Interaction diagram of peptide YQLREHMQDF with RBD site of SARS-CoV-2 (Where, amino residues of RBD site of SARS-CoV-2 are showed in Green in color and peptide is shown in sky blue color.)

Amino residues of RBD site of SARS-CoV-2 are showed in Green color and peptide is shown in sky blue color. Inset shows extended conformation of ligand and its interactions with surrounding amino acids of the S1 protein. Ligand showed good pi-pi stacking interaction with Y489. Y405, T500 and N501 showed hydrogen bonding with ligand. But, Surface diagram showed that ligand had no access to the different pockets and as well as interaction with F486 was absent. Surface diagram of peptide YQLREHMQDF with RBD site of SARS-CoV-2 is shown in the Figure 8.

Therefore, we again modified and designed. (knowledge based binding site amino acid analysis) Longer peptide of 12 amino acid sequence which can bind with more extended form and could access more pockets. FSDMEHFKRLQW was the new designed 12 amino acid peptide docked against spike protein of covid-19 (6M17) using AutoDock Vina software. Interaction diagram of peptide FSDMEHFKRLQW with RBD site of SARS-CoV-2 is shown in the Figure 9.

Inset FSDMEHFKRLQW showed extended conformation of ligand which have binding energy of -5.1 kcal/mol. This result showed new interaction with 6M17. It showed pi-pi stacking interaction with Y489 and Y505. As well as S494 showed hydrogen bond network with the ligand. Apart from this N501, V483 and Q493 showed hydrogen bonding with ligand. The surface representation showed that it has more extended conformation compare to YQLREHMQDF as well it accesses more pockets of protein. Charge distribution showed that area of negatively charged residue of the protein have interaction with positive charged amino acid of the ligand. But this peptide also didn't show interaction with F486 as well it didn't show interaction with all pockets. Surface diagram of peptide FSDMEHFKRLQW with RBD site of SARS-CoV-2 is shown in the Figure 10.

Therefore, N terminus Phenylalanine is replaced with Tyr. YSDMEHFKRLQW peptide was docked using AutoDock Vina software. It showed binding of the ligand in extended conformation and binding energy was found to be of -5.1 kcal/mol. Interaction diagram of peptide YSDMEHFKRLQW with RBD site of SARS-CoV-2 is shown in the Figure 11.

YSDMEHFKRLQW showed more interaction than other two peptides. Y449, Y453, Y489 and F486 showed hydrophobic interaction with peptide whereas Y505 showed stacking interaction with tryptophan of the peptide. Interestingly residue N501 also showed cation-pi interaction with tryptophan. Q493 showed hydrogen bonding network with aspartate and glutamate of the peptide. Residue Y453 was also involved in hydrogen bonding with aspartate. Serine from the peptide inhibitor showed hydrogen bonding with R403. Due to more interaction with target amino acid residue YSDMEHFKRLQW inhibits the binding of spike protein to ACE2 receptor as shown in Figure 12. The surface representation showed that peptide has binding interaction with all pockets. Charge distribution showed that negatively charged residues of the protein are stabilised by positive charged residues of the peptide. Surface diagram of peptide YSDMEHFKRLQW with RBD site of SARS-CoV-2 is shown in the Figure 13.

