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Review

Role of Peptides in Antiviral (COVID-19) Therapy

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ABSTRACT - Trends in the developing era to discover and design peptide-based treatments throughout an epidemic infection scenario such as COVID-19 could progress into a more efficient and low-cost therapeutic environment. However, the weakening of proteolysis is one downside of natural peptide drugs. But, peptidomimetics may help resolve this issue. In this review, peptide and peptide-based drug discovery were summarized to target one key entry mechanism of severe coronavirus pulmonary emboli syndrome (SARS-CoV-2), which encompasses the association of the host angiotensin-converting enzyme-2 (ACE2) receptor and viral spike (S) protein. Furthermore, the benefits of proteins, peptides and other possible actions that have been studied for COVID-19 through new peptide-based treatments are discussed in the review. Lastly, an overview of the peptide-based drug therapy environment is comprised of an evolutionary viewpoint, structural properties, operational thresholds, and an explanation of the therapeutic area.

Keywords: Peptides, COVID-19, Angiotensin-converting enzyme-2 (ACE2) receptor, Drug therapy

Around 108 million coronavirus disease cases (COVID-19) were reported in 2019, and 2.4 million deaths up to date (COVID-19) were reported globally (Fig. 1)[1,2]. At the turn of the twentieth century, numerous zoonotic occurrences have contributed to epidemic outbreaks in humans, such as Influenza A, H1N1, H5N1, H7N9, Zika virus Ebola virus populations[3]. The epidemics attributable to affiliates in term of spread and survival of COVID family has been particularly prevalent, starting with the emergence of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002-2003, accompanied in 2012 by Middle East Coronavirus Respiratory Syndrome (MERS-CoV) and in late 2019 by SARS-CoV-2 (COVID-19)[4]. Based on the spikes protein's and virulence factors, a large trimeric crown-like complex forming the namesake complex is a coronavirus family in humans. As noted in the microscopic examination, 'corona' (Fig. 2)[5]. The functional annotation on the coronavirus strains and their function of the spiked protein depends on the host species, and tissue tropism was found in bats. The SARS-CoV, MERS-CoV, and SARS-CoV-2 were correlated with the current outbreaks, which share their entry receptors' similarity, linking host cell post-translational. Still, coronaviruses may distinguish other COVID based on specific alterations like glycans or type of molecule binding. Whereas a) MERS-CoV applies dipeptidyl peptidase-44 primarily (DPP4), which is responsible for the deprivation of incretins such as Glucagon-like peptide-1 (GLP-1) is a 30 or 31 amino acid long peptide hormone)., b) SARS-CoV and c) SARS-CoV-2 can apply angiotensin-converting enzyme-2 (It is an enzyme attached to the cell membranes of cells in different human organs (lungs, arteries, heart, kidney, and intestines)) to penetrate human cells (ACE2) as the primary receptor (Fig. 2 and Fig. 3)[6]. In addition to perception and integration, the prior binding site was regulated by secondary pathways through signaling mediated by S protein, including C-type lectins and high-mannose glycans. It is also suggested that viral entry is possible through endocytosis[7]. The framework is arising in endosomes, with viral signal transduction. SARS-CoV and SARS-CoV-2 S protein are strongly glycosylated (It is an enzyme-directed chemical reaction that takes place in the Endoplasmic Reticulum (ER) and the Golgi Apparatus body (directs the

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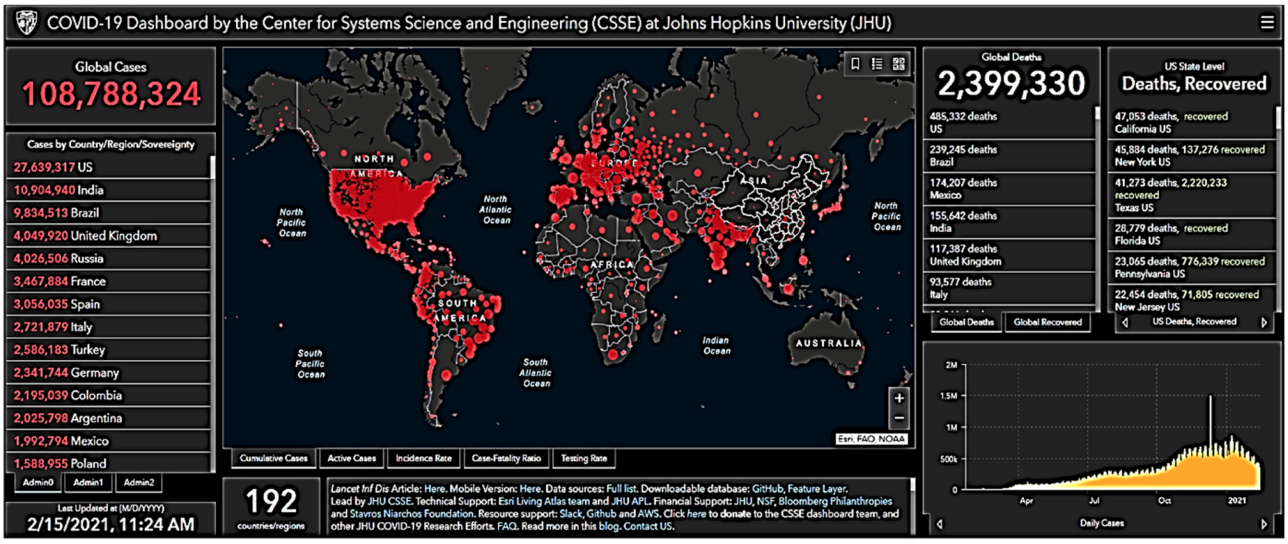
(a)



(b)

Fig. 1. (a) Data on this page is taken from the COVID-19 Dashboard on 15 February, 2021 and (b) Data collected on 23 September, 2021 by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (https://coronavirus.jhu.edu/map.html)[2].

