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Antiviral peptides from aquatic organisms: Functionality and potential inhibitory effect on SARS-CoV-2

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ABSTRACT

Several antiviral peptides (AVPs) from aquatic organisms have been effective in interfering with the actions of infectious viruses, such as Human Immunodeficiency Virus-1 and Herpes Simplex Virus-1 and 2. AVPs are able to block viral attachment or entry into host cells, inhibit internal fusion or replication events by suppressing viral gene transcription, and prevent viral infections by modulating host immunity. Therefore, as promising therapeutics, the potential of aquatic AVPs for use against the COVID-19 pandemic caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is considered. At present no therapeutic drugs are yet available. A total of 32 AVPs derived from fish and shellfish species are discussed in this review paper with notes on their properties and mechanisms of action in the inhibition of viral diseases both in humans and animals, emphasizing on SARS-CoV-2. The molecular structure of novel SARS-CoV-2 with its entry mechanisms, clinical signs and symptoms are also discussed. In spite of only a few study of these AVPs against SARS-CoV-2, aquatic AVPs properties and infection pathways (entry, replication and particle release) into coronaviruses are linked in this paper to postulate an analysis of their potential but unconfirmed actions to impair SARS-CoV-2 infection in humans.

1. Introduction

The global morbidity and mortality caused by viral infections are increasing incrementally, drawing attention to the importance of developing effective therapeutics against viruses (Barlow et al., 2014). Effective treatments are costly and require early and specific viral identification, requiring extensive processing time for vaccine development and testing of antiviral therapeutics (Falco et al., 2009; Findlay et al., 2013). The emergence of the new 2019 novel coronaviruses (nCoV) pandemic strain underscores the necessity of broader-spectrum antiviral drugs (Zhang Wen et al., 2020) and research efforts are underway to identify novel antiviral drugs or therapeutics (Gurwitz, 2020; Kuebutornyé et al., 2020; Wang, Chen, H et al., 2020; Wang, Cheng, W et al., 2020; Wang, M et al., 2020; Wang, Y et al., 2020). Alternatively, antimicrobial peptides (AMPs) could have utility because of their wide range of activities against infectious viruses in both humans and animals.

AMP molecules composed of 20–50 amino acid residues, known as antiviral peptides (AVPs) (Boas et al., 2019), have emerged as new agents to combat viral infections (Boas et al., 2019; Qureshi et al., 2014; Skalickova et al., 2015). According to those reports, mechanisms of action of antiviral drugs are mainly of two types, i.e. virus targeting and...
host targeting that can act upon various transcription and replication related enzymes to destroy a viral pathogen or inactivate their infectiveness (Boas et al., 2019; Lou et al., 2014). Mechanisms of action of AVPs against viruses include binding with specific viral subunits, blockage of viral entry into host cells, interaction with viral envelopes and modulation of host immune pathways. Small defense peptides can inhibit infection by human immunodeficiency virus (HIV-1) (Chang et al., 2005), influenza A virus (IAV) (Hartshorn et al., 2006), herpes simplex virus (HSV) (Hazzari et al., 2006), human adenovirus (HAdV) (Bastian and Schäfer, 2001) and human papillomavirus (Buck et al., 2006).

A number of potentially valuable AVPs have been characterized from fish, shellfish, marine sponge and other aquatic organisms. Recently, fish- and shellfish-derived AVPs have been found to have preventative actions against several fish infectious viruses such as viral haemorrhagic septicaemia virus (VHSV), Singapore grouper iridovirus (SGIV), nervous necrosis virus (NNV), white spot syndrome virus (WSSV) and others (Guo et al., 2012; Jin et al., 2010). Moreover, microspinosamide and Pa-MAP from sponge (Sidonops microspinosa) and winter flounder (Pleuronectes americanus) exhibited activities against HIV-1 (Rashid et al., 2001) and HSV-1 and 2 (Migliolo et al., 2012). AVPs like HR2P and mutant mucropin-M1 has gained recognition for their activities against Middle East respiratory syndrome (MERS)-CoV (Hilchie et al., 2013) and severe acute respiratory syndrome (SARS)-CoV (Li et al., 2011). In addition, two peptides (K12 and K29) derived from SARS-CoV non-structural protein ns10 reportedly inhibited replication of SARS-CoV (Ke et al., 2012). Similarly, mouse β-defensin-4 demonstrated potent and broad-spectrum antiviral effects against multiple respiratory infectious viruses in vitro and in vivo (Zhao et al., 2016).

In late December 2019, a cluster of cases of pneumonia of uncertain aetiology was reported to China National Health Commission, subsequently leading to the discovery of a new coronavirus on 07 January 2020 from patients in Wuhan (Chen Wang et al., 2020). The World Health Organization (WHO) consequently named this infection as novel coronavirus disease 2019 (COVID-19) on 11 February 2020 and declared it a pandemic on 11 March 2020 (UI Qamar et al., 2020), after its spread to at least 219 countries and territories (WHO, 2020). Presently, the world is heavily impacted by and struggling to deal with SARS-CoV-2, which led to ~111 million confirmed cases and 2.5 million deaths as of 20th February 2021 (WHO, 2020). Different kind of activities like genome sequencing (Zhang and Holmes, 2020), trialling existing drugs and medicines e.g. remdesivir (Beigel et al., 2020), hydroxychloroquine and azithromycin (Gautret et al., 2020), including drug suggestions by bioinformatics tools namely drug repurposing and molecular docking approach (Hasan et al., 2020; Parvez et al., 2020) were evaluated as potential treatments of COVID-19 pathology. At present no reports are available on the use of AVPs from aquatic or marine organisms or any other sources against SARS-CoV-2 infection. However, as there are some AVPs that inhibit viruses similar to SARS-CoV-2, like SARS-CoV (Ke et al., 2012), MERS-CoV (Hilchie et al., 2013) and some other respiratory viruses (Zhao et al., 2016), which are also very common in the aquatic organisms like in fish, shellfish and even in aquatic plants. The present study discusses properties, history and actions of AVPs from aquatic organisms that are used against infectious viruses including CoVs in human and animals. In addition, the potential of aquatic AVPs for the inactivation and destruction of CoV-2 infection pathway in human is explored according to their mechanisms of action and history of interactions with similar types of viruses. This discussion on aquatic AVPs and their possible use against SARS-CoV-2 might illuminate the prospects of developing fisheries-based therapeutics for the treatment of COVID-19.

2. History of antiviral peptides

Nisin, a 34-residue peptide produced by the lactic acid bacterium Lactococcus lactis, was the first AMP reported in 1928 (Desriac et al., 2013). It contains unsaturated stereo-inverted amino acids and thioether bridges in the structure, as explained by Gross and Morell (1971). Another AMP, gemicidin, isolated from soil bacterium Bacillus brevis, is active against gram-positive microorganisms in vivo (Dubos, 1939) and is among the first commercially produced antibiotics (Van Epps, 2006). Although, the discovery of AMPs from eukaryotes dated back to 1896 (Jago and Jago, 1926), AMP isolated from wheat (Triticum aestivum) endosperrn in 1942 and was found to be active against Pseudomonas solanacearum and Xanthomonas campestris (De Caley et al., 1972). Another of the initially-discovered AMPs is mellitin, a 26-non-modified residue peptide derived from the venom of European honeybee (Apis mellifera) (Fischer and Neumann, 1961). However, isolation and characterization of AMP gained momentum after the discovery of penicillin and streptomycin in 1943. To date, 123 peptides from human, 222 from mammals, 1057 from amphibians (Wang et al., 2016), and 122 from fish and shellfish have been characterized (Masso-Silva and Diamond, 2014).

Pardaxin is the first AMP characterized in fish, moses sole (Pardachirus marmoratus) found in the Red Sea (Primor and Tu, 1980). In 1997, a 25-residues amino acid peptide pleurocidin was identified from the secreted mucous of winter flounder (Cole et al., 1997) and another 21-residue amino acid containing AMP misugin was characterized from mudfish (Misgurnus anguillicaudatus) with strong antimicrobial activity (Park et al., 1997). Some additional AMPs have been isolated from various fish, shellfish, sponge and other marine organisms, displaying antiviral properties either in vitro, in vivo or both. For instance, hepcidins from turbot (Scophthalmus maximus; Pereiro et al., 2012), medaka (Oryzias melastigma; Cai et al., 2012); EcDefensin (Guo et al., 2012), β-defensin (Jin et al., 2010) from orange-spotted grouper (Epinephelus coioides), Scygonadin from green mud crab (Scylla paramamosain, Peng, Liu, Chen, Hao, & Wang, 2012), and microspinosamide from marine sponge (Rashid et al., 2001).

Despite the introduction of specific therapy and drugs for treating viral infections in 1946, AMPs are a promising alternative in the design of therapeutics to control viral diseases (Field and De Clercq, 2004). In the 1980s, only a few AVPs were reported from different sources. Of those, Didemmins are among the earliest AVPs identified, from the Caribbean tunicate Trididemnum; this compound is capable of inhibiting activities of DNA and RNA viruses in vitro and in leukemic cells (Rinehart et al., 1981). Ganz et al. (1985) identified a defensin from human neutrophils named HNP, which was effective inactivating HSV-1 directly (Ganz et al., 1985). Later, defensins (HNP-1, HNP-2 and HNP-3) were extensively tested and found to inactivate HSV-2, cytomegalovirus (CMV), vesicular stomatitis virus (VSV) and IAV (Daher et al., 1986). In the next decade, several AVPs were isolated from various sources, viz. tachyplesin (Morimoto et al., 1991) and polyphemusin (Nakashima et al., 1993) from horseshoe crab (Tachypleus tridentatus), PAP from pokeweed (Phytolacca americana); Chen et al., 1991) and magainin from the aquatic frog (Xenopus laevis, (Aboudy et al., 2009). The majority of the AVPs from fish and shellfish have been isolated in the 21st century. Among them, Pa-MAP was isolated from winter flounder and found interactive with viral envelope of HSV (Miglioli et al., 2012). In addition, Chia et al. (2010) described Epinecidin-1, tilapia hepcidin (TH) 1-5 from the euryhaline tilapia (Oreochromis mossambicus) and cyclic shrimp anti-lipopolyascharide factor (cALF) from tiger shrimp (Penaeus monodon), which induced clumping of fish NNV particle or virion. AVPs isolated from aquatic organisms are listed in Table 1.

