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REVIEW

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Antimicrobial peptides for novel antiviral strategies in the current post-COVID-19 pandemic

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The recent pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has highlighted how urgent and necessary the discovery of new antiviral compounds is for novel therapeutic approaches. Among the various classes of molecules with antiviral activity, antimicrobial peptides (AMPs) of innate immunity are among the most promising ones, mainly due to their different mechanisms of action against viruses and additional biological properties. In this review, the main physicochemical characteristics of AMPs are described, with particular interest toward peptides derived from amphibian skin. Living in aquatic and terrestrial environments, amphibians are one of the richest sources of AMPs with different primary and secondary structures. Besides describing the various antiviral activities of these peptides and the underlying mechanism, this review aims at emphasizing the high potential of these small molecules for the development of new antiviral agents that likely reduce the selection of resistant strains.

KEYWORDS
antimicrobial peptides, antiviral activity, innate immunity, severe acute respiratory syndrome coronavirus 2

1 | INTRODUCTION

Over the course of human civilization, infectious diseases caused by microbial pathogens (bacteria, viruses, fungi, and parasites) claimed millions of deaths per year worldwide and nowadays have become a serious challenge to global human health.[1] While there is a continuous increase of bacterial strains resistant to all classes of antibiotics, the eyes of the scientific community are always focused on the spread of viruses between animals and humans. The 20th and 21st century have been marked by pathogens emergence from wild or domestic animal reservoirs to human populations, from the 'Spanish flu' (1918) caused by influenza virus to the latest outbreaks of the last decades. Among these, the most important were the 2002 severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak, the influenza A(H1N1) pdm09 pandemic, the 2012 Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak, the 2013–2016 Ebola virus disease epidemic, and the 2015 Zika virus (ZIKV) disease epidemic.[2] Lastly, the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has provided a warning about the easy and rapid spread of viral infections, which, despite all the advances in human health care, are able to cause tremendous morbidity and mortality.[3,4] Efforts to control viral replication, infection, and spread among various species have led to notable achievements such as the eradication of smallpox or the reduction of polio transmission.[5,6] Furthermore, the

production of antiviral vaccines has totally changed the fate of viral infections in the world.[7] However, the production of effective vaccines requires time and resources, often insufficient to curb the contagion especially in the poorest or developing regions of the world.[8] The causes of this phenomenon are (i) the different properties of individual viruses; (ii) regulatory/economic restrictions; (iii) the absence of relevant animal models; and (iv) ethical problems for the conduction of clinical trials.[9]

Since the development of the first antiviral drug, named idoxuridine (5-iodo-20-deoxyuridine) and approved in 1963, antiviral drugs with different mechanisms of action have been approved for clinical treatment of human infectious diseases caused by RNA or DNA viruses, including COVID-19 caused by SARS-CoV-2.[10] Most of the approved antiviral drugs targets the viral structure, and they are administrated as mono or in combined therapies. The majority are small molecules with diverse roles in clinical use.

There are also antiviral therapies aimed at improving the host immune response, like interferons and monoclonal antibodies, or acting on specific steps of viral replication into host cell including small molecules like oligonucleotides or peptides.[11] In this review, we summarize the main properties of a class of naturally occurring molecules with antiviral activity: the antimicrobial peptides (AMPs). The sources, features, and mechanisms of antiviral action of AMPs, with particular interest to the most recent SARS-CoV-2, are highlighted. All coronaviruses, including SARS-CoV-2, are spherical particles with a diameter of about 200 nm; they are enveloped viruses and possess club-shape spikes projecting from the surface, the Spike glycoprotein (S). This latter, through the receptor-binding domain (RBD), mediates the viral entry by the cell surface receptor of the angiotensin-2 converting enzyme (ACE2).[12] The SARS-CoV-2 life cycle begins with membrane fusion occurring at the plasma membrane or within acidified endosomes after endocytosis, which is mediated by conformational changes in the S glycoprotein triggered by ACE2 binding.[13,14] During the viral entry, a cellular serine protease TMPRSS2, localized in the human respiratory tract, induces proteolytic cleavage of protein S at S1/S2 and S2 sites (protein S priming), and after cleavage, both heptapeptide repeat 1 (HR1) and 2 (HR2) regions of the S2 subunit interact to form the six helix bundle fusion core (6HB). The assembling of 6HB fusion core is essential to promote the viral membrane fusion and its following entry into the host cell.[15] Following viral entry, SARS-CoV-2 releases its genomic RNA into the host cell cytoplasm.[14]

We have collected and discussed the results obtained with natural or synthetic peptides of different sources, with a special focus on those derived from amphibian skin, which represents one of the richest natural sources of AMPs.