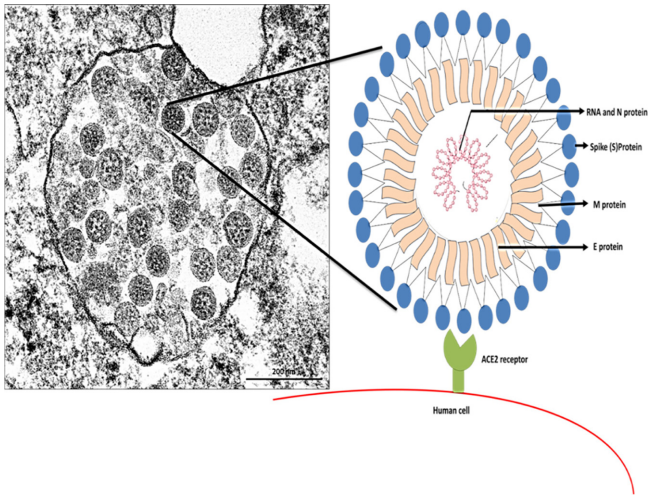


Fig. 2. Transmission electron microscopic image of SARS-CoV-2 (which shows corona viral particles' presence in the cross-sections of the rough endoplasmic reticulum (RER). These spherical structures were surrounded by dark layers, which are the spikes on coronavirus particles). Schematic representation general structure of SARS-CoV's and host cell entry receptor ACE2.

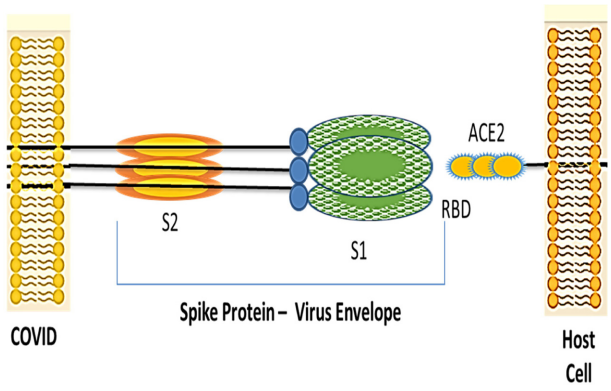


Fig. 3. Transmission electron microscopic image of SARS-CoV-2 (which shows corona viral particles' presence in the cross-sections of the rough endoplasmic reticulum (RER). These spherical structures were surrounded by dark layers, which are the spikes on coronavirus particles).

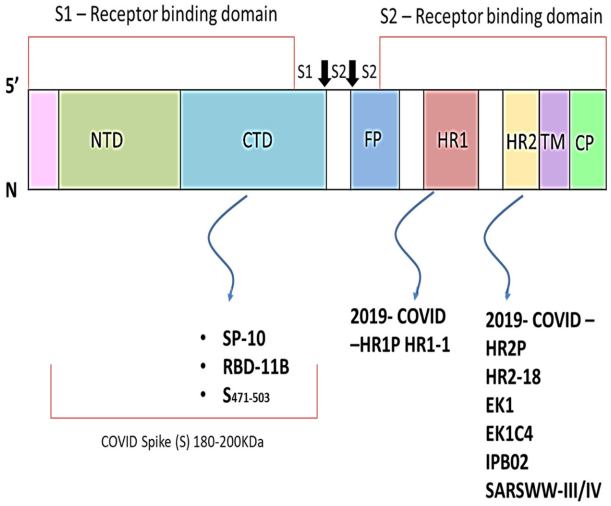


Fig. 4. A 2 Dimensional-representation of the critical domains of the COVID protein. The spike (S) protein was combined with the two subunits: S1 and S2. The S1 domain poses the N terminal domain (NTD), the C terminal domain (CTD), and it is responsible for recognition and binding to the host cell receptor. The S2 domain, responsible for membrane fusion, contains the Fusion protein (FP), heptad repeat 1 (HR1), heptad repeat HR2, the transmembrane^{TM}, and cytoplasmic tail regions (CP tail). Two cleavage sites were indicated with arrows. The major peptide-based therapeutics indicated below are associated S protein regions. Kilodalton (kDa), Severe Acute Respiratory Syndrome (SARS).

protein binding) of the cell. Type I transmembrane glycoprotein of 180-200 kDa with its N-terminus existing on the Virus's outer surface and a short C-terminal region of viral space inside the intramembrane. The S protein consists of subunits S1 and S2, which have a protease cleavage site. The S1 subunit facilitates the new promoter binding structure to ACE2, while the transmembrane machinery is present in the S2 region[8]. The comprised fusion peptides and domains of heptad-1 (HR1) and heptad-2 (HR2), which initiate the conjugation of the viral and outer membrane of the host cell-based on host receptor (Fig. 4)[9,10]. The S1 terminal forms the receptor-binding site (RBS) in the C terminal domain is composed of the amino acid residues.

