



Potential “biopeptidal” therapeutics for severe respiratory syndrome coronaviruses: a review of antiviral peptides, viral mechanisms, and prospective needs

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Received: 23 December 2020 / Revised: 25 March 2021 / Accepted: 4 April 2021 / Published online: 19 April 2021
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Abstract

Although great advances have been made on large-scale manufacturing of vaccines and antiviral-based drugs, viruses persist as the major cause of human diseases nowadays. The recent pandemic of coronavirus disease-2019 (COVID-19) mounts a lot of stress on the healthcare sector and the scientific society to search continuously for novel components with antiviral possibility. Herein, we narrated the different tactics of using biopeptides as antiviral molecules that could be used as an interesting alternative to treat COVID-19 patients. The number of peptides with antiviral effects is still low, but such peptides already displayed huge potentials to become pharmaceutically obtainable as antiviral medications. Studies showed that animal venoms, mammals, plant, and artificial sources are the main sources of antiviral peptides, when bioinformatics tools are used. This review spotlights bioactive peptides with antiviral activities against human viruses, especially the coronaviruses such as severe acute respiratory syndrome (SARS) virus, Middle East respiratory syndrome (MERS) virus, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or SARS-nCoV19). We also showed the data about well-recognized peptides that are still under investigations, while presenting the most potent ones that may become medications for clinical use.

Keywords Antiviral therapeutics · Bioactive peptides · Coronaviruses · COVID-19 pandemic · Pharmaceuticals

Key points

• *The mechanisms of limitedly available antiviral peptides show that they are potent.*

• *The peptides could be derived from animal venoms, mammals, plants, or artificial synthesis.*

• *They are potent against human coronaviruses-related diseases like SARS, MERS, and SARS-nCoV19.*

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Introduction

Viruses are found in birds, animals, and humans and are responsible for numerous epidemics or even pandemics. Since the last century, major breakthroughs regarding the control of viral replication, infection, and the production of vaccines have led to remarkable advances in human-virus interactions, such as smallpox eradication and the control of measles and poliomyelitis transmission (Vilas Boas et al. 2019). The same last century has been characterized with 5 pandemic respiratory diseases associated with influenza viruses (H1N1 or Spanish flu, H2N2 or Asian flu, H3N2 or Hong Kong flu, H5N1 or Bird flu and H1N1 Swine flu) with pigs serving as the natural hosts, infecting humans, pigs, and birds (Boopathi et al., 2020). The most recent pandemics are from the coronavirus family, which caused severe acute respiratory syndrome (SARS), Middle East respiratory

syndrome (MERS), and novel coronavirus (SARS-nCoV19) in this present century.

The present respiratory disease (SARS-nCoV19 or COVID-19) is caused by novel coronaviruses. The disease has taken over the world with symptoms like cold, fever, cough, sore throat, runny nose, and breathing difficulty. For reasons like this, the most utilized treatment for viral control is the use of antiviral drugs (Lou et al. 2014). Due to the side effects of certain antiviral drugs that have developed over the past decades, advances into newer and safer antiviral molecules are being made. Isolation of new compounds and peptides from diverse sources with the aid of molecular, structural, and bioinformatic analyses has contributed to the prospects of antiviral peptides discovery for therapeutic purposes against various human viruses (Wang et al. 2010; Rothan et al. 2014).

Therefore, this present pandemic situation versus available information on antiviral peptides putative of antiviral therapy or drugs are instigators of the present study. The therapeutic potentials of antiviral bioactive peptides against the human viruses, especially the severe respiratory syndrome coronaviruses, were examined. This review comprehensively summarizes the occurrence of antiviral peptides, mechanisms of peptide inhibition and viral action, along with futuristic needs and recommendations. Most importantly, we systematically discussed the antiviral peptides against SARS, MERS, and SARS-nCoV19. We do believe that this kind of ordered knowledge will guide researchers to extend their studies and explore the promising peptides with antiviral effects.

To do that, we used “antiviral peptides,” “bioactive peptides,” “peptides sources,” “coronavirus,” and “COVID-19” as research terms, applied Boolean operators “AND/OR” combination, performed in April 2020 from the following electronic databases: Scopus, PubMed, ScienceDirect, Wiley Online, Springer, Web of Science, ACS pubs, RCS-website, and Google Scholar. We initially checked the content of the English published articles to detect both included or excluded criteria, and therefore, some irrelevant articles were omitted according to the eligibility criteria published by Peterson et al. (2006). Then, we narrated the extractable data in the following sections.

Occurrence of antiviral peptides

Production of bioactive peptides

Bioactive peptides are short fragments of food proteins capable of providing positive influence and health-promoting properties when consumed by humans. They act as nutrients that potentiate physiological functions and disease prevention when passed through the absorptive pathways in the digestive system (Ashaolu 2020a). Based on the bioactive peptide sequence, their functions may include satiety and antiobesity

(gastrointestinal system), antithrombotic, antihypertensive, antioxidant, hypocholesterolemic (cardiovascular system), opioid (nervous system), cytomodulatory, immunomodulatory, antiviral, and antimicrobial effects (immune system) (Vilas Boas et al. 2019; Mora et al. 2019; Ashaolu 2020a, 2020b and Ashaolu 2020c).

