REVIEW ARTICLE

ISSN: 2455-8095
doi: https://doi.org/10.21477/ijapsr.8.1.02

A Review on Peptide-based Therapeutics For Combatting COVID-19

Anil K. Tallam[1], Alapati Sahithi[2], Mohana V. Nuli[3]

[1]Department of Pharmacy, Shri Venkateshwara University, Rajabpur, NH-24, Gajraula, Uttar Pradesh, India

[2]Department of Pharmaceutical Analysis, Nalla Narasimha Reddy Education Society's Group of Institutions, Hyderabad, Telangana, India

[3]Raghavendra Institute of Pharmaceutical Education and Research K.R. Palli Cross, Anantapuramu, Andhra Pradesh, India

ABSTRACT

Recent breakthroughs in peptide exploration have led to revolutionary medicinal discoveries for a number of different infectious illnesses. An immediate need exists for the development of viable treatment alternatives in light of the continuing danger of the COVID-19 pandemic. Peptide inhibitors have notable potential for the management of developing viral infections since they are safe, effective, and selective. Antiviral peptides may be rationally engineered and optimally formulated using information about the 3D structures of viral proteins and the cells they target. The resultant peptides may have broad antiviral action or be extremely selective for certain targets and targeted viral infections. In this article, we discuss the research done so far on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) peptide medicines. Thus far, attempts to repurpose peptide medicines with antiviral and antibacterial properties have failed. Targeting the link between the SARS-CoV-2 spike protein and the ACE-2 (Angiotensin-Converting Enzyme-2) that initiates cellular infection and viral replication has yielded the most promising discoveries, albeit by no means the only ones. While there exists no approved therapy for SARS-CoV-2, the experience gained in developing peptide drugs for this virus suggests that this approach may now be preferable to the use of smaller molecules.

Keywords: Coronavirus disease 2019, Peptides, Peptide-based therapeutics, Severe acute respiratory syndrome coronavirus 2, Treatment, Vaccines.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19), brough about by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), speedily spread all across the globe, resulting in many deaths and having far-reaching effects on healthcare systems, economies, and communities. Although significant attempts are being undertaken to rapidly create vaccines, it cannot be guaranteed that immunizations against this virus will give long-lasting, robust protection and a vaccine would probably not benefit individuals who are already affected.[1,2] For this reason, it is crucial to create therapeutic drugs that can combat this pandemic virus.

In the search for a medication that can neutralize COVID-19, researchers have tried a number of approaches. When used for COVID-19, peptide therapies show great promise. Peptides are subunits of proteins that can be easily synthesized at a low cost and in a short amount of time.[3] By adjusting the peptides in terms of their sequence length, side-chain reactivity, and other artificial components, the door to progress in peptide-based treatments was pushed wide open.[4,5] Peptides have advantages over other pharmaceuticals due to their high selectivity and low toxic effects, both of which stem from their limited chances for clumping in the body.[6-8] Several approaches to combat COVID-19 viral infection are discussed, including the use of peptide vaccines, peptide immune modulators, and peptides that suppress viral reproduction and release. There is not yet an exact cure for COVID-19. This highlights the need of identifying potential targets in order to develop and repurpose medications. Table 1 contains examples of some of the commercially available peptide-based products against Covid-19.

Corresponding author
Anil K. Tallam
Email : anil.tallam31@gmail.com

Received: 21-09-2022 **Accepted:** 15-12-2022 **Available Online:** 01-01-2023

Table 1: Marketed peptide-based compounds for covid-19

Company	*Product name*	*Peptide design*	*References*
Axon neuroscience	ACvac1	Pluri-epitope peptide vaccine	9
CytoDyn	Leronlimab	Leronlimab (PRO 140)	10
Vaxxinity	UB-612	Multi-tope protein; UB-612	11
Flow pharma	Flovid-20	T-cell targeted immunotherapy	12
Axon neuroscience	ACmab1	Humanized monoclonal antibody	9
Vir biotechnology	Sotrovimab	Monoclonal antibody	13

1.1. Importance of Peptide Drug Delivery System

- Proteins and peptides have critical roles in biological cells and organic molecules.
- A deficiency in proteins and peptides may lead to health problems including diabetes mellitus. (As a result of a deficiency of the protein "Insulin")
- R-DNA technology and hybridoma procedures are now being applied in protein and peptide-based medicines.[14]

1.2. Advantages of Protein and Peptide Drug Delivery System[15-21]

- Erythropoietin is mostly used in the formation of red blood cells.
- Tissue plasminogen activator is a protein that is used to treat heart attacks and strokes.
- Oxytocin is used to relieve labor pain.
- Bradykinin stimulates peripheral circulation.
- Somatostatin lessens bleeding from stomach ulcers.
- Gonadotropin is a peptide hormone that causes an ovulation to occur.
- Insulin maintains steady glucose levels in the blood.

1.3 Functions of Protein and Peptide Drug Delivery System[22-28]

- Small molecules and biomolecules are transported and stored.
- Muscle contraction allows for synchronized movement.
- Fibrous protein provides mechanical support.
- Nerve impulse generation and transmission
- Catalysis by enzymes in biological reactions.
- Antibodies provide immune defense.
- Hormones are used to control growth and differentiation.

2. Incorporation of proteins and peptides into drug delivery matrix

The drug incorporated into the Protein and Peptide drug delivery system is subjected to three different processes, which are as follows:[29-34]

2.1. Emulsification

Aqueous (water solution) -soluble medicines first dissolve in aqueous (water solution). Mixing the two liquids produces an emulsion-free mixture. The emulsifier is added to the primary emulsion to make it w/o/w. Finally, the organic solvent is removed from the emulsion by filtration and increasing the temperature.[35]

2.2. Extrusion And Spray Drying

There are two ways to make microspheres: with the help of extrusion and spraying. The core material or matrix, which is made of drug-filled Solution, and the Particulate, which comes out of the orifice, fine tubes or nozzles to make small droplets. The size of the droplet is mostly determined by the properties of the liquid (melt, solution, and suspension) and the diameter of the orifice to the speed of the jet.