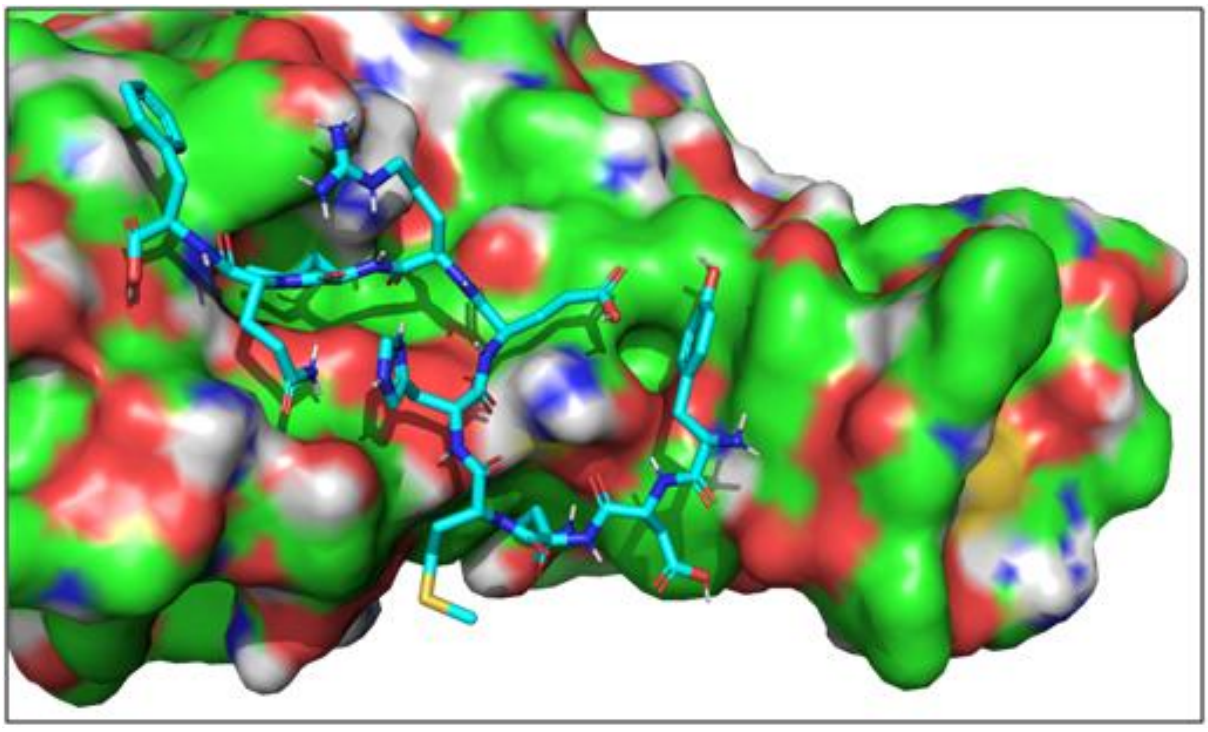


Figure 8. Surface diagram of peptide YQLREHMQDF with RBD site of SARS-CoV-2.