Recently, AVPs have drawn attention for their contribution in combating SARS-CoV-2. Two peptides S2P25 and S2P26, which inhibit SARS-CoV-1 previously, were found through molecular dynamics simulation to have some promise of blocking the cellular entry of SARS-CoV-2 (Chowdhury et al., 2020). Other studies have predicted the efficacy of antiviral peptides against SARS-CoV-2 through computational approaches. For instance, Dermaseptin-s9 peptide showed the best affinity to the active site of SARS-CoV-2 macromolecule in protein-peptide docking simulation (Fakhri, 2020). Similarly, Ling et al. (2020) designed antiviral peptides through in silico modelling seeking compounds capable of preventing SARS-CoV-2 membrane fusion, which could be
Table 1
Properties and activities of AVPs from aquatic organisms effective against viruses.

| Peptide Source | Target virus | Mechanisms of action | Reference |
|----------------|--------------|----------------------|-----------|
| Tilapia hepcidin (TH) 1–5 | Tilapia (Oreochromis mossambicus) | IPNV | Positive modulation of interleukin, annexin, and other anti-viral gene expressions | Rajanbabu and Chen, 2011 |
| TH 1–5          | Tilapia      | Grouper NNV          | Agglutination of virions into clumps to inhibit their entry into host cells | Chia et al., 2010 |
| TH 1–5          | Tilapia      | JEV                  | Modulation of immune responsive gene expressions | Huang et al., 2011 |
| Hecpidin 1–5    | Tilapia      | NNV                  | Disruption or digestion of viral capsid proteins | Wang et al., 2010 |
| Hecpidin 1 and hcep2-2 | Turbot (Scophthalmus maximus) | Megalocytivirus | Disruption of viral envelope or capsid | Zhang, J et al., 2014; Zhang, M et al., 2014 |
| Hecpidin-1 and hcep2-2 | Turbot | VHSV | Increase peptide in host body tissues to suppress viral infection | Pereiro et al., 2012 |
| EC-hecpidin1 and EC-hecpidin2 | Orange-spotted grouper (Epinephelus coioides) | SGIV | Inhibition of viral replication | Zhou et al., 2011 |
| Om-hep1 and Pro-omhep1 | Medaka (Oryzias melastigma) | WSSV | Inhibition of viral replication | Cai et al., 2012 |
| SA-hepcidin2 | Spotted scat (Scatophagus argus) | SCRV and MsReV | Not characterized | Gai et al., 2016 |
| HAMP2-1/4 and HAMP2-3 | Large yellow croaker (Larimichthys crocea) | SGIV | Suppression of viral ORF072 and ORF086 gene expression; Inhibition of viral replication | Mu et al., 2018 |
| omBD-1         | Rainbow trout (Oncorhynchus mykiss) | VHSV | Modulation of immunity by upregulating MX1 gene and IFN-related antiviral response | Falco et al., 2009 |
| zLB2D         | Zebrafish (Danio rerio) | SCVC | Modulation of immunity by upregulating IFN stimulated MX gene | García-Valtanen et al., 2014 |
| EcDefensin     | Orange-spotted grouper | SGIV and NNV | Modulation of immunity and suppression of viral gene expressions; Reduction of structural proteins (MCP and CP) accumulation; Inhibition of viral replication | Guo et al., 2012 |
| Grouper β-defensin | Orange-spotted grouper | RGV | Not characterized | Jin et al., 2010 |
| TroBD          | Golden pompano (Trachinotus ovatus) | NNV | Not characterized | Zhou et al., 2019 |
| Epinecidin-1   | Hybrid striped bass (Morone saxatilis × Morone chrysops) | NNV | Reduction of virion spreading through aggregation | Wang et al., 2010 |
| Piscidin 1 N, 1H, 2 and 3 | Red drum (Sciaenops ocellatus) | ISKNSV | Not characterized | Ie et al., 2018 |
| TO24          | Winter flounder (Pleuronectes americanus) | HSV | Disruption of viral envelope | Migliolo et al., 2012 |
| Pa-map         | Common dab (Limanda limanda) | VHSV | Disruption of viral membrane | Falco et al., 2009 |
| MDPle         | European bass, (Dicentrarchus labrax) | RRV-1 | Inhibition of viral infection by upregulating expression of genes (TLR9 and Myd88) | Zhang, M et al., 2014 |
| NK-lysin (NK1 derived) | Tongue sole (Cynoglossus semilaevis) | Nodavirus | Not characterized | Valero et al., 2020 |
| Cyclic shrimp anti-lipopolysaccharide factor (csALF) | Tiger Shrimp (Peneaus monodon) | NNV | Modulation of gene (MyD88, Toll like receptor 4, and MX) expressions | Chia et al., 2010 |
| PEN5          | Tiger Shrimp (Penaeus monodon) | WSSV | Increase the peptide load in WSSV infected shrimp to inhibit infection | Woramongkolchai et al., 2011 |
| ALFPm3 (P. monodon anti-lipopolysaccharide factor 3) | Tiger Shrimp | WSSV | Binds with the virus envelope protein WSSV189 | Somboonwiewat et al., 2005 |
| rLxHcL48     | Pacific white shrimp (Liopsetus vannamei) | WSSV | Suppression of viral wsv069 and wsv421 gene expression | Zhan et al., 2019 |
| Mj-city       | Kuruma shrimp (Marpessa japonicas) | WSSV | Modulation of post-infection immune response | Liu et al., 2015 |
| LBD (AFLs domain) | Chinese shrimp (Fenneropenaeus chinensis) | WSSV | Inhibition of viral replication | Li et al., 2015 |
| Scygonadin    | Green mud crab (Scylla paramamosain) | WSSV | Inhibition of viral replication through reducing IE1 gene expression | Peng et al., 2012 |
| SpALF1 and Sp-ALF2 | Green mud crab | WSSV | Inhibition of viral replication through reducing IE1 gene expression | Liu et al., 2012 |
| rCQALF        | Red claw crayfish, Cherax quadricarinatus | WSSV | Disruption of virus envelop; Inhibition of virus replication through reducing IE1 gene expression | Lin et al., 2016 |
| Microspinosamide | Marine sponge (Sidonops microspinosa) | HIV | Inhibition of cytopathic effect of HIV-1 infection | Rashid et al., 2001 |

CCV: Channel catfish virus; FV3: Frog virus 3; GCRV: Grass carp reovirus; HIV: Human immunodeficiency virus; HSV: Herpes simplex virus; IPNV: Infectious pancreatic necrosis virus; ISKNV: Spleen and kidney necrosis virus; JEV: Japanese encephalitis virus; MsReV: Micropterus salmoides (largemouth bass) reovirus; NNV: Nervous necrosis virus; VHSV: Viral haemorrhagic septicaemia virus; NNV: Singapore grouper iridovirus; SCRV: Siniperca chuatsi rhabdovirus; SVCV: Spring viraemia of carp virus; WSSV: White spot syndrome virus.
used in the prevention and treatment of COVID-19 pandemic.

3. Properties of AVPs from aquatic organisms

AMPs are small, gene encoded, amphipathic peptides with molecular weight < 13 kDa, and majority of them are positively charged with a few known to be anionic in nature (Hancock and Sahl, 2006; Zasloff, 2002). Cationic AMPs typically possess 20–50 amino acid residues and are enriched with basic amino acids like lysine and arginine (Hancock, 2001). AMPs have demonstrable broad-spectrum antimicrobial abilities against bacteria, fungi, parasites, viruses and even tumor cells (Cuesta et al., 2001). Since AMPs are evolutionary preserved components of innate immunity, their presence in organisms ranging from prokaryotes to higher animals including aquatic organisms are well documented (Bowdish et al., 2005; Lai and Gallo, 2009). AMPs are a primary defensive weapon of fishes innate immune systems (Smith et al., 2010). Based on the structure, 122 AMPs are reported from fish into five families namely hepcidins, β-defensins, histone-derived peptides, cathelicidins and fish-specific piscidins (Wang et al., 2016), of which the first three were antiviral against certain viral infections in aquatic organisms and humans (Table 1).

Hepcidins are versatile cysteine rich cationic peptides first characterized in human liver and therefore known as liver expressed-antimicrobial peptide or LEAP (Park et al., 2001). Moreover, it is found in tissues of different vertebrates including fish, amphibians and reptiles, and acts as a regulator of iron absorption in the intestines (Nemeth, 2004; Park et al., 2001). However, a diverse group of hepcidins were identified in teleosts and the first one was reported from hybrid striped sea bass, Morona chrysops × M. saxatilis (Shike et al., 2002). Since then, hepcidins with antiviral properties have been identified in more than thirty different fish species. For instance, tilapia derived TH 1–5 showed antiviral activity against infectious pancreatic necrosis virus (IPNV) (Rajanabanu and Chen, 2011), NNV (Wang et al., 2010), grouper NNV (Chia et al., 2010) and Japanese encephalitis virus (JEV) (Huang et al., 2011). In addition, antiviral effects of TH 1–5 and epinecidin-1 against NNV of Japanese rice fish (Oryzias latipes) were noted in vitro (Table 1). Further verification through reverse transcriptase polymerase chain reaction (RT-PCR) confirmed down regulation of NNV and interferon gene expressions (Wang et al., 2010) similarly of TroBD isolated from Golden pompano (Trachinotus ovatus) (Zhou et al., 2019). Besides, TH 1–5 and cSALF peptide limited the viral entry into cells in vitro by agglutinating NNV virions into clump (Chia et al., 2010). Although different functions of most hepcidin peptides area as yet inconclusive, some other peptides, viz. hepcidin-1, 2 characterized from trout showed inhibitory effects against megalocytovirus RBIV-C1 and VHSV (Pereiro et al., 2012; Zhang, J et al., 2019). Moreover, EC-hepcidin 1, 2 and HAMP2-1, 4, 2-3 also inhibited SGIV infection (Mu et al., 2018; Zhou et al., 2011). Similarly, SA-hepcidin 2 isolated from spotted scat (Scatophagus argus) was inhibitory against rhabdovirus and reovirus (Gui et al., 2016). Study with synthesized peptides SmHep1P and SmHep2P of hepcidin 1, 2 showed significant reduction in megalocytovirus RBIV-C1 infections, being SmHep2P more effective than SmHep1P (Zhang, J et al., 2014). Further, NKLFP27 from tongue sole (Cynoglossus semilaevis) inhibited megalocytovirus RBIV-C1 by upregulating expressions of TLR9 and Myd88 genes (Zhang, M et al., 2014).