2.3. Polymerization

Polymerization in hydrogels created by mixing monomer, drug, initiator, and cross linking agents. Intra vascular protein distribution by a photo polymerized hydro system on the inner side of a blood artery. One of the disadvantages of protein and peptide drug delivery systems is that radiators degrade protein molecule integrity.

3. Application peptide drug delivery system

- Drugs that act on the cardiovascular system Proteins and peptides (anti-Angiotensin 2 antagonists, Bradykinin, and Captopril) are critical for lowering blood pressure and increasing peripheral circulation in the therapy of heart failure.
- CNS active proteins and peptides (Cholecystokinin, B-endorphin) are required for appetite suppression and pain relief.[36]
- GI-active Proteins and Peptides (Gastrin antagonist, pancreatic enzymes) are critical for reducing gastric acid output and are necessary for digestive supplementation.[37]
- Immunomodulation of proteins and peptides (Bersin, Cyclosporin, and Interferon) is critical for selective B-cell differentiation. Inhibits T-lymphocyte activities and enhances the activity of killer cells.[38]
- Proteins and peptides that modulate metabolism (Insulin, Vasopressin) are critical in the treatment of diabetes mellitus and diabetes insipidus.[39]

4. Sars-cov-2 proteins and their role in drug discovery

The four main structural proteins of SARS-CoV-2 are the spike (S) protein, the envelope (E) protein, the membrane (M) protein, and the nucleocapsid (N) protein. Furthermore, 16 NSPs (non-structural proteins) have therapeutic potential. There are two different parts that make up a S protein: S1 and S2.[40] S1 has a receptor-binding domain (RBD) that is important in viral entrance and adherence to protein ACE-2 (Angiotensin-Converting Enzyme-2), while S2 is involved in viral fusion.[41,42] M and E proteins are engaged mostly in viral assembly. N protein is an RNA-binding protein that is required for replication and genome packaging. Due to importance of structural and nonstructural protein mutations in virulence and virus propagation, they must be taken into account when developing treatments and vaccinations.[43]

SARS-CoV-2 carries major genetic alterations that are entirely novel to human population's innate immune system. According to research, the virus doe not have the ability of infecting a sizable proportion of human population. Ganesh et al. Gathered the reports, which may be used to compare the prevalence of SARS-CoV-2 to that of SARS (Severe acute respiratory syndrome) and MERS (Middle East Respiratory Syndrome) while treatments are being developed.[44]

Scientists created three medication development strategies to combat coronaviruses. First, test existing broad-spectrum antivirals. Their spectrum is too vast, notwithstanding their advantages in terms of metabolic properties, doses, potential efficacy, and adverse effects. Another method is to search through current molecular databases quickly and efficiently for compounds with anti-coronavirus activity.[45] The third option is to create novel targeted medications based on coronavirus genetic and clinical features. On the basis of these discoveries, we compiled research findings on peptide therapies and their molecular mechanisms. This article includes an overview of SARS-CoV peptide treatments that potentially be repurposed for SARS-CoV-2 along with an update on SARS-CoV-2 peptides previously developed. Nevertheless, lab and clinical investigations are required to fully comprehend SARS-CoV-2 infection and enhance treatment development.[46]

5. Role of peptides in sars-cov-2 study

Insufficient action, resistance, safety and effectiveness difficulties, and adverse reactions are among the drawbacks of existing antiviral medicines. They are not as efficient at preventing long protein binding surfaces. Peptides are gaining popularity in the pharmaceutical business. Less toxicity, less side effects, and less selectivity make peptide-based medications a better alternative than small molecule therapies.[47] These are synthesized and chemically stabilized. Peptides and peptidomimetics are widely accepted in chemical biology. Peptides compete for binding by mimicking a protein surface. Peptide medicines are unstable, susceptible to degradation, have a quick half-life, and have poor membrane permeation. Over 400 peptide-based medications are now in clinical trials, with about 60 already authorized. Using peptide research, epitope-based vaccination screening may potentially be possible. However, no effective peptide-based medicines exist for SARS-CoV-2.[48]

Antiviral peptides (AVPs) could be an effective antiviral against SARSCoV2. AVPs are of particular relevance since they are more effective than other antiviral agents at inhibiting viral infection. AVPs block viral adsorption, permeation, endosomal discharge, uncoating, replication, and mature viri release. Studies on natural and biological sources, as well as computer methodologies like high-throughput screening, help find a potential AVP. We previously discovered seven antimicrobial peptides (AMPs) as potential MERS therapeutics. Fosgerau et al. reviewed the numerous peptide therapy techniques and potential. It has been postulated that existing antiviral peptide medicines could be repurposed to treat MERS-CoV. The current coronavirus epidemic can be managed using available antivirals and knowledge gathered previous SARS and MERS pandemic.[49-55]

Several publications have reviewed the use of peptides as COVID-19 treatment alternatives. Cherian et al. evaluated virus- and host-based medication repurposing potential for these viruses, particularly SARS-CoV-2.[56] Many publications stress the importance of repurposing medications for SARS-CoV-2. It is clear that peptides may be employed as anti-SARS-CoV-2 components. On the other hand, we give a complete assessment of peptides having therapeutic and preventive activities in SARS-CoV that might be used against SARS-CoV-2. As seen in Tables 1–3, tremendous Following SARS-CoV's identification, several positive developments have taken place.[57-60]

6. Mechanism-based categorization of covid-19 peptide therapies

Anti-coronavirus treatments may be of two types based on the target: those that work on the virus itself or those that work on host's immune response. Depending on how the peptides might work, we put them into three groups: virus entry/fusion inhibitors, replication blockers, and immunomodulators.