2 | THE NEED FOR NEW ANTIVIRAL COMPOUNDS AND THE POTENTIAL OF AMPS

Due to the drug shortage for treatment of various viral infections and the increasing viral resistance to the available drugs, there is a pressing task to identify and develop novel compounds to counteract the ever-changing viral diseases.[16,17] To this purpose, the traditional approach of random screening and subsequent optimization of lead compounds by the systematic chemical synthesis are highly resource and time consuming.[18] Despite several new synthetic and natural molecules with promising antiviral properties have been designed in the last years, based on three-dimensional structures of pathogenic viral proteins,[19–21] the need for new molecules is still an emergency. In this scenario, AMPs of innate immunity hold great promise. AMPs are encoded by genes and produced by all living organisms as indispensable components of their innate immune system. In eukaryote, they act as the first-line defense against microbial pathogens, while in prokaryote, they are produced as a competition strategy to limit the growth of other microorganisms. Most AMPs are cationic with an overall net positive charge (+1 to + 7) at pH 7 and contain less than 60 amino acid residues. They commonly form an amphipathic α-helical or disulfide-driven β-sheet conformations, which are essential for the interaction of AMPs with target proteins or cell membranes.[22–24] Given their high variability in terms of primary and secondary structures, biological activities, sources, and mechanisms of action, they can be classified in different ways. Regarding the primary structure, AMPs are subdivided based on amino acid-rich type: proline-rich peptides,[25] histidine-rich peptides,[26] glycine-rich peptides,[27] and tryptophan- and arginine-rich peptides.[28,29] Regarding the secondary structures, AMPs are classified as linear α-helical peptides, β-sheet peptides, peptides with extended structure, and peptides with both α-helix and β-sheet conformation or with more complex topologies.[30] Based on their biological activity, we can distinguish between AMPs with antibacterial,[31] antifungal,[32] antiviral,[33] antiparasitic,[34] and anticancer properties.[35] Based on their primary mechanism of action, AMPs can be divided in two major groups: non-membrane targeting and membrane targeting AMPs, even if recent evidence showed that some AMPs not only act on the membrane but they can also activate a cascade of reactions within bacterial cells.[36,37] To the first group belong the peptides that enter the cell and interact with specific targets by inhibiting intracellular processes such as protein biosynthesis,[38] nucleic acid biosynthesis,[39] protease activity and cell division.[40,41] To the second group belong the peptides that disrupt biological membranes through interaction between the positively charged amino acids and the negatively charged phospholipids with consequent membrane permeabilization, following one of the suggested models, that is, toroidal-pore, barrel-stave, and carpet-like models.[42–45] In the first model, peptide molecules are placed in parallel direction with respect to the membrane, and they are always in contact with phospholipid head groups even when they are perpendicularly inserted into the lipid bilayer.[46] In the barrel-stave model, peptide molecules are inserted perpendicularly to the plane of the membrane bilayer with the hydrophobic surfaces of the helices interacting with the fatty acid chains of the membrane phospholipids, while the hydrophilic surfaces pointing inward, with the consequent formation of a transmembrane pore.[47] In the carpet-like model, peptide molecules line parallel to the membrane surface via electrostatic interactions and cover it as a 'carpet', with the consequent reorientation such that

TABLE 1 List of antimicrobial peptides (in alphabetical order) with demonstrated antiviral activity and classified in the database APD3

