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REVIEW

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Peptides and peptidomimetics as therapeutic agents for Covid-19

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Abstract

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) Covid-19 pandemic has caused high morbidity and mortality rates worldwide. Virus entry into cells can be blocked using several strategies, including inhibition of protein-protein interactions (PPIs) between the viral spike glycoprotein and cellular receptors, as well as blocking of spike protein conformational changes that are required for cleavage/activation and fusogenicity. The spike-mediated viral attachment and entry into cells via fusion of the viral envelope with cellular membranes involve PPIs mediated by short peptide fragments exhibiting particular secondary structures. Thus, peptides that can inhibit these PPIs may be used as potential antiviral agents preventing virus entry and spread. This review is focused on peptides and peptidomimetics as PPI modulators and protease inhibitors against SARS-CoV-2.

KEYWORDS
Covid-19, peptides, peptidomimetics, protein-protein interaction, SARS-CoV-2

1 | INTRODUCTION

A novel zoonotic beta coronavirus related to bat coronaviruses crossed humans in the Chinese city Wuhan in the late quarter of 2019.[1–4] Infection with this novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), results in coronavirus disease (Covid-19), which is causing extreme hardship and havoc worldwide as a global pandemic.[5,6] SARS-CoV-2 can infect the respiratory, gastrointestinal, hepatic, and central nervous systems of humans, livestock, birds, bats, mice, and many other wild animals.[7,8] This virus was named SARS-CoV-2 owing to its similarities with the previous SARS CoV discovered in 2003.[5] SARS-CoV-2 hijacks the host cell machinery after infection and replication in infected cells involving viral attachment, fusion, penetration, uncoating, transcription, translation, and ultimately release of infectious virions. As a result, more than 178 million people have been infected, with nearly 3.85 million deaths worldwide due to Covid-19 as of June 2021. Hence, the need for a variety of effective therapeutics against this virus to curtail this epidemic and provide efficient therapeutic modalities for the emergence of SARS-CoV-2 variants that may resist existing vaccine approaches.

At present, there are no specific drugs approved against SARS-CoV-2 infection, but several vaccines have been approved for emergency use to prevent the severe infection of the virus, including Pfizer-BioNTech, Moderna RNA-based vaccines, and adenovirus vector-based vaccines of AstraZeneca and Johnson and Johnson companies.[9–12] The currently available antiviral drug remdesivir is approved for emergency use, and several other antiviral drugs are under investigation.[13] Since the virus enters the host system by attaching to particular cell receptors followed by uncoating, reverse transcription, transcription, and translation, there are several strategies for targeting the infection at any of these viral replication steps.

The spike (S) glycoprotein consists of an N-terminal S1 subunit (700 amino acids) and a C-terminal S2 subunit (600 amino acids). The S1/S2 subunits form a trimeric S protein. SARS-CoV-2 binds to the human angiotensin-converting enzyme-2 (ACE2)[14] via the S glycoprotein.[15,16] The S1 subunit contains a receptor-binding domain (RBD). The binding of the spike RBD domain to the ACE2 receptor triggers a large change in the conformation of the S protein. Subsequent cleavage of the S by a cellular membrane-bound protease exposes the hydrophobic fusion peptide (FP) to the apposed

membrane. The FP induces the formation of a six-helix bundle causing fusion of the viral envelope with cellular membrane and entry of the nucleocapsid into the cytoplasm of infected cells.[17–19]

Virus entry into cells can be blocked using several strategies, including inhibiting host-receptor protein-protein interactions (PPIs), and blocking the required for function change in conformation of the helix bundle, FPs, or protease inhibitors that inhibit cleavage/activation of the S glycoprotein. Virus entry by fusion of the viral envelope with cellular membranes involves PPIs mediated via short peptide fragments with particular secondary structures. Therefore, peptides that can target these PPIs can be used to modulate/inhibit the entry of the SARS-CoV-2 virus into the host cell. Previous studies have indicated that peptides could be used as fusion inhibitors of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection.[20] Furthermore, during viral entry, proteolytic cellular enzymes cleave part of the S protein resulting in conformational changes of the helical bundles of the spike fusion region that increase S-mediated membrane fusion. Thus, enzymes that cleave the S protein serve as additional targets for peptide antagonists. Several peptides have already been designed based on the PPI domain of the ACE2 receptor and the fusion domain of the S glycoprotein. In this review, we will cover structural aspects of the S protein, PPI of the S protein, and its interaction with ACE2, peptides designed to modulate the intra and inter PPI, as well as selected protease inhibitors. Other known antiviral agents are also discussed as possible therapeutic agents for Covid-19.[13] This review covers recent developments of peptides and peptidomimetics as PPI inhibitors between SARS-CoV-2 receptor and ACE2, heptad repeat 1 (HR1), and heptad repeat 2 (HR2) region. Apart from PPI inhibition, peptides directly or indirectly acting on the host proteases and viral proteases, which have the potential to be developed as antiviral agents against Covid-19, are also discussed. We believe that with several advances in peptide-based drug design and nearly 60 peptide drugs on the market and another 150 in clinical trials,[21] it is time to cover peptides that have been developed and tested for Covid-19.

Although PPI sites are most suitable for targeting peptides, recent literature related to infection and spread of SARS-CoV-2 in different geographical locations has suggested that the RBD region of the S protein undergoes mutation to escape neutralizing antibodies.[22,23] Therefore, caution should be used in the design of peptides or other drugs. We have included the structural and functional aspects of this S mutation. This review is important because it provides information on recent developments in peptides and peptidomimetic design for SARS-CoV-2 infection. Since this is an ongoing and evolving disease with many antiviral approaches being studied continuously, our review is restricted to the currently available information.

2 | PEPTIDES AND PEPTIDOMIMETICS

Linear peptides, cyclic peptides, grafted peptides, and modified peptides (peptidomimetics) have been designed for PPI inhibition in various diseases, including cancer and autoimmune diseases. Linear peptides suffer from low stability in serum and gastrointestinal (GI) tract due to cleavage/inactivation by cellular proteases. Hence, techniques such as cyclization, grafting of peptides to a stable framework (cyclotides), and chemical modification of peptides are necessary to increase stability. Peptides are modified by N and C terminal

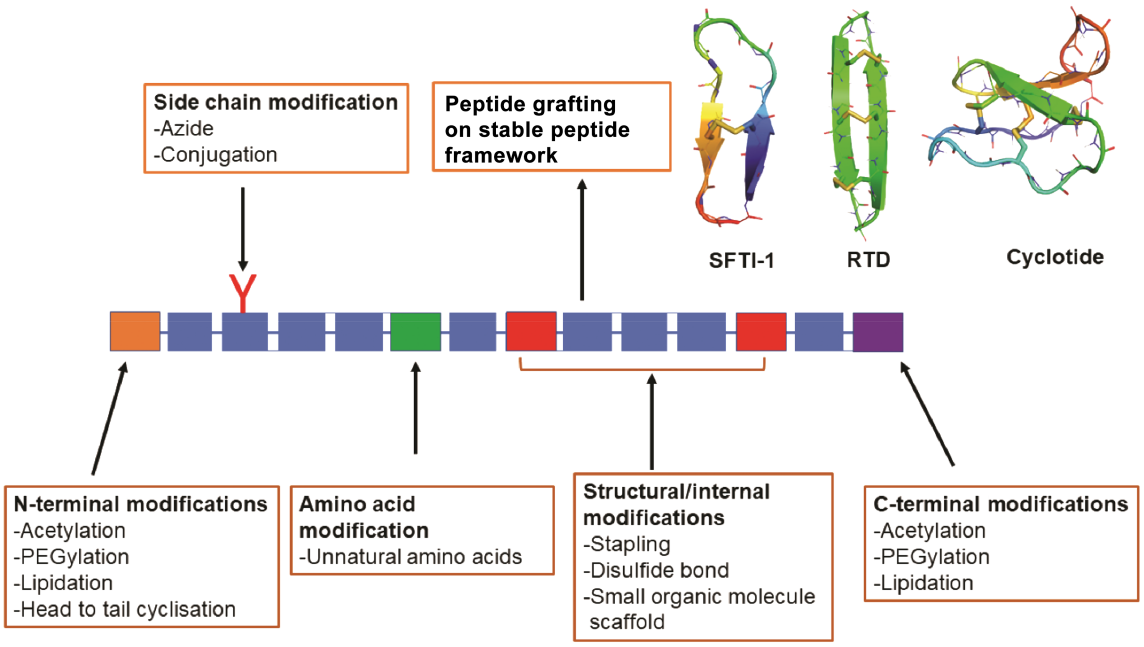

FIGURE 1 Schematic diagram of different peptide modification approaches. The structure of peptides was generated using PyMol software (Schrodinger LLC). SFTI-1 (PDB ID: 1JBL), RTD (PDB ID: 2M77), Cyclotide Kalata B1 (PDB ID: 1NB1), cysteine residues, and disulfide bonds are shown in yellow

modification, cyclization, stapling, modification of peptide bond, change in the chirality of amino acids, substitution by unnatural amino acids and small molecules scaffolds (peptidomimetic), and grafting to a stable framework of natural cyclotides like Kalata B1, or other stable frameworks such as sunflower trypsin inhibitor (SFTI)[24–26] (Figure 1). These approaches significantly enhance stability and increase the resistance of peptides to proteolytic degradation improving both the bioavailability and pharmacokinetic parameters.