Mechanism of COVID viral infection

After the SARS-CoV outbreak (2002-2003), the Virus was sequenced, and based on proteomic analysis; the receptor binding domain (RBD) was reported to contain 318-510 aminoacid, which represents to code for S proteins[11]. Likewise, the minimum binding domine (MBD) was described in combination with RBD based on a short loop structure which consists of 424-494 region containing Sproteins with 14 amino acids. Similarly, the SARS-CoV compared with the SARS-CoV 2 strain proteomic analysis revealed that the RBD sequence residue was found to be similar in the 331-524 residue region[12]. Furthermore, based on the detailed proteomic reports, the conserved residues and sequence variation were observed in SARS-CoV 2, SARS-CoV 2, and MERS. The similarity in the sequence index of the S2 domine. Based on the review, the data on applying the drug target to the S2 domine region for the development of SARS-CoV therapeutics[13].

Previous studies indicate that after virus binding with the angiotensin-converting enzyme (ACE) receptor, the S protein present in the virus initiates host cell proteases[14]. The cleavage of the S1/S2 boundary releases the strain into the cell. Besides, the S2 subunit (fusion peptide) domine also binds the host cell membrane with the virus. Further, the S2 cleavage site exposes the fusion peptide penetration to form six alpha-helix bundle, which assembles the host cell and virus membrane fusion, leads to the release of viral genetic (Fig. 5). The tissue-specific spread of proteases designed to progress the S protein, therefore, restricts the pathogenicity of different COVID, far beyond the primary receptor's cell and organ-specific position, angiotensin-converting enzyme 2 (ACE-2)[15].

The COVID targeted tissue expression occurs in many organs, but the higher ex-pression occurs in lunge-based alveolar epithelial cells and intestinal absorptive cells (simple columnar epithelial cells). The overexpression depends on ACE2 receptor-based glycoprotein leads to carboxy-peptidase (protease enzyme that hydrolyzes (cleaves) a peptide bond at the carboxy-terminal (C-terminal) end of a protein or peptide)[16]. Its main functions lead to convert vasoconstrictive and inflammatory peptide (Angiotension-2 into Angiotension-1-7 through the cleavage of the C - terminal; likewise, the angiotensin 1 converted