The production of bioactive peptides may involve classical or bioinformatic (in silico) approaches (Daliri et al. 2017). The classical way includes enzymatic hydrolysis or microbial fermentation, both of which involve using enzymes or microorganisms to hydrolyze proteins into a pool of hydrolysates. This will be followed by bioassay purification, peptide size separation via membrane filtration, high-performance liquid chromatography (HPLC), and in vitro and in vivo bioactivity tests (Ashaolu 2020a). There would also be a further peptide purification and sequencing step to isolate the desired bioactive peptide for the final in vitro and in vivo biological tests. The in silico method employs database sets composing of already isolated and identified peptide sequences to match the target protein. Based on the information, the identified sequences in the target protein are hydrolyzed by specific enzymes associated with their cleavage sites. It enhances the identification of known peptides from unknown proteins (Daliri et al. 2017). Proteins from microorganisms, fungi, plants (soy, wheat, barley, rye, oats, rice, corn, sorghum, and millet), and animals (meat, eggs, milk, and fish) have been recognized as main sources of bioactive peptides (Mora et al. 2015; Ashaolu 2020a). Almost half of the past century has been invested into peptides research with numerous angles to their bioactivities. Till now, characterizing the bioactive peptides has more often favored antibacterial or antimicrobial functions, of which the cationic and amphipathic properties of the antimicrobial peptides are not dissimilar to antiviral peptides (Vilas Boas et al. 2019).

Antiviral peptides

Antiviral peptides have several commonalities with antimicrobial peptides targeted at all microorganisms but need special attention since their targets are between living and non-living organisms; they are replicative, non-metabolizing, and lack self-generated energy (Pärm et al. 2015). As there are numerous examples of antiviral peptides, which are predominantly cell-based, in vivo protective studies are lacking (Shartouny and Jacob 2019). The demerits of antiviral peptides usage include their expensiveness, short half-life, limited upper gastrointestinal absorption, and poor immunogenicity, while on the other hand, they can be very effective, less toxic, enzymatically biodegradable, and specific (Galdiero et al. 2013). Peptides with antiviral activity against human viruses are listed in Table 1.

Table 1 Isolated peptides with antiviral activity against human viruses

Name of peptide	Source of isolation	Sequence	Target virus	References
Caerin 1.1	Frog (Australia)	GLLSVLGSVAKHVLPHVVPVIAEHL	HIV	VanCompermolle et al. (2005)
Melittin	Honeybee (<i>Apis mellifera</i>)	GIGAVLKVLTTGLPALISWIKRKRQQ	HIV, HSV-1 and HNP-2; Junin virus	Wachinger et al. (1998); Matanic and Castilla (2004); Yan et al. (2011); Hong et al. (2014)
Urumin	Frog (India)	IPLRGAFINGRWDSQCHRFSNGAIACA	IAV (H1)	Holthausen et al. (2017)
NYAD	Page display, hydrocarbon stapled	ITFXDLLXYYGP	HIV-1	Zhang et al. (2008)
Deca-(Arg)8	Synthetic analog of Tat-1 with additional fatty acid	domainDeca-WRRRRRRRRRG	Duck-HBV	Abdul et al. (2012)
G1, G2	Phage display	LRSRTKIIRIRH, MPRRRRIRRRQK	HSV-1	Tiwari et al. (2011)
Kalata B1	<i>Oldenlandia affinis</i>		HIV-1, DENV	Daly et al. (2004); Craik and Du (2017)
Cyruilin A & B	<i>Chassalia parviflora</i>		HIV-1	Gustafson et al. (1994)
Phaseococcin	<i>Phaseolus coccineus</i>		HIV	Kiczler et al. (2010)
Sesquin	<i>Vigna sesquipedalis</i>		HIV	Hultmark et al. (2005)
Latarcin 1	Spider (<i>Lachesana tarabaeve</i>)	SMWSGMWRRKLLKLRNALKKKLKG	DENV-2	Rothan et al. (2014)
Mastoparan 7	<i>Vespula lewisii</i>		VSV, HSV-1, YFV, RSV, WNV	Li et al. (2011)
Mucroporin-M1	<i>Lychas mucronatus</i>		Measle virus, Influenza H5N1, SARS-CoV, HBV	Chemysch et al. (2002); Zeng et al. (2018)
Epinecidin 1	Groupers	GFIFHIIKGLFHAGKMIHGLV	JEV	Huang et al. (2011)
Kn2-7	<i>Mesobuthus martensii</i>		HIV-1 subtype B	Kuczer et al. (2011)
Alloferon 1, 2 and 1 analogs	<i>Calliphora vicina</i>		CBV-2	Egal et al. (1999); Marcocci et al. (2018); Shartouny and Jacob (2019)
Magainin 1, 2, variants	<i>Xenopus laevis</i>		HSV-1, HSV-2, vaccinia virus	Lorin et al. (2005); Bergaoui et al. (2013); El-Bitar et al. (2015)
Cecropin A	Silk moth (<i>Hyalophora cecropia</i>)	KWKLFKKIEKVGQNIRDGIIKAGPAVAVVGQATQIAK	HIV, HSV-1 and 2, Junin virus	Wachinger et al. (1998); El-Bitar et al. (2015)
Clavanin A, AK, B	<i>Styela clava</i>		Rotavirus, adenovirus, HSV-1, HIV	Wang et al. (2010); Lu et al. (2011); Migliolo et al. (2012)
HNP-1, HNP-2, HNP-4	Human neutrophil		HIV, Influenza A, HIV	Salvatore et al. (2007); Howell et al. (2007); Meyer-Hoffert et al. (2008)
Beta-defensin 1	Mouse	DQYKCLQHGGFCLRSSCSNTKLQGTCKPDKPNCKS	IAV	Li et al. (2014)
Temporin B	<i>Rana temporaria</i>		HSV-1	Dean et al. (2010)
Dermaseptins	<i>Phyllomedusa</i>		HSV-1, HSV-2, rabies virus, HIV-1	Holthausen et al. (2017); Mechlia

Table 1 (continued)