Recently, two variants of hepcidine Om-hep1 and 2 have been isolated from medaka (O. melastigma), and those transformed into synthetic mature Om-hep1 and recombinant pro-Omhep1 leading to a dramatic inhibitory activity against WSSV in the hematopoietic (Hpt) cells of crayfish (Cherux quadracarinatus; Cai et al., 2012). Besides, seygonadin, a novel crab antimicrobial peptide biologically produced in Pachypanoros reportedly interferes with WSSV replication in vitro in Hpt cells of crayfish (Peng et al., 2012).

Defensins are cysteine-rich, 3–6 kDa cationic antimicrobial peptides acting as a first line defence against both enveloped and non-enveloped viruses predominantly found in plants, vertebrates and invertebrates (Bais et al., 1998; Bulet et al., 2004; Weinberg et al., 2006; Zhu, 2008). Defensins consist of α-helical and β-sheet structures stabilized by disulphide bridges (Selsted et al., 1985), and broadly categorized into α, β and θ defensins subfamilies based on their intra-molecular disulphide bonds. Reported of the antiviral activity of defensins in mammalian hosts have detailed inhibitory effects against HIV-1, IAV, HSV-1, 2, HADV, human papillomavirus, parainfluenza virus 3 (PIV-3), respiratory syncytial virus (RSV), vaccinia and chandipura viruses (Bastian and Schäfer, 2001; Buck et al., 2006; Chang et al., 2005; Chattopadhyay et al., 2006; Grubor et al., 2004; Hazrati et al., 2006; Howell et al., 2007; Meyerholz et al., 2007; Zhang et al., 2002).

EcDefensin, a defensin peptide from the liver cells of orange-spotted grouper exhibited strong antiviral activity against enveloped DNA virus and non-enveloped RNA virus like SGIV and NNV (Guo et al., 2012). Similarly, β-defensin from grouper pituitary cDNA showed higher expression on both pituitary and testis. The antiviral effect revealed by β-defensin transfected EPC cells exhibited pivotal role of the peptide in regulation of both innate immunity and endocrine activity (Lin et al., 2010). Furthermore, β-defensin has demonstrated antiviral activity against frog-specific Rana grida virus (RGV). Falco et al. (2008) confirmed antiviral activity of rainbow trout (Oncorhynchus mykiss) derived β -defensin through fish cells transfected with omBD1 peptide against one the devastating rhabdovirus VHSV. Interestingly, defensin was considered as an AMP in the early stages of research (Kagan et al., 1990), but subsequent studies revealed other vital roles of defensins such as cell signalling, immature dendritic cell recruitment to the place of infection and immunomodulation (Biragyn et al., 2002). García-Válden et al. (2014) suggested zebrafish (Danio rerio) derived β-defensin 2 (zBD2) as potent adjuvant of viral DNA vaccine possessing both antiviral and immunomodulatory properties against VHSV in vivo and in vitro (Table 1).

Peptide piscidins 1 N, 1H, 2 and 3 are a family of amphipatic cationic α-helical AVPs recognized from the mast cells of hybrid striped bass (Silphaduang and Noga, 2001); these have exhibited antiviral activity against both enveloped channel catfish virus and non-enveloped frog virus 3 (Chinchar et al., 2004). Other AVPs, anti-lipopolysaccharide factors (ALF) have been isolated and characterized from crustaceans (Table 1), with potential inhibitory activity against WSSV in crustaceans (Lin et al., 2016; Liu et al., 2012). These small protein molecules bind and neutralize lipopolysaccharides found in hemocytes of horseshoe crab (Morita et al., 1985). Several studies have reported inhibition of WSSV replication through reduction of early gene transcription by ALFs, isolated and characterized from Chinese shrimp (Fenneropenaeus chinensis), red claw crayfish (Li et al., 2015; Lin et al., 2016) and by Mj-sty peptide from Kuruma shrimp (Marsupenaeus japonicas; Hong-tao Liu et al., 2015). Furthermore, ALFpm3 (Somboonwivat et al., 2005) and PENS5 (Woramongkolchai et al., 2011) from tiger shrimp were found to inhibit WSSV by disrupting the virus envelope protein WSSV189 and increasing the peptide load after infection. Similarly, expression of wss069 and wsv421 genes of WSSV have been suppressed by rLVHcL48 peptide isolated from Pacific white shrimp (Litopenaeus vannamei; Zhan et al., 2019).

The Pa-MAP peptide from winter flounder inhibited HSV-1 at 80% and HSV-2 at 90%, although 90 μM maximum non-toxic concentrations (MNTC) raised the level of inhibition to 94 and 97% for HSV-1 and HSV-2, respectively, with ability to disrupt the viral envelope or capsid (Migliolo et al., 2012; see Table 1). In addition, Pa-MAP characterized from marine sponge was inhibitory against HIV-1 infection through a cell proliferation (XTT) in vitro with approximately 0.2 μg/mL of EC50 (Rashid et al., 2001).

However, FASTA sequence of three common AVPs such as ‘Defensin’, ‘Hepcidin’ and ‘Piscidin’ were retrieved from NCBI (https://www.ncbi.nlm.nih.gov/) and RCSB PDB databases (https://www.rcsb.org/) and considered for multiple sequence alignment (MSA) by using Clustal Omega software (https://www.ebi.ac.uk/Tools/msa/clustalo/). These attempts were employed for brief documentation and analysis of the
conserved regions or identical sites of AVPs from aquatic organisms with reported purified or commercial AVPs from human or synthetic origins. For example, in case of defensins, four alpha-defensins from human source were retrieved, and allowed to MSA with five other AVPs from aquatic organisms including Atlantic cod (Gadus morhua), Atlantic salmon (Salmo salar), puffer fish (Tetraodon nigroviridis), crocodile icefish (Pseudochoanichthys georgianus), and killifish (Fundulus heteroclitus). MSA revealed nine conserved positions among the sequences including different identical positions. Again, five hepcidin sequences of aquatic source (striped bass, Morone saxatilis; Rio pearlfish, Nematolebias whitei; European sea bass, Dicentrarchus labrax; tuberculated flathead, Soro- gona tuberculata) were aligned with two hepcidins of human origin. Here, around nineteen positions were conserved including the availability of a specific site ‘CCNC’ (Cysteine-Asperginie-Cysteine-Cysteine) among all hepcidin sequences. In addition, MSA of two synthetic constructs of piscidin and five homologous piscidin sequences from striped bass also exhibited the conserved pattern and identical sites. Though the analysis had been done within a minimal number of sequences, results indicated that the AVPs from aquatic sources shared conserved regions with human or commercial synthetic constructs of AVPs. The detailed alignment results are illustrated in Fig. 1.

4. AVPs mechanisms of action against viruses

AVPs, isolated from various animals, plants, insects, fish and humans reportedly display broad antiviral activities against viruses through different mechanisms of action, such as blocking virus fusion or entry into the host cells, preventing the spread of virus through suppression of its gene expression, and inhibition of translation through an immune modulatory mechanism (Jenssen et al., 2006; Mulder et al., 2013) (Fig. 2).

AVP blocks viral entry through interaction with heparan sulfate,
which is the most important glycosaminoglycan molecule related to viral attachment with host cells (Fig. 2a). It has been reported that lactoferricin is able to inhibit HSV infection by binding to heparan sulfate (Andersen et al., 2003; Jenssen et al., 2004). Similarly, human α-defensin, LL-37 and magainin also bind with glycosaminoglycans to prevent viral attachment with host cells (Jenssen et al., 2006). AVPs utilize another mechanism that interacts with specific cellular receptors to inhibit viral entry into the hosts (Fig. 2b). Polypehnumus analogue T22 has been shown to have potent antiviral activity against HIV-1, 2 in vitro, where the peptide binds to a chemokine receptor CXCR4, a coreceptor for the entry of HIV-1 into T cells (Nakashima et al., 1992; Tamamura et al., 1998). Besides, θ-defensin interacts with HSV-2 glycoprotein B and HIV-1 glycoprotein 120 with high affinity, thus blocking the entry of HSV-2 and HIV-1 into host cells (Münk et al., 2003; Yasin et al., 2004).

A proposed mechanism of action has suggested that melittin obtained from honey bee inhibited HSV-1 by preventing cell fusion through interference with the activity of ATPase enzyme (Fig. 2c), thereby disrupting the membrane fusion process (Matanic and Castilla, 2004). AVPs protect the host cell from different viral infection through interaction with the virus envelop or disrupting virus envelop/capsid (Fig. 2d). To exert anti-HIV activity, dermaseptin directly interacts with the viral particle, eventually disrupting the membrane of the virus (Lorin et al., 2005). Moreover, peptide Pa-MAP isolated from the winter flounder has been found to inhibit HSV-1, 2 infection by interacting with viral envelop (Migliolo et al., 2012; Teixeira et al., 2013).

Inhibition of viral replication or protein synthesis is another mechanism triggered by various peptides to prevent virus spreading within the host cell (Fig. 2e). The PAP from American pokeweed, for example, prevented tobacco mosaic virus (TMV) infection by inactivating ribosomes, thereby blocking viral protein synthesis (Taylor et al., 1994). A similar mechanism was also exhibited by protegrin-1 to exert antiviral activity against HIV-1 (Steintraesser et al., 2005). Suppression of viral gene expression and modulation of immunity are two important inhibitory mechanisms of AVPs (Fig. 2f), as in the cases of melittin and cecropin A, both found to inhibit HIV-1 infection by suppression of viral gene expression (Brack-Werner et al., 1998). The peptide omBD1 isolated from rainbow trout inhibited VHSV infection by upregulating the expression of mx1 gene, suggesting an immune modulatory mechanism of peptides (Falco et al., 2007).

5. Aquatic AVPs against human and animal viruses

A number of studies reported the efficacy of AVPs against human and animal viruses, but their application as therapeutics is limited in animals. Peptide TH 1–5 was found effective against IPNV (Rajanbabu and Chen, 2011) and NNV (Wang et al., 2010). Likewise, cecropin B and its synthetic analogue CF17 were active against a range of fish viruses including infectious hematopoietic necrosis virus (IHNV), VHSV, snakehead rhabdovirus (SHRV) and IPNV (Chiou et al., 2002).

