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ORIGINAL RESEARCH

Peptide modelling and screening against human ACE2 and spike glycoprotein RBD of SARS-CoV-2

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Abstract

Outbreak of Coronavirus Disease 2019 (COVID-19) has become a great challenge for scientific community globally. Virus enters cell through spike glycoprotein fusion with ACE2 (Angiotensin-Converting Enzyme 2) human receptor. Hence, spike glycoprotein of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a potential target for diagnostics, vaccines, and antibodies. Also, virus entry can be prevented by blocking ACE2 thus, ACE2 can be considered potential target for therapeutics. As being highly specific, safe and efficacious, peptides hold their place in therapeutics. In present study, we retrieved sequence of 70 peptides from Antiviral Peptide Database (AVPdb), modelled them using 3D structure predicting web tool and docked them with receptor binding domain (RBD) of spike protein and human host receptor ACE2 using peptide-protein docking. It was observed that peptides have more affinity towards ACE2 in comparison with spike RBD. Interestingly it was noticed that most of the peptides bind to RBM (residue binding motif) which is responsible for ACE2 binding at the interface of RBD while, for ACE2, peptides prefer to bind the core cavity rather than RBD binding interface. To further investigate how peptides at the interface of RBD or ACE2 alter the binding between RBD and ACE2, protein–protein docking of RBD and ACE2 with and without peptides was performed. Peptides, AVP0671 at RBD and AVP1244 at ACE2 interfaces significantly reduce the binding affinity and change the orientation of RBD and ACE2 binding. This finding suggests that peptides can be used as a drug to inhibit virus entry in cells to stop COVID-19 pandemic in the future after experimental evidences.

Keywords SARS-CoV-2 · Spike glycoprotein · Molecular docking · Active site · RBD · ACE2 · Viral fusion

Introduction

In the end of December 2019, China reported 99 patients who had pneumonia associated with the novel coronavirus (SARS-CoV-2) in Wuhan city of Hubei province (Chen et al. 2020). World Health Organization (WHO) termed this disease as Coronavirus Disease 2019 (COVID-19) on 11 February 2020 (WHO 2020). As of August 5th, total number of confirmed cases and deaths are 18,614,177 and 702,642 respectively globally (WHO Situation Report-199).

With unavailability of specific vaccines and medicines, antiviral, antimalarial drugs and convalescent plasma therapy are being used as primary treatment (Duan et al. 2020; Mitjà and Clotet 2020; Vincent et al. 2005). Furthermore, researchers have screened molecular databases of natural products, marine natural compounds, and previously reported virus inhibitors from terrestrial fungi against various SARS-CoV-2 proteins (Khan et al. 2020a, b; Quimque

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et al. 2020) along with drug repurposing (Khan et al. 2020c; Maurya et al. 2020). To find an effective treatment, researchers have identified potential protein targets of the virus. Few examples are Papain-Like Protease 2 (PLP2), 3C-Like Protease (3CL), RNA-dependent RNA polymerase (RdRp), Nucleoside Triphosphatase (NTPase) or Helicase, Hemagglutinin Esterase (HE), Spike Glycoprotein (S Protein), Envelop Protein (E Protein), Membrane Protein (M Protein), Nucleocapsid Protein (N Protein) and Endoribonuclease Nonstructural Protein 15 (NSP15) (Kim et al. 2020; Prajapat et al. 2020; Wu et al. 2020). Virus enters human cells by its spike glycoprotein which recognizes the human cell receptor and fuses with host cell membrane (Gallagher and Buchmeier 2001; Simmons et al. 2013). Spike glycoprotein is a trimeric protein in which every monomer is composed of S1 and S2 subunits. S1 domain in spike protein contains RBD (receptor binding domain) which binds to the ACE2 (angiotensin-converting enzyme 2) and S2 domain is responsible for membrane fusion (Belouzard et al. 2009). ACE2 is an enzyme located at the cell membrane and expressed in heart, kidney, intestines, lungs and arteries (Donoghue et al. 2000; Hamming et al. 2004). ACE2 in human is known as hACE2 (Bolles et al. 2011) and it mediates the coronaviruses entry into human cells (Nicholls and Peiris 2005). Recent study shows that RBD of S1 subunit in SARS-CoV-2 binds strongly (10–20 folds) to the ACE2 compared to RBD of SARS-CoV (Wrapp et al. 2020).