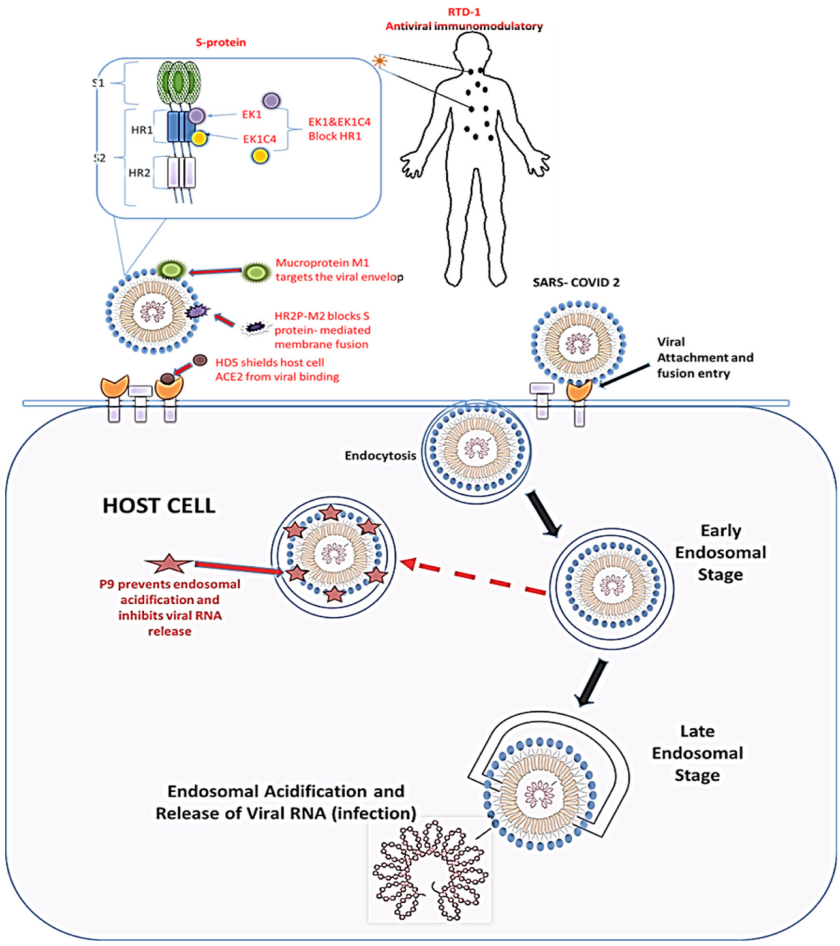


Fig. 5. Mechanism of actions of Antiviral protein with potential anti-SARS-CoV-2 activities. Numerous antiviral protein target the major morphology components of the Virus to exert antiviral effects: mucroporin-M1 (Cationic Peptide), which mainely acts by disrupting viral envelope, HR2P-M2 targets the viral Spike protein-mediated fusion, EK1 and EK1C4 block the HR1 subunit domain of viral S2 subunit and P9 peptide act towards stopping late host endosome cell layer degradation (acidification) and thus preventing viral RNA release. Anti-viral peptide confers antiviral protection to the host: RTD-1 is a potent antiviral immuno-modulatory to initiates immune enhancement, and HD5 adheres and protects ACE2 from viral specification docking.

into angiotensin (1-9)[17].

As for the year 2019-2020, many published research studies focused, initially on the history of outbreak, correlation of previous COVID strains with the current COVID-19 strain, and finally focused on therapeutic medicines to control the severance and to maintain the mortality, based on the therapeutic aspect, antibiotics were prescribed initially. Still, there is no effect on the COVID 19 virus. Eventually, the antibiotics helped control the bacterial infection as per the complication that emerged by COVID-19[18]. Further, the antimalarial drugs (chloroquine and hydroxychloroquine) showed effective treatment of SARS-CoV and other viruses such as HIV and Zika Virus. Few manuscripts were published on natural therapeutic peptides, which target the ACE2 - S protein (protein-protein interaction)[19]. Hence the current review focus on the therapeutic peptides which were involved COVID treatment and further other application and importance of the developed therapeutic peptides were reviewed in detail. Further, the rapid multiplication of COVID-19 virus in kidney cells (Unpublished data).

The invention of peptide therapy

Peptides constitute a particular class of molecularly regulated but biochemically and therapeutically distinct pharmaceutical compounds. Peptides represent an opportunity for therapeutic intervention that closely imitates natural pathways as inherent signaling molecules for several physiological functions. Also, many peptide medicines are simply “replacements” that add or substitute peptide hormones in cases of insufficient or lacking endogenous concentration. This can be demonstrated

by the isolation and initial therapeutic use of insulin in diabetics in the 1920s who did not produce enough hormone[20]. Currying adrenocorticotrophic hormone (ACTH) in livestock pituitary glands to treat different endocrine conditions in patients was accompanied by insulating peptides from whole livestock tissue[21]. Peptides have evolved as therapeutics over time and continue to grow as drug development and treatment paradigms (Table 1). In the first half of the 20th-century, peptides, which were insulin-isolated and ACTH, gave life-saving medicines. In mid of the 90s, synthetic oxytocin and vasopressin were applied in clinical terms before sequence clarification, and peptides' chemical syntheses became feasible. As the venom of arthropods and cephalopods has become recognized as a store of bioactive peptides, it has become a popular strategy for isolating natural products from exotic sources. The genomic age allowed many important peptide hormones to be recognized and molecularly characterized by the receptors, and industry and academia started to pursue new peptide ligands for such receptors. The enthusiasm for peptide therapy was later tempered by some native peptide limits, for example, short plasma halving life and low oral bioavailability. The short half-life of many peptide hormones modulates the hormone levels quickly but is complicated for several clinical developments. These peptide limitations were described elsewhere in detail[22]. We will concentrate on peptide characteristics recommended for human clinical development. Scientists have started using medicinal chemistry techniques to make candidates more like medicines by improving half-life, physiological stability, and receptor selectiveness. The clinic also provided peptide analogs of native hormones with enhanced medicinal properties.

Oral bioavailability is another barrier to the production of peptide drugs: The enzymes designed to decompose amide bands of ingested proteins are effective at cleaving peptide hormones with the same interactions, and the high polarity and molecular weight of peptides severely restrict intestinal permeability. Since oral delivery is often desirable for promoting compliance with the patient, the need for injection decreases the appeal for evidence requiring ongoing, external care. Besides, the availability of an extensive combinatorial chemistry library and high percussion (HTS) technology has pendulum to small molecules aimed at peptide receptors in a new direction. The general challenge is to find a small molecule that mimics a peptide ligand's receptor binding and selective modulation; small molecules are more appropriate for oral delivery and more accessible to produce than peptides. In the new screening library, the number and variety of scaffolds support the idea that leads molecules could be detected, optimized, and transformed into drugs. Structural biology applied an arrow to the carcass by delaminating main molecular interactions that any molecule could exploit at receptor active locations.