Moreover, several peptides are found active against human viruses, viz. influenza, rabies, HIV, HSV, hepatitis C virus (HCV) and West Nile virus (WNV) (Thakur et al., 2012). Peptides isolated from invertebrates such as melittin, cecropin and alloferon were inhibitory against different infectious viruses. Melittin, an antitumor peptide has been reported to inhibit the activity of HIV-1, HSV-1 and Junin virus through a membrane fusion process (Matanic and Castilla, 2004). Alloferon-1, 2 are two potential biopharmaceutical compounds having the ability to improve host innate immune response as they shown activity against influenza virus (Chernysh et al., 2002). Another AVP T22, which is synthesized by a solid-phase method based on 9-fluorenyl-methyloxycarbonyl (Fmoc) (Akaji et al., 1989), has shown strong activity against HIV-1, 2 strains in vitro through virus-cell fusion, or uncoating process after virus adsorption (Nakashima et al., 1992).

Mulder et al. (2013) reviewed a number of peptides from vertebrates that are active against diseases causing viruses in humans like defensins HNP-1, which is a type of α-defensin peptide capable of inactivating HSV-1, 2, CMV, VSV and IAV/WSN (Daher et al., 1986). Retrocyclin is a θ-defensin 18-residue peptide capable of blocking the entry of HIV-1 into host cell (Münk et al., 2003). In addition, lactoferricin (LfcinB) peptide derived from multifunctional glycoprotein lactoferrin has shown inhibitory action against HIV-1, CMV (Swart et al., 1998) and HSV-1, 2 (Andersen et al., 2003). Another peptide isolated from bovine neutrophils, i.e. indolicidin has shown antiviral mechanism while interacting with HIV-1 (Robinson et al., 1998). There are other examples of peptides that are active against human viruses, such as PAP (Kaur et al., 2011) and dermaseptin (Belaid et al., 2002) against HIV and HSV, and Hp1090 against HCV (Yan et al., 2011).

Peptides originated from marine organisms have exhibited antiviral activity against both animal and human viruses. As for instance, microspinosamide from sponge has been found to be active against HIV-
Recent updates report that many peptides are active against infectious viruses causing illness in humans and animals. For example, P1 peptide derived from a phage displayed peptide library found to inhibit JEV in vitro and in vivo (Wei et al., 2020). Besides this, Brice and Diamond (2020) suggested innate antiviral defense by three human host peptide derived from a phage displayed peptide library found to inhibit HCoV-229E spike protein (Xia et al., 2018). Similarly, a defensin-like peptide P9R has exhibited pH dependent activity against respiratory viruses like SARS-CoV and MERS-CoV (Zhao et al., 2020a).

6. Insights of AVPs against human coronaviruses and SARS-CoV-2

Potentially effective vaccine and antiviral therapeutic options are being studied with different collaborative efforts toward the development of anti-SARS-CoV-2 drug compounds. Though some likely therapeutic agents appear to have prospects for treatment of COVID-19, AVPs or AMPs have not been given a similar level of attention to date (Daly et al., 2020; Ledford, 2020; Ohashi et al., 2020; Vanden Eynde, 2020; Wang, Shen, H et al., 2020; Wang, Cheng, W et al., 2020; Wang, M et al., 2020; Wang, Y et al., 2020). Few recent reports have strong evidence that AVPs could provide alternative options of therapeutic agents against the SARS-CoV-2. For example, a study suggested that a natural lectin-like defensins-5 (HD5) peptide (ATCYCRTGRC ATRESLSGVCEISGR) can successfully block the ACE2 receptors on the host, in which it is already established that ACE2 receptor plays vital role in the entry of SARS-CoV-2 into the human cellular system (Mahendran et al., 2020; Cheng Wang et al., 2020). Another analysis of the likely effectiveness of AVPs against coronaviruses was reported by Xia et al. (2019). From their experimental data, they suggested that ‘EK1’ (SLDQINVTFLDLEYMKLEEAKKLEESYDDKEL) exhibited significant level of cross-reactivity against all MERS-CoV and SARS-CoV (Xia et al., 2019). EK1 was found to be effective in the inhibition of viral fusion entry as well as the challenges of HCoVOC43, alpha-coronavirus and MERS-CoV virus also could be protected by its intranasal use (Mahendran et al., 2020; Xia et al., 2020, 2019). In addition, the viral envelope protein of SARS-CoV, MERS-CoV, and influenza H5N1 viruses were been disrupted by the strong electrostatic affinity with a AVP named ‘mucroporin-M’ (LFRILLSKLRVLSAFK), which was designed as peptide analogue from the parent peptide mucroporin (FLGLPISGLGLVSAFK) extracted the venom of the scorpion Lychas mucronatus (Dai et al., 2008; Li et al., 2011). Viral uncoating for the successful release of viral RNA is a critical step during the disease progression by this group of pathogens, and hence endosomal acidification is crucial for pH-dependent activation of viral fusion proteins. This endosomal acidification step was found to be misled by the mouse b-defensins-4 derived P9 (NGAICWGPCTAPFRQ IGNCGHFVKRCCKIR) in MERS-CoV (Zhao et al., 2016). Moreover, another cyclic peptide RTD-1 (GFCRCLRGRVCRGICTR) was also reported against the SARS-CoV infection which could act as an immunomodulatory effector molecule via a cytokine response combating against SARS-CoV progression (Wohlford-Lenane et al., 2009). Responding to the pandemic and infectious disease outbreaks is urgently needed for defending against COVID-19. The above mentioned reports suggested that AVPs could be an alternative option of effective drug response against the coronaviruses. Additionally, aquatic organisms have already been described as promising sources of AVPs. Hence, aquatic AVPs might be among preferred therapeutic candidates of COVID-19 for evaluation through proper scientific experimental and clinical validation.

6.1. Possible action of aquatic AVPs against SARS-CoV-2

6.1.1. Structure of SARS-CoV-2, entry mechanisms and disease symptoms

The whole genome sequence of novel SARS CoV-2 was 1st published on 10 January 2020 which has facilitated the identification of SARS CoV-2-infected patients using RT-PCR (Zhu et al., 2020). The very first literature (published on 22 January 2020) described SARS CoV-2 belonging to β-coronavirus group carrying ancestry of bat coronavirus HKU9-1, which is similar to other SARS-CoVs as its spike protein strongly interacts with human angiotensin-converting enzyme (ACE)-2 receptor (Xu et al., 2020). The viral genome of SARS-CoV-2 is ~29.8 kilobase with a GC content of ~38%, and virus diameter and surface spike length varies from 60 to 140 nm and 8–12 nm, respectively (Chan et al., 2020; Zhou et al., 2020). Genetic analysis demonstrated that SARS-CoV-2 matches 88%, 79% and 50% identity with two bat SARSr-CoV, normal SARS-CoV, and MERS-CoV, respectively, indicating distinct/novel characteristics of SARS-CoV-2 (Tu et al., 2020). Pangolins and bat identified CoV02 demonstrated maximum similarity ~85.5–92.4% and 96.2%, respectively, with CoV2 (Lam et al., 2020; Zhou et al., 2020), although the intermediate host of CoV2 is still unknown (Benvenuto et al., 2020).

Under electron microscope, this single stranded RNA virus showed spherical shape with spike-like projections on surface similar to coronas, and named after the Latin meaning of corona (Barcena et al., 2009). Its molecular arrangement consists of S and S’ untranslated region (UTR), nonstructural proteins encoded replicase complex, spike protein (S), envelope protein (E), membrane protein (M), nucleocapsid protein (N) and some unidentified nonstructural open reading frames (ORF) (UL Qamar et al., 2020; Zhu et al., 2020). Viral envelope (human cell membrane derived lipid bilayer) anchored S, E and M proteins. Entry of CoVs into the host cell is mediated mainly by S glycoprotein, which possesses two functional subunits described as S1 and S2 domains (S1/ S2 sites) to bind with host cells and trigger the fusion of viral and cellular membranes (Tortorici and Veesler, 2019). CoV-2 and other CoVs have affinity for binding with human ACE2 and host proteases cleaved S, whereas S2 domain placed upstream of fusion peptide (S2’ site) (Millet and Whittaker, 2015). Interestingly, CoV-2 has a furin-like protease cleavage site (RRAR,SV) between S1 and S2 boundary (AYT,M) which is processed during biogenesis, but the comparable sites are absent in other CoVs (Coutard et al., 2020; Walls et al., 2020). Among three (S, M and E) different proteins in viral envelope of CoVs, M protein is comparatively abundant and responsible to provide virus shape, whereas combination of M and E protein orchestrates virus internal assembly and helps to mature the outer envelope (Siu et al., 2008). Transfer of virus particles into the host cell is performed by E protein and N protein which binds/interacts with viral RNA during particle assembly to form nucleocapside (Asbour et al., 2020; Masters, 2006). In β-CoVs cis acting RNA extends 3’ to S’ into ORF and association between S’ and 3’ UTR act as a potential molecular switch for the synthesis of subgenomic RNA (Yang and Leibowitz, 2015).

Although fatality rates of SARS, MERS and SARS-CoV-2 are 10, 36, and 2.3%, respectively (Wu and McGoogan, 2020), CoV-2 S protein showed 10 to 20-fold higher affinity to bind with human ACE2 compared to others, making CoV-2 a super-spreader during 2020 pandemic (Wrapp et al., 2020). Like other CoVs, CoV-2 entry into host cells depends on recognition and binding of S protein with ACE2 receptor. After cleaving of S protein by host proteases, S1 further divided into N- and C-terminal domains having ACE2 receptor binding entity, and S2 causing the fusion of viral and host cell membranes (Tu et al., 2013; Zhang Wei, et al., 2020). Protease enzymes activity of S1/S2 cleaving completely dependent on amino acid profile of virus, and similar to SARS-CoV, S protein of CoV-2 is cleaved by cathepsin L and...
TMPRSS2 at S2′ site during cellular entry (Ashour et al., 2020). Fusion of host cell membrane and viral envelope triggers the entry of viral genome into the cell cytoplasm for multiplication. Following receptor binding SARS-CoV S1/S2 site (ATY↓M) is cleaved by cathepsin L during entry in the host cell endosome (Bosch et al., 2008). Human organs like alveolar epithelial cells in lung or enterocytes in small intestine are enriched with higher amount of ACE2, the potential site of SARS-CoV-2 attack (Zou et al., 2020). The development of cathepsin L inhibitor or neutralizing antibodies may be useful to control SARS-CoV-2 infection in humans.