To inhibit virus entry into human cells, targeting spike protein RBD or host receptor ACE2 can be considered a compelling approach. Thus, small molecules and peptides have been screened for spike protein and ACE2 receptor (Abdelli et al. 2020; Han and Král 2020; Huentelman et al. 2004; Sinha et al. 2020; Xia et al. 2020). Peptide therapeutics has been evolving since the isolation of first peptide, insulin for diabetic patients in 1920s. Peptides are biochemically and therapeutically different from small molecules and proteins. With limitation of short half-life in plasma and insufficient bioavailability of peptides, more than 150 peptides entered human trials and more continue to be added (Tong 2009). Literature review shows that peptides have been designed and used as ACE2 inhibitors (Huang et al. 2003; Iwaniak et al. 2014; Luhtala et al. 2009).

Here, we present molecular docking of 70 peptides from Antiviral Peptides Database (AVPdb) (Qureshi et al. 2014) with SARS-CoV-2 spike glycoprotein RBD and human ACE2. Peptides were modelled computationally from their sequences and the best model was selected for further docking with RBD and ACE2 (peptide-protein docking). To explore the impact of peptide binding on RBD and ACE2, best peptide-RBD complex with ACE2 and peptide-ACE2 complex with RBD were docked and results were compared with RBD-ACE2 docked structure (protein–protein docking). Docking results reveal that peptides decrease the binding affinity and deviate the binding between RBD and ACE2 significantly. Figure 1 illustrates the binding complex of Spike Glycoprotein RBD with ACE2 and the modeling structure of potent peptides, AVP0671 and AVP1244 for RBD and ACE2 respectively.

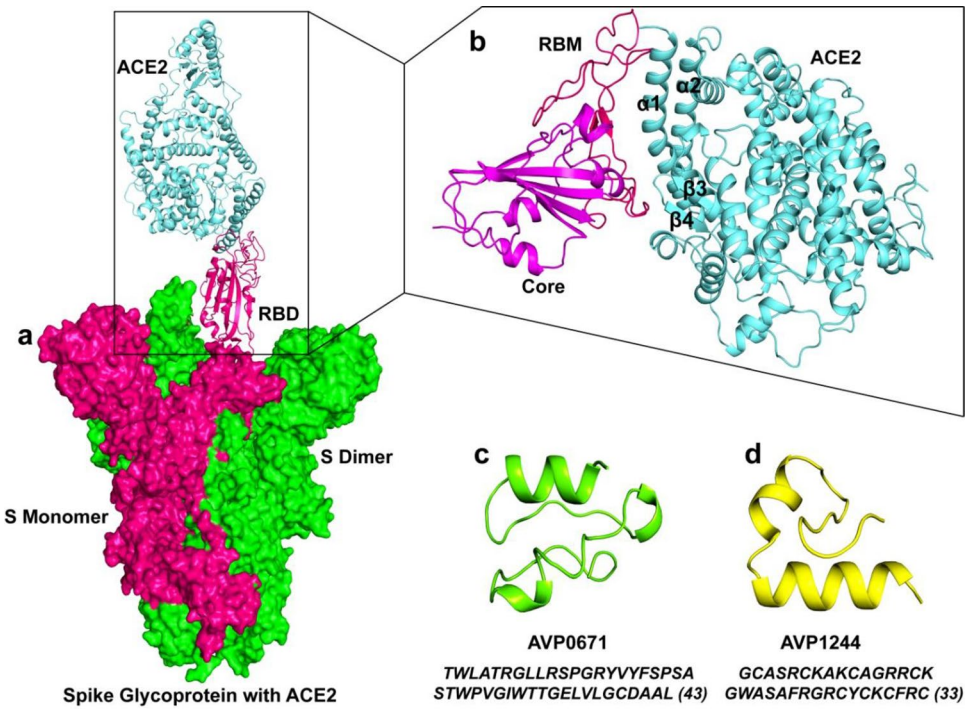

Fig. 1 **a** Structure of spike glycoprotein bonded to ACE2. **b** Complex between RBD and ACE2. In RBD, RBM and core are shown in magenta and pink colors respectively. **c**, **d** Modelled peptide inhibitors for RBD and ACE2 respectively with their codes and amino acid sequences

Material and methods

Peptides and modelling

Previously reported and experimentally confirmed antiviral peptides deposited in AVPdb Database (Qureshi et al. 2014) are available at https://crdd.osdd.net/servers/avpdb/index.php as an open source. Selecting Virus Entry as a target in database, peptides of sequence length ≥ 30 were obtained. Widely used de novo structure predicting PEP-FOLD3 web server (https://bioserv.rpbs.univ-paris-diderot.fr/services/PEP-FOLD3/) was used to model selected peptides (Lamiable et al. 2016).