In some cases, the small molecular approach has been better than in others. Small molecules are less effective than peptides in peptide receptors, and small molecules that function like antagonists can be detected more easily than agonists. For small molecular drug discovery, especially in class B GPCRs, the large ligand connecting site for some peptide GP CRS and extraordinary conforming changes needed for signal transduction are significant challenges[23-26]. Nevertheless, small molecules, including losartan and valsartan available orally, substituted peptide (SARENIN) as hypertension receptor blockers and other small molecules of the class A G protein-coupled receptors (GPCRs) for which no peptide drugs was marketed as Class A GPCRs (Table 2)

Although resolving some problems in peptide medicines, the potential for liabilities associated with peptides, such as CYP inhibition leading to drug/drug interactions (DDI) and side effects arising from off-target binding, remains unchanged. While a significant discovery, small molecule ligands for peptide receptors are no substitute for peptide

Table 1. List of exRNA-EVs and their description and functional roles

Peptide	Source	Introduction to the clinic	Sequence description	Ref.
Insulin	Isolated from canine and bovine pancreata	1920s	Native	21
Vasopressin	Synthetic	1962	Native	
Calcitonin	Isolated from the salmon ultimobranchial gland	1971	Native	
Oxytocin	Synthetic	1962	Native	
Adrenocorticotropic hormone (ACTH)	Isolated from bovine and porcine pituitary glands	1950s	Native	
Leuprorelin	A synthetic analog of gonadorelin	1984	Nonapeptide analog of decapaptide gonaddorelin	
Octreotide	A synthetic analog of somatostatin	1988	Cyclic octapeptide analog of somatostatin-14	

Table 2. Small molecule drugs act on peptide receptors

Drug or drug class	Primary molecular targets	Action at receptor	Liabilities of small molecules	Current status	Ref.
Bosentan and others	Endothelin receptors	Antagonism	Hepatotoxicity; DDIs	Marketed; no peptides was approved in significant markets	23-26
Tolvaptan and other vaptans	Vasopressin V2 receptor	Antagonism	Hepatotoxicity	Marketed; no peptides was approved in significant markets	
Small-molecule opioids (natural, synthetic, and semi-synthetic)	Opioid receptors	Agonism	Multiple effects caused by lack of receptor subtype specificity	Marketed; no peptides was approved in major markets	
Losartan and other sartans	Angiotensin II receptor 1	Antagonism	DDIs; fetal toxicity	Marketed; displaced the peptide angiotensin receptor blocker saralasin	
Elagolix and others	Gonadotrophin-releasing hormone receptors	Antagonism	DDIs (sufugoix)	Small molecules have entered Phase 3; multiple peptides are currently marketed	
Aprepitant and others	Neurokinin 1 receptor	Antagonism	DDIs	Marketed; no peptides are approved in major markets	

compounds. In recent times, the potential of peptide therapeutics has been further understood and nuanced (characterized).

Novel synthetic drug strategies depend on drug absorption, distribution, metabolism, and excretion to be modulated through amino acid or backbone changes. Consequently, the characteristics of peptides previously seen as liabilities are no more problematic: for example, for some indications, injection is considered an acceptable route of administration partly because of the production of peps or depots, which reduce the injection frequency. Although several classes of oral medications for type 2 diabetes mellitus are available, the market of injectable GLP-1 peptide agonists has continued to expand since the exenatide approval in 2005, and several next-generation medicines candidates are currently in development[27,28]. Teriparatide, an osteoporosis-approved parathyroid truncated hormone, provides an anabolic mechanism of action that is distinct from orals and supports routine injection by oral bisphosphonates[29]. The Peptide drug applicants were produced against various molecular targets beyond the historically prevailing epithelial hormone receptors. The clinic contains peptides that disturb protein-

Table 3. Updated peptide-based therapeutic against SARS-CoV and SARS-CoV-2.[34-41]

Year of infection	Sequence / Structure	Target	Potential therapeutic update	Stage of development	Ref.
SARS COVID -19	ACE2-based peptides	S protein-RBD	Inhibitor 1-4	Proposed in theory	33-40
	ISGINASVVNIQKEIDRLNEVAKNL-NESLIDLQELK(Chol)	HR1 domain of CoV S protein (MFM)	IPB02	Preclinical *in vitro* models	
	DISGINASVVNIQKEIDRLNEVAKNL-NESLIDLQEL	HR1 domain of CoV S protein (MFM)	2019-nCoV-HR2P	Preclinical *in vitro* models	
	IEEQAKTFLDKFNHEAEDLFYQS	S protein-RBD	SBP1 (peptidase domain of ACE2)	Preclinical *in vitro* models	
	SLDQINVTFLDLEYEMKLEE-AIKLEESYIDLKEL	HR1 domain of CoV S protein (MFM)	EK1	Preclinical *in vitro* models	
	(N)EK1-GSGSG-PEG4-(Chol)	HR1 domain of CoV S protein (MFM)	EK1C4 (lipopeptide)	Preclinical in vitro and *in vivo* models	

Table 3. (Continued) Updated peptide-based therapeutic against SARS-CoV and SARS-CoV-2.[34-41]