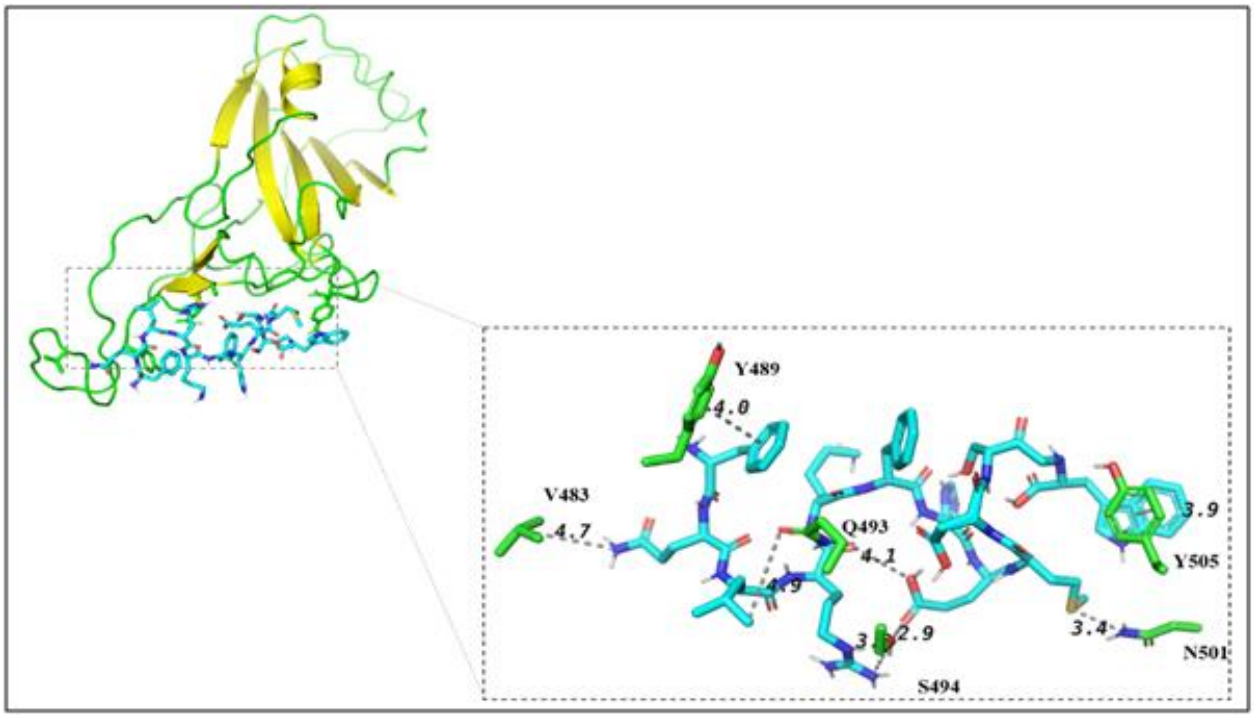


Figure 9. Interaction diagram of peptide FSDMEHFKRLQW with RBD site of SARS-CoV-2. (Where, amino residues of RBD site of SARS-CoV-2 are showed in Green in color and peptide is shown in sky blue color.)