Target protein preparation

Spike glycoprotein RBD and ACE2 were prepared for peptides and antibodies docking at COVID-19 Docking Server (Kong et al. 2020) available at https://ncov.schanglab.org.cn/index.php. Docking structures of both the targets prepared from complex (PDB: 6M0J) of SARS-CoV-2 and ACE2 recently deposited on RCSB Protein Databank (Berman et al. 2002) (https://www.rcsb.org/) by Wang and Zhang's group from Tsinghua University (Lan et al. 2020). Water molecules were removed during protein preparation. RBD contains 194 amino acid residues (sequence, 333–526) and single *N*-Acetyl-D-Glucosamine (NAG) molecule while, ACE2 has 597 amino acid residues (sequence, 19–615) along with Zinc metal ion and three *N*-Acetyl-D-Glucosamine molecules in the prepared structures.

Active site prediction

Binding pockets in RBD and ACE2 were identified using Active Site Prediction Server (Singh et al. 2011) (https://www.scfbio-iitd.res.in/dock/ActiveSite.jsp). Server predicts multiple cavities and classifies them according to their sizes. For each cavity, surrounding residues at proximal distance (10 Å) are listed with their numbers, coordinates and participating atoms in interactions.

Molecular docking

Peptide-protein and protein–protein dockings were employed in the study. Initially, peptides were docked with spike protein RBD and ACE2 using COVID-19 Docking Server (Kong et al. 2020). This server uses CoDockPP docking algorithm (Kong et al. 2019) for peptide and antibody docking. For each job, server predicts 10 best models. Hence, screening of 70 peptides with RBD and ACE2 gave 700 models for each target. Among the 700 peptide-RBD models, the model in which peptide binds at the RBD surface that is responsible for ACE2 binding, were selected. Same protocol was used for Peptide-ACE2 models and best model based on its docking score for each target was chosen for further protein–protein docking. To investigate the effect of peptides on RBD-ACE2 binding, the best models of peptide-RBD and peptide-ACE2 were docked with ACE2 and RBD respectively using template-based docking at HDOCK web server (Yan et al. 2020a) available at https://hdock.phys.hust.edu.cn/. In HDOCK, docking score is not a true binding energy but, it gives relative scores of predicted models. Docking of RBD and ACE2 was also performed on same server and results were compared with the peptide embedded complexes. Peptide-protein and protein–protein interactions of complexes were investigated using PDBePISA web tool (https://www.ebi.ac.uk/msd-srv/prot_int/cgi-bin/piserver).

Results and discussion

Peptide-protein docking

Binding between spike RBD and ACE2 can be inhibited using small molecules (Zhou et al. 2020), peptides (Han and Král 2020; Xia et al. 2020) and neutralizing antibodies (Zhou and Zhao 2020). Recent experimental study shows that natural antimicrobial peptide, Human Intestinal Defensin 5 (HD5) secreted by intestinal Paneth cells significantly inhibits the interaction between ACE2 and RBD at higher concentration when it was preincubated in the bioassay (Wang et al. 2020). SARS-CoV-2 spike protein fragment, Tyr-Lys-Tyr-Arg-Tyr-Leu (Sequence length, 438–443), hexapeptide has been identified as an inhibitor for the ACE2 and RBD interactions as determined from the experimental as well as theoretical study (Peter and Schug 2020). Additionally, spike protein RBD inhibitory peptides have been designed and studied elsewhere (Baig et al. 2020; Chatterjee et al. 2020; Zhang et al. 2020). Here, we used large peptides to bind RBD and ACE2 to hinder the formation of RBD-ACE2 complex. Binding affinity of modelled peptides with spike RBD and ACE2 was determined computationally using molecular docking tools. Structures of modelled peptides and their docking scores with RBD and ACE2 are given in Fig. S1 and Table S1 respectively.