Name of peptide	Source of isolation	Sequence	Target virus	References
Mirabamide E, F, G, and H	<i>Stelletta clavosa</i>		HIV	et al. (2018); Monteiro et al. (2018); Vilas Boas et al. (2017)
HS-1	<i>H. semilineatus</i>		DENV-2 and -3	Carriel-Gomes et al. (2007)
LK-3	Artificial peptide (dimer)	LKKLCKLLKKLCKLAG, LKKLCKLLKKLCKLAG	HIV-1	Jang et al. (2014)
HBD-2, 3			HPV, HIV, vaccinia virus, VZV	Quiñones-Mateu et al. (2003); Barlow et al. (2011)
LL-37	Human neutrophil granules		VZV, VV, HSV-1, adenovirus, HIV, RSV, HCV, influenza A, HCV, Aichi virus, DENV 2, rhinovirus	Gordon et al. (2005); Matsumura et al. (2016); Sousa et al. (2017); He et al. (2018); Ahmed et al. (2019)
Hp1036	Scorpion (<i>Heterometrus petersii</i>)	ILGKIWEGIKSIF	HSV-1, HCV	Zhao et al. (2012); Chen et al. (2012); Hong et al. (2014)
Hp1239	Scorpion (<i>Heterometrus petersii</i>)	ILSYLWNGIKSIF	HSV-1, HCV	Zhao et al. (2012); Chen et al. (2012); Hong et al. (2014)
Lactoferrin, Lactoferricin	Mammals' secretions		HPV, CMV, HSV-1 and HSV-2, adenovirus, rotavirus, poliovirus, RSV, HIV, influenza, HCV, HBV, DENV, chikungunya, Zika	Van der Strate et al. (2001); Li et al. (2009); Chen et al. (2017); Carvalho et al. (2017); Andersen et al. (2001); Mistry et al. (2007); Marr et al. (2009); Shestakov et al. (2012)
CYVIP	Human filtrate		HSV-1	Borst et al. (2013)
Protegrin-1	Swine white blood cells		DENV, HSV-1, and HSV-2	Lu et al. (2011); Rothan et al. (2014)
Indolicidin	Bovine	ILPWKWPWWPWRR	HIV	Robinson et al. (1998)
Pa-MAP1	<i>Pleuronectes americanus</i>		HSV-1, HSV-2	Wang et al. (2004); Holly et al. (2017)
Turtle egg white protein (TEWP)	Sea turtle	QKKCPGRCTLCKGKHERPTLPYNGKYICCVVKVK	CHPV	Chattopadhyay et al. (2006)
Antiviral peptides	Spike glycoprotein	AVPs viz. , Seq12, Seq12m, and Seq13m	SARS-CoV-2	Dutta et al. (2020)

Animal-derived antiviral peptides

The antiviral peptides may be obtained from animal or plant sources. The animal-derived antiviral peptides have been scantily sourced from marine organisms, amphibians, mammals, and arthropods. The commonest peptides from the

marines are the clavanins from *Styela clava* and mirabamides E, F, G, and H obtained from *Stelletta clavosa*, which demonstrated antiviral activities against rotavirus, adenovirus, and human immune deficiency virus (HIV) (Yasin et al. 2000; Lu et al. 2011; Ireland et al. 2008). An antiviral peptide nomenclated as Pa-MAP 1 and capable of interference with

the herpes simplex virus (HSV-1 and HSV-2) glycoprotein surface was derived from *Pleuronectes americanus*, an arctic fish (Migliolo et al. 2012; Vilas Boas et al. 2017). Didemnim (A and B) have also shown virucidal actions against parainfluenza, dengue, and human papillomavirus (HPV) (Canonico et al. 1982). Didemnins-like depsipeptides derived from tunicates such as *Didemnins* X, Y, M, *Nordidemnin* N, and *Epididemnin* A were also found to possess antiviral properties (Aneiros and Garateix 2004).

The physiological and morphological characteristics of amphibians suggest that they can produce antimicrobial and antiviral peptides. *Rana temporaria* is a frog species capable of producing temporin B peptide against HSV-1 and was found to rupture the viral envelope (Marcocci et al. 2018). Magainin 1 and 2 peptides from *Xenopus laevis* demonstrated virucidal action against vaccinia virus (VV), HSV-1 and HSV-2, with clear indications that their lysine-rich and alanine-rich regions stimulated certain unclear mechanisms that associated their cationic charge with an amphipathic structure to cause interactions with the anionic phospholipids of the viral envelope, consequently, causing their disruption and death (Egal et al. 1999; Matanic and Castilla 2004; Dean et al. 2010). Obviously, the dermal glands of frogs have proven to be the source of many amphibian-derived peptides because they can release cationic, amphipathic α -helical secondary structure, with 10–50 amino acids when stressed (Marcocci et al. 2018; Vilas Boas et al. 2019).

Other than HSV, peptides targeting HIV-1 envelope were also derived from the genus *Phyllomedusa*, the dermaseptins (Belaïd et al. 2002; Lorin et al. 2005; Bergaoui et al. 2013). The derivatives (S3, S4) of dermaseptins showed virucidal activity against rabies virus when amino acid exchange (methionine-lysine) was involved, using bioassays and mice models (Mechlia et al. 2019). *Hydrophylax bahuvistara* frog can produce urumin, which demonstrated inhibitory and destructive actions against influenza (H1N1, H1N2) virus when bioassays and mice models were employed (Holthausen et al. 2017). This apparently indicated that hemagglutinin 1 was switched into a reactive mode with the peptide urumin.

In addition, dengue virus (2 and 3) could be attacked by HS-1 peptide isolated from the skin of *Hypsiboas semilineatus*. This is based on the studies of Monteiro et al. (2018) who observed HS-1 peptide activity at the early stages of dengue viral infection in vitro, subsequent reduction in viral load, and the disruptive impact of the peptide on the viruses that caused some envelopes to invaginate.

Apart from lactoferrin or protegrin-1, the antiviral peptides that mammals commonly produce are defensins and cathelicidins, which are also antimicrobials with cationic and amphipathic characteristics. Cathelicidins were demonstrated to inhibit or destroy influenza A virus, HSV, HIV, respiratory syncytial virus (RSV), varicella zoster virus (VZV), VV, hepatitis C virus (HCV), Zika virus, adenovirus, rhinovirus, Aichi

virus, and certain serovars of dengue virus with no same mechanisms of action, which often involve viral envelope and components damage or host cell protection (Gordon et al. 2005; Barlow et al. 2011; Matsumura et al. 2016; Sousa et al. 2017; Alagarasu et al. 2017; He et al. 2018; Ahmed et al. 2019).