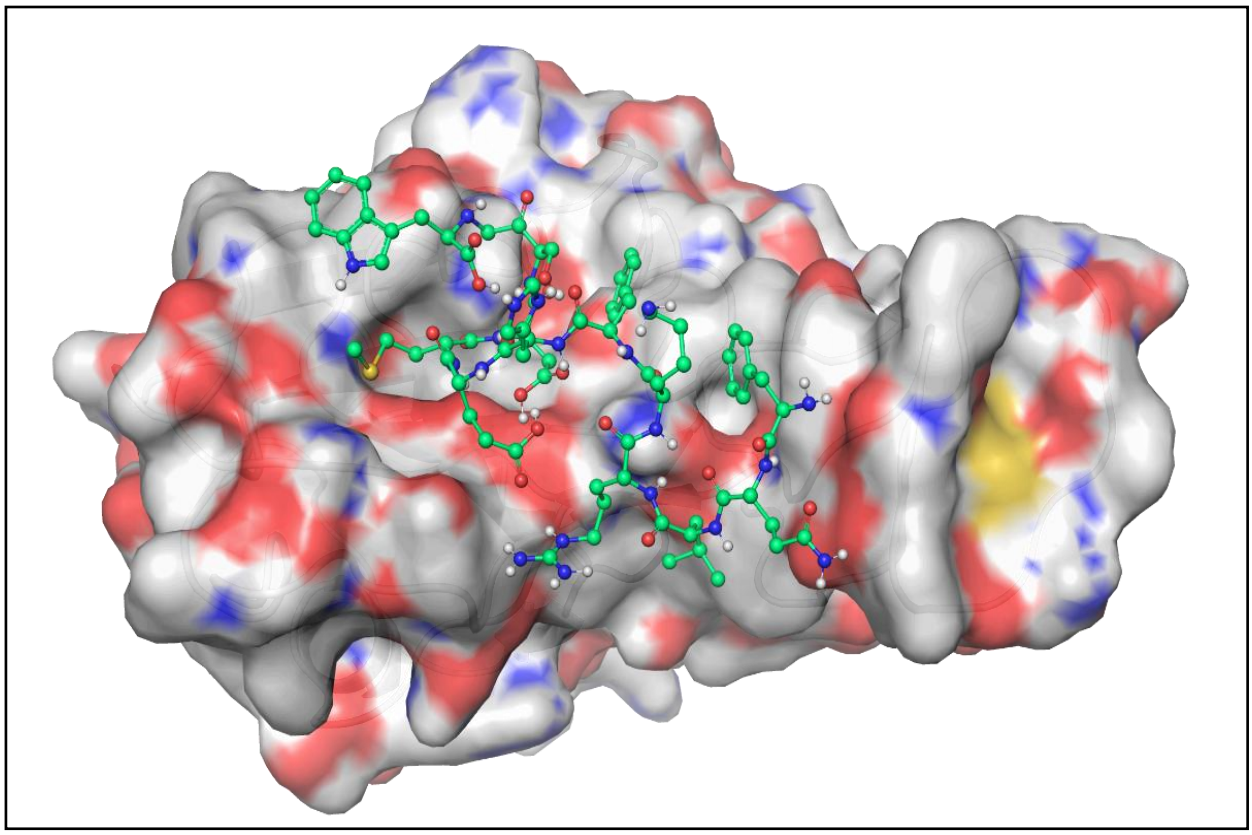


Figure 10. Surface diagram of peptide FSDMEHFKRLQW with RBD site of SARS-CoV-2.

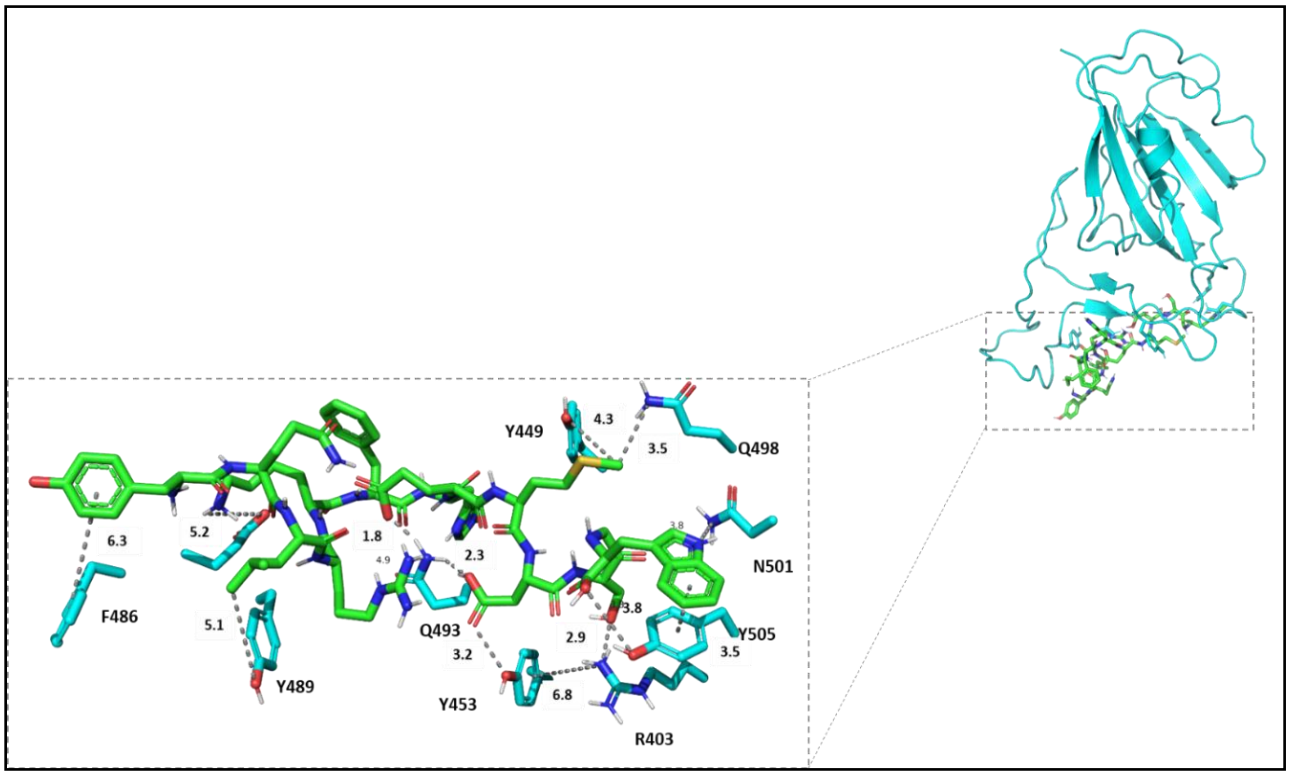


Figure 11: Interaction diagram of peptide YSDMEHFKRLQW with RBD site of SARS-CoV- 2. (where, amino residues of RBD site of SARS-CoV-2 are showed in sky blue in color and peptide showed in green in color).