Active site prediction results show that RBD has one large cavity (1024 $Å^3$) and seven cavities are located on the site where ACE2 binds (Table S2) whereas, in ACE2, three cavities on the RBD binding site along with main cavity (3037 $Å^3$) were observed near α1 and α2 helices and it is approximately three times bigger than the RBD main pocket (Table S3). It was seen that peptides have stronger binding tendency towards ACE2 in comparison with spike RBD. Figure 2e indicates that the docking scores of peptide-RBD

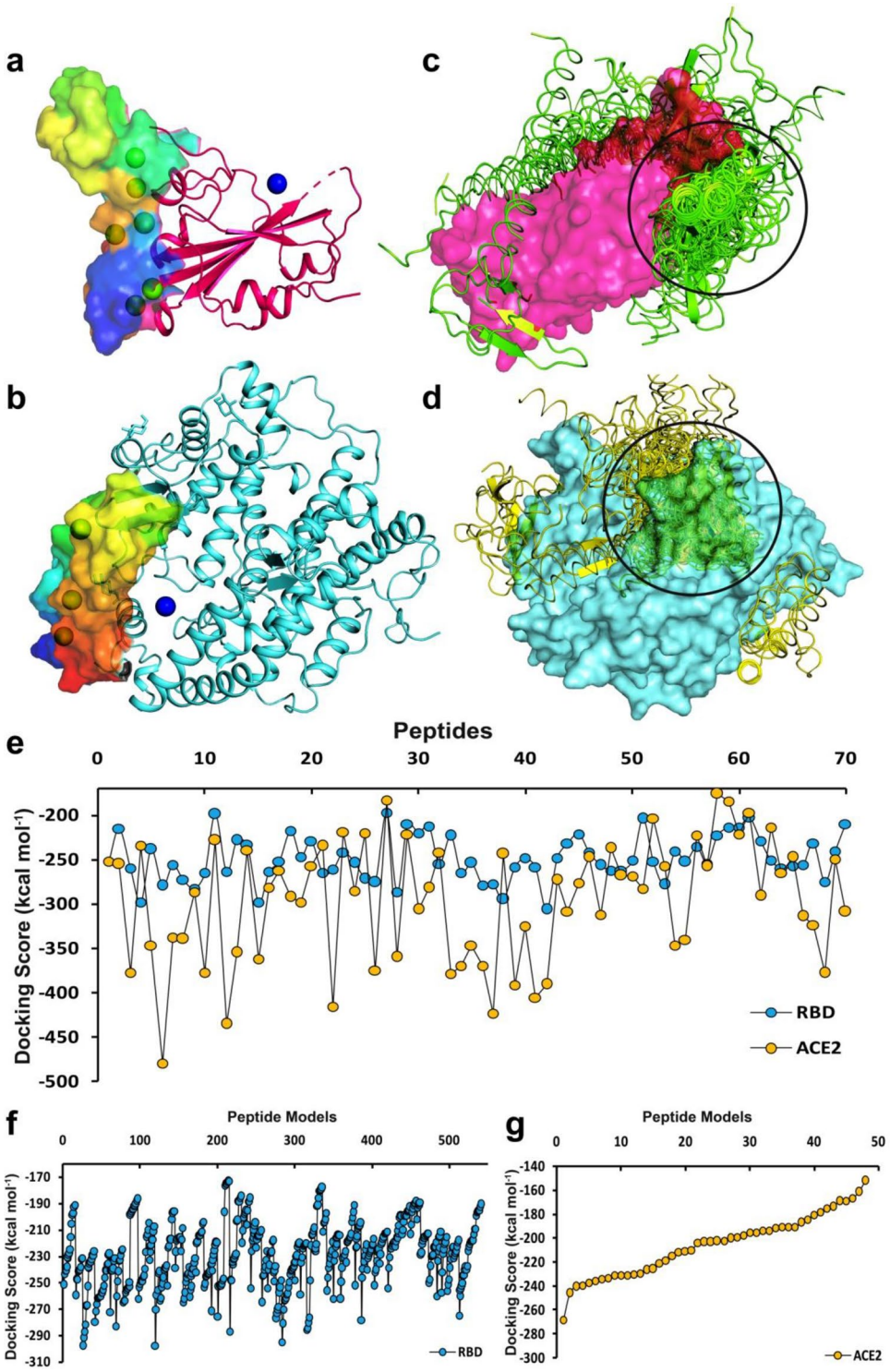

Fig. 2 **a**, **b** Binding cavities of RBD and ACE2 respectively, green sphere- cavity on interface, blue sphere- largest cavity, rainbow surface- RBD or ACE2 binding Interface. **c**, **d** Peptide-RBD and peptide-ACE2 models respectively, black circle indicates the site where most of the peptides are bound. **e** Docking scores of top 70 peptide-RBD and peptide-ACE2 models. **f**, **g** Docking scores of peptide-RBD and peptide-ACE2 models respectively in which peptide is attached at the RBD or ACE2 binding interface