Pneumonia has characteristics in common with the SARS-CoV-2 infection, now known as COVID-19 disease. Similar to other influenza viruses, signs and symptoms of COVID-19 include high temperature, continuous cough, expectoration, headache, pharyngalgia, dyspnoea and diarrhoea. Recently, the UK government included “loss of smell and taste” to the list of symptoms induced by COVID-19. Zheng (2020) reported that 90, 68 and 96% infected patients showed fever, cough and fatigue, respectively. Besides these, bilateral and unilateral pneumonia as well as multiple mottling and ground glass opacity were identified in lungs as revealed from chest X-ray and CT scanning (Chen et al., 2020). The U.S. Centers for Disease Control and Prevention reported that COVID-19 cause respiratory illness and in particular, that elderly, immune compromised and people with other health related problems are more vulnerable to this disease (Gralinski and Menachery, 2020). Since COVID-19 has spread across the world, mutation over time can make it more virulent and for this reason, proper surveillance and research are necessary to monitor and understand the change of its genetic materials in different environments. Incidentally, Asian males showed higher expression levels of ACE-2 receptor that are more susceptible to COVID-19 (Zhao et al., 2020b) compared to non-Asian counterparts (European and North American countries) demonstrating severe symptoms and sickness (Rothe et al., 2020).

6.1.2. Inhibitory mechanism of aquatic AVPs against SARS-CoV-2

Peptide based antimicrobial therapy has become a promising field in pharmaceutical research and a large number of peptides are being currently tested for medicinal use (Fosgerau and Hoffmann, 2015). AVP derived from aquatic organisms could initiate a new avenue in searching candidate drugs against SARS-CoV-2. Features of APV that are preferable as antiviral agents include – (i) interfering with protein-protein interactions, (ii) blocking the substrate binding site of key viral proteins, (iii) having high half-life in cellular environment, and (iv) minimum marketable time (Kaspar and Reichert, 2013). The absence of effective remedy against SARS-CoV-2 has drawn attention to unique therapeutics candidates with the possibility of combating adverse health complications during the COVID-19 pandemic. Most of the antiviral peptides including AVPs from aquatic organisms are found to inhibit or destabilize key proteins of virus (Reddy et al., 2004). The life cycle of SARS-CoV-2 and other coronaviruses have following steps – (i) recognition of viral spike protein by host receptor, (ii) viral entry into the host cell, (iii) release of viral RNA for replication, (iv) translation of viral replicase polyproteins using the translation machinery of host cell, (v) synthesis of viral structural and nonstructural proteins, and (vi) assembly and release of viral particles from the host cell through exocytosis (Bar-On et al., 2020; Wan et al., 2020).

Candidate drugs with the most therapeutic potential focus on the above-mentioned steps, without which normal process of viral disease progression in the host environment may be disturbed or interrupted. The possible mechanisms behind the action of aquatic AVPs against coronaviruses include – (1) inhibition of the viral entry through interfering with viral protein and host receptor-binding protein, (2) blocking of key proteins involved in the replication process, and (3) inhibition of the assembly and release of viral particles. These three mechanisms against SARS-CoV-2 including the known actions of aquatic AVPs

![Fig. 3. The life cycle of SARS-CoV-2 in host cells (i–vii), and possible antiviral role of aquatic AVPs against different stages of SARS-CoV-2 (A–C).](image-url)
against other member of coronaviruses are illustrated in Fig. 3.

6.1.2.1. Inhibition of viral entry. The entry of SARS-CoV-2 into human cell is initiated by S protein. S1 subunit of S protein usually interacts with ACE2 of human cell and S2 subunit strengthens the fusion between human cell membranes and viral envelope protein (Coutard et al., 2020; Holmes, 2003). Since S protein plays vital roles in the membrane fusion and viral entry into the host cellular environment, it could be a potential therapeutic target for SARS-CoV-2. Aquatic AVPs are reported to interfere with this entry step of different viral pathogens (Fig. 3A), including CoVs. β-defensin-like peptides isolated from aquatic sources (Zou et al., 2007) are biologically similar to human and other organism derived defenses (Cuesta et al., 2011). Besides, β-defensin was able to combat the emerging respiratory viruses such as H1N1, H7N7, H3N2, H7N9, H5N1, SARS-CoV and MERS-CoV. It was found that P9, one of the 11 investigated β-defensins, could bind to the viral glycoproteins leading to blockade of membrane fusion for respiratory viruses (Zhao et al., 2016). Moreover, it could block the entry of HSV by binding its envelope glycoprotein (Hazzati et al., 2006). RSV β-defensin could destabilize the envelope protein responsible for inhibiting viral entry into the intracellular host environment (Kota et al., 2008). Immunomodulatory effects were reported for IAV that promote the uptake of IAV by neutrophils before viral entry (Tecle et al., 2007). Piscidins are another group of widely reported aquatic AVPs (such as Fiscidin-1) isolated from the mast cells of the hybrid striped bass and other fish species (Silphaduang et al., 2006; Silphaduang and Noga, 2001). Potent antiviral activity by obstructing viral entry (such as HIV-1) into the host cellular environment has been reported (Wang, 2012; Wang et al., 2010). Moreover, polyphemusins, isolated from horsehoe crab, and their modified derivative (T22) have also been investigated as viral fusion inhibitor (Hikichi et al., 2016). Another aquatic antiviral peptide Cathelicidin is capable of inhibiting viral entry, hence that AVP may be an effective therapeutic against SARS-CoV-2. Cathelicidin peptides LL-37 also showed potent antiviral efficacy against two important respiratory viruses, RSV and IAV (Mansbach et al., 2012; Tripathi et al., 2013). LL-37 initiates peptide-mediated membrane disruption with influenza virus leading to the inhibition of viral fusion and viral propagation within the host cell (Tripathi et al., 2013). Moreover, LL-37 mediated membrane disruption was reported with vaccinia virus (Dean et al., 2010). Cathelicidins peptides were successfully evaluated as potential antiviral therapeutics against HIV, HSV and Adenovirus (Levinson et al., 2012; Matanic and Castilla, 2004; Smith et al., 2010) and thus, cathelicidins also appear to be among prospective therapeutics against SARS-CoV-2.

6.1.2.2. Blocking proteins in replication process. The expression of several structural and nonstructural proteins coded within the viral genome usually precede the replication process, using host cell machinery. SARS-CoV-2 releases genomic materials into the host cytoplasm for initiating replication (Channappanavar et al., 2016; Chu et al., 2020). Replicate polyproteins are synthesized from viral RNA which lead to the formation of RNA-dependent RNA polymerase (RdRp) and helicase with other non-structural proteins. These RdRp and helicase and other nonstructural proteins (NSP 3, 4, 6) participate in the translation of important proteins and full-length positive-strand genomic RNA for further processing of new viral particles (Gordon et al., 2020; Li et al., 1999). Aquatic AVPs hold some potential as options for targeting the replication process of SARS-CoV-2 (Fig. 3B). CoVs are mostly dependent on iron-containing enzymes to complete their replication processes (Adejei and Lazarus, 2016; Jia et al., 2019). Hence, depriving iron supply could be a better therapeutic option for the treatment of COVID-19. Incidentally, human ferroportin protein expressed in the duodenal enterocytes and macrophages can govern iron release, and human hepcidins underegulate this ferroportin leading to iron deficiency and compromised viral replication (Ganz, 2007; Liu et al., 2016). Hepcidins (cysteine rich peptides isolated from hybrid striped bass and other fish species; Shike et al., 2002), could also play a role in interference with normal iron supplies within the host cell. Although extensive research on iron regulation in COVID-19 patients and hepcidins supplements is underway, adjuvant based therapeutic option for battling against SARS-CoV-2 could be a promising alternative (Liu et al., 2020). Further, cathelicidins AVPs were found to inhibit RT enzyme in HIV (Bergman et al., 2007). Several other aquatic AVPs such as Scyga-nadin, SpALF1, SpALF2, cQALF and HAMP2 also have demonstrated their capacity to inhibit the replication cycle of different viral pathogens (Cheung et al., 2014; Lin et al., 2016; Neves et al., 2017), raising another option for retarding the replication of SARS-CoV-2.

6.1.2.3. Prevent assembly and release of virus particles. There are limited investigations into the coronavirus assembly and release process, although some studies suggest that viral nucleocapsid proteins are involved in the genomic RNA assembly and viral particles are released through exocytosis process (Kota et al., 2008; Stertz et al., 2007). This step or information could be useful for targeting candidate AVPs after extensive research. The AVP database suggested that only a few peptides have potential inhibition efficacy during the release of SARS CoVs particles (Fig. 3C). The database also includes several peptides with potential antiviral activity showing various mechanisms of action against different CoVs including MERS and SARS (Qureshi et al., 2014). A modified peptide sequence ‘dec-RVKR-cmk’ was reported to be efficient for blocking coronavirus release (Bergeron et al., 2005). But there are no aquatic AVPs known to be effective in this step, which requires further research.

Aquatic AVPs have already been inhibitory against different coronaviruses including other deadly viruses. Therefore, AVPs derived from aquatic sources have the potential ability to combat SARS-CoV-2, although validation is necessary to determine the effectiveness of AVPs as a therapeutic option for COVID-19 patients. Overall, peptide based therapeutics, especially aquatic AVPs could be promising as they have established capability to inhibit the life cycle of a variety of respiratory viruses.

