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REVIEW

Antimicrobial peptides and other peptide-like therapeutics as promising candidates to combat SARS-CoV-2

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ABSTRACT

Introduction: There are currently no specific drugs and universal vaccines for Coronavirus disease 2019 (COVID-19), hence urgent effective measures are needed to discover and develop therapeutic agents. Applying peptide therapeutics and their related compounds is a promising strategy to achieve this goal. This review is written based on the literature search using several databases, previous studies, scientific reports, our current knowledge about the antimicrobial peptides (AMPs), and our personal analyses on the potential of the antiviral peptides for the treatment of COVID-19.

Areas covered: In this review, we begin with a brief description of SARS-CoV2 followed by a comprehensive description of antiviral peptides (AVPs) including natural and synthetic AMPs or AVPs and peptidomimetics. Subsequently, the structural features, mechanisms of action, limitations, and therapeutic applications of these peptides are explained.

Expert opinion: Regarding the lack and the limitations of drugs against COVID-19, AMPs, AVPs, and other peptide-like compounds such as peptidomimetics have captured the attention of researchers due to their potential antiviral activities. Some of these compounds comprise unique properties and have demonstrated the potential to fight SARS-CoV2, particularly melittin, lactoferrin, enfuvirtide, and rupintrivir that have the potential to enter animal and clinical trials for the treatment of COVID-19.

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the third coronavirus causing outbreaks in humans in the current millennium. The virus was first identified in patients with pneumonia-like disease in Wuhan, China [1,2]. SARS-CoV -2 constitutes a serious threat to human health due to high mortality and spreading rate. The disease is spreading rapidly worldwide [3]. Coronaviruses belong to Coronaviridae family and are classified into four classes of alpha, beta, gamma, and delta coronaviruses [4,5]. Coronaviruses can typically cause respiratory, gastrointestinal, liver, and neurological diseases with varying severity in humans, birds, bats, mice, and possibly many other animals [1,6]. Of the seven coronaviruses that infect humans, HCoV-NL63, HCoV-229E, HCoV-OC43, and HKU1 represent the most common ones and cause mild respiratory illness, but they can sometimes cause severe clinical symptoms in immunocompromised patients, infants, children, and the elderly [2,4]. The other three coronaviruses (Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and SARS-CoV-2) belong to the highly pathogenic class of beta-coronaviruses which can cause severe pneumonia. SARS emerged in 2002/2003 and MERS emerged in 2012 with mortality rates of 10% and 37%, respectively. Both of these viruses are transmitted from animal to human and from human to human [6,7]. Despite the lower case fatality rate of SARS-CoV-2 in comparison to SARS and MERS, it has killed many more people [8]. It has caused more than 119 million infected cases and 2,642,826 deaths worldwide as of 14 March 2021 [9].

There are currently no specific antiviral drugs and universal vaccines against coronaviruses in the world [10]. Given the high prevalence, rapid transmission, and growing mortality of SARS-CoV2, urgent effective measures are needed to discover and develop therapeutic agents and vaccines. Due to the shortage and limitations of antiviral drugs for various infections and the emergence of drug resistance in several viruses, natural or synthetic antimicrobial peptides (AMPs), antiviral peptides (AVPs), and peptidomimetics have captured the attention of researchers hence they can be potential antiviral agents to fight viruses.

In this review article, after literature searches in several databases such as PubMed, Web of science, Scopus and Google patents, we begin with a brief description of SARS-CoV2 followed by a comprehensive description of antiviral peptides including natural and synthetic AMPs or AVPs and antiviral peptidomimetics. Subsequently, the structural features, mechanisms of action, limitations, and therapeutic applications of these peptides are explained. Eventually, some of the most important peptides that may demonstrate the potential to fight SARS-CoV2 are introduced.

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Article highlights

- Antiviral peptides and other peptide-like therapeutics are promising candidates to combat SARS-CoV-2.
- Many of the peptides or peptidomimetics have the potential to enter animal and clinical trials for the treatment of Covid-19.
- The most important limitations of AVPs are cytotoxicity, low serum stability, allergic and inflammatory responses, low and relative selectivity, and high synthesis costs.
- The AVPs can be designed before synthesis using bioinformatics tools and protein engineering strategies to bypass most of their limitations.
- Peptidomimetics are more stable and have more powerful drug-like properties than natural peptides.
- We recommend a clinical trial on Enfuvirtide as a fusion inhibitor for the treatment of COVID-19.

2. SARS-CoV-2 structure properties

Coronaviruses genome is a 26–32 kb non-segmented positive sense single-strand RNA accumulated with nucleocapsid proteins. The genome is surrounded by a membrane containing different proteins including spikes glycoproteins that represent a crown-like appearance to the viruses [11,12]. The genome sequence of SARS-CoV-2 has been determined and represented in the GeneBank database by accession number MN908947.3. Homology analysis of SARS-CoV-2 genome with other coronaviruses showed an 88–89% similarity with two other bat-derived coronaviruses namely bat-SL-CoVZC45 and bat- SL-CoVZXC21. Also, SARS-CoV-2 genome sequence had 82% and 50% similarity with SARS-COV and MERS-CoV, respectively [13,14]. SARS-CoV-2 genome is a 29.9 Kb RNA with at least 10 open reading frames (ORFs). The two-third of the genome from the 5′ terminal (called ORF1a/1b) is responsible for the virus replication and encodes two large polyproteins of pp1a and pp1ab. The remaining regions are known as structural regions which encode main structural proteins including the glycosylated spike (S), the envelope (E), the membrane (M), and the nucleocapsid (N) proteins [15].