complexes fall under the range of approximately − 200 to − 300 kcal mol^{-1} while for peptide-ACE2 complexes, the range is − 160 to − 480 kcal mol^{-1}. This major difference in docking scores is observed due to ACE2 having a big void, where most of the peptides bind in comparison with small void of RBD. Thus, it is possible that peptides can still block the functions of ACE2 by incorporating steric hindrance in the overall structure without binding to the RBD locus of ACE2. Both targets have multiple binding sites but in RBD, surprisingly, it was observed that peptides mainly bind at the surface (Fig. 2c) which is responsible for ACE2 binding. However, in ACE2, peptides positioned themselves in the core part of the target (Fig. 2d) unlike in RBD. Considering multiple binding sites in RBD, its ACE2 binding site has

large cleft that is formed by multiple binding sites (Fig. 2a) which contains all the hydrophilic and hydrophobic residues except His and Met at the10 Å proximity. It has also another large cavity (1024 $Å^3$) that is surrounded with all the amino acid residues except Gln and Met. Furthermore, ACE2 has three small binding pockets between α1 and α2 helices on its RBD binding surface (Fig. 2b).

To block the RBD and ACE2 binding, peptide should be on the surface of either RBD or ACE2. Hence, we looked at total 1400 docking models (700 of each) of peptide-RBD and peptide-ACE2 in PyMOL (Schrodinger 2010) and unexpectedly found that ACE2 has only 48 models in which peptides are present on the RBD binding interface while, there were 541 models of peptide-RBD in which peptides are located on the ACE2 binding site. Docking scores of 541 of peptide-RBD and 48 of peptide-ACE2 models are represented in Fig. 2f, g and given in Table S4 and S5. Docking results suggest that peptides have higher affinity (− 297 to − 173 kcal mol^{-1}) for RBD at the ACE2 binding site than the RBD binding site of ACE2 (− 267 to − 152 kcal mol^{-1}). Here, it is a good indication that peptides will prefer spike RBD of virus over human ACE2 to bind and that can be considered more beneficial way to block the virus entry into the human cells. Table 1 shows the peptide-protein and protein–protein docking results of best models of studied complexes. The best model of each, AVP0671-RBD_1 (D1) from peptide-RBD and AVP1244-ACE2_6 (D2) from peptide-ACE2 models was selected for further protein–protein docking analysis based on its highest docking score among all models (D1 model: − 297.98 kcal mol^{-1}, D2 model: − 267.85 kcal mol^{-1}).

In D1, interface interaction analysis shows that peptide forms hydrogen bonds and salt bridge with RBD. It mainly binds through hydrogen bonds to the RBD. The number of interacting residues in D1 is higher than the residues in D2. It was noted that hydrogen bonds and salt bridges contribute equally to the interactions in D2. Figure 3a and b illustrate the docking of peptide with RBD and ACE2 respectively whereas, docking between RBD and ACE2 is shown in Fig. 3c. Additionally, some proximal interface interactions in D1, D2 and D3 are shown in Fig. 3. Total number of interactions in D1, D2 and D3 is given in Table S6 and S7.

It was observed that AVP0671 peptide interacts with Asn487, Gly496 and Tyr505 residues of RBD which form hydrogen bonds with ACE2 at the interface while, AVP1244 peptide forms hydrogen bond with Glu37 and salt bridges with Arg393 residues of ACE2 which interact with RBD at the interface. From these results, peptides turned out to be a huge barrier between the ACE2 and RBD interface during virus entry since their strong interactions with interface residues are responsible for binding to both the targets. Hence, these peptides block the RBD and ACE2 residues which are responsible for their interface interactions.

Protein–protein docking

To investigate how peptides hamper the RBD and ACE2 binding, protein–protein docking of peptide embedded models, D1 and D2 with ACE2 and RBD respectively was performed using HDOCK tool. For the structural comparison between complexes, RBD and ACE2 were also solely docked using same server. Docked D3 complex was superimposed with experimentally derived structure (PDB: 6M0J) and it was found that docked structure slightly deviates (RMSD: 0.417 Å) from the experimental structure (Fig. S2). Protein–protein docked complexes of

Table 1 Docking score and interactions for peptide-protein and protein–protein complexes of peptides, RBD and ACE2