Defensins have shown activity against HIV, influenza A virus, VV, and varicella zoster virus among others (Quiñones-Mateu et al. 2003; Salvatore et al. 2007; Howell et al. 2007; Crack et al. 2012; Zapata et al. 2016), indicative of being used as futuristic antiretroviral peptides. Protegrin-1 originating from pigs is a cyclic peptide shown to inhibit dengue virus replication via the replication enzyme pathway, while its mirror structure demonstrated activity against HSV-1 and HSV-2 (Yasin et al. 2000).

Lactoferrin and its derivative, lactoferricin, are peptides obtained from the milk of mammals and have antiviral multiactivity against influenza virus, HPV, HIV, RSV, adenovirus, poliovirus, rotavirus, hepatitis B virus (HBV), HCV, Zika virus, dengue virus cytomegalovirus (CMV), and HSV (Andersen et al. 2001; Van der Strate et al. 2001; Mistry et al. 2007; Marr et al. 2009; Li et al. 2009; Chen et al. 2017; Shestakov et al. 2012; Wang et al. 2016).

Insects, crustaceans, arachnids, and every other member of the arthropodal community are not left out of the supplies of antiviral peptides. *Calliphoridae* member blowfly peptides and alloferons (1 and 2) have been shown to inhibit influenza virus serovars, coxsackievirus B2 (CBV-2), and HSV-1 (Chernysh et al. 2002; Kuczer et al. 2011, 2013), with less vivid action mechanism. Cecropia moth can produce cecropin A peptide, which has activity against HSV, Junin virus (JV), and HIV (Wachinger et al. 1998; Albiol Matanic and Castilla 2004; Hultmark et al. 2005).

Apart from studies on morphological parts of arthropods, their venoms have widely been investigated by researchers for potential antiviral peptides. Asian spider venom peptide, Lactarcin 1 (from *Lachesana tarabaeve*) possesses antiviral property against dengue virus-2 through protease activity blockage (Rothan et al. 2014). Melittin, which is derived from bees' venom, as well as melittin-incorporated nanoparticulates showed activity against HSV, JV, and HIV via lysis of their envelopes (Albiol Matanic and Castilla 2004; Galdiero et al. 2013; Hood et al. 2013). Similarly, wasp venom contains mastoparan capable of rupturing and separating the envelope of vesicular stomatitis virus (VSV) from its capsid (Sample et al. 2013). Mucroporin-M1 peptide from aquatic scorpion (*Lychas mucronatus*) had inhibitory effects against severe acute respiratory syndrome coronavirus (SARS-CoV), influenza H5N1, measles virus, and HBV (Li et al. 2011; Zhao et al. 2012) while *Euscorpions validus* venom-derived peptide, Eva 1418, inhibited the replication of HSV-1 (Zeng et al. 2018). Three peptides derived from scorpion venom, namely Hp1090, Hp1239, and Hp1036, were also demonstrated to act against

HSV-1 and HCV replication (Hong et al. 2014; Yan et al. 2011).

Plant-derived antiviral peptides

As a means of self-defense, plants produce multifarious poisonous substances against pathogens and pests. These substances include molecules, proteins, peptides, and toxins that fight against impending viral attacks. This backdrop has led to numerous investigations into these plant defense substances, especially peptides as putative human antiviral peptides (Shartouny and Jacob 2019). Among this group of plant defense peptides, cyclotides have gained vast attention due to their rigid structure and numerous biological activities such as molluscicidal, insecticidal, nematocidal, antimicrobial, and anthelmintic (Weidmann and Craik 2016; Vilas Boas et al. 2019). They have also shown inhibitory actions against dengue virus, HIV, and influenza H1N1 virus (Henriques and Craik 2010; Sencanski et al. 2015). Other related peptides including 2000 Da fractionated peptide, sesquin, and phaseococcin, isolated from *Sorghum bicolor* seeds, *Vigna sesquipedalis*, and *Phaseolus coccineus*, respectively, have demonstrated inhibitory activities against HSV-1 and HIV (Camargo Filho et al. 2008; Jack and Tzi 2005; Ngai and Ng 2005). Moreover, antiviral peptides from pokeweed (PAP-1, PAP-2, and PAP-3) were reported to cause genomic mutations of poliovirus, HSV, HIV-1, influenza virus and lymphocytic choriomeningitis mammarenavirus (LCMV) via depurination (Rajamohan et al. 1999; Uckun et al. 2003; Aron and Irvin 1980; Tomlinson et al. 1974; Uckun et al. 2005), as well as inhibit Japanese encephalitis virus both in vitro and in vivo (Ishag et al. 2013; Domashevskiy and Goss 2015).

Mechanism of inhibition

Peptides with antiviral or virucidal activities integrate into the envelope of the target virus or cell membrane of the host to create an unstable membrane. Some peptides prevent viral spike proteins from binding to host cells (Belaid et al. 2002). The cellular pathways including DNA replication and protein synthesis may be altered in this process, thereby stopping viral infection (Sitaram and Nagaraj 1999; Pärn et al. 2015). Since many antiviral peptides can be obtained from previously demonstrated antimicrobial molecules (Chinchar et al. 2004; Crack et al. 2012), it is logical to relate the idea that peptides with positive charges can have direct interaction with negatively charged host cellular membranes to cause viral inhibition.