6.1 Viral Entrance and Fusion-inhibiting Peptides

Specifically, the S protein of SARS-CoV interacts with the ACE2 receptor to allow coronavirus entrance into cells. Lu et al. used bioinformatics for detecting peptides with B cell epitopes inside S protein of SARS-cove that could be used in diagnosis. RBD in the spike protein's S1 subunit is a target for virus fusion inhibitors, neutralising antibodies, and vaccinations. Barh et al. reported possible SARS-CoV-2 spike RBD inhibitor peptides. Using bioinformatics, they identified critical fragments adhering to spike RBD. -helices from ACE2's protease domain were employed to create SARSCoV-2 peptide inhibitors. RBD S1 binds directly to ACE2 PD. SBP1 (Spike-binding protein 1), can inhibit the SARS-CoV-2 spike protein from binding with ACE2.[61]

The spike proteins of coronaviruses are examples of class I fusion proteins; they consist of two halves, human receptor (HR) 1 and 2. An essential and constant method for viral fusion and entry is the formation of a six-helical bundle by the heptad repeat via interaction with the ACE2 receptor on the target cell. As a result, numerous researchers have looked for fusion inhibitors that might be employed for treating CoV infections. The HR1 and HR2 regions of SARS-CoV and SARSCoV-2 have 92.6% and 100% sequence homology, correspondingly, indicating that HR 2 peptides demonstrated to suppress SARS-CoV may potentially impede SARSCoV-2.[62,63] It is now possible to develop peptide or small molecule derived anti-CoV fusogenics to halt SARS-CoV-2 membrane fusion according to the work of Tang et al., who investigated HR2-derived inhibitory compounds for SARS-CoV and MERS-CoV. Several HR2 sequence-derived fusion blockers were discovered to block SARS-CoV-2 cell fusion in a latest investigation. In order to stop the spread of coronaviruses, Xia et al. developed an inhibitor called EK1 that specifically blocks the HR1 domain. They also created the very powerful lipopeptide EK1C4, which targets the spike protein in pan-coronavirus fusion.[64] To increase inhibitory efficacy against SARS-CoV-2, EK1C4 was created by merging together cholesterol fragment and EK1. The EKIC4 protein blocked the entrance of pseudotyped viruses, particularly, SARS-CoV and MERS-CoV and also blocked membrane fusion facilitated by the SARS-CoV-2 S-protein. EK1C4, having an EC_{50} of 36.5 nm, is more potent than that of EK1 peptide, which has an EC_{50} of 2.47 M. SARS-CoV-2 S-protein-mediated fusion and pseudovirus transmission were suppressed by the HR2-based lipopeptide fusion inhibitor IPB02.

Unlike previous peptide medicines, EK1C4 may be breathed as aerosol, lowering viral accumulation in lungs and minimising inflammatory reaction. Intranasal injection of EK1C4 shows promise as a SARS-CoV-2 therapy. This is because HR1 domain present in S2 subunit of S protein is extensively regulated, making drug resistance mutations difficult to develop (Figure 1).[64,65]

6.2 Peptides that Suppress Viral Multiplication and Release

Once within the host cell, the virus modifies the transcription pathway to manufacture its proteins. With open reading frames, ORF1a and ORF1b, two polyproteins (pp1a & pp1b) are encoded by the positive-stranded RNA of SARS-CoV. Enzymatic degradation of such polyproteins yields sixteen non-structural proteins essential for replication, including two proteases, papain-like protease (PLpro/Nsp3), and 3-chymotrypsin-like protease (3CLpro/Nsp5). SARS-3CLpro CoV-2's shares 99.02 percent sequence identical with that of SARS-CoV. Two peptidomimetic aldehydes, 11a and 11b, were found after researchers investigated the possibility of designing peptide inhibitors to block the substrate binding domain of SARSCoV-2 3CLpro. Both were quite effective in preventing SARS-CoV-2 infection. The replicase polyprotein is also processed by another protease called PLpro, is an attractive antiviral therapeutic target. Glutathione, used to treat liver problems, was found to be effective against PLpro with a docking score of 20.[66-68]

In a recent randomized placebo-controlled experiment, remdesivir was found to reduce respiratory tract infection in COVID-19-infected individuals.

SARS-CoV-2 Nsp12 shares significant homology with SARS-CoV, signifying a well-regulated mode of action validated by cryo-EM structural analyses. Nsp12 has a nidovirus RdRp (RNA-dependent RNA polymerase)-derived nucleotidyl transferase structure and a right hand RdRp domain. Nsp12 may help synthesise viral RNA with Nsp7 and Nsp8 serving as cofactors. The Nsp7-Nsp8 complex boosts Nsp12's RNA binding and RdRp enzymatic activity by synthesising a 6-nucleotide primer for RdRp RNA production. The Nsp12-Nsp8 interaction offers tremendous therapeutic potential.

Nsp9 is responsible for viral replication, pathogenicity, and viral RNA translation. Selinexor is a synthetic peptide that inhibits the nuclear export protein CRM1 (Chromosomal Maintenance 1), sometimes referred to as exportin 1 (XPO1). Currently, its low dosages are being evaluated against COVID19. In addition to inhibiting adipogenesis, the mushroom-derived Ternatin 4-N-methylated cyclic hexapeptide impedes the translation pathway. Because ternatin 4 affects host translation, it is incorporated as a potential preclinical compound.