Complex	Code	Docking Score (kcal mol^{-1})	RMSD (Å)	Number of interacting residues		Interface area ($Å^2$)	Bonds		
							[a]N_{HB}	[b]N_{SB}	[c]N_{DS}
Peptide-protein docking									
				Peptide	RBD/ACE2				
AVP0671-RBD_1	D1	− 297.98	–	24	31	958.3	8	1	0
AVP1244-ACE2_6	D2	− 267.85	–	17	28	815.0	4	4	0
Protein–protein docking									
				RBD	ACE2				
RBD-ACE2	D3	− 349.50	00.34	27	30	960.3	19	3	0
AVP0671-RBD_1:ACE2	T1	− 242.70	168.91	35	30	957.2	10	10	0
AVP1244-ACE2_6:RBD	T2	− 292.75	69.17	35	33	1114.8	14	0	0

[a]Number of hydrogen bond

[b]Number of salt bridge

[c]Number of disulfide bond

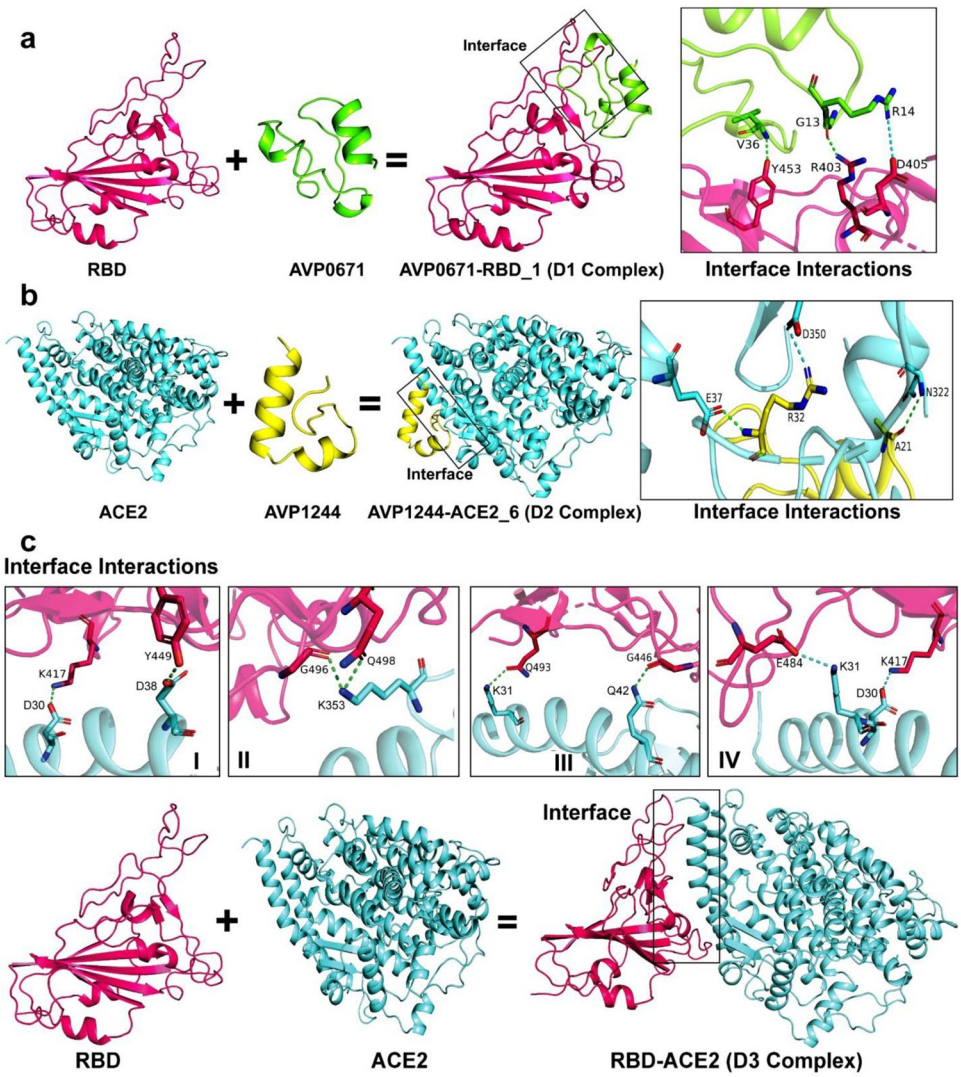

Fig. 3 **a** Spike protein RBD and AVP0671 docked structure and its interface interactions. **b** Human cell receptor ACE2 and AVP1244 docked structure and its interface interactions. **c** Protein–protein docked structure of RBD and ACE2 and its interface interactions (I–II) Hydrogen bond interactions (III–IV) Salt bridge interactions. In interactions, green and cyan colors indicate the hydrogen bonds and salt bridges respectively

RBD (AVP0671-RBD_1:ACE2, T1) and ACE2 (AVP1244-ACE2_6:RBD, T2) were compared with RBD-ACE2 complex (RBD-ACE2, D3).