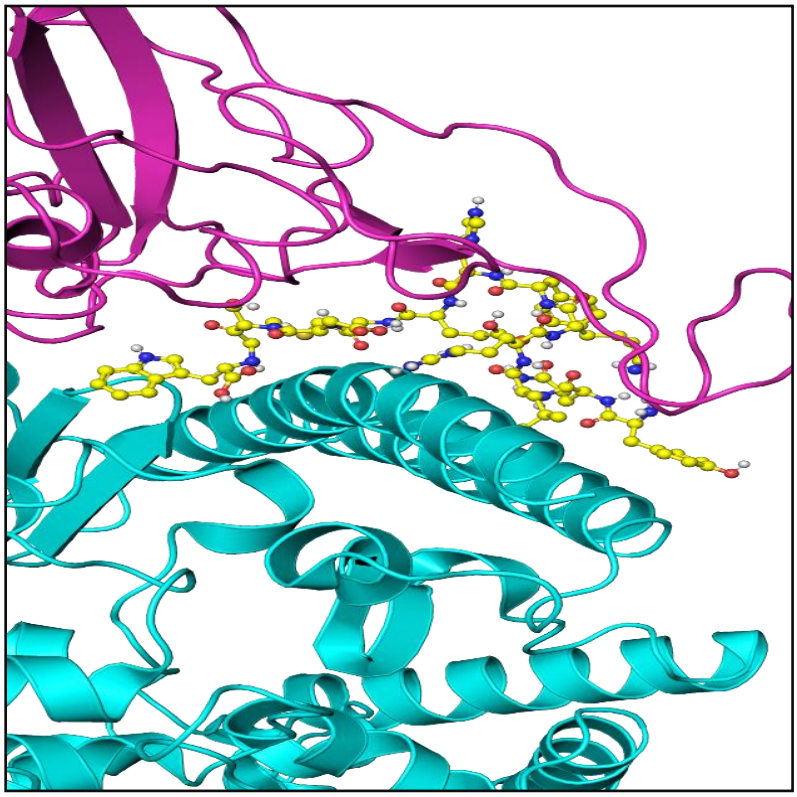


Figure 12. Complex of ACE2 and spike protein with YSDMEHFKRLQW. (where, ACE 2 is shown in sky blue in color, spike protein shown in pink color and peptide shown ball stick model).