Peptidomimetics are generally obtained from slight modifications of either backbone or side chain on a parent peptide by the inclusion of an unnatural amino acid, modifications of the peptide bond, replacement by small molecular scaffold, and sometimes by non-peptide templates topologically similar to the parent peptide. Peptidomimetics exhibit increased rigidity in structure, improve target specificity, stability, and cell membrane permeability.[27]

Traditionally peptidomimetics have been classified into three subtypes: type I, type II, and type III.[28,29] These classifications were found to be ambiguous in including all the different classes of modified peptides, and hence, Grossmann *et al*. proposed a new classification of peptidomimetics based on the degree of their similarity to their natural peptide precursor.[30] The revised classification includes four different classes: Classes A-D, where Class A shows the highest similarity, and D showing the least to parent peptide.[31,32]

3 | PPI AS BIOLOGICAL TARGET—CHALLENGES AND PERSPECTIVES

Advancement of structural and computational biology has significantly increased our knowledge of PPI interfaces, and has aided in the design of several peptides as lead molecules that can specifically target PPI.[33] Various strategies and techniques have facilitated the design and discovery of peptides as PPI modulators, including phage display, high throughput screening, computational studies, and structure-based design.[34–36] Targeting the abnormal and aberrant PPIs is of great clinical importance, but it has been a significant challenge to target and regulate specific PPIs. Historically, PPIs are considered as unattractive targets for drug discovery, less than 0.01% of the PPIs have been targeted with an inhibitor.[37] The nature of the PPI surface makes it a very difficult site to target, and unlike conventional drug targets such as enzymes and ligand binding sites of G protein-coupled receptor (GPCR), most of the binding surfaces between proteins are usually large 1500 to 3000 $Å^2$ involving many polar and hydrophobic interactions. Along with that flat nature of the binding interface with no definite binding cavity, PPI inhibition is challenging since the binding surface is not well defined like small molecule binding surfaces.[38] Hence, targeting PPIs with small molecules with high specificity has been incredibly difficult. Due to the diverse nature of PPIs, a thorough and detailed knowledge of the interaction at the molecular level is required for a successful drug design and discovery approach.[39] The drug discovery process has taken a significant leap in targeting difficult PPI sites, and scientists have successfully targeted so-called "undruggable sites" with the help of advanced drug screening techniques and rational drug design.[40] Recent advances in structure-based drug design have led to the identification and prediction of binding surface between the proteins, and molecular details of binding, including the key amino acids that dominate PPI binding sites. The key residues that determine the fate of PPI are termed as "hot-spot" residues. Specific and selective modulation of PPI can be achieved by the study of these key residues and by the nature and role of their interactions in mediating binding.[41] Analysis of the PPI binding sites has shown that 15% to 40% of PPIs are mediated by short linear peptides.[42] Small synthetic molecules, peptides, and proteins are designed to specifically target PPIs. Each class of these targeting agents has advantages and disadvantages regarding efficacy, specificity, bioavailability, and synthesis process. Targeting PPIs with peptides and peptidomimetics that can bind to hot spot regions of the binding interface are studied extensively.[38,43] Certain PPIs that are sufficiently exposed can be effectively targeted with specific antibodies; however, antibodies generally cannot bind to intracellular PPIs and deeply embedded PPIs, while antibodies also have substantial stability issues. Peptides and peptidomimetics are explored as simple and effective alternatives for targeting PPI as they have high affinity and specificity.[44–46]

4 | SARS-COV-2 VIRUS: STRUCTURE

The virion particle contains the Spike glycoprotein (S), an envelope protein (E), membrane protein (M), and the nucleocapsid protein (N), which are structural proteins that form the viral particle[47] (Figure 2). Each of these proteins possesses specific functions. S forms the crowns on the surface of the viral envelope and has important roles in viral entry through receptor recognition and membrane fusion of the viral envelope with cellular membranes.[48] The E protein has a major role in assembly, budding, envelope formation, and virulence. The M protein is involved in viral assembly, and the N protein packages and protects the viral RNA genome forming the ribonucleoprotein complex.[47] Among these structural proteins, the S glycoprotein has been a major focus of research for the discovery of therapeutics and vaccines for Covid-19 that interfere with viral entry and spread since it is the principal protein involved in virus entry and a target of the immune system.

The S glycoprotein is a transmembrane protein with 1200 to 1400 amino acid residues, which mediates the SARS-CoV-2 virus entry to host cells by recognizing and attaching to specific host receptors present on the surface of the cells and mediating fusion of the viral envelope with cellular membranes. S binds to the ACE2 receptor mediating the viral entry to the cells.[49] S is present as a homotrimer in its functional form, S-protein in its monomeric unit is composed of two subunits S1 and S2. The S1 subunit is involved in host recognition, whereas the S2 subunit guides the fusion of the virus to the host cell membrane. The S1 subunit consists of the N-terminal domain (NTD), RBD, and C-terminal domain (CTD). RBD is responsible for host receptor recognition and helps in the interaction of S protein to ACE2 receptor. Within RBD, a region directly interacts with the ACE2 receptor called the receptor-binding motif (RBF). The S2 domain

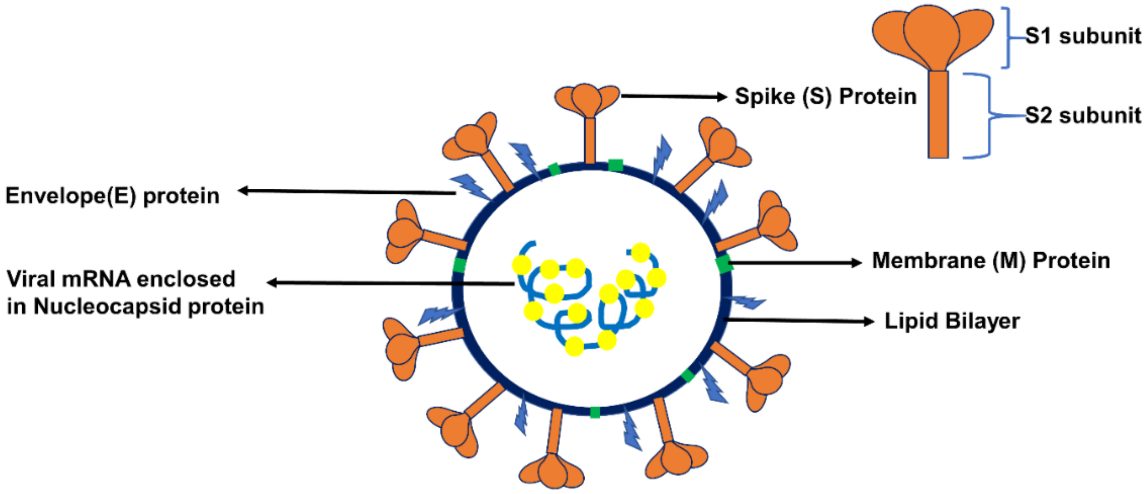

FIGURE 2 SARS-CoV-2 with structural and nonstructural proteins and genomic elements