Coronaviruses enter the host cells through the interaction of the S protein with its receptor [11]. Recently, Hoffmann et al. demonstrated that SARS-CoV2, like SARS-COV, enters the target cell via the angiotensin-converting enzyme-2 (ACE2) receptor. They also showed that SARS-CoV2 S protein is processed by the target cell proteinase of Transmembrane Serine Protease 2 (TMPRSS2) [16]. Using Cryo-Electron Microscope, Wrapp et al. structurally compared SARS-CoV2 and SARS-COV S protein and showed that SARS-CoV2 S protein was remarkably similar to that in SARS-COV but with a higher affinity for ACE2 [17]. It can be assumed that the high transmission potency of SARS-CoV2 compared to SARS-COV is related to the strong binding affinity of its S protein with ACE2. Therefore, S protein plays an important role in the viral infection and pathogenicity and it can be a target for developing vaccines and antiviral compounds [14].

After receptor binding and fusion to the host cell membrane, the virus entry is mediated by clathrin-dependent and clathrin-independent endocytosis [15]. The positive-sense RNA of the virus is translated into pp1a/1ab and structural proteins using host ribosomes. These polyproteins are cleaved by viral proteases 3 C-like protease (3 CLpro) and papain-like protease (PLpro) and converted into 16 nonstructural proteins (NSPs) required for transcription, replication, and packaging of new viruses during infection [14,18,19]. NSPs also contain many RNA-processing enzymes such as RNA-dependent RNA polymerase (RdRp), endonuclease, RNA helicase, and triphosphatase [20]. After RNA amplification by RdRp, the structural proteins S, E, and M enter the endoplasmic reticulum and the viral genome is encapsulated within the N proteins. Eventually, vesicles containing mature viruses germinate toward the plasma membrane and release the viruses [11,15]. Homology analyses of SARS-CoV-2 and SARS-CoV showed 76% similarity between their S proteins with numerous genetic variations in their receptor-binding domain (RBD) regions [14] that this difference may undermine the previously approved therapeutic agents' effectiveness for the treatment of COVID-19.

3. Antimicrobial peptides with antiviral properties

Because of drug limitations for the treatment of many viral infections, nowadays there is much focus on antiviral researches [21]. Despite existing drugs and vaccines, using AVPs is a potential alternative strategy to control new and drug-resistant viruses [21–23]. AVPs represent a type of AMPs with antiviral properties. AMPs are present in almost all organisms. These short (10–50 amino acids), positively charged, and amphipathic oligopeptides have a high structural and functional diversity [24] and are part of the innate immune system. AMPs have been identified in a wide range of organisms, from microbes to plants, insects, and vertebrates, including humans [25,26]. AMPs are the first line of defense against various pathogens including bacteria, fungi, and viruses [27]. AVPs act against numerous of both coated and uncoated viruses [22,28], hence are promising prospects for the treatment of viral infections [29].

4. Structural and functional characteristics of AVPs

Structurally, AVPs can be composed of α-helix, beta sheets, extended strands, or a mixture of them (Figure 1). In terms of amino acid content, statistical analysis at the APD showed that glycine, cysteine, leucine, lysine, valine, and isoleucine were the most frequent amino acids in AVPs, respectively. Interestingly, AVPs are rich in cysteine in contrast to other classes of AMPs that have higher levels of lysine, glycine, leucine, and isoleucine and lower levels of cysteine (http://aps.unmc.edu/AP/database/antiV.php.).

The most important mechanisms of action of AVPs are as follows [30,31]:

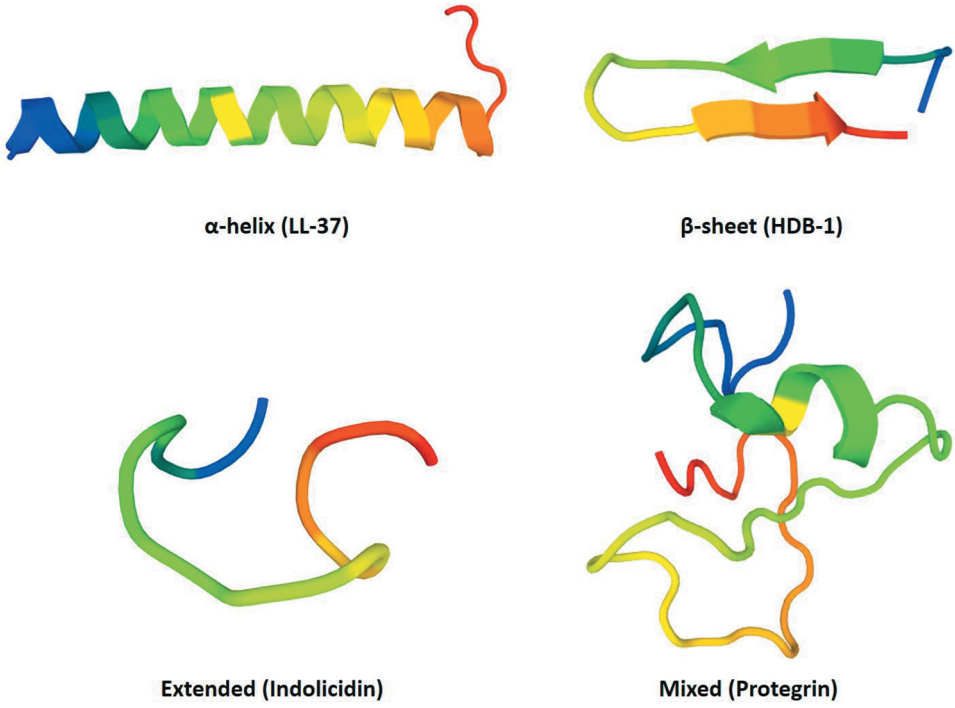

Figure 1. Examples of the possible structures of antiviral peptides that include α-helix, beta sheets, extended strands, and mixed.

1) Interacting with glycosaminoglycans which act as receptors for viruses, so the peptides can compete with viruses for binding to these receptors. 2) Preventing the virus from entering the cell by binding to the receptors needed for the virus entrance. 3) Inhibition of fusion or integration of the virus to the target cell membrane. 4) Inhibition of the viral gene expression. 5) Inactivation of ribosomes and inhibition of the viral protein chain elongation. 6) Induction of inflammatory and immunomodulatory responses that indirectly induce antiviral properties. 7) Direct degradation and deformation of the lipid coating of the viruses. As an instance, some AVPs mimic sialic acid behavior and are recognized by the receptor-binding site of the viral Hemagglutinin (HA). The RLxRxMxxxK motif seems to be important for the inhibitory activity of many of these peptides because it is homologous to highly conserved sequences in HA in many influenza strains [32].