7. Concluding remarks

AVPs produced by aquatic organisms (fish, shellfish, aquatic plants and other organisms) have potential as novel therapeutics or drugs against both aquatic and terrestrial infectious viruses. Despite having antiviral activity against numerous viruses, no studies have been reported on the application of aquatic AVPs as drugs against viral infections. The mechanisms of action of some AVPs derived from aquatic sources are yet to be characterized (Gui et al., 2016; He et al., 2018; Jin et al., 2010; Valero et al., 2020; Zhou et al., 2019). Some aquatic AVPs showing in vitro activity against viruses might lack similar actions in vivo. Also, AVPs induced immune pathways in humans or animals are still under investigation (Chia et al., 2010; Rashid et al., 2001). However, aquatic organisms derived AVPs could inhibit SARS-CoV-2 in a number of mechanisms, even though there is no previous study in relevant of this topic. The potential of aquatic AVPs according to the history of other AVPs and the mechanism of their inhibition of viruses are discussed here which could broaden the research scopes of the development of anti-SARS-CoV-2 therapeutics and hence could defeat COVID-19.
Brack-Werner, R., Erleve, V., von Pechmann, N., Neumann, M., Winder, D., Kleinschmidt, A., Salmos, B., Ludvigsen, A., Wachtinger, M., Holle, R., 1998. Antimicrobial peptides mediate and cecropins inhibit replication of human immunodeficiency virus 1 by suppressing viral gene expression. J. Gen. Virol. 79, 731–740. https://doi.org/10.1099/0022-1317-79-4-731.

Brice, D.C., Diamond, G., 2020. Antiviral activities of human host defense peptides. Curr. Med. Chem. 27, 1420–1433. https://doi.org/10.2174/0929867366666666968008515154.

Buck, C.B., Day, P.M., Thompson, C.D., Lubkowski, J., Lu, W., Lowy, D.R., Schiller, J.T., 2006. Human -defensins block papillomavirus infection. Proc. Natl. Acad. Sci. 103, 1516–1521. https://doi.org/10.1073/pnas.0509029103.

Bulet, P., Stocklin, R., Menin, A., 2004. Anti-microbial peptides: from invertebrates to vertebrates. Immunol. Rev. 198, 169–184. https://doi.org/10.1111/j.0161-202x.2004.00414.x.

Cai, L., Cai, J.J., Liu, H.P., Fan, D.Q., Peng, H., Wang, K.J., 2012. Recombinant medikin (Oryzias melastigma) pro-hepcidin: multifunctional characterization. Comp. Biochem. Physiol. B Biochem. Mol. Biol. 161, 140–147. https://doi.org/10.1016/j.cbb.2011.09.006.

Calý, L., Druce, J., Catton, M.G., Jans, D.A., Wagstaaf, K.M., 2020. The FDA-approved drug ivmecin inhibits the replication of SARS-CoV-2 in vitro. Antivir. Res. 178, 104787. https://doi.org/10.1016/j.antiviral.2020.104787.

Carriél-Gomes, M.C., Kratz, J.M., Barcena, M., Oostergetel, G.T., Bartelink, W., Faas, F.G.A., Verkleij, A., Rottier, P.J.M., 2020. The 2019-new coronavirus epidemic: evidence for virus evolution. J. Med. Virol. 92, 180–187. NEJMoa2007764. NEJMoa2007764.

Chan, J.F.-W., Kok, K.-H., Zhu, Z., Chu, H., To, K.K.-W., Yuan, S., Yuen, K.-Y., 2020. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg. Microbes Infect. 9, 223–236. https://doi.org/10.1080/22279573.2019.1719992.

Chang, T.L., Vargas, J., Delpech, V.B., 2020. Dual role of α-defensin 1 in anti-HIV-1 innate immunity. J. Clin. Invest. 115, 765–773. https://doi.org/10.1172/JCI91948.

Channappanavar, R., Fehr, A.R., Vijay, R., Mack, M., Zhao, J., Meyerholz, D.K., Perlman, S., 2016. 2009 pandemic H1N1 influenza virus polymerase inhibitors target human α-defensins. Science 352, 559–562. https://doi.org/10.1126/science.aaa5778.

Chen, Z.C., White, R.F., Antoniw, J.F., Liu, Q., 1991. Effect of pokeweed antiviral protein (PAP) on the infection of plant viruses. Plant Pathol. 40, 622–628. https://doi.org/10.1111/j.1365-3059.1991.tb0246x.x.

Chen, N., Zhou, M., Dong, X., Qi, J., Geng, F., Han, Y., et al., 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet 395, 507–513.

Chernysh, S., Kim, S.I., Bekker, G., Plesekach, V.A., Filatova, N.A., Anikin, V.B., Platonov, V.G., Bulet, P., 2002. Antiviral and antitumor peptides from insects. Proc. Natl. Acad. Sci. 100, 12628–12632. https://doi.org/10.1073/pnas.1921018100.

Cheung, R.C.F., Wong, J.H., Pan, W.L., Chan, Y.S., Yin, C.M., Dan, X.L., Wang, X.H., Fang, E.F., Lam, S.K., Ngai, P.H.K., Xia, L.L., Fu, Y.Y., Zhang, G.Q., Liu, H.Q., Sha, O., Lin, P., Ki, C., Bekhit, A.A., Bekhit, A.E.D., Wan, D.C.C., Ye, X.J., Xia, J., Ng, M.Y.J., 2014. Antifungal and antimalarial products of marine organisms. Appl. Microbiol. Biotechnol. 98, 3475–3494. https://doi.org/10.1007/s00253-014-5575-0.

Chia, T.-J., Wu, Y.C., Chen, Y.-J., Chi, S.-C., 2010. Antimicrobial peptides melittin and cecropin inhibit replication of human adenovirus. Biochem. Physiol. B Biochem. Mol. Biol. 161, 140–147. https://doi.org/10.1016/j.bjp.2011.09.006.

Chiu, P.P., Lin, C.M., Perez, L., Chen, T.T., 2002. Effect of cecropin B and a synthetic analogue on propagation of fish viruses in vitro. Mar. Biotechnol. 4 (3), 294–302.

Chowdhury, S.M., Talukder, S.A., Khan, A.M., Afrin, N., Ali, M.M., Islam, R., Parves, R., Islam, R., Zaman, A., Rabee, A., Al Mamun, A., Sufian, M.A., Hossain, M.N., Hossain, M.A., Halim, M.A., 2020. Antiviral peptides as promising therapeutics against SARS-CoV-2. J. Phys. Chem. B 124, 9785–9792. https://doi.org/10.1021/acs.jpcb.0c05621.

Chu, H., Chan, J.F.W., Wang, Y., Yuan, T.T.T., Chai, Y., Hou, S., Huang, Y., Sun, H., Huang, X., Zhang, X., Cai, J.P., Zhou, J., Yuan, S., Kok, K.-H., To, K.K.W., Chan, H.I.Y., Zhang, A.J., Sir, K.-Y., Au, W.K., Yuen, K.-Y., 2020. Comparative replication and immune activation profiles of SARS-CoV-2 and SARS-CoV-in human lung cells: an ex vivo study with implications for the pathogenesis of COVID-19. Clin. Infect. Dis. 71, 1400–1409. https://doi.org/10.1093/cid/ciaa140.

Cole, A.M., Weis, P., Diamond, G., 1997. Isolation and characterization of pleurocidin, an antimicrobial peptide in the skin secretions of winter flounder. J. Biol. Chem. 272, 27160–27163. https://doi.org/10.1074/jbc.272.42.27160.

Coutard, B., Valle, C., de Lamballerie, X., Canard, B., Seidah, N.G., Decroly, E., 2020. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antivir. Res. 176, 104742. https://doi.org/10.1016/j.antiviral.2020.104742.

Couture, C., Watanabe, K., 2007. Pathogenicity comparison of synthetic LL-37 and natural peptidoglycan. J. Leukoc. Biol. 79, 471–479. https://doi.org/10.1189/jlb.V79I3.471.

Cotter, P.A., Hill, C., Tindall, B.J., 2005. The antimicrobial activity of β-defensins against bacteria in the bony fish gilthead sea bream (Sparus auratus). J. Mol. Microbiol. Biotechnol. 7, 151–157. https://doi.org/10.15252/jmmb.2005.7.3.151.

Coutinho, V., Rayes, F., Belaid, A., Aouni, M., Khelifa, R., Trabelsi, A., Jemmali, M., 2002. Recombinant hepcidin inhibits replication of herpes simplex virus 1, adenovirus, and rotavirus. Mem. Inst. Oswaldo Cruz 102, 469–472. https://doi.org/10.2147/microbio.0050002005000200.

De Vos, P.W., Weiser, J.M., 2010. Impact of LL-37 on anti-infective immunity. J. Leukoc. Biol. 77, 451–459. https://doi.org/10.1189/jlb.0409430.
García-Valtanen, P., Martinez-Lopez, A., Ortega-Villaizan, M., Perez, L., Coll, J.M., Ganz, T., 2007. Molecular control of iron transport. J. Am. Soc. Nephrol. 18, 394-401.

Gross, E., Morell, J.L., 1971. Structure of nisin. J. Am. Chem. Soc. 93, 4634-4635.

Ganz, T., Selsted, M.E., Szklarek, D., Harwig, S.S., Daher, K., Bainton, D.F., Lehrer, R.I., 1986. Direct inactivation of viruses by human β-defensin 3 against vaccinia virus. J. Allergy Clin. Immunol. 119, 1022-1025. https://doi.org/10.1016/j.jaci.2007.01.044.

He, S., Wang, J., Du, X., Yue, B., Wang, G., Zhou, S., Xie, B., Zhang, M., 2018. A teleost TFP-2 peptide that possesses a broad antibacterial spectrum and immune-stimulatory properties. Fish Shellfish Immunol. 82, 469-475. https://doi.org/10.1016/j.fsi.2018.08.051.

Hikichi, Y., Yokoyama, M., Takeamura, T., Fujino, M., Kumakura, S., Maeda, Y., Yamamoto, N., Sato, H., Matano, T., Murakami, T., 2016. Increased HIV-1 sensitivity to neutralizing antibodies by mutations in the Env V3-codon region for resistance to CXCR4 antagonists. J. Gen. Virol. 97, 2427-2440. https://doi.org/10.1099/jgv.0.005536.

Hilchey, A.L., Wuertz, K., Hancock, R.E.W., 2013. Immune modulation by multifaceted cationic host defense (antimicrobial) peptides. Nat. Chem. Biol. 9, 761-768. https://doi.org/10.1038/nchembio.1393.

Holmes, K.V., 2003. SARS-associated coronavirus. N. Engl. J. Med. 348, 1948-1951. https://doi.org/10.1056/NEJMep030708.