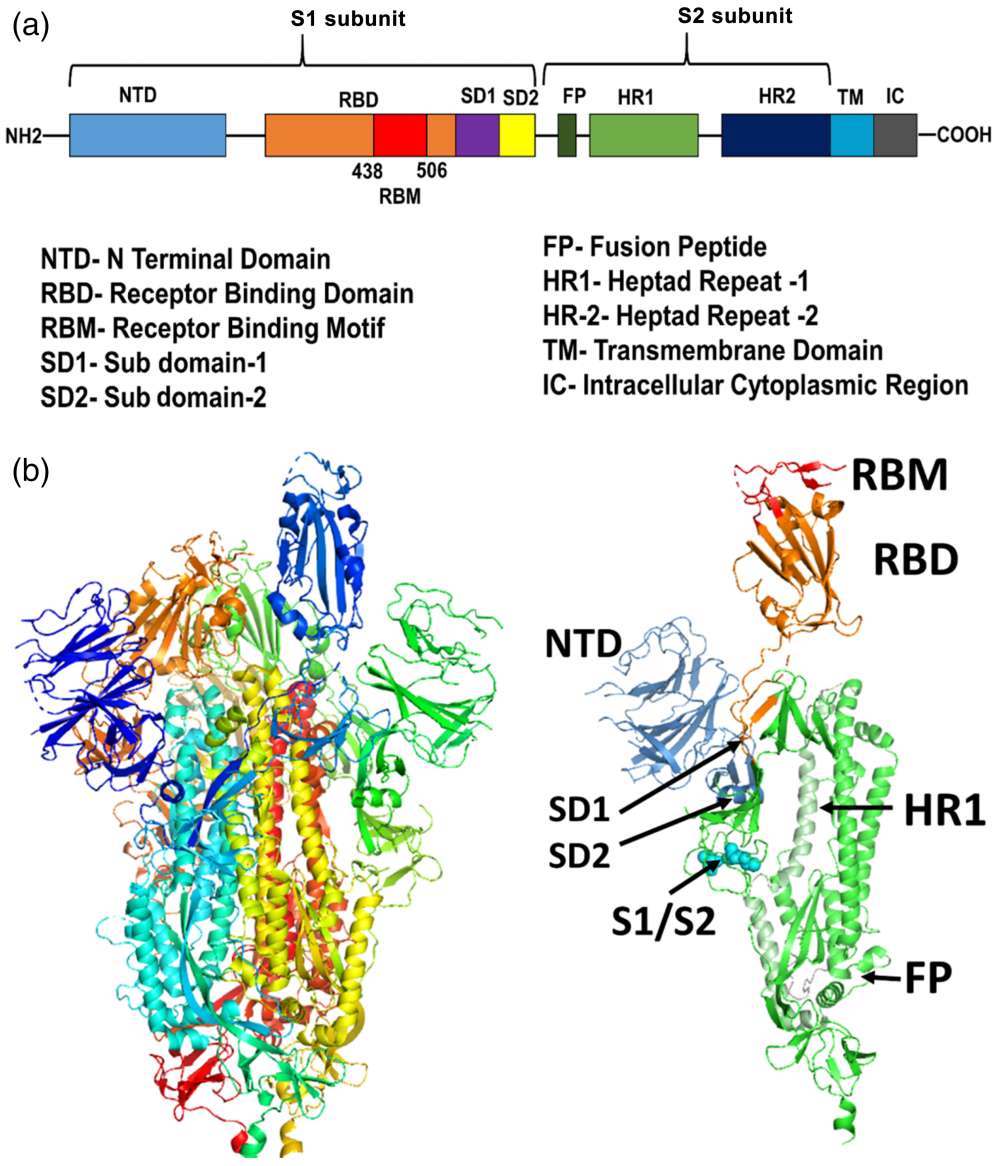

FIGURE 3 (A) Schematic representation of different regions of the monomer of the Spike (S) glycoprotein of SARS-CoV-2. (B) S homotrimer of SARS-CoV-2 (PDB ID: 6VSB) and monomer with different regions of S labeled. Schematic diagram generated based on the structural data available[17,50,51]

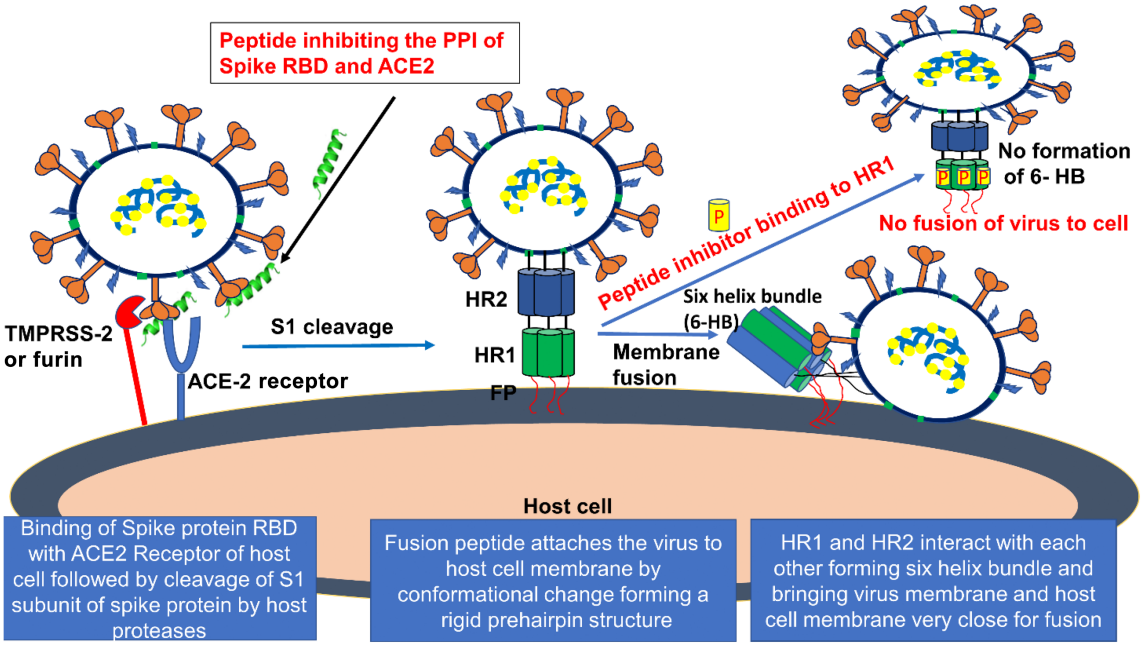

FIGURE 4 Membrane fusion process of SARS-CoV-2 with host cell membranes and approaches of peptide inhibitors for the SARS-CoV-2-mediated membrane fusion with cellular membranes

consists of a C-terminal transmembrane domain, which attaches the S glycoprotein to the virus membrane. The S2 subunit also consists of the FP, HR1, and HR2 regions. S1 and S2 are divided by cleavage sites S1/S2[17] (Figure 3).

The S glycoprotein is a homotrimeric fusion glycoprotein present as large protrusions on coronavirus surfaces that undergo drastic conformational changes for receptor recognition, membrane fusion, and cell entry.[17,50,52] The prefusion structures of S protein of SARS-CoV-2 have been widely researched and studied using crystal and cryogenic electron microscopy (cryo-EM) methods of structure determination in the quest to provide scientists a platform to develop vaccines and therapeutics targeting S protein.[17,52–56] In the prefusion state of S-glycoprotein, the RBD remains at the top of the trimeric S above the fusion core, and the nature of the RBD conformation depends upon S conformational changes. In the closed prefusion states, all the three RBD of the trimeric S glycoprotein remains flat on the S surface (down conformation), hindering the receptor binding site, whereas, in the open prefusion state, one RBD on up conformation exposes the receptor binding site to aid the recognition and binding of the virus to host ACE2 receptor.[49,50,52,54] This is a critical step for viral-host recognition, binding, and cellular entry (Figure 4). Receptor binding of the S-protein to ACE2 is followed by a structural transition to the postfusion form of S-glycoprotein.[54]

4.1 | PPI of ACE2 and RBD of S-protein of SARS-CoV-2 interaction

X-ray crystallographic, as well as cryo-EM structures of SARS-CoV-2 S-glycoprotein-ACE2 complex, revealed that S-trimer binds to ACE2 receptor through the RBD domain with only one RBD domain in up conformation, while the other two remain in the down conformation. Studies suggested that one of the RBD domains in the homotrimer S-protein must be in the up conformation for binding with ACE2 receptor.[17,50,57,58] Studying this interaction between RBD and ACE2 receptors can lead to the discovery of therapeutics like peptides and peptidomimetics using a rational drug design approach (Figure 5). SARS-CoV-2 RBD interaction involves a twisted five stranded antiparallel beta sheets (β1, β2, β3, β4, and β7) with short connecting helices and loops forming the core of RBD. The region containing the short β5 and β6 strands, α4 and α5 helices, and loops in between β4 and β7 strands is called RBM. RBM contains the majority of the contacting residues of SARS-CoV-2 that interacts with ACE2.