5. Natural antiviral peptides

Natural AMPs are produced as the first lines of defense in many organisms [33]. Due to their characteristics such as selectivity, relative specificity, low level of side effects, and high range of synthetically production levels (from milligrams to kilograms), AVPs can be suitable candidates for the treatment of many diseases. However, their use also has some limitations. For example, natural AVPs in the body are prone to proteolytic degradation and are rapidly eliminated from the bloodstream. They may also be highly cytotoxic or cause inflammatory and allergic responses [34]. The following are some of the most important antimicrobial peptides with antiviral properties.

5.1. Defensins and cathelicidins peptides

Defensins and cathelicidins are the two well-known natural peptides used to fight viruses. These peptides induce immune responses and play an essential role in innate immunity. In mammals, defensins and cathelicidins are the two major families of Cationic Host Defense Peptides (CHDPs) which have direct antimicrobial and immunomodulatory properties [35]. Defensins are classified into three subgroups α, β, and θ. To date in humans, six α-defensin and 31 β-defensin peptides have been identified [36]. Both defensins and cathelicidins have amphipathic properties. Defensins often have beta-sheets that are stabilized by three disulfide bonds and consist of 18–45 residues [37]. Salvatore et al. reported the activity of human neutrophil peptide-1 (HNP-1), an α – defensin, against influenza A virus and stated that this peptide inhibits the virus in its earliest infection stages. The influenza virus uses the cellular protein kinase C (PKC) signaling pathway to infect host cells. Studies showed that PKC phosphorylation is reduced in infected cells treated with HNP-1, indicating interference with the viral cycle [38].

5.1.1. Defensins

Defensins modulate viral infection through several mechanisms that are performed by direct interaction with viral envelopes or through interactions with the virus potential target cells. They may also indirectly interfere with various stages of the viral life cycle [39] or modify the innate immune response to viral infections. Defensins involve in many activities include differentiation/maturation of T cell, macrophage, and dendritic cell, as well as recruiting of dendritic cells into infection sites,

wound healing, regulation of cell death pathways, and induction of the production of pro-inflammatory cytokine by macrophages, mast cells and keratinocytes [40]. Also, defensins, more importantly, HNP-1, 2 and 4, possess antiviral activity against HIV [41]. The antiviral effects of HNP-4 against herpes simplex virus (HSV) [42], human papillomavirus (HPV) [43,44], respiratory syncytial virus (RSV) [45] have also been investigated. A study by Yongjie et al. found that HNP1-3 and their rabbit homolog, RNP1-5, could not evoke innate immune responses or have a direct effect on inhibiting SARS-CoV [46]. It has been reported that Rhesus θ-defensin (RTD1) could reduce pathological lung lesions in SARS-infected mice compared to the untreated group. The results of this study showed that RTD1 had no effect on the viral load, but it indirectly reduced pulmonary complications and the death of mice due to its anti-inflammatory effects [47].

It has been shown that a high concentration of HNPs is dangerous and can cause inflammation in the lungs of mice with SARS-CoV [48]. Direct injection of HNP into the lungs of mice caused inflammation and deterioration of the infection [47,49]. The influx of neutrophils in severe pneumonia caused by viruses such as SARS-CoV and influenza causes the secretion of large amounts of neutrophil proteases and HNPs in the lungs, which destroys Surfactant-Protein-A (SPA) and Surfactant-Protein-D (SPD) in the lungs. SPA and SPD play an important role in the direct inhibition of viruses and inhibiting inflammation in the lungs. This issue highlights the deleterious effect of HNPs in infectious and inflammatory lung diseases [50,51]. Therefore, in viral infectious diseases involving the respiratory system, AVPs should be used that have less affinity for lung proteins.

5.1.2. Cathelicidins

Cathelicidins are typically 12 to 88-residues linear peptides composed of amphipathic α-helix structures with an N-terminal signal sequence, a conserved Cathelin-like domain, and a variable C-terminal domain [52]. In contrast to the extended family of defensins, only a single cathelicidin is expressed in humans, mice, and rabbits. However, in other species, multiple cathelicidins are found (such as protegrins in pigs) [35]. These antiviral peptides disrupt viral capsids and activate a number of protective mechanisms in the host, such as promoting repair systems, producing chemokines and cytokines, modulating the differentiation of dendritic cells and T cells polarization, and activation of effective antiseptic and anti-inflammatory factors in the host [53]. The human LL-37, a cathelicidin, which is produced as a precursor of hCAP-18 peptide and accumulates in neutrophil granules, is likely to be produced in epithelial cells as an acute phase reagent [54]. The mechanism of action of LL-37 is related to the formation of oligomers following interaction with the viral capsid that leads to generating fibril-like supramolecular structures on the surface of the viral phospholipid bilayer [55]. Through expressing a variation of the toroidal pore model, the peptide further assembles into the transmembrane pores and causes destabilization of the viral membrane [55]. LL-37 improves the healing outcome in mice infected by Influenza A Virus (IAV) through inhibiting virus replication and reducing the production of inflammatory cytokines. LL37 does not block hemagglutination activity and does not cause virus accumulation or decrease in virus uptake by epithelial cells, but it inhibits virus replication in the post-cell stage before synthesis of the virus RNA or proteins [56]. This peptide has been effective against IAV [56], respiratory syncytial virus (RSV) [57], hepatitis C virus (HCV) [58], and dengue virus (DENV) [59]. The effect of vitamin D deficiency and air pollution on inhibiting LL-37 expression has been suggested to exacerbate COVID-19 [60] because LL-37 can inhibit a wide range of coated viruses [61,62]. However, LL-37 stimulates inflammation in the lungs after infections caused by IAV and SARS-CoV [47].