Epigenetic modifications which govern chromatin rear-

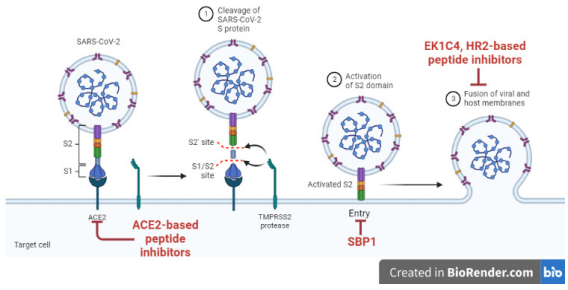

Figure 1: SARS-entrance CoV-2's and fusion mechanism is depicted in this diagram. Peptide molecules that have been identified as being involved in the entry and fusion of the coronavirus are depicted.

rangement are linked to viral pathogenesis. The significance of epigenetic regulators in SARS-CoV research has been emphasized. Lately, DNA methylation studies of ACE2 protein shed light on SARS-CoV-2 epidemiology. The BET (bromodomain and extra-terminal domain) proteins function as epigenetic readers and control the expression of ACE2. Gordon et al discovered a BRD4 (Bromodomain-containing protein 4)-SARSCoV-2 E protein interaction, raising the prospect of peptide-derived bromodomain blockers as SARS-CoV2 treatments. An interaction between HDAC2 (Histone deacetylases-2) and the viral protein Nsp5 was discovered in SARS-CoV-2 investigation. Nucleus transport of HDAC2 is thought to be inhibited by Nsp5. We propose exploring for Nsp5 peptide inhibitors, as this appears to be a shift in COVID-19. Futhermore, HDAC blockers may be used to prevent COVID-19. Epigenetic therapies such as epidrugs may be useful therapeutic or preventative tools. Intriguingly, Apicidin was discovered by using a cyclic 3-tetrapeptide scaffold, a method that can be applied to find other anti-coronaviral peptide inhibitors.[69-73]

6.3 RNA Processing

Apart from RNA polymerase, RNA helicase, and protease capabilities, the coronavirus replicase utilises a range of RNA enzymes that are specific to it. This is followed by ribose 2-O-methylation of the cap, which permits viruses to evade detection by the host immune system. These include Nsp13, an RNA/NTP triphosphate triphosphatase and helicase; Nsp14, an RNA cap N7 methyltransferase; and Nsp16, an RNA cap ribose-O methyltransferase and an unknown guanylyl translocator. N7-Methyltransferase domain of Nsp14 serves as an intriguing target because it differs from cellular methyltransferases in its fold. The methyltransferase of coronaviruses is a potential and promising antiviral therapeutic target.[74-78]

6.4 Virus Maturation

The RTC employs negative-stranded intermediates to generate progeny genomes and subgenomic mRNAs.

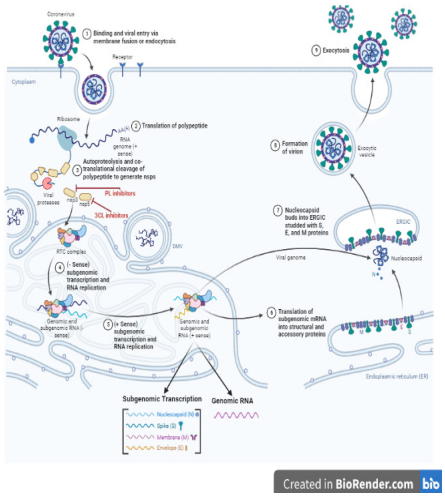

Figure 2: A graph depicting SARSCoV2 replication and maturation mechanism, highlighting peptide treatments. The viral replicase coordinates both continuous and discontinuous RNA production. These proteins form membranebound replication-transcription complexes (RTC) with viral and perhaps cellular proteins. Nsp12 (non-structural protein-12) is the principal target in case of remdesivir, a nucleoside analogue antiviral agent utilized for SARSCoV-2. The drug has antiviral action against numerous viruses, particularly RSV, Ebola, Nipah, SARS-CoV, and MERS-CoV. In the three coronaviruses, this chemical may impact viral RNA production by delaying chain termination (MERS-CoV, SARS-CoV and SARS-CoV-2). It is now being evaluated in numerous countries for COVID-19 emergency treatment.

Translation of these mRNAs results in the structural proteins S, M, E, and N. The E protein is responsible for many steps of viral replication, particularly envelope production, pathogenicity, budding, and assemblage. When the CoV RNA sequence is bound to N, it forms the nucleocapsid, contrary to the other important structural proteins. Cascarina et al recently discovered that the N protein can regulate biomolecular interactions with RNA and critical host cell proteins. N protein interacts with stress granules, triggering the host immunological system. Modification of stress granules may be effective in reducing coronavirus replication. N protein interacts with G3BP1, which limits the RNA virus replication (Figure 2).[79-81]

6.5 Modulatory Peptides for the Immune System

Once within the target cell, the virus triggers an immune response (innate or adaptive). The virus enters the nose and mouth, then enters the lungs, infecting ACE2 receptor-expressing cells. These viruses evade immune cells, culminating in the unrestricted viral reproduction. Activated macrophages and other immune cells produce cytokines.[82]

A) Innate Immune Response

When the SARS-CoV-2 virus infects the upper or lower respiratory airways, it may lead to the development

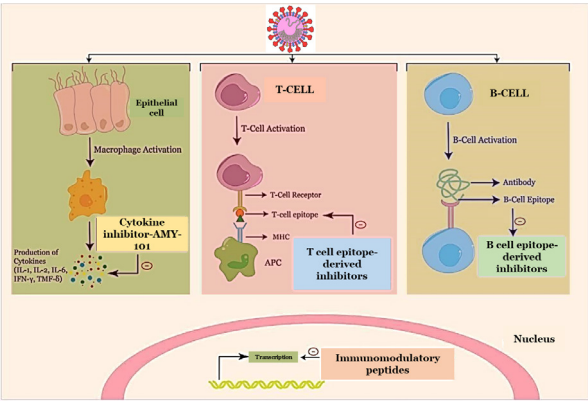

Figure 3: Illustration of how SARS-CoV-2 affects the immune system, with peptide therapeutics in the foreground.