ACE2 interacts with the SARS-CoV-2 RBD with its N-terminal peptidase domain. The NTD of ACE2 consists of two lobes with the peptide substrate binding site between them. The N-terminal helix of ACE2 is located within the concave outer surface of RBM, while the extended RBM in SARS-CoV2 RBD interacts with the small lobe of ACE2. A total of 19 to 20 residues of ACE2 are in contact with 17 to 19 residues of the SARS-CoV-2 RBD, and most of the contacting residues reside in the N-terminal helix of ACE2.[55,57] Hydrophobic and hydrophilic interactions such as hydrogen bonds and salt bridges are involved in the binding of RBD with ACE2. The SARS-CoV-2 RBD-ACE2 interface has 13 hydrogen bonds and two salt bridges. In addition, the T470-F490 loop and Q498-Y505 within RBD are key contacting elements forming several aromatic interactions with ACE2.[57] Identification of the key residues in the PPI interface of ACE2 and SARS-CoV-2 and their importance in binding to form a stable complex of proteins is important in designing specific inhibitors. Xu *et al.* in their study demonstrated through mutagenesis that residues

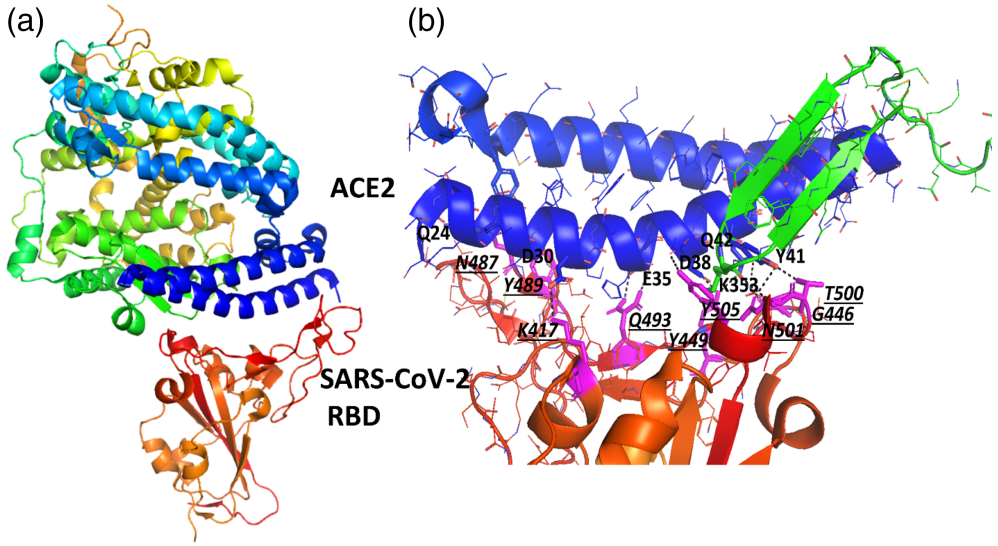

FIGURE 5 (A) ACE2 and SARS-CoV-2 RBD interaction. N-terminal helix of ACE2 (blue) interacts with SARS-CoV-2 RBD. (B) Key interacting residues between the receptor-binding motif (RBF) of SARS-CoV-2 and the ACE2 receptor (PDB ID: 6M0J). Single-letter amino acid code is used for labeling. Residues labeled in italics and underlined are amino acid residues from the RBD region of SARS-CoV-2

(470-TEIYQAGST-478) of RBM compose a critical region of RBD for specific recognition of SARS-CoV-2 RBD by the ACE2 receptor. Also, the single point mutation Y505A of RBD leads to the complete abolishment of binding of SARS-CoV-2 RBD to ACE2, making it one of the most critical residues for binding to ACE2 receptor.[57]

4.2 | Design of peptide and peptidomimetics for inhibiting SARS-CoV-2 binding to ACE2

Interaction between the S RBD domain and the ACE2 receptor has been extensively studied by cryo-EM, X-ray crystallography, and computational methods providing valuable insight for discovering the therapeutics for Covid-19.[17,55,56] Zhang *et al*., through molecular dynamics simulation based on the cryo-EM structure of SARS-CoV-2 RBD and ACE2 complex, demonstrated that the ACE2 peptidase domain (PD) α1 helix is important for binding the RBD. Based on this idea, they designed and synthesized the natural 23-mer peptide SBP1 composed entirely of proteinogenic amino acids from the human ACE2 PD alpha helix. SBP1 represents the first peptide inhibitor that was shown to disrupt the interaction of ACE2 and SARS-CoV2 interaction. Biolayer interferometry revealed SBP1 associates with a micromolar affinity to insect-derived SARS-CoV-2-RBD protein.[59] Computational approaches are being widely used for the design and discovery of RBD-ACE2 PPI modulators. Han *et al*. designed a promising ACE2 based peptide inhibitor for Covid-19 using classical molecular dynamics and modeling techniques. Based on the critical interfacial residues (Figure 5), four peptides were designed, inhibitor 1 with a single α1 helix and inhibitors 2 to 4 consisting of double helices extracted from the peptidase domain of ACE2. The molecular dynamics simulation study showed that inhibitors 2 to 4 containing the double helices retain their bent shape providing the right conformation for binding with RBD, whereas inhibitor 1 was deemed unstable due to single helix[60] (Table 1). Inhibitors 2 to 4 showed initial promise in a computational[74] study by conformational matching to the RBD of SARS-CoV-2 and a full cover of the RBD surface; however, *in vitro* and *in vivo* studies are required to validate the efficacy of these peptides. Sitthiyotha *et al*. employed a computational drug design and molecular dynamics to design 25-mer peptides (SBP25) as SARS-CoV-2-RBD binders with better predicted binding affinity than the previously reported SBP1. Using SBP25 peptide (21IEEQAKTFLDKFNHEAEDLFYQSSL45) as a template, several peptides were designed with the strategy to enhance SPB25 binding affinity to SARS-CoV-2-RBD by employing Rosetta.[74] Among the designed peptides, molecular dynamics results showed five designed peptides (SPB25F8N, SPB25F8R, SPB25L25R, SPB25F8N/L25R, and SPB25F8R/L25R) with better predicted binding affinity to SARS-CoV-2 RBD than SPB25 and SBP1.[62] Barh *et al*. used three different bioinformatics approaches to identify and design 17 chimeric peptides that can bind to the SARS-CoV-2 RBD. Among these 17 peptides, 10 peptides showed promising therapeutic potential as SARS-CoV-2-RBD-ACE2 PPI inhibitors.[75] Larue *et al*. rationally designed a panel of ACE2-derived peptides based on the RBD ACE2 binding interfaces of SARS-CoV-2 and SARS-CoV. These subsets of peptides could inhibit the S-mediated entry at low millimolar range and also inhibited the live SARS-CoV-2 infection.[63] Recently, a series of stapled peptides NYBSP-1, NYBSP-2, and NYBSP-4 designed based on human ACE2 were reported to bind to SARS-CoV-2 RBD and may potently inhibit the SARS-CoV-2 infection *in vitro*[64] (Table 1).

Recently, lactam-based i, i + 4 stapled hACE2 peptides ($hACE2_{21\text{-}55}$A36K-F40E) targeting SARS-CoV-2 demonstrated their ability to inhibit the RBD interactions with ACE2 in an *in vitro* setting.[66] Stapled peptides and peptidomimetics generally show a higher degree of *in vitro* and *in vivo* stability compared to their linear counterparts and could form the basis for the development of therapeutics against Covid-19.[76] Another strategy to block the ACE2 and SARS-CoV-2 interaction