5.2. Transferrins

Transferrins are iron-binding proteins with antiviral activity. The most well-known transferrin is lactoferrin (LF), which is a multifunctional 80-kDa glycoprotein and is widely available in various secretory fluids. LF, first discovered in cow's milk, is evolutionarily highly conserved and is found in humans, mice, and pigs. Its structure consists of a polypeptide chain that has a positively charged N-terminal region. The LF chain has two circular loops connected to three spiral α-helixes, each of which has an iron-binding site. There is a strong connection between two loops when iron binds (the holo-form), which makes LF resistant to proteolysis [40]. Reports have indicated that bovine lactoferrin is a potent inhibitor of a broad number of viruses and has higher antiviral effects than human lactoferrin. Lactoferrin specifically binds to the subunit A2 of the hemagglutinin and inhibits influenza virus infection and related hemagglutination [63]. Lactoferrin has been shown to inhibit infection by binding to adenovirus III and IIIa structural polypeptides targets [64]. The inhibitory effect of LF on DENV [65], Marek's Disease Virus (MDV) [66], and HCV [67] has been investigated. Recent studies showed that LF can interfere with some of the receptors involved in SARS-CoV-2 pathogenesis and also prevents the entering of the virus via ACE2 to host cells [68]. Therefore, LF may contribute to the prevention and treatment of COVID-19 [68].

5.3. Hepcidin

Hepcidin is a cysteine-rich peptide with four disulfide bonds [69] and a length of 25 amino acids, which is primarily expressed by liver cells and is also known as Liver-Expressed Antimicrobial Peptide 1 (LEAP-1). This peptide was first isolated from human blood. Hepcidin is made as a pro-peptide with two cleavage sites. The first cleavage site leads to releasing an N-terminal signal sequence while the second one leads to forming the mature Hepcidin from the pro-peptide. Hepcidin has an important role in iron regulation and systemic hemostasis of iron in hepatic cells and other cell types [40]. The chronic HCV infection can lead to iron accumulation in the liver, which may cause liver damages. However, little is known about the mechanism of iron accumulation in the liver due to HCV. It has been shown that patients infected by HCV have lower levels of Hepcidin in their livers, suggesting that HCV may inhibit Hepcidin expression [69]. Recent studies showed that there was a low similarity between Hepcidin and

cytoplasmic end of the S protein of SARS-CoV-2, suggesting that there is similar iron dysmetabolism in COVID-19 patients [70]. The S protein mimics the function of Hepcidin, resulting in the toxic function of iron in COVID-19 pathophysiology. The S protein can cause the internalization, negative regulation, and blocking of ferroportin which leads to progressive anemia and hyperferritinemia [71]. Using Hepcidin as an AVP to treat COVID-19 seems to be more complex and needs more comprehensive studies.

5.4. Melittin

Melittin is one of the most well-known virus membrane-disrupting peptides, which is an amphipathic peptide with 26 residues and is one of the main components of European bee venom (*Apis mellifera*). This peptide consists of two α-helices connected by a flexible linker [69]. It exerts various effects on lipid bilayer membranes, including vesicle deformation, creating pores, causing disruption and lysis [72]. Melittin was tested against HIV-1 and IAV by assaying infected T lymphoma cells, and the results showed that the cell culture treated with Melittin was almost completely free of viral particles [73].

The pore-forming peptides, like Melittin, represent a subset of AMPs that binds to the virus coating and forms a channel-like structure or pore in two lipid bilayers [25]. To date, no studies have been performed on the efficacy of Melittin or its derivatives on SARS-CoV-2. However, in a study in China, bee venom was effective in preventing COVID-19 in beekeepers exposed to bee stings [74]. In this study, apitherapy in 121 people prevented them from developing COVID-19, while three of them were in close contact with COVID-19 patients [74]. Apitherapy is a branch of alternative medicine that uses honey bee products, including honey, pollen, propolis, royal jelly, and bee venom [75]. Regarding previous research on the antiviral role of Melittin and its immunomodulatory function, it can be suspected that in their study the most important effective component in bee venom has been Melittin.

In addition to the peptides mentioned above, various studies have shown that antimicrobial peptides derived from amphibian skin such as Caerin and temporin have antiviral properties. An *in silico* study by Liscano et al. indicated that two amphibian AMPs, caerin 1.6 and caerin 1.10, had a high affinity for spike proteins of SARS-CoV-2. These two AMPs interact particularly with Arg995 located in the S2 subunit of the spike protein, which is a key subunit in viral fusion and entry into the host cell through ACE2 [76]. A family of the AMPs that their antiviral activity has been well studied is temporins. The temporins are linear, small cationic peptides with 10 to 14 residues that isolated originally from the skin secretion of the European red frog (*Rana temporaria*) [77]. There are several studies about the antiviral activity of temporins. For example, De Angelis et al. showed that temporin G can act against influenza and parainfluenza respiratory viruses [78]. Also in other research, the antiviral effect of temporins was reported against the MERS-CoV [79] and herpes simplex virus 1 (HSV-1) [77].

Other bioactive peptides including cryptides or cryptins, may be created from proteolytic cleavage of a member of physiological proteins such as hemoglobins or apolipoproteins. In fact, cryptides are peptides embedded in the sequence of physiological proteins in the body that show antimicrobial properties after the cleavage from the parental proteins. The activity of these peptides is typically against bacteria, fungi, and protozoa but they may also possess antiviral effects [26].

6. *In silico* modified and synthetic antiviral peptides

To date, 190 AVPs have been registered in the Antimicrobial Peptide Database (APD) (http://aps.unmc.edu/AP/database/antiV.php.). AVPs can exert their antiviral effects in two ways; first, they have direct antiviral effects that usually inhibit the virus by interfering with one of the vital components or processes involved in the life cycle of viruses. Second, they can induce immune and inflammatory responses in different ways such as inducing the secretion of pro-inflammatory cytokines. To achieve the therapeutic properties of AVPs, sometimes their modulating and pro-inflammatory effects are required to be prevented to inhibit further damages to the infected tissues.