Year of infection	Sequence /Structure	Target	Potential therapeutic update	Stage of development	Ref.
SARS-CoV (COVID-2003)	SLDQINVTFLDLEYEMKLEE-AIKLEESYIDLKEL	HR2 domain of CoV S protein (MFM)	EK1	Preclinical in vitro and *in vivo* models	33-40
	YKYRYL	ACE2 receptor	RBD-11b	Preclinical *in vitro* models	
	STSQKSIVAYTM	ACE2 receptor	SP10	Preclinical *in vitro* models	
	EEQAKTFLDKFNHEAEDLFYQSSGL-GKGDFR	S protein-RBD	P6	Preclinical *in vitro* models	
	NGIGVTQNVLYENQKQIANQFNKAI-SQIQESLTTTSTA IQKEIDRLNEVAKNLNESLID-LQELGK	HR2 domain of S protein (MFM)	HR1 and HR18	Preclinical *in vitro* models	
	SLDQINVTFLDLEYEMKLEE-AIKLEESYIDLKEL	HR2 domain of CoV S protein (MFM)	EK1	Preclinical in vitro and *in vivo* models	
	GYHLMSFPQAAP-HGVVFLHVTW GVFVFNGTSW-FITQRNFFS	ACE2 receptor (MFM)	SARS WW-III SARS WW-IV (derived from S2 subunit)	Preclinical *in vitro* models	
	ALNCYWPLNDYGFYTTTGIGY-QPYRWVLSFEL	ACE2 receptor	S471-503	Preclinical *in vitro* models	

protein interactions, target the tyrosine kinases receiver and inhibit intracellular targets[30,31]. Phage screen has recognized new peptides as the point of departure for scientific and medicinal chemical study and introduced new peptide scaffolds to the clinic[32,33]. This resulted in the production of therapeutic peptides in a complex and robust environment. In the USA, Europe, and Japan, more than 60 peptide products have been approved; more than 150 are under active clinical development. We will discuss molecular drug targets on COVID based on therapeutic peptides application (Table 3).

Among several peptides, Mucroporin, (LFGLIPSLIGGLV SAFK) is one of the cati-onic Host Defense Peptide collected from a type of Scorpian Venom of Lychas mucronatus applied as a drug.

Likewise, the four different mutation-based Mucroporin-M1 (LFRLIKS-LIKRLVSAFK) were applied as a more efficient drug than the raw peptide antiviral efficiency aginst SARS-CoV - 14.46 μg/mL; influenza H5N1 - 2.10 μg/mL; measles - 7.15 μg/mL[34]. The mucoprotein (M1) showed higher and immediate interaction with measles-based viral material and showed pre-treatment efficacy; besides, it also acts as a blocker towards molecular binding before the virus attachment to the host cells. The peptide mucoprotein (M1) binds with the virus outer-membrane showed higher electrostatic affinity, could block the interaction and distortion of the viral envelope, with act as an anti-viricidal effect against SARS-CoV, MERS-CoV, and influenza H5N1 viruses[35].

Peptide target on the spike (s) glycoprotein

The 36-residue peptide designed by Xia and colleagues EK1 (SLDQINVTFLDLEYEMKKLEEAIKKLEESYIDLKEL) act as a pan - CoV combined in-hibitor against SARS-CoV, MERS-CoV, and three SARS-related COVID-19 from As shown in Fig. 1 tested in bats, besides, the EK1 peptide targets on blocking the HR1 rho-binding domain to avoid the formation of fusion glycoprotein into a trimer of hair-pins with a 6-helix bundle (6HB) core, which prevents the entry of the Virus into the host cell[36].

Additionally, EK1 acts as an intra-nasal drug for the treatment of human corona-virus OC43, which acts as an antiviral remedy for middle east respiratory syndrome-based coronavirus (MERS-CoV)[37]. This indicates that some single peptides can be applied against multiple therapeutic agents against different types and strains of coronavirus. This broad spectrum of antiviral (Anti-coV) function strongly indicates that EK1 will be an effective drug against the upcoming evolved SARS-CoV infection[38]. Recently as an alternative therapy, lipoprotein (EK1C4), synthesized through c terminal of peptide conjugate with a lipid moiety based on the serine

and glycine (amino acid) as stronger binding affinity (-2.02). This binding affinity was enhanced based on the addition of polyethylene glycol (PEG) (EK1-GSGSGPEG4- Lipid)[39].

Similarly, based on lipid conjugation, antiviral therapy reported for HIV C34 inhibitor. Apart from EK1, HR2P-M2 peptides were designed as a drug target against 6HB core of H1 and 2 domains of middle east respiratory syndrome based coronavirus strain. The previous report conducted by channappanavar[40] indicates that intranasal treatment of MERS-CoV with HR2P-M2 showed more potent antiviral efficacy, but the same peptide showed nil effect against SARS-CoV; these experimental outcomes showed the selective antiviral efficiency towards the COVID and other beta coronaviruses.

Peptide targeting towards inhibition of endosomal/lysosomal acidification

A novel peptide P9 (β-defensin-4) reported the potent and broad-spectrum antiviral activity with S2 subunit against MERS- CoV, which prevents the viral entry into the host cell based on the endocytosis[41]. The P9 possesses the peptide's polycationic property (NGAICWGPCPTAFRQIG NCGHFKVRCCKIR), which triggers the micro-environment to prevent the acidification of endosomes. The potential hydrogen ion concentration (pH) of peptide plays a significant role in the activation of viral fusion with the endosomal membrane; if the acidification of the endosome was prevented, the endosomal fusion failed and leads to the uncoating mechanism of viral RNA release[42]. This broad spectral antiviral mechanism was also documented in SARS- CoV, different influenza virus strains, H1N1swin flue, H3N2, H5N1, H7N7, further the cytotoxicity (IC50) for P9 peptide was determined to be 380 μg/mL using the mammalian kidney cells. Thus, the broad therapeutic advantage re-opens a solution for the current COVID19 and upcoming mutated covid strains[43].