From the initial to the final phase of a typical viral cycle, most virucidal peptides inhibit virions by direct contact, or suppress their gene expression, or interfere with the linkages, movements, and adsorption of proteins in the host cell membrane (Galdiero et al. 2013; Zapata et al. 2016). An example is

the Tat antiviral peptide, which interacts with CXCR4, a co-receptor (protein) of HIV-1, and inhibits the replication of HIV-1 (Keogan et al. 2012; Pärn et al. 2015). The mechanism of inhibition of antiviral peptides is described within the viral replication cycle in Fig. 1. The antiviral activity of any peptide will be affected by its chemical and structural properties including charge, amino acid sequence, and profile while bioinformatics and in silico designs have paved the edge-cutting way for more modern peptide analysis (Mooney et al. 2012; Sharma et al. 2014).

Coronavirus family

An overview about coronavirus

Coronaviruses (CoVs) are enveloped, positive-sense, single-stranded RNA viruses with genomic lengths of ≤ 32 kb and can cause liver, intestinal, respiratory, and nervous system diseases in mammals such as animals and humans (Monajjemi et al. 2020; Liya et al. 2020). Their genomes encode between four and five structural proteins, including hemagglutinin esterase, nucleocapsid, membrane, envelope, and spike proteins (Esper et al. 2005). Spike protein is the most important surface membrane protein of coronavirus, which determines the host range and specificity of the virus (Liya et al. 2020). The coronavirus family belongs to the order Nidovirales, and it can be categorized into 3 chief groups: α -coronavirus (group 1), β -coronavirus (group 2), and γ -coronavirus (group 3), while the β -coronavirus is subsequently sub-classified into group 2A and 2B (Chuck et al. 2011). The α - and β -genera are responsible for human CoVs infections, the HCoV. α -CoVs include HCoV-229E and HCoV-NL63 while β -CoVs include HCoV-HKU1, HCoV-OC43, SARS-CoV, MERS-CoV, and SARS-nCoV19 (Rabaan et al. 2020).

SARS, MERS, and SARS-nCoV19

SARS-CoV, MERS-CoV, and SARS-nCoV19 cause a variety of severe flu-like symptoms and were responsible for recent epidemics (in 2002/3, 2012/5, and 2019/2020, respectively) (Bauchner et al. 2020). Despite of this classification, the ability of CoVs to generate novel strains with high virulence through high frequency of mutations and recombination remains a potential threat to human health.

SARS-CoV is a newly identified member of *Coronaviridae* family identified in 2002/2003. Coronavirus envelope S-protein is a class I viral fusion protein which is categorized by the presence of two heptad repeat regions (HR₁ and HR₂), making a multifaceted complex called fusion central. MERS-CoV initially came into the spotlight in 2012, and dispersed worldwide with a high death rate, and now, the

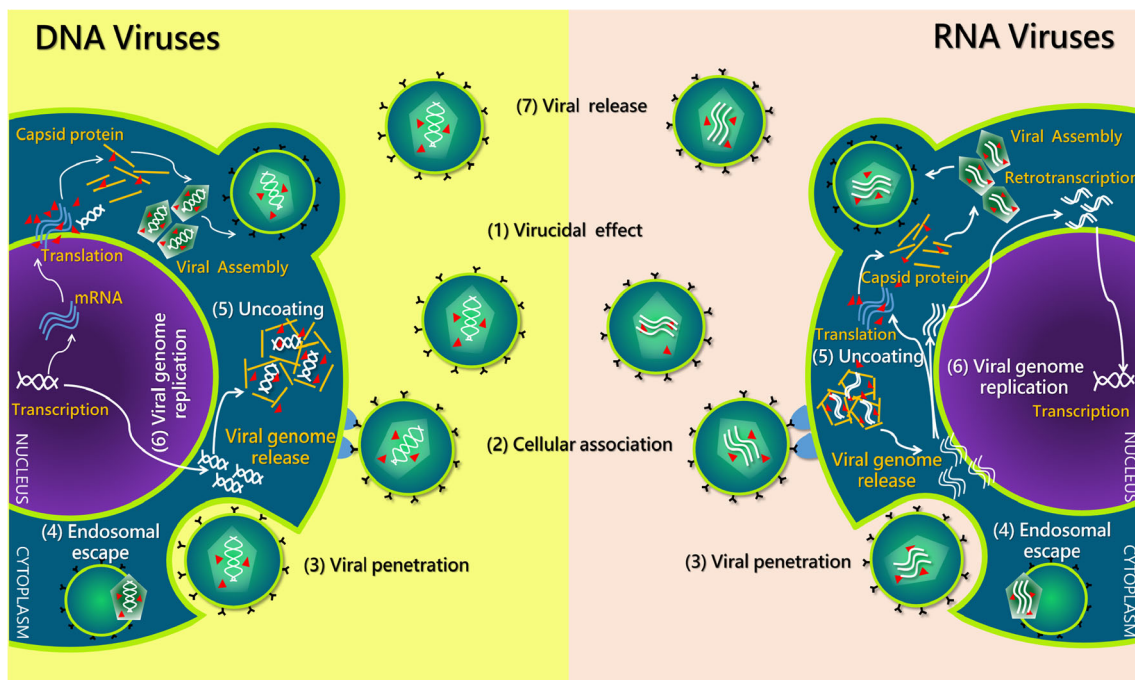


Fig. 1 Annotated action mechanism of antiviral peptides based on inhibition sites within a viral replication cycle adapted from different studies. Adapted from Vilas Boas et al. (2019)

world is underneath another severe COVID-19 pandemic instigated by SARS-nCoV19 or novel coronavirus (nCoV-19) (Lai et al. 2020; Prompetchara et al. 2020). So far, more than 120 million people have been infected with close to 3 million deaths recorded across the world (www.worldometers.info/coronavirus). SARS-nCoV19 is vastly spreadable in humans, and so far, no medication has been industrialized to treat the virus infection (Shereen et al. 2020). While drugs such as hydroxychloroquine, remdesivir, and lopinavir (Rosa and Santos 2020) are presently being proposed to hinder SARS-nCoV19 infection, there is no clinical study so far to verify their efficiency in treating these patients. Thus, presently, there is a worldwide search for suitable medication for SARS-nCoV19.