of acute respiratory syndrome (ARS). The compstatin-derived complement C3 peptidic antagonist AMY-101 proved effective in treating extreme ARDS (Acute respiratory distress syndrome) due to COVID-19 pneumonia in an individual. The pathogenic immunological response to SARS-CoV-2 may be mitigated by using an IL-1 receptor inhibitor in conjunction with remdesivir.[83]

To fight viral infection, natural killer (NK) cells lyse infected cells. Peripheral blood in COVID-19 individuals has a lower amount of NK cells. In a SARS-CoV mouse model, enhanced chemokine production linked with increased NK cell migration towards the lungs. Elevated chemokines production in COVID-19 patients' lungs may also help NK cells migrate towards the lungs. A transcriptome signature suggested NK cell penetration into lungs, potentially via the CXCR3 (C-X-C Motif Chemokine Receptor 3) pathway. Because chemokines recruit NK cells for removing the virus, peptide blockers that block chemokine receptors are prospective SARSCoV-2 treatments. Furthermore, peptide blockade is a well-proposed means for NK cell activation, so new peptide treatments are needed here.[84]

B) Adaptive Immune Response

Antibody and immunological response are critical for vaccination effectiveness. A successful vaccine should stimulate antigen-specific B-cells, or T cells. In response to SARS-CoV-2 infection, antibodies, cluster of differentiation (CD) cells including CD4+ and CD8+ cells are produced. As a result of this recognition, T cells produce cytokines. Others provide SARS-CoV peptides to CD4+ cells (Figure 3). Effective vaccines should be designed such that it stimulates immunological responses against the infection. Vaccines that work against a specific pathogen are those that successfully elicit a protective immune response. Kiyotani et al. detected 781 HLA (human leukocyte antigens) class I and 418 Class II antigenic determinants for SARS-CoV-2 by computerized examination of potential determinants expressed on HLA class I molecules. SARS-CoV-2 proteome was studied immunologically and an epitope, ITLCFTLKR, was discovered as a vaccine candidate. When using envelope protein as an immunogenic target, peptides that attach to MHC (major histocompatibility complex) class I and II are attractive vaccine candidates. Ten epitopes derived from structural proteins created by molecular docking of MHC-I are discovered as possible SARS-CoV-2 peptide vaccine epitopes. They are immunogenic elements that may be utilised to discover new vaccines. Because traditional experimental methods are costly and take time, in silico strategies are chosen.[85-88]

7. CONCLUSION

Effective vaccinations and antivirals must be developed quickly for battling the SARS-CoV-2 pandemic and reduce the number of deaths caused by the disease. Peptides are an excellent framework for developing novel medications because of their rapid design and development, extreme selectivity, and low adverse reactions. Although synthetic peptide vaccines are currently in the research and development phase, vaccine development has proved to be both effective and quick. Drug repurposing has shown to be the superior technique for developing new chemical medicines. Furthermore, innovative drug delivery systems might be designed for improving their administration approaches. This article will be very helpful in hastening the design of new therapies for COVID-19, despite the fact that its accuracy and scope will be temporary owing to the quick improvements being made in this field.

REFERENCES

1. Konatham TK, Satyanarayana Reddy K, Masipogu A, Vallakeerthi N. A Review on viruses that originated from china; Sars, mers and covid-19. World Journal of Pharmaceutical Research, 2020;9(5):2010-2015.
2. Tannock GA, Kim H, Xue L. Why are vaccines against many human viral diseases still unavailable; an historic perspective?. Journal of medical virology. 2020;92(2):129-38.
3. Tizzano B, Palladino P, De Capua A, Marasco D, Rossi F, Benedetti E, Pedone C, Ragone R, Ruvo M. The human prion protein α2 helix: a thermodynamic study of its conformational preferences. Proteins: Structure, Function, and Bioinformatics. 2005;59(1):72-9.
4. Bagwe PV, Bagwe PV, Ponugoti SS, Joshi SV. Peptide-based vaccines and therapeutics for COVID-19. International Journal of Peptide Research and Therapeutics. 2022;28(3):94.
5. Buckton LK, Rahimi MN, McAlpine SR. Cyclic peptides as drugs for intracellular targets: The next frontier in peptide therapeutic development. Chemistry–A European Journal. 2021;27(5):1487-513.
6. Diao L, Meibohm B. Pharmacokinetics and pharmacokinetic–pharmacodynamic correlations of therapeutic peptides. Clinical pharmacokinetics. 2013;52:855-68.
7. Bruno BJ, Miller GD, Lim CS. Basics and recent advances

in peptide and protein drug delivery. Therapeutic delivery. 2013;4(11):1443-67.