TABLE 1 Peptides and peptidomimetics targeting the PPI in Covid-19

Protein-protein interaction	Targeted protein	Peptide	Reference
ACE2: SARS-CoV-2 RBD	RBD	**AHB1**-DEDLEELERLYRKAEEVAKEAKDASRRGDDERAKEQMERAMRLFDQVFE-LAQELQEKQTDGNRQKATHLDKAVKEAADELYQRVR **AHB2-** ELEEQVMHVLDQVSELAHELLHKLTGEELERAAYFNWWATEMMLELIKS-DDEREIREIEEEARRILEHLEELARK	[61]
ACE2: SARS-CoV-2 RBD	RBD	**SBP-1** IEEQAKTFLDKFNHEAEDLFYQS	[59]
ACE2: SARS-CoV-2 RBD	RBD	**SBP-25** IEEQAKTFLDKFNHEAEDLFYQSSL **SPB25F8N-** IEEQAKTNLDKFNHEAEDLFYQSSL **SPB25F8R-** IEEQAKTRLDKFNHEAEDLFYQSSL **SPB25L25R-** IEEQAKTFLDKFNHEAEDLFYQSSR **SPB25F8N/L25R-** IEEQAKTNLDKFNHEAEDLFYQSSR **SPB25F8R/L25R-** IEEQAKTRLDKFNHEAEDLFYQSSR	[62]
ACE2: SARS-CoV-2 RBD	RBD	**Inhibitor-1 (single helix)** IEEQATFLDKFNHEAEDLFYQSSLASWNYNTNIT **Inhibitor-2 (double helix)** (1) IEEQATFLDKFNHEAEDLFYQSSLASWNYNTNITEENVQNMNAAGDKESA FLKWQSTLAQMYPLQEI (2) WDLGKGDFR **Inhibitor-3 (double helix)** (1) IEEQATFLDKFNHEAEDLFYQSSLASWNYNTNITEENVQNMNAAGDKES AFLKWQSTLAQMYPLQEIQALTVKLQLQALQQNGS (2) MTQGFWENSMLTDPGNVQAVCHPTAWDLGKGDFRILMCT **Inhibitor-4 (double helix)** (1) IEEQATFLDKFNHEAEDLFYQSSLASWNYNTNITEENVQNMNAAGDKES AFLKWQSTLAQMYPLQEIQALTVKLQLQALQQNGS (2) PGNVQAVCHPTAWDLGKGDFRILMCTKVTMDDFDTAHHEMGHIQYDM AYAAQPFLLRNGANEGF	[60]
ACE2: SARS-CoV-2 RBD	RBD	**SAP-1** TFLDKFNHEAEDLFYQ **SAP-6** EDLFYQ	[63]
ACE2: SARS-CoV-2 RBD	RBD	Double Stapled peptides: **NYBSP-1** **NYBSP-2** **NYBSP-4**	[64]
ACE2: SARS-CoV-2 RBD	RBD	Peptide 13 IDWQFWFHYDKWDHEWEDEWYQSS	[65]
ACE2: SARS-CoV-2RBD	RBD	**Stapled peptide- hACE$_{221-55}$A36K-F40E**	[66]
ACE2: SARS-CoV-2RBD	ACE2	**CSP-4 -** NNYLWWMTEYHD **CSP-13** CLLCKNAEHARY **CSP-4 dimer**	[67]
ACE2: SARS-CoV-2RBD	ACE2	**Dalbavancin** (glycopeptide antibiotic)	[68]
ACE2: SARS-CoV-2 RBD	ACE2 RBD binding site	**SARS-BLOCK**	[69]
HR1:HR2 of S2 domain	HR1	**EK1** - SLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKEL	[70,71]
HR1:HR2 of S2 domain	HR1	**EK1C4** -SLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKELGSGSG-PEG4-Chol	[71]
HR1:HR2 of S2 domain	HR1	**2019-nCoV-HR2P** DISGINASVVNIQKEIDRLNEVAKNLNESLIDLQEL	[51]
HR1:HR2 of S2 domain	HR1	**[SARSHRC-PEG4] $_2$-Chol** [DISGINASWNIQKEIDRLNEVAKNLNESLIDLQEL -PEG4]$_2$-Chol	[72]
HR1:HR2 of S2 domain	HR1	**IPB01-IPB-09** ISGINASVVNIQKEIDRLNEVAKNLNESLIDLQELK(Chol)	[73]

Abbreviations: Chol, cholesterol; PEG, polyethylene glycol.

is to develop anti-ACE2 inhibitors.[77] Small and highly specific peptides may be ideal for serving this purpose for SARS-CoV-2 infection. Also, specifically blocking the ACE2 binding region with SARS-CoV-2 S protein by anti-ACE2 peptides have an additional advantage because they can be designed to target all the mutating variants of SARS-CoV-2. There are also reports that peptide sequences from ACE2 to design stapled peptides do not prevent virus internalization.[78]

ACE2 receptor targeting peptides blocking the ACE2/SARS-CoV-2 RBD interactions have also been studied. Recently, small anti-ACE2 peptides that bind to ACE2 and inhibit the PPIs between ACE2 and SARS-CoV-2 were discovered by using a novel phage biopanning method.[67] Among the several peptides discovered, two peptides, namely CSP4 and CSP-13 peptides, exhibited the highest PPI blocking effect with an IC_{50} of 635 nM and 709 nM, respectively (Table 1). Using the multimerization technique to increase the potency of the peptides, dimers of CSP-4 with 20-fold more potency (IC_{50} 31 nM) than CSP-4 were obtained. The binding efficiency of these peptides to ACE2 and the ability to inhibit the PPI of ACE2 and SARS-CoV-2/SARS-CoV-1 was assessed by surface plasmon resonance. These peptides were found to inhibit SARS-CoV-2 infection in Vero-E6 cells and exhibited minimal toxicity in *in vivo* studies.[67] Wang *et al*. showed that dalbavancin, a peptide-based antibiotic, binds to human ACE2 with high affinity and blocks the interaction with SARS-CoV2 S proteins. Dalbavancin effectively inhibited the SARS-coV-2 infection *in vitro* and in mice and in rhesus macaques *in vivo* animal models.[68] Paidi *et al*. engineered a hexapeptide corresponding to the ACE2-interacting domain of SARS-CoV-2 (AIDS) that inhibits the PPI of SARS-CoV-2 and ACE2 using an *in silico* modeling approach. Interestingly the designed hexapeptide (wtAIDS) was able to inhibit the interaction between SARS-CoV-2 S protein and ACE2 *in vitro* and *in vivo* (Table 1). Intranasal administration of the wtAIDS peptide reduced the fever and protected the lungs and heart with enhanced locomotor activities in SARS-CoV-2 spike S1 challenged mice, but the mutant form of the peptide (mtAIDS) was unable to show any protective effects.[79] Watson *et al*. demonstrated SARS-BLOCK synthetic peptide scaffolds act as antidotes to SARS-CoV-2 S protein-mediated infection of human ACE2 expressing cells. These synthetic peptides demonstrate a significant reduction of infection in the pseudo-SARS-CoV-2 virus model in nanomolar doses.[69] Wang *et al*. studied the role of intestinal defensins in the SARS-CoV-2 infection and found that the human defensin-5 (HD-5), which is present abundantly in the intestine, prevents the SARS-CoV-2 invasion by binding to ACE2. HD-5 binding to ACE2 was demonstrated by biolayer interferometry, which might prevent the PPI of ACE2 and SARS-CoV-2 interaction. Although the role of HD-5 in preventing the SARS-CoV-2 pseudoparticle has been shown, further *in vitro* and *in vivo* studies are needed to validate its role in genuine SARS-CoV-2 infections.[80]

4.3 | Peptides targeting the PPI of HR1 and HR2 domains of the S2 domain of S-glycoprotein

The S1 RBD domain is involved in host receptor recognition and binding, while the S2 domain, which consists of the HR1 and HR2 regions, plays an important role in membrane fusion. The binding of RBD to ACE2 is followed by cleavage of the S1 domain followed by a significant conformational change in the S2 domain. The FP binds to the host cell membrane, and HR1 and HR2 regions interact with each other forming a six-helix bundle, subsequently bringing the virus and cellular membranes in close proximity for membrane fusion to occur (Figure 6). Efforts toward blocking the interaction of HR1 and HR2 regions are being pursued for the development of fusion inhibitors. Based on this approach, the EK1 peptide was developed as a pan coronavirus fusion inhibitor targeting the HR1 domain (Table 1). Further lipidation of EK1 was used to obtain the potent fusion inhibitor EK1C4 which inhibited SARS-CoV-2 S protein-mediated membrane fusion and pseudovirus infection with an IC_{50}s of 1.3 nM and 15.8 nM, respectively. Furthermore, EK1 C4 potently inhibited the live SARS-CoV-2 infection *in vitro*. Another study has shown that intranasal administration of the lipopeptide ([SARSHRC-PEG4]2-chol) targeting the HR1 region completely prevented the direct contact SARS-CoV-2 infection in ferrets.[81] HR1 and HR2 fusion core is highly conserved and less prone to mutations across the coronavirus' family. Therefore, targeting this region may result in more potent fusion inhibition. Peptides and peptidomimetics targeting ACE2: SARS CoV2 PPI, HR1, and HR2 PPI may also lead to the development of potent SARS-CoV-2 fusion inhibitors.