The AVPs can be designed before synthesis using bioinformatics tools and protein engineering strategies to bypass most of their limitations. In the modification of natural peptides by *in silico* methods, the amino acid contents, their charge, and many other physicochemical and structural properties that may affect their antiviral activity, are important. Therefore, it can be remarked that the production of AVPs is done with two main approaches, including their extraction from natural resources and their design, modification, and bioinformatics predictions (based on their interaction with primary viral structures or enzymes) [22].

The peptides are synthesized through three general methods include synthesis in a soluble medium, synthesis on a solid base, or a combination of both states. Although peptide synthesis is often performed by the solid-phase method, the soluble method was preferred by pharmaceutical companies in the 1970s and 1980s [80].

Zhao et al. investigated the antiviral activity of 11 synthetic peptides derived from β-defensin-4 in a mouse model infected by H1N1 influenza. The results showed that a short peptide, called P9, had robust antiviral effects against a variety of respiratory viruses *in vitro* and *in vivo*, including influenza A virus (H1N1, H3N2, H5N1, H7N7, H7N9), SARS-CoV, and MERS-CoV. The antiviral activity of the P9 peptide was related to its high affinity for viral glycoproteins as well as the abundance of essential amino acids for antiviral activity in its composition. After binding of the viral particles via surface glycoproteins, the P9 peptide enters the cells through endocytosis and prevents acidification of the endosome, which causes membrane occlusion and subsequently inhibits the viral RNA release [81]. Also in a study by Kim et al., the ability of human β-defensin-2 (HBD 2) to improve antiviral immune responses against MERS-CoV was studied *in vitro* and *in vivo* using the S protein RBD on different cell lines (HG23, CRFK, RAW267.4, MRC-5, FRhK-4, HeLa, ST, CCL-9.1, and Vero cells). When fusion protein containing HBD2 and S protein RBD (HBD2-RBD) was applied on THP-1 cells (human monocytic

cells), the expression levels of the antiviral molecules (IFN β, IFN-γ, MxA, PKR, and RNase L) and molecules that induce the innate immune response (NOD2, TNF-α, IL-1β, and IL-6) were increased compared with the cells treated with only S protein RBD. The expression of chemokines was also increased after treatment with the HBD2-RBD fusion protein. As previously mentioned, HDB2 can clinically cause more inflammation in the body, especially in the lungs of COVID-19 patients, and can increase the mortality rate [82].

Mucroporin is a cationic defense peptide derived from the venom of a scorpion (*Lychas mucronatus*) that can effectively inhibit many bacteria. Mucroporin-M1, a synthetic optimized mucroporin, can inhibit gram-positive bacteria and antibiotic-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant coagulase-negative *Staphylococcus* (MRCNS), at low concentrations [83]. Li et al. studied the antiviral activity of mucroporin and optimized mucroporin-M1 on Vero cell lines. The results showed that optimized mucroporin-M1 had significant antiviral activity against measles, SARS-CoV, and influenza H5N1, while the parental peptide or mucroporin did not show antiviral activity against any of these three viruses. Based on these results, they concluded that defense peptides derived from scorpion venom can be rationally designed and modified in order to demonstrate antiviral activity, especially against RNA viruses [84].

Interferons (IFNs) are cytokines that induce the synthesis of several active antiviral proteins in the cells [85]. Different expensive recombinant interferons are available in the market including IFN α-2a, IFN α-2b, IFN α-n1, IFN α-n3, IFN α -con 1, IFN β-1a, IFN β-1b, IFN β − 1a, IFN β − 1b, IFN α − 2a, IFN α − 2b, IFN α P-2b and IFN γ-1b [86]. Studies have shown that alpha and beta interferons and their recombinant forms have good antiviral properties against SARS-CoV-2, inhibit virus replication and protein synthesis and considerably diminish the disease symptoms [87]. Truncated peptides of human interferons IFNα1 (152–189) and human IFNβ (150–187) were used to treat allergic encephalomyelitis, and showed that these peptide derivatives mimic the interferons and induce their signaling pathway [88]. The question is whether these synthetic peptide derivatives that show interferon-like effects, can inhibit SARS-CoV-2? The answer to this question could be useful in developing a new and cheaper treatment way for COVID-19 compared to using intact interferons.

The entry of HIV-1 virus is remarkably similar to the entry of SARS-CoV2 virus into their target cells [89,90]. HIV-1 virus enters the host cell with two glycoprotein subunits on its surface, namely the gp120 subunit (equivalent to S1 of SARS-CoV-2) which is responsible for binding to the receptor, and the gp41 subunit (equivalent to S2 of SARS-CoV-2) which is responsible for fusion to the host cell membrane. Refolding of the N-terminal heptad repeat (NHR) and the C-terminal heptad repeat (CHR) of the gp41 subunit in the form of a 6 helixes bundle (6-HB), brings the virus and the cell membranes closer together, leading to a fusion reaction. NHR and CHR sequence-derived antiviral peptides, such as the FDA-approved drug T20 or Enfuvirtide, can competitively inhibit the formation of viral 6-HB, thereby inhibiting the fusion of the virus to the host cell membranes and ultimately inhibiting the virus entry [22,91]. Because HIV-1 gp41 protein is structurally and functionally similar to SARS-CoV2 protein S2, the question is whether Enfuvirtide can inhibit SARS-CoV2 entry into the cell as well. In an *in silico* study using molecular docking and molecular dynamic (MD), Calligari et al. suggest Enfuvirtide as a SARS-Cov2 inhibitor [92]. More researches on this FDA-approved drug and conducting clinical trials in this area could help develop drug discovery and treatment for COVID-19.