In general, SARS-nCoV19 has exposed 80% genome uniqueness with SARS-CoV. It was found that the viruses could be contracted from their normal hosts (bats) based on their 96.2% genomic similarity (Zhou et al. 2020) through intermediates (civet cats, camels). This is laudable, but information on the number of hosts during transmission process and how humans contract them *via* animals has not been substantiated. While some reports suggest direct contact with raw meat or milk of intermediate hosts as means of getting HCoV infections, SARS-CoV and MERS-CoV transmission routes were identified as mainly via infectious droplets and close contact (NHFPC 2015). It has also been reported that COVID-19 thrives in densely concentrated areas and can be transmitted via aerosols to the general population (Liya et al. 2020).

Beyond the mechanism of the antiviral drugs, the viral particle is molded by S-glycoprotein, envelope (E), membrane (M), and nucleocapsid (N) (Boopathi et al. 2020). The spike is a type 1 transmembrane protein and is shaped by two subunits (S_1 and S_2) which are elaborate in the fusion/entry procedure. While S_1 has receptor-binding domain (RBD) and is accountable for assembling to the cellular receptor, S_2 has fusion-peptide, HR₁, HR₂, transmembrane-domain, and a cytoplasmic domain-peptide and turns in the viral synthesis before being passed into the cell (De Haan et al. 2006). Both HR₁ and HR₂ have 3 pieces each that, altogether, form a six-helix bundle synthesis central. Disturbance of this central creation is critical to viral union reserve, thus stopping infection (Steffen and Pohlmann 2010). Meanwhile, HR₁ and HR₂ of S-protein of SARS-CoV are vastly preserved areas and are attractive boards of passive inhibitors.

On the other hand, assembling CoVs-S-protein to cellular angiotensin-converting enzyme 2 (ACE₂) is the first step in CoV infection. The receptor for SARS-CoV is ACE₂, which is a surface molecule located on arteriovenous endothelial cells, arterial smooth muscle cells, small intestinal epithelium, and the respiratory tract (Ren et al. 2008; Liya et al. 2020). Investigation of SARS pathogenesis in different parts and organs of humans has shown that ACE₂ is expressed on the surfaces of alveolar epithelial, small intestinal epithelial cells, endothelial cells, and smooth muscle cells (Hamming et al. 2004). Thus, in the bronchial epithelial cells, SARS-nCoV19 may be able to use alveolar type II epithelial cell ACE₂ as a receptor for penetration. Speculation arises that there may be

similarities in the clinical characteristics of SARS-CoV and SARS-nCoV19 as the amino acid sequence and predicted protein structure between their RBD in the spike protein are highly similar. In fact, the affinity of SARS-nCoV19 to ACE₂ binding is higher than SARS-CoV (Wrapp et al. 2020).

Two possible mechanistic pathways have been postulated at this stage. First, the virus particle uses its S₁ subunit domain to bind to ACE₂ receptor on the human host cell membranes such as alveolar epithelial cells, followed by fusion with S₂ subunit at a low pH (Li 2016). Otherwise, the virions undergo membrane fusion after fusion peptide is released from the S₂ subunit site and then eat the virus via endocytosis. Here, the virus may exercise receptor-binding reorientation in S-protein, cathepsin L cleavage by host enzymes, and completion of other endosomal fusion mechanisms (Simmons et al. 2005). Then comes the viral release and uncoating of its genetic materials through the proteasomes into the cytoplasm. This process is mediated by the nsp replication-transcription complex (RTC), encoded in the genome and important for double-membrane structural inducement in susceptible cell cytoplasm. The synthesis of M, S, and E proteins ensues and is inserted into the endoplasmic reticulum (ER), which become transferred to endoplasmic reticulum-Golgi intermediate compartment (ERGIC) (Boopathi et al. 2020). After the formation of nucleocapsids by N-protein, new viruses migrate from the cytoplasm toward the cell membrane with vesicular walls to be released in the exocytotic process that leads to host cell death, hence continuing the replication cycle in other susceptible living cells.

The single-stranded RNA genome of CoVs encodes two polyproteins, which are treated into at least 15 mature proteins by papain-like protease and 3C-like protease (3CL^{pro}) (Lu et al. 1998). The 3CL^{pro} of CoVs is therefore a promising target for development of drugs against CoVs infection due to the inhibition of the proteolytic dispensation, which can diminish viral replication and viral-made cytotoxic effect (Yao et al. 2018). Antiviral peptides are preferred to conservative drugs and may also be effective against SARS-nCoV19, due to the continual outbreaks of COVID-19. Thus, it is necessary to enlarge a wide-spectrum drug that can battle against all types of CoVs infection.

Possible antiviral peptides against SARS, MERS, and SARS-nCoV19

The emergence of COVID-19 outbreak needs imperative solutions for operative antiviral tactics. Using the computational chemistry could help in this regard (Zhu et al. 2018). One of these strategies is to inhibit the viral infections using HR-based peptides, which could compete with endogenous HR counterparts and thereby prevent the virus replication and infection. This strategy was successfully used to mitigate the replication

of human immunodeficiency (Kliger et al. 2001; Wild et al. 1993), Ebola (Watanabe et al. 2000), and SARS-CoV viruses (Bosch et al. 2004; Zhu et al. 2004). Generally, it is supposed that a sequence of conformational fluctuations happens in the coronavirus HR regions during the viral fusion progression.