8. Muttenthaler M, King GF, Adams DJ, Alewood PF. Trends in peptide drug discovery. Nature reviews Drug discovery. 2021;20(4):309-25.
9. Together against alzheimer's disease since 1999, AXON Neuroscience SE. Available at: https://www.axon-neuroscience.eu/ (Accessed: March 9, 2023).
10. Covid-19, CytoDyn Inc. Available at: https://www.cytodyn.com/pipeline/covid-19 (Accessed: March 9, 2023).
11. Our pipeline (2022) Vaxxinity. Available at: https://vaxxinity.com/our-pipeline/ (Accessed: March 9, 2023).
12. Flovid-20 (2022) Flow Pharma. Available at: https://flowpharma.com/product/flovid-20/ (Accessed: March 9, 2023).
13. Development Pipeline | Vir Biotechnology. Available at: https://www.vir.bio/pipeline/ (Accessed: March 9, 2023).
14. Hatmal MmM, Alshaer W, Al-Hatamleh MA, Hatmal M, Smadi O, Taha MO, et al. Comprehensive structural and molecular comparison of spike proteins of SARS-CoV-2, SARS-CoV and MERS-CoV, and their interactions with ACE2. Cells. 2020;9:2638.
15. Premkumar L, Segovia-Chumbez B, Jadi R, Martinez DR, Raut R, Markmann AJ, et al. The receptor-binding domain of the viral spike protein is an immunodominant and highly specific target of antibodies in SARS-CoV-2 patients. Science immunology. 2020;5:eabc8413.
16. Tomaszewski T, DeVries RS, Dong M, Bhatia G, Norsworthy MD, Zheng X, et al. New pathways of mutational change in SARS-CoV-2 proteomes involve regions of intrinsic disorder important for virus replication and release. Evolutionary Bioinformatics. 2020;16:1176934320965149.
17. Ganesh B, Rajakumar T, Malathi M, Manikandan N, Nagaraj J, Santhakumar A, et al. Epidemiology and pathobiology of SARS-CoV-2 (COVID-19) in comparison with SARS, MERS: An updated overview of current knowledge and future perspectives. Clinical epidemiology and global health. 2021;10:100694.
18. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen K-Y. Coronaviruses-drug discovery and therapeutic options. Nature reviews Drug discovery. 2016;15:327-47.
19. Chan JF, Chan K-H, Kao RY, To KK, Zheng B-J, Li CP, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. Journal of Infection. 2013;67:606-16.
20. De Wilde AH, Jochmans D, Posthuma CC, Zevenhoven-Dobbe JC, Van Nieuwkoop S, Bestebroer TM, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrobial agents and chemotherapy. 2014;58:4875-84.
21. Dyall J, Coleman CM, Venkataraman T, Holbrook MR, Kindrachuk J, Johnson RF, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. Antimicrobial agents and chemotherapy. 2014;58:4885-93.
22. Mohammadi Pour P, Fakhri S, Asgary S, Farzaei MH, Echeverria J. The signaling pathways, and therapeutic targets of antiviral agents: focusing on the antiviral approaches and clinical perspectives of anthocyanins in the management of viral diseases. Frontiers in Pharmacology. 2019;10:1207.
23. Smith MC, Gestwicki JE. Features of protein–protein interactions that translate into potent inhibitors: topology, surface area and affinity. Expert reviews in molecular medicine. 2012;14:E16.
24. Cretich M, Gori A, D'Annessa I, Chiari M, Colombo G. Peptides for infectious diseases: From probe design to diagnostic microarrays. Antibodies. 2019;8(1):23.
25. Cunningham AD, Qvit N, Mochly-Rosen D. Peptides and peptidomimetics as regulators of protein–protein interactions. Current opinion in structural biology. 2017;44:59-66.
26. Di L. Strategic approaches to optimizing peptide ADME properties. The AAPS journal. 2015;17:134-43.
27. Lee AC-L, Harris JL, Khanna KK, Hong J-H. A comprehensive review on current advances in peptide drug development and design. International journal of molecular sciences. 2019;20(10):2383.
28. Madhavan M, Mustafa S. En route to peptide therapeutics for COVID 19: harnessing potential antigenic mimicry between viral and human proteins. Transactions of the Indian National Academy of Engineering. 2020;5:411-5.
29. Chowdhury SM, Talukder SA, Khan AM, Afrin N, Ali MA, Islam R, et al. Antiviral Peptides as Promising Therapeutics against SARS-CoV-2. Journal of Physical Chemistry B. 2020;124:9785-92.
30. Ahmed A, Siman-Tov G, Hall G, Bhalla N, Narayanan A. Human antimicrobial peptides as therapeutics for viral infections. Viruses. 2019;11:704.
31. Vilas Boas LCP, Campos ML, Berlanda RLA, de Carvalho Neves N, Franco OL. Antiviral peptides as promising therapeutic drugs. Cellular and Molecular Life Sciences. 2019;76:3525-42.
32. Agarwal G, Gabrani R. Antiviral Peptides: Identification and Validation. International Journal of Peptide Research and Therapeutics. 2021;27:149-68.
33. Fosgerau K, Hoffmann T. Peptide therapeutics: current status and future directions. Drug discovery today. 2015;20:122-8.
34. Mustafa S, Balkhy H, Gabere MN. Current treatment options and the role of peptides as potential therapeutic components for Middle East Respiratory Syndrome (MERS): a review. Journal of infection and public health. 2018;11:9-17.
35. Kiplin Guy R, DiPaola RS, Romanelli F, Dutch RE. Rapid repurposing of drugs for COVID-19. Science. 2020;368:829-30.
36. Harrison C. Coronavirus puts drug repurposing on the fast track. Nature biotechnology. 2020;38:379-81.
37. Khavinson V, Linkova N, Dyatlova A, Kuznik B, Umnov R. Peptides: Prospects for Use in the Treatment of COVID-19. Molecules. 2020;25:4389.
38. Mousavi Maleki MS, Rostamian M, Madanchi H. Antimicrobial peptides and other peptide-like therapeutics as promising candidates to combat SARS-CoV-2. Expert Review of Anti-Infective Therapy. 2021;19:1205-17.
39. Cherian SS, Agrawal M, Basu A, Abraham P, Gangakhedkar RR, Bhargava B. Perspectives for repurposing drugs for the coronavirus disease 2019. Indian J Med Res. 2020;151:160-171.
40. Chen YW, Yiu C-PB, Wong KY. Prediction of the SARS-CoV-2 (2019-nCoV) 3C-like protease (3CL pro) structure: virtual

screening reveals velpatasvir, ledipasvir, and other drug repurposing candidates. F1000Research. 2020;9:129.

41. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020;19:149-50.
42. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life sciences. 2020;248:117477.
43. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell discovery. 2020;6:1-18.
44. Han DP, Penn-Nicholson A, Cho MW. Identification of critical determinants on ACE2 for SARS-CoV entry and development of a potent entry inhibitor. Virology. 2006;350(2):15-25.
45. Huang Y, Zhao R, Luo J, Xiong S, Shangguan D, Zhang H, et al. Design, synthesis and screening of antisense peptide based combinatorial peptide libraries towards an aromatic region of SARS-CoV. Journal of Molecular Recognition. 2008;21:122-31.
46. Guo Y, Tisoncik J, McReynolds S, Farzan M, Prabhakar BS, Gallagher T, et al. Identification of a new region of SARS-CoV S protein critical for viral entry. Journal of molecular biology. 2009;394:600-5.
47. Chu LHM, Chan SH, Tsai SN, Wang Y, Cheng CHK, Wong KB, et al. Fusion core structure of the severe acute respiratory syndrome coronavirus (SARS-CoV): In search of potent SARS-CoV entry inhibitors. Journal of Cellular Biochemistry. 2008;104:2335-47.
48. Struck A-W, Axmann M, Pfefferle S, Drosten C, Meyer B. A hexapeptide of the receptor-binding domain of SARS corona virus spike protein blocks viral entry into host cells via the human receptor ACE2. Antiviral research. 2012;94:288-96.
49. Lu W, Wu X-D, Shi MD, Yang RF, He YY, Bian C, et al. Synthetic peptides derived from SARS coronavirus S protein with diagnostic and therapeutic potential. FEBS letters. 2005;579:2130-6.
50. Yuan K, Yi L, Chen J, Qu X, Qing T, Rao X, et al. Suppression of SARS-CoV entry by peptides corresponding to heptad regions on spike glycoprotein. Biochemical and biophysical research communications. 2004;319:746-52.
51. Bosch BJ, Martina BEE, Van Der Zee R, Lepault J, Haijema BJ, Versluis C, et al. Severe acute respiratory syndrome coronavirus (SARS-CoV) infection inhibition using spike protein heptad repeat-derived peptides. Proceedings of the National Academy of Sciences of the United States of America. 2004;101:8455-60.
52. Xia S, Yan L, Xu W, Agrawal AS, Algaissi A, Tseng C-TK, et al. A pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. Science advances. 2019;5:eaav4580.
53. Sainz B, Jr, Mossel EC, Gallaher WR, Wimley WC, Perter CJ, Wilson RB, Garry RF. Inhibition of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) infectivity by peptides analogous to the viral spike protein. Virus Research. 2006;120(1-2):146-155.
54. Liu I-J, Kao C-L, Hsieh S-C, Wey M-T, Kan L-S, Wang W-K. Identification of a minimal peptide derived from heptad repeat (HR) 2 of spike protein of SARS-CoV and combination of HR1-derived peptides as fusion inhibitors. Antiviral research. 2009;81:82-7.
55. Zhu GX, Tao H, He W, Tien P, Shan GFM, Tang J, et al. Screening and identification of severe acute respiratory syndrome-associated coronavirus-specific CTL epitopes. Am Assoc Immnol. 2022;177:2138-45.
56. He Y, Zhou Y, Siddiqui P, Niu J, Jiang S. Identification of immunodominant epitopes on the membrane protein of the severe acute respiratory syndrome-associated coronavirus. Journal of Clinical Microbiology. 2005;43:3718-26.
57. Choy W-Y, Lin S-G, Chan PK-S, Tam JS-L, Lo YD, Chu IM-T, et al. Synthetic peptide studies on the severe acute respiratory syndrome (SARS) coronavirus spike glycoprotein: perspective for SARS vaccine development. Clinical Chemistry. 2004;50:1036-42.
58. Hu H, Li L, Kao RY, Kou B, Wang Z, Zhang L, et al. Screening and identification of linear B-cell epitopes and entry-blocking peptide of severe acute respiratory syndrome (SARS)-associated coronavirus using synthetic overlapping peptide library. Journal of Combinatorial Chemistry. 2005;7:648-56.
59. Tai W, He L, Zhang X, Pu J, Voronin D, Jiang S, et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. Cellular & Molecular Immunology 2020;17(6):613-620.
60. Barh D, Tiwari S, Silva Andrade B, Giovanetti M, Almeida Costa E, Kumavath R, et al. Potential chimeric peptides to block the SARS-CoV-2 spike receptor-binding domain. F1000Research. 2020; 9:576.
61. Han Y, Král P. Computational Design of ACE2-Based Peptide Inhibitors of SARS-CoV-2. ACS nano. 2020;14:5143-7.
62. Xu Y, Zhu J, Liu Y, Lou Z, Yuan F, Liu Y, et al. Characterization of the heptad repeat regions, HR1 and HR2, and design of a fusion core structure model of the spike protein from severe acute respiratory syndrome. ACS Publications. 2004;43:14064-71 .
63. Xia S, Zhu Y, Liu M, Lan Q, Xu W, immunology YWm, et al. Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein. naturecom.
64. Tang T, Bidon M, Jaimes JA, Whittaker GR, Daniel S. Coronavirus membrane fusion mechanism offers a potential target for antiviral development. Antiviral research. 2020;178:104792.
65. Cannalire R, Stefanelli I, Cerchia C, Beccari AR, Pelliccia S, Summa V. SARS-CoV-2 entry inhibitors: Small molecules and peptides targeting virus or host cells. Int J Mol Sci. 2020;21(16):5707.
66. ul Qamar MT, Alqahtani SM, Alamri MA, Chen L-L. Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. Journal of pharmaceutical analysis. 2020;10:313-9.
67. Yang H, Xie W, Xue X, Yang K, Ma J, Liang W, et al. Design of wide-spectrum inhibitors targeting coronavirus main proteases. PLoS Biology. 2005;3.
68. Dai W, Zhang B, Jiang XM, Su H, Li J, Zhao Y, et al. Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. Science. 2020;368:1331-5.
69. Corley MJ, Ndhlovu LC. DNA Methylation Analysis of the COVID-19 host cell receptor, Angiotensin I Converting Enzyme 2 gene (ACE2) in the Respiratory System Reveal Age and Gender Differences. 2020;10.20944/preprints202003.0295.v1.
70. Qiao Y, Wang XM, Mannan R, Pitchiaya S, Zhang Y, Wotring