Howell, J.L., Streb, J.E., Lehrer, R.I., 2007. Antiviral activity of human β-defensin 3 against vaccinia virus. J. Allergy Clin. Immunol. 119, 1022-1025. https://doi.org/10.1016/j.jaci.2007.01.044.

Huang, H.-N., Rajanbabu, V., Pan, C.-Y., Chan, Y.-L., Hui, C.-F., Chen, J.-Y., Wu, C.-J., 2013. Modulation of the chemokine responses to protect mice against Japanese encephalitis virus using the antimicrobial peptide, tlpia hepcidin 1-5. Biomaterials 32, 6804-6814. https://doi.org/10.1016/j.biomaterials.2011.05.053.

Jago, W., Jago, W., 1926. Toxic action of wheat flour to brewer’s yeast. Ind. Ferment. 17, 1427-1467.

Jenssen, H., Andersen, J.H., Uhlén-Hansen, L., Guteberg, T.J., Rekkel, Ø., 2004. Anti- HSV activity of lactoferricin analogues is only partly related to their affinity for heparan sulfate. Antivir. Res. 61, 101–109. https://doi.org/10.1016/j.antiviral.2003.09.001.

Jenssen, H., Hamill, P., Hancock, R.E.W., 2006. Peptide antimicrobial agents. Clin. Microbiol. Rev. 19, 491-511. https://doi.org/10.1128/CMR.00056-05.

Jin, J.-Y., Zhou, L., Wang, Y., Li, Z., Zhao, J.-G., Zhang, Q.-Y., Gui, J.-F., 2010. Antibacterial and antiviral roles of a fish β-defensin expressed both in pituitary and testis. PLoS One 5, e10283. https://doi.org/10.1371/journal.pone.0010283.

Kagan, B.L., Selsted, M.E., Ganz, T., Lehrer, R.I., 1990. Antimicrobial defensin peptides from vertebrates have antiviral activity. J. Immunol. 144, 128-135. https://doi.org/10.4049/jimmunol.144.1.128.

Kaur, I., Gupta, R.C., Puri, M., 2011. Ribosome inactivating proteins from plants possess antibacterial and antiviral functions in vitro. Fish Shellfish Immunol. 32, 828-835. https://doi.org/10.1016/j.fsi.2011.04.005.

Kotze, A., Meseguer, J., Esteban, M., Cuesta, A., Falco, A., Estepa, A., 2007. Dual antiviral activity of human alpha-defensin-1 against viral haemorrhagic septicaemia rhabdovirus (VHSV): inactivation of virus particles and induction of a type I interferon-related response. Antivir. Res. 76, 114-123. https://doi.org/10.1016/j.antiviral.2007.06.006.

Krause, M.J., Revak, M.L., Alford, J.C., 1983. The chemotactic activity of human α-defensins with surfactant protein D. J. Immunol. 176, 6962-6966. https://doi.org/10.4049/jimmunol.177.12.8658.

Lai, Y., Gallo, R.L., 2009. AMPed up immunity: how antimicrobial peptides have multiple roles in innate immune defense. Trends Immunol. 30, 131-141. https://doi.org/10.1016/j.ti.2008.12.003.

Lam, T.T.Y., Jia, N., Zhang, Y.-W., Shum, M.H.-L., Jiang, J.-F., Zhu, C.-G., Tong, Y.-G., Shi, Y.-X., Ni, X.-B., Liao, Y.-S., Li, W.-J., Jiang, B.-G., Wei, W., Yuan, T.-T., Zhang, K., Cai, X.-M., Li, J., Pei, G.-Q., Qiang, X., Cheung, W.Y.-M., Li, X.-F., Sun, F.-D., Qin, S., Huang, J.-C., Leung, G.M., Holmes, E.C., Hu, Y.-L., Guan, Y., Cao, W.-C., Zheng, K., Cui, X.-M., Li, J., Pei, G.-Q., Qiang, X., Cheung, W.Y.-M., Li, X.-F., Sun, F.-D., Qin, S., Huang, J.-C., Leung, G.M., Holmes, E.C., Hu, Y.-L., Guan, Y., Cao, W.-C., 2020. Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. Nature 583, 282-285. https://doi.org/10.1038/s41586-020-2169-0.

Ledford, H., 2020. Coronavirus breakthrough: dexamethasone is first drug shown to save lives. Nature 582, 469.
Liu, H., Chen, R., Zhang, Q., Wang, Q., Li, C., Peng, H., Cai, L., Zheng, C., Wang, K., 2012. Identification and expression analysis of a novel stylicin antimicrobial peptide from Kuruma shrimp (Marsupenaeus japonicus). Fish Shellfish Immunol. 35, 469–477. https://doi.org/10.1016/j.fsi.2011.12.002.

Liu, Z., Sun, Y., Rao, Z., 2014. Current progress in antiviral strategies. Trends Pharmacol. Sci. 35, 86–102. https://doi.org/10.1016/j.tips.2013.11.002.

Liu, G., Hu, Y., Wang, L., Y. Zhang, Y., Zhang, B., Zhao, B., Wang, X., Yuan, Y., Bao, J., Zhang, B., Shi, Y., Yan, G., Guo, M.F., 2013. Molecular basis of binding between novel human coronavirus MERS-CoV and its receptor CD26. Nature 500, 227–231. https://doi.org/10.1038/nature12328.

Liu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Millet, J.K., Whittaker, G.R., 2015. Host cell proteases: critical determinants of human immunodeficiency virus in vitro. Chemotherapy 37, 205–212. https://doi.org/10.1159/000530256.

Masters, P.S., 2006. The molecular biology of coronaviruses. Adv. Virus Res. 66, 1–95. https://doi.org/10.1016/S0065-3527(06)66003-3.

Mori, T., Ohshubo, S., Nakamura, T., Tanaka, S., Iwamatsu, S., Ohashi, K., Niwa, M., 1985. Isolation and biological activities of lipopolysaccharide (LPS) from the bacterium Bacteroides fragilis. J. Biochem. 97, 1611–1625.

Mu, Y., Huo, J., Guan, Y., Fan, D., Xiao, X., Wei, J., Li, Q., Mu, P., Ao, J., Chen, X., 2018. An improved genome assembly for Larimichthys crocea reveals hepcidin gene expansion with diversified regulation and function. Commun. Biol. 1, 195. https://doi.org/10.1038/s42003-018-0030-y.

Mulder, K.C.L., Lima, L.A., Miranda, V.J., Dias, S.C., Franco, O.L., 2013. Current scenario of peptide-based drugs: the key roles of cationic antimicrobial and antiviral peptides. Front. Microbiol. 4, 1–23. https://doi.org/10.3389/fmicb.2013.00051.

Munk, C., Wei, G., Yang, O.O., Waring, A.J., Wang, H., Tong, H., Lehrer, R.I., Landau, N. B., Cole, A.M., 2003. The ß-defensin, reticulin, inhibits HIV-1 entry. AIDS Res. Hum. Retrovir. 19, 875–881. https://doi.org/10.1089/08908280322940949.

Nakashima, H., Masuda, M., Murakami, T., Koyanagi, Y., Fujii, N., Yamamoto, N., 1992. Antiviral and antidiabetic virus activity of a novel synthetic peptide, T22 (Tyr-Ser-Lys)-polyphemusin I: a possible inhibitor of virus-cell fusion. Antimicrob. Agents Chemother. 36, 1249–1255. https://doi.org/10.1128/AAC.36.6.1249.

Nakashima, H., Yamamoto, N., Masuda, M., Fujii, N., 1993. Defensins inhibit HIV replication in vitro. AIDS 7, 1129.

Nemeth, E., 2004. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science (80-. ). 306, 2090–2093. https://doi.org/10.1126/science.1104742.

Neves, M.A., Karim, M.A., Hasan, M., Jamar, J., Karim, Z., Fahim, T., Hosen, M.J., 2020. Prediction of potential inhibitors for RNA-dependent RNA polymerase of SARS-CoV-2 using comprehensive drug repurposing and molecular docking approach. International journal of biochemistry macromolecules 163, 1797–1797.

Peng, H., Liu, H.-P., Chen, B., Hao, H., Wang, K.-J., 2012. Optimized production of cyclosporin in Pichia pastoris and analysis of its antiviral activity. Protein Expr. Purif. 82, 37–44. https://doi.org/10.1016/j.peppat.2011.11.008.

Pereiro, P., Figueras, A., Novoa, B., 2012. A novel hepcidin-like in turbid (Scopelothalix maximus L.) highly expressed after pathogen challenge but not after iron overload. Fish Shellfish Immunol. 32, 879–889. https://doi.org/10.1016/j.fsi.2012.02.019.

Primor, N., Tu, A.T., 1980. Conformation of pardaxin, the toxin of the flatfish Paralichthys olivaceus. J. Mol. Biol. 141, 767–777. https://doi.org/10.1016/0022-2836(80)90124-5.

Primor, N., Tu, A.T., 1980. Conformation of pardaxin, the toxin of the flatfish Paralichthys olivaceus. J. Mol. Biol. 141, 767–777. https://doi.org/10.1016/0022-2836(80)90124-5.

Primor, N., Tu, A.T., 1980. Conformation of pardaxin, the toxin of the flatfish Paralichthys olivaceus. J. Mol. Biol. 141, 767–777. https://doi.org/10.1016/0022-2836(80)90124-5.

Primor, N., Tu, A.T., 1980. Conformation of pardaxin, the toxin of the flatfish Paralichthys olivaceus. J. Mol. Biol. 141, 767–777. https://doi.org/10.1016/0022-2836(80)90124-5.
Wang, Cheng, Wang, S., Li, D., Zhao, X., Han, S., Wang, T., Zhao, G., Chen, Y., Chen, F., Wang, G., 2012. Natural antimicrobial peptides as promising anti-HIV candidates. Curr. Med. Chem. 19, 149–158. https://doi.org/10.2174/092986712798379876.

Teixeira, L.D., Silva, O.N., Migliolo, L., Fensterseifer, I.C.M., Franco, O.L., 2013. Antimicrobial modulation in juveniles by nodavirus. Dev. Comp. Immunol. 103, 103516. https://doi.org/10.1016/j.dci.2013.09.016.