Concerning SARS-CoV, Bosch et al. (2004) found that membrane-proximal HR₂-peptide of S-protein inhibited SARS-CoV in Vero cells, where the membrane-distal HR₁-peptide showed no inhibition activity. Its effectiveness was, however, significantly ($P < 0.05$) inferior to those of corresponding HR₂-peptides of the murine coronavirus and hepatitis virus (MHV) during the inhibition of MHV infection. Interestingly, SARS-CoV HR₁- and HR₂-peptide mixtures showed a better stability than the individual peptide that was validated using heat-accelerated, biochemical, and electron microscopical analyses, thus providing an appealing basis for developing a therapeutic medication against SARS-CoV. The octapeptide AVLQSGFR was manufactured and tested toward SARS-CoV (BJ-01) (Gan et al. 2006). The results implied that, compared with other components testified, AVLQSGFR is the most potent peptide capable of inhibiting SARS-replication, and that no measurable toxicity is detected in Vero cells. In another study, Ho et al. (2006) evaluated the inhibitory effects of small peptides resultant from S-protein on the interaction of S-protein to ACE₂ and on S-protein-pseudotyped retrovirus infection. SP-4 (residues of 192–203), SP-8 (residues of 483–494), and SP-10 (residues of 668–679) pointedly jammed the binding between S-protein and ACE₂, with IC₅₀ values of 4.30, 6.99, and 1.88 nM, separately. It was also suggested that SP-10 may be industrialized as an anti-SARS-CoV drug, due to its blocking effects on S-protein which was tested in Vero E6 cells. The HR₂ peptide, especially P6 of 23-mer, was found to block the SARS-CoV-fusion with an IC₅₀-value of 1.04 μM (Liu et al. 2009). Most importantly, combination of HR, N46, and its mutated type like N46eg, display synergistic effect with an IC₅₀-value of 1.39 μM and amalgamation index of 0.75, signifying a communal tactic to accomplish hopeful inhibition by HR₁-peptide for SARS-CoV. The HR₂, either as artificial peptides or as GST-fusion polypeptides, is a powerful inhibitor of SARS-CoV and has been reported to bind with HR₁ to create a normal 6-helix bundle (Zhu et al. 2004). Alternatively, Chuck et al. (2013) created 4 nitrile-based peptidomimetic inhibitors with diverse N-terminal defensive clusters and diverse peptide span and scrutinized there in vitro antienzymatic activity of 3CL^{pro} of SARS-CoV. They found out that the nitrile-based peptidomimetic inhibitors are applicable by blocking 3CL^{pro} from a wide series of SARS-CoV with an IC₅₀ value of 4.6–49 μM. This activity was ensured by making a covalent bond with the catalytic Cys145, where AVLQ-peptide creates a sum of auspicious bonds with the S1-S4 substrate-binding pouches. Cbz-AVLQ-CN, which is a peptidomimetic inhibitor, has a wide-spectrum activity on

3CL^{PRO} of human-COV strains 229E, NL63, OC43, HKU1, and transferable bronchitis virus, but no noticeable embarrassment on caspase-3. In general, numerous peptides, as anti-SARS-CoV, resulting from HR₂ have been recognized, such as P₁ (Lu et al. 2013), HR₂P (Chambers and Easton 1990), and CP-1 (Otwinowski 1997), which avert fusion core formation by reasonably binding with HR₁ and blocking the innate bond betwixt HR₁ and HR₂.

Regarding MERS-CoV, which is another high-mortality risk kind of coronavirus family, precise, extremely effective therapeutics and vaccines are instantly needed to protect human lives and control the pandemic fears. The antiviral peptides pointing to the membrane fusion architecture signify a favorable type, which had activities towards some viruses, including HIV, SARS-CoV, and MERS-CoV. The HR-based peptide-inhibitor T₂₀ (enfuvirtide) had been used to treat HIV-patients (Cuzin and Alvarez 2003; Imai et al. 2000; Kilby et al. 1998). In a comparison study, the peptide corresponding to the full length of HR₂-sequence potently inhibited pseudotyped MERS-CoV with an EC₅₀-value of ~3.013 μM, where a similar peptide (HR₁) showed no effect even at the supreme concentration (Gao et al. 2013). The changes among similar variance of different peptides were also found in other HR₂-peptides of class-I enveloped viruses, but the detailed mechanism explaining these differences has not yet been explored. In a related assay, Gao et al. (2013) characterized the six-helix bundle fusion central construction of MERS-CoV S₂-subunit protein and studied the binding of two peptides with each other to form 6-HB-core of MERS-CoV via X-ray crystallography and biophysical investigations. They found that the spanning residues of HR₁ (998-1039) and HR₂ (1251-1286) peptides formed a stable six-helix bundle fusion central structure, signifying that MERS-CoV goes into the host cell mostly *via* membrane fusion mechanism. The hydrophilic residues of HR₂ (1251-1286) peptide significantly ($P<0.05$) improved its stability, solubility, and most importantly enhanced its antiviral activity against MERS-CoV duplication and its S-protein mediated cell-cell fusion, hindering viral fusion central formation, as well as interacting with the viral HR₁-domain in a dose-dependent means. Lastly, the authors recommended that HR₂ (1251-1286) peptide should be used as a template for design of analogs with enhanced activity against MERS-CoV infection and possibly used in clinical patients. Another study of Sun et al. (2017) inspired by the same fusion core proteins, designed a peptide named MERS-5HB, which contains 3 replicas of HR₁ and two copies of HR₂. He found that MERS-5HB could bind with HR₂P, a peptide resulting from HR₂, with a sturdy affinity value of up to 0.24 nM, thereby inhibiting pseudotyped MERS-CoV, pass efficiently with IC₅₀ of ~1 μM. In addition, MERS-5HB significantly inhibited S-glycoprotein-mediated syncytial formation in a dose-dependent means ($P<0.05$). Further biophysical description displayed that MERS-5HB was a thermo-