Previous studies have shown that peptides that target the heptad repeat (HR) regions of S2 subunit of coronaviruses the S protein can inhibit the virus infection at the micromolar levels [93,94]. Also, targeting the binding site of RBD can block the initial stages of the virus entry [95]. Significant mutations in the S protein-coding region, which lead to 12 amino acid substitutions, may be a key to understand why and how the virus crosses barriers of different species from animals to humans. It can be declared that factors that can interact with the S protein domains can prevent infections caused by coronaviruses such as SARS [96,97]. Bosch et al. designed two peptides namely HR (96 amino acids) and HR2 (39 amino acids) based on the HR1 and HR2 regions of the coronavirus S protein and produced them in an *E. coli* expression system. When mixed together, the two peptides are integrated into a highly stable anti-parallel oligomeric complex. Using biological assays, they showed that the HR2 peptide acts as a potent inhibitor of virus entry into the cell as well as the cell-cell fusion [98]. Zheng et al. synthesized and analyzed 10 peptides based on the virus S protein (namely P1 to P10) and reported that peptides P2, P6, P8, and P10 effectively inhibited SARS-CoV-2 entry into the cell. P2 does not compete directly for binding to ACE2 but may inhibit binding site reconfiguration. The other three active peptides (P6, P8, and P10) are located on the surface of the S1 and S2 subunits and exhibit a ring conformation [96].

In another study, the HR2 antiviral peptide (designed based on the HR2 region of MERS-CoV) which was conjugated to cholesterol and palmitate lipids, prevented the relatively slow entry of MERS-CoV into the host endosomes. The conjugated lipids allow the HR2 peptide to accumulate in the endosome, preventing the entry of the viruses. Lipidization of antiviral peptides locates them in the areas rich in coronavirus fusion proteases, which protects cells from the entry of a variety of coronaviruses [99]. Xia et al. designed the antiviral peptides HR1P (residues 924 − 965) and HR2P (residues 1168–1203) based on HR1 and HR2 regions of SARS-CoV-2 and studied their inhibitory effects using Surface Plasmon Resonance (SPR), precipitation equilibrium analysis, polyacrylamide gel electrophoresis, high-performance liquid chromatography, computer-aided homologous modeling, and molecular docking. They stated that these two peptides inhibited the entry of SARS-CoV2 virus into the host cell by inhibiting the virus-host cell fusion [100].

Previously, Xia et al. assessed the effect of the EK1 antiviral peptide, which was designed based on the HR2 of the MERS-CoV, on mice infected by MERS-CoV. The results showed that EK1 can inhibit the fusion of MERS-CoV to the host cells [101]. The researchers also studied the inhibitory effect of the

antiviral peptide EK1C4, a lipopeptide derivative of EK1, on mice infected by SARS-CoV-2 and showed that the peptide inhibited the virus entry by inhibiting the fusion process [100,102]. Zhu et al. studied the effect of IPB02 antiviral peptide, a lipopeptide designed based on the SARS-CoV-2 HR2 region, on cell cultures infected by SARS-CoV-2 and found that this peptide has a high potential inhibitory effect on virus-host cell fusion [103].

Zhang et al. investigated the effect of the antiviral peptide SBP1 (designed based on the ACE2 peptidase domain) using Bio-Layer Interferometry, a method that assesses protein–protein interactions. They showed that SBP1 disrupted the interaction of ACE2 and the virus S protein by binding to the RBD domain [104].

Some antiviral peptides focus on inhibiting important enzymes involved in virus replication such as proteases and polymerases [29]. RNA-dependent RNA polymerase, RdRp, is one of the enzymes that limit the rate of transcription and replication of influenza virus and coronaviruses, which consists of three subunits of PB1, PB2, and PA. The PB1 subunit is responsible for the polymerization reaction and endonuclease cleavage, while the PB2 subunit is responsible for detecting and binding the cap structure of host mRNAs. The N-terminal region of the PA subunit forms a domain with endonuclease activity which is responsible for the cleavage of the host pre-mRNA. $PB1_{731\text{-}757}$ is an antiviral peptide derivative from the PB1 subunit which can inhibit the viral polymerase activity and the virus proliferation by interfering with the interaction between the C-terminal region of PB1 and the N-terminal region of PB2 [34].

Watson et al. designed and synthesized the SARS-BLOCKTM peptide, which acts as an AVP against SARS-CoV-2 infection. This synthetic peptide is potently and competitively able to inhibit SRS-CoV-2 protein binding to ACE2, by binding to the RBD domain of the virus S protein [105].

7. Peptidomimetics and other peptide-like therapeutics

Peptidomimetics are designed based on small protein-like chains or small molecules that mimic the behavior of a peptide and have regulated molecular properties, such as high stability or biological activity. The use of peptidomimetics is a very powerful strategy for designing small molecule-based drugs as enzyme inhibitors or receptor ligands [106]. These compounds mimic a natural peptide or a protein of the viruses and have the ability to interact with their biological targets and produce the same biological effects [107]. There are different types of changes to create peptidomimetics with improved drug properties, including local changes, such as the binding of nonstandard amino acids, and general changes, such as forming a circular end in polypeptide chains during a cyclization process. Cyclization is one of the most common strategies used to convert peptides into drugs and pharmacologically active agents [108].

Other changes to create peptidomimetics include the binding of β-peptides, peptoids (N-substituted glycines), peptide-peptidomimetic hybrid structures, and lipidization [109]. Peptidomimetics can detect intracellular targets by crossing cell membranes independently (e.g. cyclosporine) or by binding to the cell-penetrating carrier peptides [110]. They can also inhibit protein-protein interactions [111]. Since short peptides are often flexible and unstructured, they can increase their inhibitory potency by stabilizing or inducing the desired secondary structures. Interference of peptidomimetics with protein–protein interactions can occur in all three major structural motifs of the protein: α- helix, β-sheet, and turns. Peptides that mimic these motifs are stabilized in a variety of ways [110].

The human rhinovirus (HRV) 3 C protease inhibitor peptidomimetic, rupintrivir, originally developed from HRV or its derivatives, has shown extensive antiviral activity against picornaviruses and coronaviruses *in vitro* [112].