Host defense mechanism: protecting the receptor of the cell

The primary point of COVID infection, based on the Angiotensin-converting enzyme 2 precursor (ACE2), which acts as a key entry point of viral into the host cell. The human α-defensin-derived natural lectin peptide HD5(1-9) (ATCYCRTGRCATRES-LSGVCEISGRLYRLCCR) synthesized plays a defensive role against COVID. Based on the structural and chemical properties of HD5 were predicted to recognized the inhibi-tion of SARS- CoV (Spike protein subunit) towards the host cell ACE2[44]. But some research studies indicated that HD5 targeted specifically on S1 peptide subunit, instead targeted on the entire ACE2 receptor of the host cell. The higher binding strength of HD5 peptide towards the ACE2 receptor mainly depends on hydrogen bonding based on hydrophobic and hydrophilic interactions, which protects the host from viral attachment and infection[45].

Immunomodulatory based antiviral therapy

The cyclic-based peptide (Rhesus θ-defensin-1 (RTD-1) synthesized from leukocytes of (Rhesus macaque (Macaca mulatta)), which substantially reduces the necrotizing bronchiolitis caused by SARS- CoV[46]. Besides, among the cytokines level, the interleukin -6 (IL6), keratinocyte, and granulocyte (white blood cells in the innate immune system pigeonholed by the occurrence of specific granules in their cytoplasm[47]. They are also called polymorphonuclear leukocytes (PMN, PML, or PMNL)) in lung tissue homogenates, thus RTD-1 peptide act as immuno-modulatory effector compound through the production of proinflammatory based cytokines response in eradicating SARS- CoV[48].

Likewise, the lactoferrin (LF) is a globular glycoprotein (molecular mass - 80 kDa) antiviral peptide, act as an iron-binding protein present in the different mucosal secreted matrix (milk, saliva, tears, and nasal secretions), which has a vital role in the function towards immune enhancement. Besides, the lactoferrin act as a multifunctional (protein of the transferrin family) mechanism (bacteriocide, fungicide)[49]. The critical part of antiviral therapy for humans and animals-based Virus (containing DNA or RNA genetic material) is that the LF acts as an immune enhancement. Further, LF functions as a viral binding inhibitor in the cellular receptors[50]. LF is present in human breast milk as one of the major constituents. Hence breast milk will be one of the natural remedies as antiviral therapy; most of the proven research aspects indicate that LF has multifunction therapeutic target against HCV, HSV, HIV, polio-, and the rotavirus. The significant spread of coronavirus through the oral and nasal, in which the LF binds directly to the virus particle. Hence it may act as an effective remedy against the coronavirus[51]. Further, LF can be applied as an individual drug or drug conjugate (synergetically functions as a combined antiviral drug with the conventional medicine)[52]. This will avoid drug resistance mechanisms caused by mutated strains.

Antiviral peptide therapy's towards future directions

Globally, due to the pandemic condition's emergency, the need for an effective drug for controlling infectious disease (COVID-19 and the mutated strains of COVID 19[53]. In search of the most effective antiviral agent against COVID -19, we

believe natural antiviral protein could be a potential class of antiviral drug towards COVID-19[54]. It is an exciting and impressive discovery that how the peptide (short amino acid) acts on the Virus and controls the viral mechanism, and preventing the receptor binding; likewise specific target and selectivity of the peptide depends on the viral strain. From this review, we like to bring attention to the application of Antiviral peptide against COVID viral envelope, HR2P targets the viral S protein, which mediates the binding mechanism, EK1, and lipid binding Ek1 (lipopeptide), which blocks the HR1 domine (S2 protein) and P9 peptide stops the acidification of the endosome and prevent the viral RNA release[34]. Besides the antiviral protein towards protecting the host. RTD -1 act as an immunomodulatory, which triggers proinflammatory cytokines, HD5 binds to the ACE 2receptor, which prevent the viral attachment[36]. Recent findings show the more substantial proof on host serine protease (TMPRSS2) is one of the multifunction S proteins against SARS - CoV, which prevents the viral membrane fusion mechanism[41].

Furthermore, the novel Sprotein furin (cleavage site) and CD147 based viral entry pathway were prevented SARS - CoV virulence. These are the major peptides based compounds, which targets different site. Furthermore, the combined therapy of antiviral peptides could provide a promising treatment strategy that will further study their synergetic efficacy towards clinical studies. As per the United states of Food and Drug Administration, a total of 36 amino acids based combination based inhibitor was approved in 2003 for the treatment against HIV (Human immunodeficiency virus) in combination with other synthetic-based antiviral drug therapy. In China, some of the studies were ongoing to prevent the viral-based HR1 (viral envelope) based glycoprotein-based clinical trial (3rd Phase)[55]. Further, the clinical trial of antiviral peptide therapy against covid could effectively replace the drug therapy discovery, leading to the development of operation warp speed by the United States government (April 2020) for the Covid-19 vaccine therapeutic and diagnostic development[56].