steady α-helical secondary structure. Finally, the author recommended that MERS-5HB-peptide may offer a decent basis for empathy of an original inhibitor on MERS-CoV. Newly, the same group designed, synthesized, and characterized peptides for HR₁ and HR₂ regions from the HCoV-229E and tested them against HCoV-229E S-protein-mediated cell-cell fusion, and both pseudotyped and live HCoV-229E. Both 229E-HR1P and 229E-HR2P peptides showed inhibition of cell-cell spread with IC₅₀ of 5.7 and 0.3 μM, respectively, and inhibition of the pseudovirus poison with IC₅₀ of 0.5 and 1.7 μM, respectively. Besides, in mouse-model assays, 229E-HR2P retained its antiviral effects in both higher and inferior breathing areas when intranasally managed. Eventually, the authors proposed that 229E-HR2P could be utilized as an antiviral medication to be utilized lengthwise with diverse antiviral fragments with a diverse underlying mechanism, probably employing synergistic effects (Xia et al. 2018). On the other hand, Ying et al. (2014) identified m336, m337, and m338, as human monoclonal antibodies, directing the receptor (CD₂₆/DPP₄), and assembling domain (RBD) of MERS-CoV S-glycoprotein. The extraordinarily utmost nullification effect of such antibodies, especially m336, proposes that they have an inordinate potential for prophylaxis and therapy of MERS-CoV contagion in humans and as a tool for developing vaccine immunogens.

Newly, no known medicines or vaccines to control the COVID-19 pandemic caused by SARS-nCoV19 were found. Interestingly, Barh et al. (2020) disclosed that 3 amino acid in hACE₂ bind with nCoV-RBD. AC20 and AC23 derived from hACE₂ blocked two key critical positions, where DBP6, which was recognized from databases, blocked 3 sites of nCoV-RBD and assembled with one critical position Gln498. Likewise, it was found that 7 chimeric peptides were measured as promising among which cnCoVP-3, cnCoVP-4, and cnCoVP-7 are the top three, and cnCoVP-4 fits all the criteria as anti-COVID-19 peptide. Generally, the effective peptides ought to bind with 3 key sites of nCoV-RBD, namely Gly485/Phe486/Asn487, Gln493, or Gln498/Thr500/Asn501, or Phe486, Gln493, and Asn501. These are motivating issues that are worth searching in further studies. Small molecules to block 6-helix bundle formation ought to be followed in further studies on the current fusion central structure. As the EC₅₀ is in the micromolar range, for any ideal peptide inhibitors, a thorough screening for peptides of better efficacy should be pursued in the future.

On the other hand, phytochemicals such as anthocyanins and tannins were previously reported to have possible inhibition against SARS-CoV-2. For example, Khalifa et al. (2020a) found that pedunculagin, tercatin, and castalin which are hydrolysable tannins interacted with Cys145 and His41 of SARS-CoV-2-3CL^{PRO}. Likewise, Khalifa et al. (2020b) revealed that the polyacylated anthocyanins, including phacelianin, gentiodelphin, cyanodelphin, and tecophilin,

were found to authentically bind with the receptor binding site and catalytic dyad (Cys145 and His41) of 2019-nCoV-3CL^{pro} and could be used as effective anti-COVID-19 natural components. It was also shown that other polyphenols could be believed as promising biologically active substances for the inhibition of COVID-19, mostly due to their antiviral activities and the immune-regulation functions. It was also found that triterpenoid, anthraquinone, flavonoids, and other polyphenols are potential keys to cunning antiviral therapies for inhibiting SARS-CoV-2-^{pro} (Mehany et al. 2021). Additionally, vitamin A, vitamin D, and/or minerals, especially Zn, with their derivatives could provide a promising alternative for CoV therapy (Alpert 2017). These functional compounds are essential substances at the molecular and cellular levels that play critical functions (Khalifa et al. 2020c; Khalifa et al. 2019). The advantage of using mixtures containing polyphenols, bioactive peptides, vitamins, and minerals could be further considered against the SARS-CoV-2 infections.

Further needs

General safety issues associated with all bioactive peptides are not strange to antiviral peptides. It is pertinent to investigate the immunogenicity and toxicities of peptides due to intestinal wall disruption, erythrocytes and lymphocytes toxicity, free radical production, enzymopathic, and immunopathic tissue damage and cytotoxicity (Bhandari et al. 2020). The quality of delivery and treatment processes should be critically guarded, be it by conjugating with nanocarriers, antibodies, carbohydrates, or lipids. Other suggestions on the use of antiviral peptides as adjuvants or combined therapeutic agents (Vilas Boas et al. 2019) cannot be oversighted.

Other needs to be met include reproducibility of antiviral peptides and the design of kinetic model peptide synthesis to keep their bioactivity intact (Daliri et al. 2017). Moreover, several peptides have shown antiviral properties, but their sequencing information are still lacking. Kaspar and Reichert (2013) previously suggested stabilizing peptides in vivo with a probe tail structure or peptide sequence clipping for optimal bioavailability. This is due to the ever-challenging issue of poor oral absorption and short half-life of biopeptides inspired by gut digestive enzymes. Post-translational modifications like acetylation and amidation, membrane permeability improvement by adding fatty acid chains, or D-enantiomers usage for decreased target sensor and binding affinity to proteases (Shartouny and Jacob 2019) can help to solve this need for good oral absorption and peptide stability.

Using the available new technologies, antiviral peptides should be enriched for a complete set of in vitro, in vivo, and human-based studies. Proteases of genetically improved microbial strains could be useful in the industrial production of peptides meant for antiviral therapy. It is also important that

validated all-round characterization of antiviral peptides is essential to commence therapeutic claims against HCoVs and all other human viral diseases.

Acknowledgements The authors acknowledge database websites mentioned and Ms. Itthanan Suttikhana for assisting with the figure in this article.

Availability of data and material Available upon request

Code availability Available upon request

Author contribution TJA and IK conceptualized, wrote, and revised the manuscript. AN and NW proofread it. All authors read and approved the manuscript.

Declarations

Ethics approval Not applicable

Consent to participate Not applicable

Consent for publication Not applicable

Competing interests The authors declare no competing interests.

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