Lee et al. reported that Aza-peptide epoxides (APEs) can be used to inhibit the activity of coronaviruses. Each APE has an aza-peptide component and an epoxide moiety attached to the carbonyl group of P1 residue. P1 is the first position of the cleavage sites of a protein to be digested by the target peptidase. Therefore, the P1 residue determines the specificity of the APE target peptidase. In addition, the substitution of the atom or functional group present on the C2 epoxide atom regulates the inhibitory and activity of APE on a specific peptidase. APE contains Aza-glutamine as a P1 residue that mimics the properties of the S1 protein of SARS-CoV and can irreversibly inhibit the virus peptidase [113].

Kim et al. synthesized dipeptidyl bisulfite (GC376) salt from GC373 and measured its activity besides other compounds such as GC373, GC375, and GC376 against various viruses [112]. GC-373 is a peptide aldehyde that is metabolized from the bisulfite adduct, GC-376 free acid [114,115]. Viral proteases are important targets for the production of antiviral drugs. Viral proteases of 3 Cpro in picornaviruses and 3 CLpro in coronaviruses have common properties, such as similar conserved active sites with a nucleophilic cysteine residue. In most viral proteases, the P1 and P2 positions at the cleavage sites of the viral polyproteins are typically occupied by Gln (or Glu) and a hydrophobic residue, respectively. GC375 and other stronger compounds of GC373 and GC376 have been tested against most coronaviruses and some picornaviruses such as *Hepato virus* (HAV) [112]. In a study by Balzarini et al., semi-synthetic glycopeptides such as vancomycin, eremomycin, teicoplanin, ristocetin A and DA-40,926 showed anti-viral activity against SARS-CoV, but there is no documented evidence of their effect on SARS-CoV2 and needs further studies [116].

8. Some reports of the development of peptide-based therapeutics against coronaviruses

The patents of peptide-based antiviral agents, especially synthetic peptides and peptidomimetics against coronaviruses are being developed (https://patents.google.com/), some of which are listed in Table 1. Further research could determine the potential use of these agents for the COVID-19.

Particularly, there are reports of several therapeutic peptides being developed to control SARS-CoV-2 and to treat COVID-19, some of which are listed in Table 2.

Table 1.. Some patents on peptides and peptidomimetics that can use against coronaviruses.

Patent ID	Subject	Property rights	Inventors	Published year
US7151163B2 (CA2524209A1)	Antiviral agents for the treatment, control and prevention of coronaviruses infection (the invention of an antiviral peptide with 7 to 50 amino acids with activity against the virus S protein)	Sequoia Pharmaceuticals Inc	Erickson, J. W., Silva A.	2004
EP1705182B1	Anti-tumor and anti-viral peptides (making a new peptide with different structure, mechanism of action and therapeutic effect from alloferon and other biologically active compounds)	European Patent Office	Chernysh, S. I., Bekker, G. P.	2004
EP0246630A2	Antiviral peptides and a means of treating herpes infections	European Patent Office	Cohen, E. A., Gaudreau, P. Michaud, J., Brauzeau,P.,Langelier, Y	1987
US7718610B2	Retrocyclins: Antiviral and antimicrobial peptides	University of California	Lehrer, R. I., Waring, A. J., Cole, A. M., Hong, T. B.	2008
US20040138137A1	Alloferons- Immune peptides	Alloferons Institute	Kim, S., Chernysh, S., Bekker, G., Makhaldiani, N., Hoffman,J., Bulet, P.	1999
EP1272510A2	Active drug antiviral peptides and methods of their use	Wisconsin Alumni Research Foundation	Brandt, C.,Bultmann, H.	2001
US5104854A	Antiviral peptides	University of Washington	Schlesinger, M.J.,Collier, N. C., Adams, S. P.	1991
US20100119479A1	Therapeutic antiviral peptides	Intermune Institute	Buckman, B.,Serebryany, V.,Seiwert, S., Beigelman, L., Stoycheva A.	2009
US9555070B2	Pan antiviral peptides to inhibit protein kinase	NUOVO BIOLOGICS LLC	Miller, K. D.,Austin, B. S., YOURIST, J. E.	2010

9. Conclusion

Regardless of their limitations, AVPs and other peptide-like therapeutics are promising candidates to combat SARS-CoV -2. Although there are reports of several therapeutic peptides being developed to control SARS-CoV-2 and to treat COVID-19, we deeply suggest paying more attention to these molecules and performing more accurate and comprehensive studies in this field. In our opinion, many of the peptides or peptidomimetics listed in this article such as melittin, lactoferrin, enfuvirtide, and rupintrivir have the potential to enter animal and clinical trials for the treatment of COVID-19.

10. Expert opinion

As previously mentioned, the use of natural AVPs in infectious diseases such as COVID-19, in which inflammatory responses and cytokine storms cause more mortality than the presence of the virus itself, the use of those peptides that in addition to antivirals properties can also inhibit inflammatory responses are in priority such as Melittin and lactoferrin (LF). For example, in addition to LF antiviral properties and inhibiting the entry of SARS-CoV2 into the cell, LF has anti-inflammatory properties, so that Campione et al. suggested a clinical trial on LF as an intranasal spray or oral formulations for the treatment of COVID-19 [133]. Despite ongoing studies, many limitations of natural AVPs have diminished their use as approved drugs. The most important of these limitations are cytotoxicity, low serum stability, allergic and inflammatory responses, low and relative selectivity, and high synthesis costs. Due to these limitations, many scientists are looking for modifications and shortening AVPs through *in silico* methods and protein engineering.