Peptides have formed a specific therapeutic role from humble beginnings as substances extracted from animal glands will remain a significant aspect of the therapeutic sector. By expanding into new applications and therapeutic goals, using new chemical approaches to increase molecular diversity and technologically improved medicinal properties, peptide-based pharmaceuticals have kept pace with innovation and progress. We expect that work will continue to view new opportunities for peptides. Peptides are a convenient baseline for discovering drugs as the catalog of peptide medicines used regularly in the medical practice is an endogenous ligand for peptide hormone towards targeted receptors.

The future application of peptide-based drugs to new targets continues to be extended. Study. Throughout the early phase, human trials or in preclinical models of infection, many peptide-added targets for which no medications have been authorized have shown as for the therapeutic values[57]. Novel peptide therapies are still available. To control the properties of drug targeting such as permeability and stability, hits are often optimized. For this purpose, an outline of the peptide chemical toolbox shows the different options. Cyclic peptides have received particular attention and modifications to achieve surface integration that bridges the conventional pharmacology gap. Sequence motives and scaffolds, which can be applied in cells, known as cell invading peptides, are primarily interest for groundbreaking peptide-based medicines.

Refinements in peptide analyzing and computational engineering will continue supporting drug development[58-61]. Improved understanding of the molecular basis for human genetic disorders will produce novel possible therapy leads. De-orphanizing poorly defined peptide targets will promote research programs for new membrane-ligand pairing[62]. Besides, new methods to the development, production, and development of peptide drugs will expand the versatility of the unique class of molecules. Initiatives will be underway to boost the oral disponibility of peptide clinical applications via increased drug stabilization in the gastrointestinal tract and peptide-formulation by enhancing the central nervous system's absorption through combining them with transporter molecules or nanotubes. We will refer you to other chapters on this topic for further information on developments in peptide chemistry and conjugation. The final sequence of mini-examinations complements this set well by providing insights into halves of life extension, formula considerations, and changes necessary to produce the new peptide generation.

Conclusion

The Antiviral peptide is structurally and biochemical versatile for developing the molecular model for the generation of therapeutic drugs against COVID-19. The scope of antiviral peptide molecules will be strengthened by modern peptide therapeutics, design, and half-life enhancement strategies. Initiatives have been undertaken to increase the oral availability of peptide therapeutics by growing the stabilization of drugs in the intestinal system and by implementing peptides with permeability enhancers and enhancing the availability of peptides in the COVID-19 by conjugating or delivering peptides through nanoparticles via carrier molecules. Therefore the objectives of the article have short and long-term parts. Regarding the short-term to ensure efficient and safe treatment against COVID-19 and further decrease the human mortality rate, which has been increased exponentially based on viral infection. Secondly, the

drugs we provide as a treatment to prevent disease spread can be designed to act dually as an immunomodulatory. A long-term objective to research is needed to continue till the human trial to bring back the natural substituents against COVID19 and other upcoming infections. Through which our future generation's health and safety can be safeguarded, this will enhance the social welfare of humans.

Supplementary Materials

The following are available online at www.mdpi.com/xxx/s1, Video S1: Rapid multiplication of COVID Virus[63]. This is a time-lapse video of a cell-culture infected with the novel coronavirus. A single layer of kidney cells is visible at the start of the footage, and slowly, black dots appear across the cell sheet. The Virus cannot be seen, but evidence of its presence can be as infected cells that appear as black dots. As more cells become infected with Virus, they lift off the cell layer and appear as black dots. More and more infected cells become visible. The video footage starts following 40hrs of culture and finishes following 80hrs of incubation. Peter Doherty Institute for Infection and Immunity (Doherty Institute) scientists have successfully grown the 2019 novel coronavirus (COVID-19) from a patient sample, providing laboratories worldwide with crucial information to help combat the Virus[63].

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국문요약

COVID-19와 같은 전염병 감염 시나리오 전반에 걸쳐 펩타이드 기반 치료법을 발견하고 설계하는 개발 시대의 추세는 보다 효율적이고 저렴한 치료 환경으로 발전할 수 있습니다. 결과적으로, 그들의 단백질 분해 약화는 천연 펩타이드 약물의 단점 중 하나입니다. 펩티도미메틱스는 이 단점을 해결하는 데 도움이 될 수 있습니다. 이 리뷰에서 펩타이드 및 펩타이드 기반 약물 발견은 숙주 안지오텐신 전환 효소-2(ACE2) 수용체 및 바이러스 스파이크(S)단백질의 연관성을 포함하는 중증 코로나바이러스 폐색전 증후군(SARS-CoV-2)의 주요 진입 기전 중 하나를 표적으로 요약했습니다. 또한, 펩타이드 기반의 새로운 치료법을 통해 COVID-19에 대해 연구된 단백질, 펩타이드 및 기타 가능한 조치의 이점을 다룹니다. 그리고 펩타이드 기반 약물 치료 환경의 개요는 진화적 관점, 구조적 특성, 작동 한계값 및 치료 영역에 대한 설명으로 구성된다

Conflict of interests

The authors declare no potential conflict of interest.

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