4.4 | Peptides targeting proteases that activate SARS-CoV-2 S-mediated membrane fusion

Proteolytic cleavage that activates the fusogenicity of the S glycoprotein occurs at two sites. The first step is the cellular protease furin's priming and cleavage at the polybasic S1/S2 site. A second cellular serine protease-2, transmembrane serine proteases-2 (TMPRSS-2), cleaves the S2 subunit allowing FPs to be released and anchor into the cellular membrane. Also, SARS-CoV-2 can enter into a host cell by endosomal uptake, where Cathepsin L activates S-protein and helps in the release of the viral genome into the host cell after fusion of the viral envelope

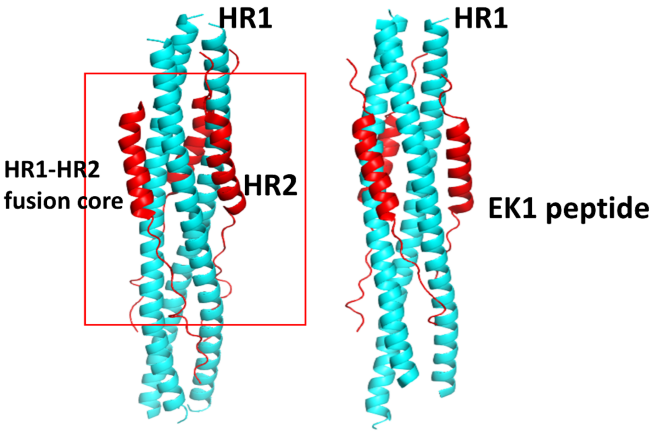

FIGURE 6 Structure of the postfusion core of human SARS-CoV-2 (PDB ID: 6LXT) HR1 (cyan), HR2 (red) form a six helical bundle.[51] Pan-coronavirus inhibitor EK1 peptide (red) in complex with HR1 motif (cyan) of SARS-CoV (PDB ID: 5ZVM)

with the endosomal membranes. Host proteases like furin, TMPRSS-2, and cathepsin-L play an important role in coronavirus fusion and infection in a host cell. Targeting these host proteases may result in efficient antiviral agents against Covid-19. Peptides and peptidomimetics are being designed and studied to target these host proteases to block the S-mediated membrane fusion and block infection.

Studies have shown that the peptidomimetic furin inhibitor decanoyl-RVKR-chloromethyl ketone (dec-RVKR-cmk) inhibits the protease-dependent activation of different viral glycoproteins. Dec-RVKR-cmk blocked the activation and cleavage of SARS-CoV-2 S, preventing syncytium formation and virus infection with an IC_{50} of 5 μM.[82] Another furin peptidomimetic inhibitor, MI-1851, prevented the SARS-CoV-2 S cleavage and a 10 μM dose of MI-1851 reduced the SARS-CoV-2 titer in Calu-3 cells by 190-fold[83] (Table 2).

Host protease TMPRSS-2, which is expressed in the epithelial lining of respiratory, gastrointestinal, and urogenital tracts, is involved in the proteolytic activation of SARS-CoV, MERS, and SARS-CoV-2.[90–92] Inhibition of TMPRSS-2 by the small-molecule camostat mesylate inhibited SARS-CoV-2 infection.[91] Inhibition of TMPRSS-2 (knockdown) prevented the activation of SARS-CoV-2 S protein and spreading of SARS-CoV-2 in Calu-3 cells.[83] Bestle *et al*. demonstrated that the polypeptide aprotinin, a broad range inhibitor of serine proteases obtained from bovine lung, inhibits TMPRSS-2 and blocks the SARS-CoV-2 infection *in vitro* for 16 to 48 hours postinfection.[83] Aprotinin's antiviral effect was abolished after 72 hours, and hence the peptidomimetic MI-432 and its analog MI-1900 were designed to target serine proteases and to enhance the stability and antiviral efficacy. Both peptidomimetics were found to be more potent than aprotinin in reducing the SARS-CoV-2 titers.[83] Recently, Azouz *et al*. demonstrated that α-1 antitrypsin (an FDA-approved drug for treating α-1 antitrypsin deficiency) could also act as a novel inhibitor of SARS-CoV-2 priming protease TMPRSS-2 and blocks the SARS-CoV-2 infection *in vitro*[93] (Table 2; Figure 7).

SARS-CoV-2 can also enter host cells through endocytosis, and they can be processed by Cathepsin L, which are present in endosomes and lysosomes. Blocking of the protease activity of the Cathepsin L by the small-molecule e64d showed reduced SARS-CoV-2 pseudo-particle infection in TMPRSS2-negative HEK293 and Vero cells.[91] Peptides and peptidomimetics are designed to interfere with the activity of the Cathepsin L. Peptide P9 derived from mouse β-defensin has a broad-spectrum antiviral activity against coronaviruses like SARS-CoV-1, MERS CoV, and SARS-CoV-2 (Table 2). Peptide P9, which has abundant basic amino acids, showed high binding affinity to viral glycoproteins, was shown to enter into cells together with the virus via endocytosis and prevented the endosomal acidification, thereby indirectly blocking the activity of protease and release of viral genomes.[84] Furthermore, the optimized peptide P9R exhibited high potency (IC_{50} in lower μg/mL) in inhibiting influenza virus, SARS-CoV-1, MERS-CoV, and SARS-CoV-2 infections and was shown to combat pH-dependent respiratory viruses.[85] A further study reported the peptide 8P9R and chloroquine (endosomal acidification inhibitor) could synergistically enhance the activity of arbidol, a spike-ACE2 fusion inhibitor, against SARS-CoV-2 and SARS-CoV in cells. Also, *in vivo* studies showed that the combination of 8P9R with arbidol and camostat (TMPRSS-2) significantly reduced the replication of SARS-CoV-2 and SARS-CoV infection by blocking both entry pathways of the virus into cells.[86]

The main protease (M^{pro}), also called $3CL^{pro}$, is an additional desirable target for antivirals.[95] M^{pro} is involved in the processing of polypeptides and proteins that are translated from viral RNA. The X-ray crystal structure of unliganded SARS-CoV-2 M^{pro} and as a complex with a potential peptidomimetics (α-ketoamide) inhibitor has been reported.[89] This information will be vital in the development of antiviral agents against Covid-19. The reported peptidomimetic inhibitor

TABLE 2 Peptides and peptidomimetics targeting host proteases furin, TMPRSS2, Cathepsin L, and virus main protease

Targeted protease	Peptide	Virus tested	Reference
Furin	dec-RVKR-cmk	SARS-CoV-2	[82]
Furin	MI-1851	SARS-CoV-2	[83]
TMPRSS-2	Aprotinin PDFCLEPPYTGPCKARIIR YFYNAKAGLCQTFVYGGCRAKRNNFKSAED CMRTCGGA	SARS-CoV-2	[83]
TMPRSS-2	MI-432	SARS-CoV-2	[83]
TMPRSS-2	MI-1900	SARS-CoV-2	[83]
Cathepsin-L	P9 (derived from mouse β defensin-4) NGAICWGPCPTAFRQIGNCGHFKVRCCKIR	SARS-CoV-2, SARS-CoV-1, MERS-CoV	[84]
Cathepsin-L	P9R (derived from mouse β defensin-4) NGAICWGPCPTAFRQIGNCGRFRVRCCRIR	SARS-CoV-2, SARS-CoV-1, MERS-CoV	[85]
Cathepsin-L	8P9R -8-branched P9R (derived from mouse β defensin-4) 8X- -NGAICWGPCPTAFRQIGNCGRFRVRCCRIR	SARS-CoV-2, SARS-CoV-1, MERS-CoV, influenza virus	[86]
Cathepsin L	Teicoplanin (glycopeptide antibiotic)	SARS-CoV-2, SARS-CoV-1, MERS-CoV	[87,88]
SARS-CoV-2 Main Protease (M^{pro})	α-ketoamide 13b	SARS-CoV-2	[89]