Interestingly, D3 docking score was observed higher (-349.50 kcal mol^{-1}) compared to the docking scores of T1 (-242.70 kcal mol^{-1}) and T2 (-292.75 kcal mol^{-1}) complexes which indicates that peptides are playing a notable role to disrupt the RBD and ACE2 binding. Details of docking analysis and interface interactions are shown in Table 1. In D3, RBD and ACE2 strongly interact through hydrogen bonds and salt bridges. There are 22 interactions observed between RBD and ACE2 interface. Tyr, Asn and Gly residues from the RBD and Lys, Asp and Tyr residues from the ACE2 have major contribution to the interface interactions. Lys417, Gly446, Tyr449, Asn487, Gln493, Gln498, Thr500, Asn501, Gly502 and Tyr505 residues from RBD and, Gln24, Asp30, Lys31, Glu35, Glu37, Asp38, Tyr41, Gln42, Tyr83, Asn330, Lys353 and Arg393 residues from ACE2 at the RBD and ACE2 interface in D3 were also reported in previous studies (Han and Král 2020; Lan et al. 2020; Yan et al. 2020b). The number of hydrogen bonds was identified significantly higher than that of salt bridges between RBD and ACE2.

Total six interactions (Asn487- 3, Gly496- 1 and Tyr505- 2) of RBD with ACE2 and two interactions (Glu37- 1, Arg393- 1) of ACE2 with RBD are inhibited due to peptide embedding to the RBD and ACE2. Protein–protein docking reveals significant role of the peptides in the inhibition of RBD and ACE2 binding. Peptides in T1 and T2 complexes significantly deflect the position of binding sites of RBD and ACE2 from their actual binding observed in D3 complex. Figure 4 shows the docking complexes of peptide embedded RBD and ACE2 (T1 and T2), their interactions and superimposed structures of T1 and T2 with D3. In the case of T1, equal number of interactions (Hydrogen bonds- 10, Salt bridges- 10) were identified while 14 hydrogen bonds were observed in T2 between RBD and ACE2. Interface interactions between