Taylor, S., Massiah, A., Lomonossoff, G., Roberts, L.M., Lord, J.M., Hartley, M., 1994. Antibacterial and antiviral properties of epinecidin-1 and hepcidin 1–12. J. Virol. 68, 4923–4931. https://doi.org/10.1128/JVI.68.6.4923-4931.1994.

Smith, V.J., Desbois, A.P., Dyrynda, E.A., 2010. Conventional and unconventional antimicrobials from fish, marine invertebrates and micro-algae. Mar. Drugs 8, 1213–1262. https://doi.org/10.3390/md8041213.

Somboonwit, K., Marcos, M., Tassanakajon, A., Klinbunga, S., Aumelas, A., 2019. Expression and anti-microbial activity of ankyrin-repeat factor (ALF) from the black tiger shrimp Penaeus monodon. Dev. Comp. Immunol. 91, 501–510. https://doi.org/10.1016/j.dci.2019.03.001.

Taylor, S., Massiah, A., Lomonossoff, G., Roberts, L.M., Lord, J.M., Hartley, M., 1994. Correlation between the activities of five ribosome-inactivating proteins in depurination of tobacco ribosomes and inhibition of tobacco mosaic virus infection. Plant J. 5, 827–835. https://doi.org/10.1046/j.1365-313X.1994.506082x.x.

Teixeira, L.D., Silva, O.N., Migliolo, L., Fensterseifer, I.C.M., Franco, O.L., 2013. In vivo antimicrobial evaluation of an alanine-rich peptide derived from Pleuronectes americanus. Peptides 42, 144–148. https://doi.org/10.1016/j.peptides.2013.02.001.

Thakur, N., Qureshi, A., Kumar, M., 2012. AVPpred: collection and prediction of highly effective antiviral peptides. Nucleic Acids Res. 40, W199–W204. https://doi.org/10.1093/nar/gkr450.

Tortoriolo, M.A., Velesler, D., 2019. Structural insights into coronavirus entry. Adv. Virus Res. 105, 93–116. https://doi.org/10.1016/bs.advr.2019.08.002.

Tripathi, S., Tecle, T., Verma, A., Crouch, E., Hartshorn, K.L., 2007. Human neutrophil defensins increase neutrophil uptake of influenza A virus and bacteria and modify virus-induced respiratory burst responses. J. Immunol. 178, 8046–8052. https://doi.org/10.4049/jimmunol.178.9.8046.

Teixeira, L.D., Silva, O.N., Migliolo, L., Fensterseifer, I.C.M., Franco, O.L., 2013. In vivo antimicrobial evaluation of an alanine-rich peptide derived from Pleuronectes americanus. Peptides 42, 144–148. https://doi.org/10.1016/j.peptides.2013.02.001.

Thakur, N., Qureshi, A., Kumar, M., 2012. AVPpred: collection and prediction of highly effective antiviral peptides. Nucleic Acids Res. 40, W199–W204. https://doi.org/10.1093/nar/gkr450.

Tortoriolo, M.A., Velesler, D., 2019. Structural insights into coronavirus entry. Adv. Virus Res. 105, 93–116. https://doi.org/10.1016/bs.advr.2019.08.002.

Tripathi, S., Tecle, T., Verma, A., Crouch, E., White, M., Hartshorn, K.L., 2013. The human cathelicidin LL-37 inhibits influenza A virus through a mechanism distinct from that of surfactant proteins D and defensins. J. Gen. Virol. 94, 40–49. https://doi.org/10.1099/0.051003-0.

Ul Qamar, M.T., Alqahtani, S.M., Alamri, M.A., Chen, L.-L., 2020. Structural basis of lentiviral replication cycle by cathelicidin host defense peptides. Retrovirology 2, 2. https://doi.org/10.1186/1742-4690-7-2.

Valero, Y., Articza, M., Cortés, J., Ramírez-Cepeda, F., Guzmán, F., Mercado, L., Esteban, M.A., Chaves-Pozo, E., Cuesta, A., 2020. NK-lysin, decorinatin and hepcidin antimicrobial peptides in European sea bass. Ontogenetic development and modulation in juveniles by nodavirus. Dev. Comp. Immunol. 103, 103516. https://doi.org/10.1016/j.dci.2019.103516.

Van Epps, H.L., 2006. René Duboc: unearthing antibiotics. J. Exp. Med. 205, 239–253. https://doi.org/10.1083/jem.20060249.

Vanden Eynde, J.J., 2020. COVID-19: a brief overview of the discovery clinical trial. Lancet 395, 1569–1578. https://doi.org/10.1016/S0140-6736(20)32232-9.

Weinberg, A., Qui, T.A. Sumon et al., 2020. Structural basis of hepcidin-1 and hepcidin-2 possession antimicrobial activity and promote resistance against bacterial and viral infection. Fish Shellfish Immunol. 98, 127–134. https://doi.org/10.1016/j.fsi.2020.03.011.

Yang, D., Leitbowitz, J.L., 2015. The structure and functions of coronaviruses genomic 3′-end viruses. J. Gen. Virol. 96, 206–223. https://doi.org/10.1099/jgv.0.086211-0.

Yang, C., Zhao, R., Shi, Z., Zhou, P., 2020. Molecular and serological investigation of 2019-nCoV infection by a highly potent pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. J. Virol. 93, 11390–11398. https://doi.org/10.1128/JVI.00311-20.

Yan, R., Zhao, Z., He, Y., Wu, L., Cai, G., Diao, H., Hong, W., Wu, Y., Cao, Z., Zheng, C., Li, W., Sun, F., Shi, Z., Zhu, Y., Jiang, S., Lu, L., 2020. Inhibition of SARS-CoV-2 (previously 2019-nCoV) infection by a highly potent pan-coronavirus fusion inhibitor targeting its spike protein that harbors a high capacity to mediate membrane fusion. Cell Res. 30, 343–355. https://doi.org/10.1038/s41422-020-0261-x.

Yan, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., Zhong, W., Hao, P., 2020. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci. China Life Sci. 63, 457–460. https://doi.org/10.1007/s11427-019-9210-7.

Yan, B., Shi, Z.L., Zhou, P., 2020. Molecular and serological investigation of 2019-nCoV infection by a highly potent pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. J. Virol. 93, 11390–11398. https://doi.org/10.1128/JVI.00311-20.

Yan, B., Shi, Z.L., Zhou, P., 2020. Molecular and serological investigation of 2019-nCoV infection by a highly potent pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. J. Virol. 93, 11390–11398. https://doi.org/10.1128/JVI.00311-20.
Zhang, Wen, Zhao, Y., Zhang, F., Wang, Q., Li, T., Liu, Z., Wang, J., Qin, Y., Zhang, X., Yan, X., Zeng, X., Zhang, S., 2020. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The Perspectives of clinical immunologists from China. Clin. Immunol. 214, 108393. https://doi.org/10.1016/j.clim.2020.108393.

Zhao, H., Zhou, J., Zhang, K., Chu, H., Liu, D., Poon, V.K.-M., Chan, C.C.-S., Leung, H.-C., Tai, N., Liu, Y.-P., Zhang, A.J.-X., Jin, D.-Y., Yuan, K.-Y., Zheng, B.-J., 2016. A novel peptide with potent and broad-spectrum antiviral activities against multiple respiratory viruses. Sci. Rep. 6, 22008. https://doi.org/10.1038/srep22008.

Zhao, H., Toe, K.K.W., Sze, K.-H., Yung, T.T.-M., Bian, M., Lam, H., Li, C., Chu, H., Yuen, K.-Y., 2020a. A broad-spectrum virus-and host-targeting antiviral peptide against SARS-CoV-2 and other respiratory viruses. Res. Sq. https://doi.org/10.21203/rs.3.rs-18687/v1.

Zhao, Y., Zhao, Z., Wang, Y., Zhou, Y., Ma, Y., Zuo, W., 2020b. Single-Cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. Am. J. Respir. Crit. Care Med. 202, 756–759. https://doi.org/10.1164/rcrm.202001-0179EL.

Zheng, J., 2020. SARS-CoV-2: an emerging coronavirus that causes a global threat. Int. J. Biol. Sci. 16, 1678–1685. https://doi.org/10.7150/ijbs.45053.

Zhou, J.-G., Wei, J.-G., Xu, D., Cui, H.-C., Yan, Y., Ou-Yang, Z.-L., Huang, X.-H., Huang, Y.-H., Qin, Q.-W., 2011. Molecular cloning and characterization of two novel hepcidins from orange-spotted grouper, *Epinephelus coioides*. Fish Shellfish Immunol. 30, 559–568. https://doi.org/10.1016/j.fsi.2010.11.021.

Zhou, Y., Lei, Y., Cao, Z., Chen, X., Sun, Y., Xu, Y., Guo, W., Wang, S., Liu, C., 2019. A β-defensin gene of *Trachinotus ovatus* might be involved in the antimicrobial and antiviral immune response. Dev. Comp. Immunol. 92, 105–115. https://doi.org/10.1016/j.dci.2018.11.011.

Zhou, P., Yang, X.-L., Wang, X.-G., Hu, B., Zhang, L., Zhang, W., Si, H.-R., Zhu, Y., Li, B., Huang, C.-L., Chen, H.-D., Chen, J., Luo, Y., Guo, H., Jiang, R.-D., Liu, M.-Q., Chen, Y., Shen, X.-R., Wang, X., Zheng, X.-S., Zhao, K., Chen, Q.-J., Deng, F., Liu, L.-L., Yan, B., Zhan, F.-X., Wang, Y.-Y., Xiao, G.-F., Shi, Z.-L., 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579, 270–273. https://doi.org/10.1038/s41586-020-2013-7.

Zhu, S., 2008. Discovery of six families of fungal defensin-like peptides provides insights into origin and evolution of the CSαβ-defensins. Mol. Immunol. 45, 828–838. https://doi.org/10.1016/j.molimm.2007.06.354.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G.F., Tan, W., 2020. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 382, 727–733. https://doi.org/10.1056/NEJMoa2001017.

Zou, J., Mercier, C., Kousounadis, A., Secombes, C., 2007. Discovery of multiple beta-defensin like homologues in teleost fish. Mol. Immunol. 44, 638–647. https://doi.org/10.1016/j.molimm.2006.01.012.

Zou, X., Chen, K., Zou, J., Han, P., Hao, J., Han, Z., 2020. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front. Med. 1–8.