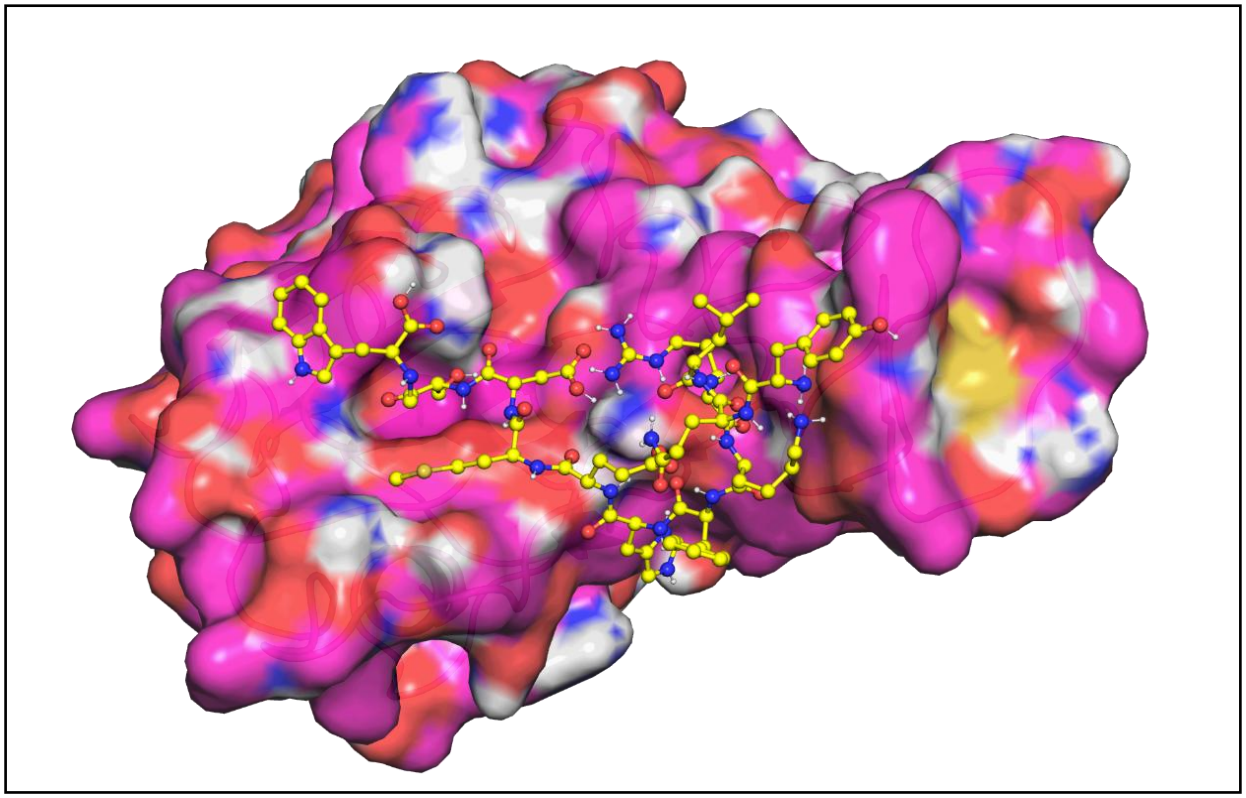


Figure 13. Surface diagram of peptide YSDMEHFKRLQW with RBD site of SARS-CoV-2.

Conclusion

The peptide derived from the interface sequence interaction by the software claims to modify the Protein-protein interaction that occurs between SARS-CoV-2 and ACE2. The systematic modification of the basic peptide were performed. The chain length of the peptide was increased so that it has access to all the binding pocket areas of the RBM of SARS-CoV-2 and binds strongly with it thus interrupting its interaction with ACE2 receptor.

The binding energies and interaction of the peptide inhibitor with protein were analyzed. It was found that 12 amino acid residue long peptide inhibitor showed more interaction than 10 amino acid residue long peptide. Among 12 amino acid peptides, YSDMEHFKRLQW showed more interaction and extended conformation which can interact with all pockets present on the surface. Therefore, YSDMEHFKRLQW can be used as peptide inhibitor against spike protein of the SARS-CoV-2 with further design and formulation development. This modified peptide sequence can act as scaffold for development of specific peptidomimetics with good pharmacokinetic and pharmacodynamic profile. *In- vitro and In-vivo* studies can be performed using both 12 amino acid peptides because FSDMEHFKRLQW also showed good interaction. Thus, both YSDMEHFKRLQW & FSDMEHFKRLQW can be used for further investigational studies. The results will validate the *in-silico* analysis and pave a way for further modification.

Abbreviations

Covid-19: Coronavirus disease 2019.
WHO: World Health Organization.
PHEIC: Public Health Emergency of International Concern.
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2 2019.
nCoV: Novel Coronavirus.
ACE2: Angiotensin Converting Enzyme 2.
RBM: Receptor Binding Motif.
RBD: Receptor Binding Domain.
S1: Subunit 1.
S2: Subunit 2.
OPLS: Optimized Potentials for Liquid Simulations.
PDB id: Protein Data Bank Identification code.
RCSB: Research Collaboratory for Structural Bioinformatics.
REU: Residue units.

Conflicts of Interest

All authors have contributed equally for the article. The authors declare no conflict of interest.

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