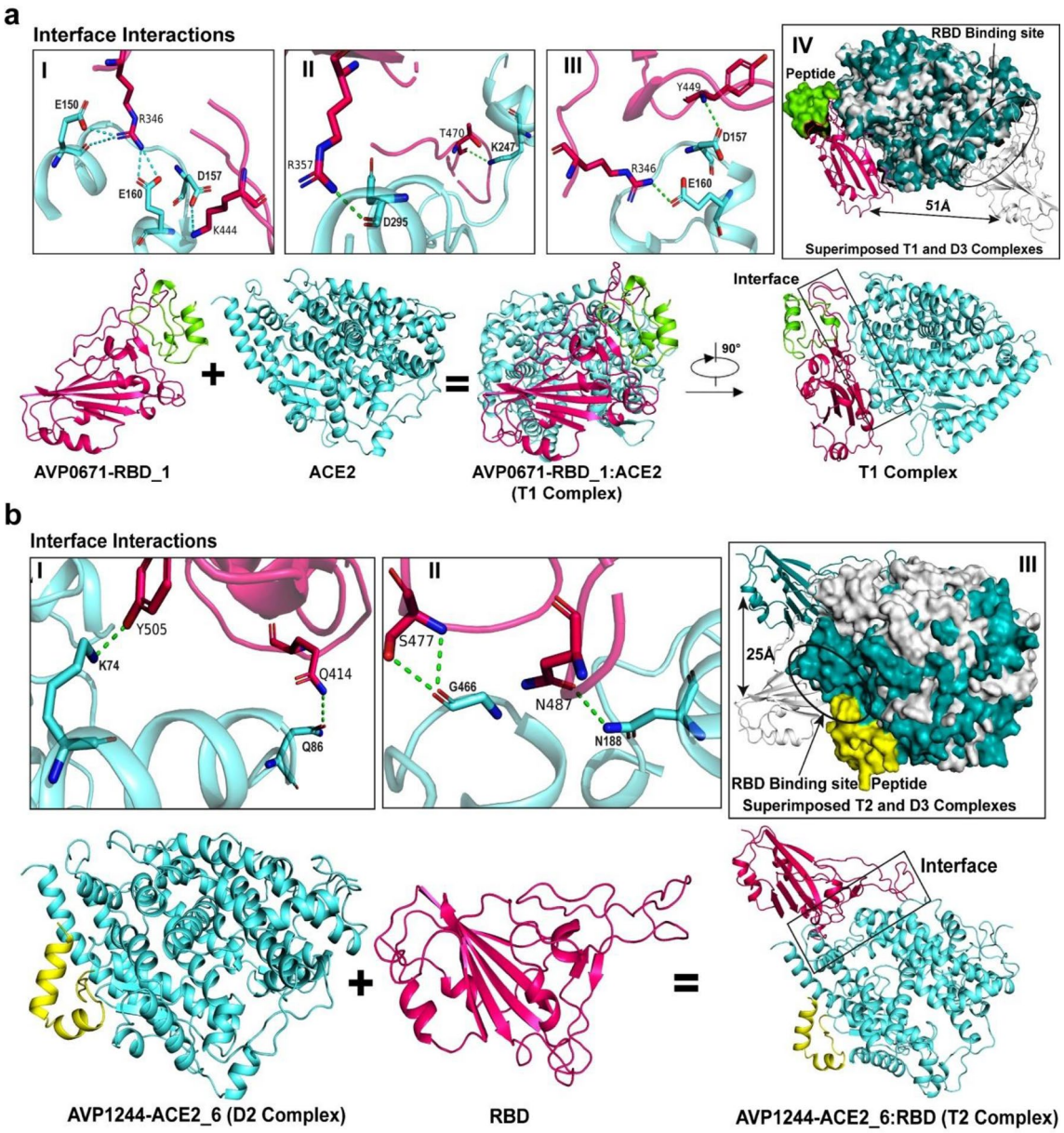

Fig. 4 Protein–protein docking structures of peptide embedded RBD and ACE2 and their interface interactions. **a** Docking between AVP0671-RBD_1 (D1) and ACE2 (I) Salt bridge interactions (II–III) Hydrogen bond interactions (IV) 3D superimposed structure of T1 and D3. **b** Docking between AVP1244-ACE2_6 (D2) and RBD (I–II) Hydrogen bond interactions (III) 3D superimposed structure of T2 and D3. In superimposed structures, D3 is illustrated in white color

RBD and ACE2 in T1 and T2 complexes are indicated in Table S7. In D2, peptide nearby β3 and β4 sheets of ACE2 shifts the position of coming RBD from its main binding site (α1 and α2 helices). Superimposed structures (3D structure alignments) support that peptide attached to RBD in T1, remarkably changes the binding position of ACE2 on RBD surface. RMSD was found 0.422 Å and the distance between T1 RBD and D3 RBD was observed 51 Å. Meanwhile, RMSD of structurally aligned T2 and D3 was found 15.443 Å and distance between RBDs in T2 and D3 was noticed 25 Å which is half of the distance observed (51 Å) between RBDs of T1 and D3. Protein–protein docking gives clear insight into molecular interactions between RBD and ACE2 and how these interactions are blocked by peptides. Hence, these findings suggest that highly selective and efficacious peptides might be a weapon against various deadly diseases in future therapeutics.

Conclusion

In this article, we used computational tools to model peptides from their sequences and the peptides were screened against ACE2 and SARS-CoV-2 RBD domain utilizing molecular docking study. From the peptide-protein docking results, it was observed that peptides have stronger tendency towards ACE2 over RBD. However, in around 77% models of peptide-RBD, peptides are situated on the ACE2 binding site of RBD whereas, only in 7% peptides-ACE2 models, peptides are located on the RBD binding site of ACE2. Thus, results drive us to significant conclusion. To further investigate the influence of peptides on binding of RBD with ACE2 or the inhibitory mechanism of peptides on this binding, protein–protein docking approach was used. From the docking results, it was observed that peptides remarkably deflect the position of RBD and ACE2 from their actual binding mode and which further stops the viral fusion with human cells. Docking results unveil the potency of peptides for target protein (RBD and ACE2) binding and build a strong foundation for peptides in COVID-19 therapeutics computationally. Thus, from our findings, we confidently state that peptides might be a possible option for the treatment of COVID-19 and can be pursued to the final step of the drug development after experimental evidences.

Author contributions SBR and PBP drafted the manuscript. SBR, PBP and MFM did literature review, designed the study and analyzed the data. SBR and PBP retrieved peptides from the database and modelled them. LBP and KNP carried out peptide-protein docking. NC performed protein–protein docking. All authors helped to prepare tables and figures. All authors read the final manuscript and approved it.

Compliance with ethical standards

Conflict of interest The authors have declared no conflict of interest.

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