In addition to natural AVPs, modified and synthetic peptides and other peptide-like structures such as peptidomimetics can also be considered in the fight against COVID-19. Synthetic peptides have various functions such as being antagonists, inhibitors of virus entry into the cell, inhibitors of key enzymes of the virus life cycle, mimics and competitors with receptors for viruses, and immune system modulators. The targets of synthetic peptides are enormously diverse. In the case of coronaviruses, some studies have reported changes in the structure of the S protein to prevent them from entering the cell as the most significant goal of drug design [93,95,96,101]. The entry of coronaviruses, including SARS-CoV-2, into the host cells depends on the binding of coronavirus glycoprotein S (spike) to the receptors. Therefore, factors used by SARS-CoV-2 to enter the cell can be used as therapeutic targets [16]. The receptors of glycoprotein S are ACE2 for SARS-CoV and SARS-CoV-2, CD209L (a type C lectin also called L-SIGN) for SARS-CoV, and DPP4 for MERS-CoV [15]. Madanchi et al. in an *in silico* study stated that Enfuvirtide, an HIV-1 fusion inhibitor synthetic peptide, can act as a potent SARS-CoV-2 fusion inhibitor [134]. Therefore, their research team strongly recommends a clinical trial on Enfuvirtide as a fusion inhibitor for the treatment of COVID-19.

Peptidomimetics are more stable and more resistant to digestion than peptides. They also have more powerful drug-like properties, for example, they have higher bioavailability

Table 2. Some therapeutic peptides and peptide-like structures in development against COVID-19.

Name	Peptide type	Clinical application	Bioactivity	References
Nelfinavir	Synthetic	HIV treatment and has been indicated to treat SARS-CoV and is being tested for COVID-19 treatment	antiretroviral protease inhibitor	[117,118]
Remdesivir	organic compounds known as alpha amino acid esters	Has been shown to have antiviral activity against numerous RNA viruses, Phase 4 clinical trials for the treatment of Ebola and SAS-CoV2	Adenosine analog/RNA polymerase inhibitor	[119,120]
Lopinavir	Peptidomimetic	treatment of HIV-1 (FDA approved), Phase 2/3 for treat MERS (NCT02845843)/Phase 4 for SARS-CoV2 (NCT04255017)	antiretroviral protease inhibitor/Inhibits 3 CLpro	[121]
Plitidepsin	synthetic (cyclic depsipeptide)	immune suppressor, antiviral and antitumor, Phase 1 clinical trial for the treatment of SARS-CoV2 (NCT04382066)	Interference with the viral cycle by Blockade of Elongation factor 1-alpha 1 (eEF1a1)	[122,123]
Aviptadil	A synthetic form of Human Vasoactive Intestinal Polypeptide (VIP)	treatment of erectile dysfunction (approved), has shown to have anti-inflammatory effects that applicable for respiratory disorders, such as cystic fibrosis, sarcoidosis, asthma and pulmonary arterial hypertension (PAH), Phase 2 clinical trial for treatment of SARS-CoV2 (NCT04311697)	Vasoactive intestinal polypeptide (VIP) analog/ Inhibitor of interleukin-6	[124]
Solnatide	synthetic (mimics the lectin-binding domain (TIP) of tumor necrosis factor)	treatment of Acute Lung Injury (trials studying), being tested to COVID-19 treatment	Activates epithelial Na+ channel, ENaC/improving alveolar fluid clearance and oxygenation of the lungs/reducing lung edema/decreases reactive oxygen species production	[125,126]
Metenkefalin	synthetic	treatment of multiple sclerosis (in Bosnia)/Phase 2 trials for COVID-19 (NCT04374032)	Targets the delta-opioid receptor and causes Immunomodulatory	[127]
Ampion	synthetic	Used to treat pain due to osteoarthritis of the knee (Phase 3 trials) (NCT03988023, NCT02024529)/ Phase 1 trials for SARS-CoV2 (NCT04606784, NCT04456452)	increase signaling molecules required for tissue repair and healing in the lungs/reduces pro-inflammatory cytokine/suppresses NF-κB and STAT1α pro-inflammatory pathways	[128]
Oseltamivir	a synthetic derivative prodrug of ethyl ester	Approved for influenza A and B treatment/Trials (phase 2 and 3) for the treatment of SARS-CoV2 (NCT04516915, NCT04338698)	inhibitor of the influenza neuraminidase enzyme/ inhibit the spread of the influenza virus in the human body	[129]
PUL-042	synthetic	Phase 2 trials for treatment of SARS-CoV2 (NCT04313023)	Bind and activate the toll-like receptor (TLRs) on lung epithelial cells/induces the epithelial cells to produce peptides and reactive oxygens species (ROS) against pathogens	[130]
APL-9A	Pegylated synthetic cyclic peptide	Phase 1/2 trials for the treatment of SARS-CoV2 (NCT04402060)	modulates the complement cascade centrally at C3/ reduce inflammation in the lungs	[131]
FX-06	fibrin-derived synthetic peptide	Used for treatment of vascular leak syndrome in Ebola virus disease, Phase 2 trials for COVID-19 treatment (NCT04618042)	stabilizes cell-cell interactions, thereby reducing vascular leak	[132]

than natural peptides and their ability to cross the blood-brain barrier has been improved. They also show more flexibility for changes and modifications. Pharmacokinetics studies have shown that the clearance of peptidomimetics is lower than natural peptides, so they have a longer half-life in the body [135]. In this regard, due to the high similarity of human rhinoviruses 3C protease with coronaviruses 3CL protease, the question arises as to what is the inhibitory efficiency of rupintrivir, a HRV 3C protease inhibitor peptidomimetic, on SARS-CoV-2 protease? Vatansever et al. found that rupintrivir was able to inhibit SARS-CoV-2 virus 3CL protease with maximal inhibitory concentration (IC_{50}) of approximately 67 μM. They also showed that the serum stability of rupintrivir was higher than other drugs studied [136]. We suggest that researchers pay more attention to AVPs and other peptide-like compounds, especially those discussed in this review article, for basic and clinical research in the field of COVID-19 control. Regarding the emergence need to combat COVID-19, we also recommend focusing on available FDA-approved peptide therapeutics which could be promising candidates for drug development studies and clinical trials for COVID-19.

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