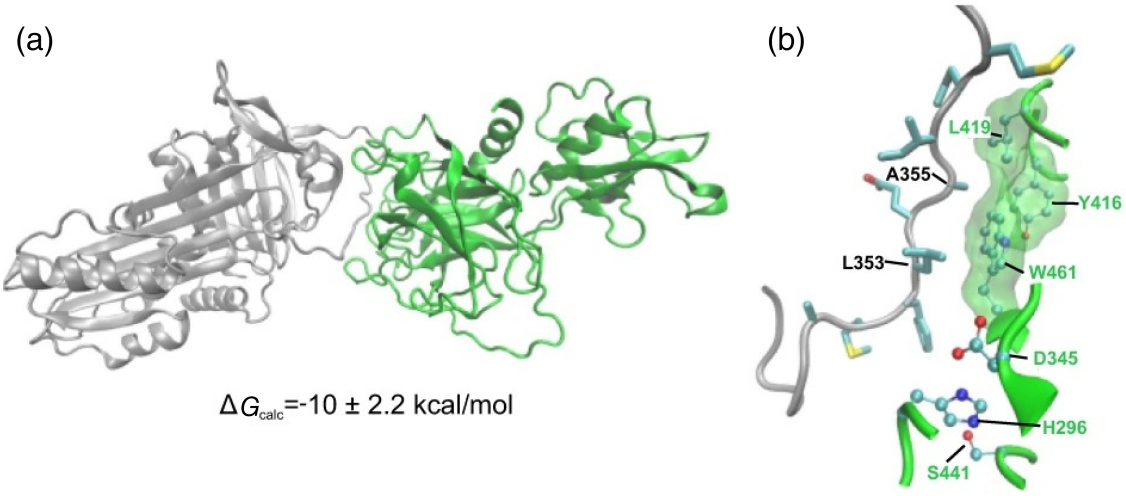

FIGURE 7 (A) Protein-protein docking analysis of a homology model for the TMPRSS2 extracellular fragment (green, PDB 1Z8G) and α1AT (gray, PDB 3CWM) and computationally calculated binding free energy (ΔG_{calc}) of the complex. (B) Detailed view on the α1AT-TMPRSS2 binding interface. The sidechains of α1AT (gray) residues are represented with sticks, while sidechains of TMPRSS2 (green) are shown with balls and sticks. Hydrogen atoms are omitted for clarity; carbon, oxygen, nitrogen, and sulfur atoms of amino acid side chains depicted in light blue, red, dark blue, and yellow, respectively. The hydrophobic patch near the TMPRSS2 catalytic triad is highlighted with a green transparent surface. Adapted and reproduced from Creative Commons Attribution[94]

has been shown to enhance half-life and to inhibit the replication of SARS-CoV-2 in human Calu-3 lung cells[89] (Table 2).

Most of the peptides being studied as therapeutic agents for Covid-19 are in the preliminary stages of development. Many of these peptides are only validated by computational studies, *in vitro* studies, and only a small number of the peptides have been studied *in vivo* as an antiviral agent. The majority of the peptides discussed are characterized for their antiviral effect by *in vitro* studies only. *In vitro* studies must be done by considering the phospholipidosis effect of the peptides in cells. Phospholipidosis is a drug-induced excessive intracellular accumulation of phospholipids.[96] Many cationic amphiphilic drugs may show the antiviral effect through phospholipidosis, and these drugs may be ineffective *in vivo*. There are reports of a strong correlation between the drug-induced phospholipidosis and SARS-CoV-2 inhibition *in vitro*.[97] Hence the peptides showing the antiviral activity in SARS-CoV-2 must be tested for their phospholipidosis effects in cells before going to *in vivo* study. Detailed *in vivo* study of the peptides in virus challenge studies can provide more insight into these peptides as potential therapeutics for Covid-19. Among the discussed peptides in this review, only a handful of peptides, EK1, EK1C4, and [SARSHRC-PEG4]2-Chol, have been evaluated for their *in vivo* antiviral efficacy in animal model.[70–72]

5 | MUTATIONS AND POSSIBLE RESISTANCE TO PEPTIDES TARGETING THE S GLYCOPROTEIN

SARS-CoV-2 is an RNA virus with a single-stranded RNA genome. RNA viruses are known to have a very high mutation that contributes to their enhanced virulence and evolution. Human genetic variations and infection in different geographical regions also lead to a selection of mutations virus (variants).[98–101] The highly mutated region in the entire genome of SARS-CoV-2 includes open reading frames (ORF1ab), S, and N proteins. More than 1800 mutations are reported in the S-protein of SARS-CoV-2. Among these, 235 mutations are in the RBD region, with multiple mutations occurring at the same sites.[102] Since RBD is involved in the PPI of the S-protein, and ACE2 binding, it is estimated that the virus will accumulate more mutations in the RBD region (Figure 8). SARS-CoV-2 variants, B.1.1.7 lineage (a.k.a. Alpha variant, 20B/501Y.V1 variant and VUI202012/01), B.1.351 lineage (a.k.a. Beta variant, 20C/501Y.V2), P.1/P.2 lineages (Gamma variant), and B.1.429 (Kappa variant) are known to be responsible for the observed increase of infections in the United Kingdom, South Africa, Brazil, and North America.[105–108] Recently, another delta variant was shown to circulate in southeast Asia, in particular the Indian subcontinent.[109–111] As the disease peaks in different geographical regions, it is important to keep track of these viral mutations to design therapeutic agents capable of dealing with these virus variants. There are efforts to keep centralized mutation data that is accessible to scientists and clinicians. CoVMT is an interactive SARS-CoV-2 mutation tracker that focuses on critical variants.[112] A genetic database such as *the global initiative on sharing avian flu data* (GISAID) is updated with genetic analysis of different variants of SARS-CoV-2 virus.[113] CoV-GLUE database has updated information about replacement, insertion, and deletion mutations observed in SARS-CoV-2 (http://cov-glue.cvr.gla.ac.uk/#/replacement). Some of the reported mutations and their origin are provided in Table 3.

Detailed structural studies of complexes of the SARS-CoV RBD and SARS-CoV-2 RBD region binding to ACE2 reveal that both

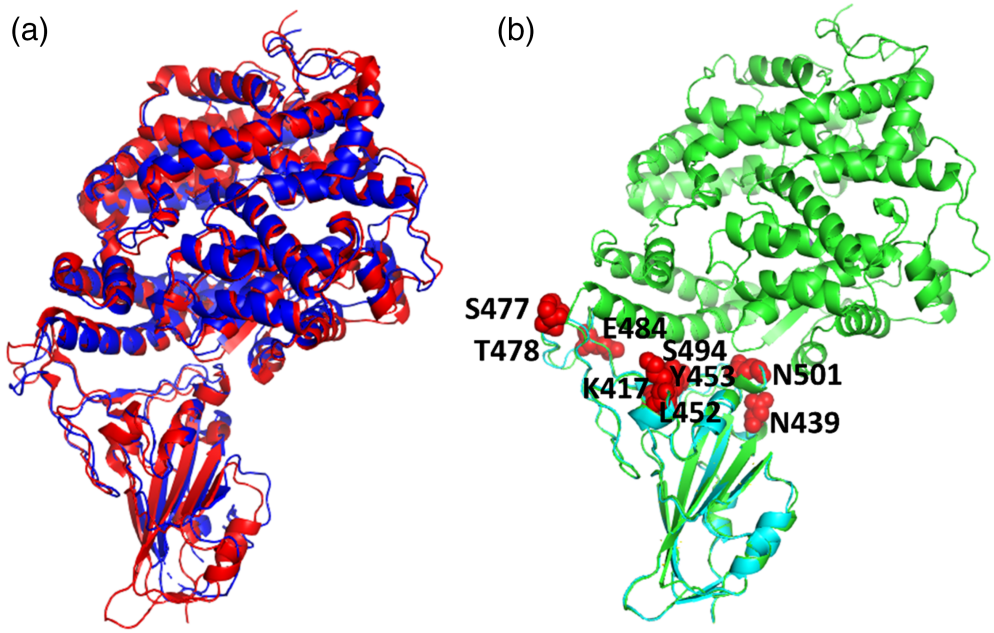

FIGURE 8 (A) Crystal structure of SARS-CoV-2 RBD and SARS-CoV-RBD complexes overlapped (PDB ID: 6M0J, 1AJF, red and blue)[55,103]; (B) Mutation (red spheres with label) in the RBD region (PDB ID: 7BWJ, 6M0J). The numbering scheme published in the crystal structure of SARS-CoV-2 antibody with RBD was used[104]

TABLE 3 Variants of SARS-CoV-2 and significant mutations in the S-protein

Mutations	Country of origin or first detected	Name of the lineage
A67V, 69del, 70del, 144del, **E484K**, D614G, Q677H, F888L	United Kingdom/Nigeria—December 2020	B.1.525 **(Eta variant)**
(L5F*), T95I, D253G, (**S477N***), (**E484K***), D614G, (A701V*)	United States (New York)—November 2020	B.1.526 **(Iota variant)**
D80G, 144del, F157S, **L452R**, D614G, (T791I*), (T859N*), D950H	United States (New York)—October 2020	B.1.526.1
L452R, E484Q, D614G	India—February 2021	B.1.617
(T95I), G142D, E154K, **L452R, E484Q**, D614G, P681R, Q1071H	India—December 2020	B.1.617.1 **(Kappa variant)**
T19R, (G142D), 156del, 157del, R158G, **L452R, T478K**, D614G, P681R, D950N	India—December 2020	B.1.617.2 **(Delta variant)**
T19R, G142D, **L452R, E484Q**, D614G, P681R, D950N	India—October 2020	B.1.617.3
E484K, (F565L*), D614G, V1176F	Brazil—April 2020	P.2
69del, 70del, 144del, (**E484K***), (**S494P***), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (K1191N*)	United Kingdom	B.1.1.7 **(Alpha variant)**
D80A, D215G, 241del, 242del, 243del, **K417N, E484K, N501Y**, D614G, A701V	South Africa	B.1.351 **(Beta variant)**
L452R, D614G	United States (California)	B.1.427 **(Kappa variant)**
S13I, W152C, **L452R**, D614G	United States (California)	B.1.429 **(Kappa variant)**
L18F, T20N, P26S, D138Y, R190S, **K417T, E484K, N501Y**, D614G, H655Y, T1027I	Japan/Brazil	P.1 **(Gamma variant)**

Note: RBD mutations are in bold. Data obtained from https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fvariant-surveillance%2Fvariant-info.html. Date: 6 January 2021.