JW, et al. Targeting transcriptional regulation of SARS-CoV-2 entry factors ACE2 and TMPRSS2. Proceedings of the National Academy of Sciences of the United States of America. 2021;118(1):e2021450118.

71. Takahashi Y, Hayakawa A, Sano R, Fukuda H, Harada M, Kubo R, et al. Histone deacetylase inhibitors suppress ACE2 and ABO simultaneously, suggesting a preventive potential against COVID-19. Scientific Reports. 2021;11(1):3379.
72. Pruimboom L. Methylation Pathways and SARS-CoV-2 Lung Infiltration and Cell Membrane-Virus Fusion Are Both Subject to Epigenetics. Frontiers in Cellular and Infection Microbiology. 2020;10:290.
73. Olsen CA, Ghadiri MR. Discovery of potent and selective histone deacetylase inhibitors via focused combinatorial libraries of cyclic α3 β-tetrapeptides. Journal of Medicinal Chemistry. 2009;52:7836-46.
74. Mousavizadeh L, Ghasemi S. Genotype and phenotype of COVID-19: Their roles in pathogenesis. Journal of Microbiology, Immunology and Infection. 2021;54:159-63.
75. Daffis S, Szretter KJ, Schriewer J, Li J, Youn S, Errett J, et al. 2′-O methylation of the viral mRNA cap evades host restriction by IFIT family members. Nature. 2010;468(7322):452-6 .
76. Viswanathan T, Arya S, Chan SH, Qi S, Dai N, Misra A, et al. Structural basis of RNA cap modification by SARS-CoV-2. Nature Communications. 2020;11(1):3718.
77. Chen Y, Cai H, Pan Ja, Xiang N, Tien P, Ahola T, et al. Functional screen reveals SARS coronavirus nonstructural protein nsp14 as a novel cap N7 methyltransferase. Proceedings of the National Academy of Sciences. 2009;106:3484-9.
78. Wang Y, Sun Y, Wu A, Xu S, Pan R, Zeng C, et al. Coronavirus nsp10/nsp16 Methyltransferase Can Be Targeted by nsp10-Derived Peptide In Vitro and In Vivo To Reduce Replication and Pathogenesis. Journal of Virology. 2015;89:8416-27.
79. De Haan CA, Rottier PJ. Molecular interactions in the assembly of coronaviruses. Adv Virus Res. 2005;64:165-230.
80. Cascarina SM, Ross ED. A proposed role for the SARS-CoV-2 nucleocapsid protein in the formation and regulation of biomolecular condensates. FASEB Journal. 2020;34:9832-42.
81. Yang W, Ru Y, Ren J, Bai J, Wei J, Fu S, et al. G3BP1 inhibits RNA virus replication by positively regulating RIG-I-mediated cellular antiviral response. Cell Death & Disease. 2019;10(12):946.
82. Gallenga CE. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by COVID-19: anti-inflammatory strategies. Article in Journal of Biological Regulators and Homeostatic Agents. 2020;10.23812/CONTI-E.
83. Franzetti M, Pozzetti U, Carugati M, Pandolfo A, Molteni C, Faccioli P, et al. Interleukin-1 receptor antagonist anakinra in association with remdesivir in severe COVID-19: A case report. International Journal of Infectious Diseases. 2020;97:215-8.
84. Fadda L, Borhis G, Ahmed P, Cheent K, Pageon SV, Cazaly A, et al. Peptide antagonism as a mechanism for NK cell activation. Proceedings of the National Academy of Sciences of the United States of America. 2010;107:10160-5.
85. Liu J, Wu P, Gao F, Qi J, Kawana-Tachikawa A, Xie J, et al. Novel Immunodominant Peptide Presentation Strategy: a Featured HLA-A*2402-Restricted Cytotoxic T-Lymphocyte Epitope Stabilized by Intrachain Hydrogen Bonds from Severe Acute Respiratory Syndrome Coronavirus Nucleocapsid Protein. Journal of Virology. 2010;84:11849-57.
86. Joshi A, Joshi BC, Mannan MAu, Kaushik V. Epitope based vaccine prediction for SARS-COV-2 by deploying immunoinformatics approach. Informatics in Medicine Unlocked. 2020;19:100338.
87. Robson B. Computers and viral diseases. Preliminary bioinformatics studies on the design of a synthetic vaccine and a preventative peptidomimetic antagonist against the SARS-CoV-2 (2019-nCoV, COVID-19) coronavirus. Computers in Biology and Medicine. 2020;119:103670.
88. Palatnik-de-Sousa CB, Soares IdS, Rosa DS. Editorial: Epitope discovery and synthetic vaccine design. Frontiers in Immunology. 2018;9:826.

How to cite this article: Tallam AK, Sahithi A, Nuli MV. A Review on Peptide-Based Therapeutics For Combatting Covid-19. Int. J. Appl. Pharm. Sci. Res. (2023);8(1): 8-16. doi: https://doi.org/10.21477/ijapsr.8.1.02

Source of Support: Nil.

Conflict of Support: None declared.