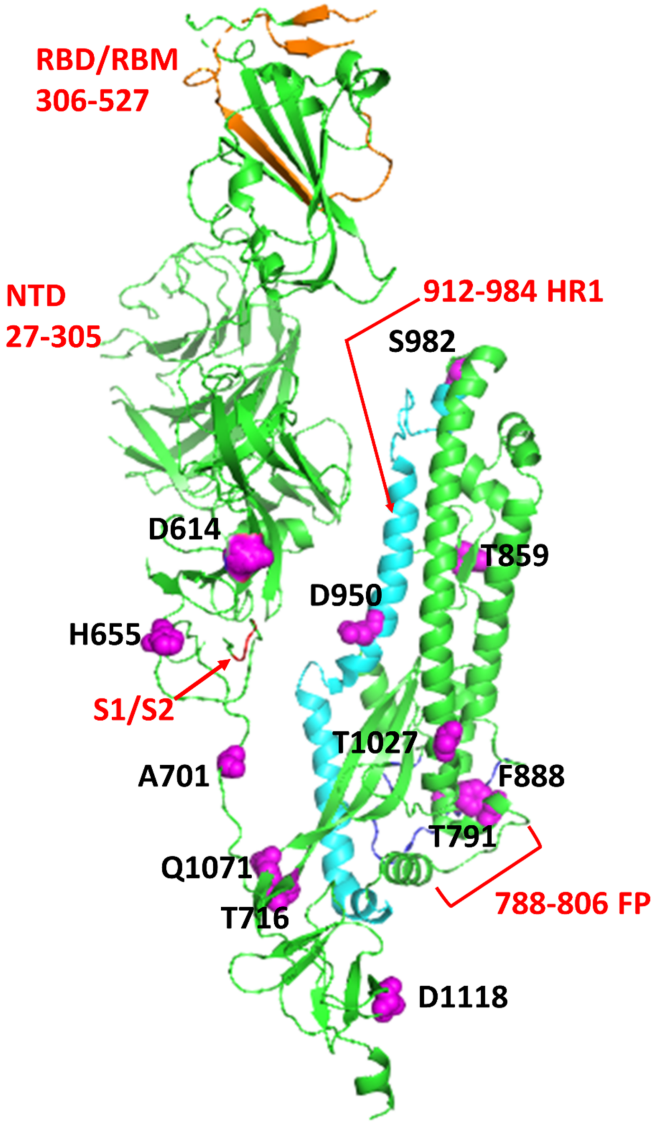

FIGURE 9 Cryo-EM structure of the S protein (PDB ID: 6VSB)[17] showing mutations in the other than RBD region of the S glycoprotein. The only monomer of the S-glycoprotein is shown for the sake of clarity. Different regions and amino acids corresponding to that region are indicated in red. Mutated amino acid residues are shown as spheres (magenta) along with a label

viruses' RBD binding region is nearly identical[55,103] (Figure 8) and share ~76% sequence identity with SARS-CoV and ~43% sequence identity with MERS-CoV. However, SARS-CoV-2 binds with a higher affinity to ACE2 than SARS-CoV, explaining the severe infectivity of SARS-CoV-2 compared to SARS-CoV.[114] Furthermore, the cleavage ability of TMPRSS2 plays a vital role in the viral entry to the host cell. Mutation in that region that helps to cleave the S glycoprotein can enhance virus entry. The RBD of human SARS CoV-2 S proteins from different continents is associated with 44 distinct mutation sites.[115] B.1.429, found in California, has an L454R mutation in RBD. A N501Y mutation in the RBD region was found in most variants and is known to enhance the transmissibility of SARS-CoV-2. These variants of RBD also have the well-known D614G mutation that was found during the early stages of Covid-19 spread outside China. The D614G mutation changes the RBD region structure and S1/S2 subunit interaction. The mutation seems to help S glycoprotein to be in open conformation that helps bind to ACE2, thus enhancing the overall binding to ACE2.[56,116–118]

Analysis of the genomes of several SARS-CoV-2 strains from across the world revealed 32 mutations in RBD. The RBD with mutations at N354D, D364Y, V367F, and W436R exhibited significantly increased affinity to human ACE2, indicating that these mutants may have acquired enhanced infectivity.[118,119] It was also reported that the two hot-spot residues that fall in the RBD of the S protein (G476S and V483A) were frequently present in a SARS-CoV-2 sample isolated from North America.[99] Other observed mutations in the RBD region are S477N, L452R, and N501Y.[120,121]

Mutations/deletions that are not in the RBD region seem to affect the mutation in the RBD region of the S-glycoprotein. The deletion ΔH69/V70 frequently occurred with RBD mutations N439K or Y453F. The N439K mutation is known to enhance the binding of RBD to ACE2 via a new salt bridge formation compared to non-mutated RBD and resistance to neutralizing antibodies.[23,121,122] Details of mutations in different regions of S-glycoprotein and genetic variation of ACE2 and TMPRSS-2 are discussed in a recent review article by Huang and Wang.[120] Mutations in the other regions of the S glycoprotein include those within the FP as well as HR1 regions (Figure 9). However, compared to the PPI of the RBD region of the S protein and ACE2, the number of mutations in the FP and HR1 regions reported so far are small in number. Thus, peptides designed in any of these regions should take into consideration of these possible mutations.

6 | CHALLENGES OF PEPTIDES AS THERAPEUTICS FOR COVID-19

Linear peptides have limited *in vivo* stability that poses a significant challenge for their development as a therapeutic agent.[123,124] Various modifications of peptides for enhancing the stability of the peptides include cyclization, use of unnatural amino acids, and stapling. In the development of peptides as a therapeutic agent in Covid-19, stapling of the linear peptides is widely used for conformational constraining that enhances the affinity and stability of the peptides.[64] Also, most of the peptides reported targeting SARS-CoV-2 in the *in vivo* study are delivered through the intranasal administration as SARS-CoV-2 viral particles are concentrated on the respiratory tract.[71] The route of administration of the peptides must be considered depending on the stability of the peptides. Recent development in nano-drug delivery approaches has been game-changing in the control of the Covid-19 pandemic. The use of lipid nanoparticles platform for the delivery of sensitive agents like mRNA (Pfizer and Moderna vaccines) has led to the successful development of vaccines against Covid-19.[9,11] A similar lipid nanoparticle drug delivery system could be used for the delivery of the peptides to enhance their stability and therapeutic effects in Covid-19. Other approaches such as

peptidomimetic approach or grafted peptides and stapled peptide approaches where peptides are stabilized for *in vivo* delivery should be considered.[76,125–128]

7 | CONCLUSIONS AND FUTURE DIRECTIONS

Different strategies to improve peptide stability and cell penetrability properties are being developed utilizing peptides as ideal tools for inhibiting PPIs in Covid-19. Certain limitations, such as the low stability of peptides, can be addressed by cyclization, stapling, peptidomimetics, and grafting techniques. Peptides and peptidomimetics can block viral entry into the host cells at very early stages and hence can be used as prophylactic and therapeutic agents. Peptides can be designed to target the receptor binding and fusion of coronavirus to host cells. Peptides can be formulated for intranasal applications acting locally on the respiratory tract where SARS-CoV-2 viral load is maximum. Extensive study, preclinical animal testing, and clinical trials are needed to develop clinically approved potential peptides as therapeutics for Covid-19. Caution should be used when designing peptides that target the RBD region of the S protein since it undergoes extensive mutation. The use of multiple peptides that target different PPIs may effectively deal with the effect of specific mutations in one of the targeted PPIs.

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CONFLICT OF INTEREST

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

This is a review article, and hence no data are available for sharing.

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