Name	Sequence	Source	Net charge	Hydrophobic residues (%)	In vitro antiviral activity	In vivoantiviral activity
Ala-6-fenycin	EKYTEAPEYI	Bacillus sp. strain P34	−2	20	EAV[144]; FHV-1[144]	n.r.
ALFpm3	QGWEAVAAAVASKIVGLWRNEKTEL LGHECKFTVKPYLKRFQVYYKGRMW CPGWTAIRGEASTRSQSGVAGKTAK DFVRKAFQKGLISQQEANQWLSS	The black tiger shrimp, *Penaeus monodon*	+9	39	WSSV[145]	n.r.
Alloferon 1	HGVSGHGQHGVHG	Blow fly *Calliphora vicina*	+4	15	HHV-1[146]	IAV[147]
Alloferon 2	GVSGHGQHGVHG	Blow fly *Calliphora vicina*	+3	16	IAV[148]; IBV[148]	n.r.
Alpha-basrubrin	GADFQECMKEHSQKQHQHQG	Edible Chinese vegetable, *Malabar spinach*	−1	20%	HIV[149]	n.r.
Alpha-MSH	SYSMEHFRWGKPV	Brain, *Homo sapiens*	+1	30	HIV[150]	n.r.
An1a	GFGCPLDQMQCHNHCQSVRYRGGYC TNFLKMTCKCY	Venom gland, female *Alopecosa nagpag*, Yunnan, China, Asia	+5	36	DENV−2[151]; ZIKV[151]	n.r.
Antiviral lectin scytovirin	GSGPTYCWNEANNPGGPNRCSNNKQ CDGARTCSSSGFCQGTSRKPDPGPK GPTYCWDEAKNPGGPNRCSNSKQCD GARTCSSSGFCQGTAGHAAA	Cyanobacterium, *Scytonema varium*	+4	23	HIV[152]; HCV[152]; SARS-CoV-1[152]; EBOV[152]	EBOV[153]; MARV[153]
Antiviral protein Y3	AACARFIDDFCDTLTPNIYRPRDNG QRCYAVNGHRCDFTVFNTNNGGNPI RASTPNCKTVLRTAANRCPTGGRGKIN	Golden oyster mushroom, *Pleurotus citrinopileatus*	+4	35	TMV[154]	TMV[154]
Apl-AvBD16	FFLLFLQGAAGNSVLCRIRGGRCHV GSCHFPERHIGRCSGFQACCIRTWG	Peking duck, *Anas platyrhynchos*	+5	48	DHV[155]	DHV[155]
Ascaphin-8	GFKDLLKGAAKALVKTVLF	Coastal Tailed Frog, *Ascaphus truei*, Pacific Northwest, USA, North America	+4	57	HIV-1[156]	n.r.
Aurein 1.2	GLFDIIKKIAESF	Southern bell frog *Litoria aurea* and *Litoria raniformis*, Australia	+1	53	HIV[156]	n.r.
Beta-amyloid peptide (1–40)	DAEFRHDSGYEVHHQKLVFFAEDVG SNKGAIIGLMVGGVV	*H. sapiens*	−3	42	HSV-1[157]; IAV[158]	n.r.
Beta-amyloid peptide (1–42)	DAEFRHDSGYEVHHQKLVFFAEDVG SNKGAIIGLMVGGVVIA	*H. sapiens*	+3	45	HSV-1[157]; IAV[158]	n.r.
BMAP-27	GRFKRFRKKFKKLFKKLSPVIPLLHLG	Cattle, *Bos taurus*	+10	40	HIV[159]	n.r.
BMAP-28	GGLRSLGRKILRAWKKYGPIIVPIIRIG	Cattle, *B. taurus*	+7	42	HSV-1[160]	n.r.
BmKDfsin4	GFGCPFNQGQCHKHCQSIRRRGGYC DGFLKTRCVCYR	*Mesobuthus martensii* Karsch	+8	32	HBV[161]	n.r.
BmKn2	FIGAIARLLSKIF	Venom, *Buthus martensii Karsch*	+3	69	HIV-1[162]	n.r.

(Continues)

TABLE 1 (Continued)

Name	Sequence	Source	Net charge	Hydrophobic residues (%)	In vitro antiviral activity	In vivoantiviral activity
Brevicillin	SDSVVSDIICTTFCSVTWCQSNCC	Brevibacillus sp. strain AF8	-2	50	SARS-CoV-2[163]	n.r.
Brevinin-1	FLPVLAGIAAKVVPALFCKITKKC	Frog, *Rana brevipoda porsa*, Japan, Asia	+4	66	HSV-1[87]; HSV-2[87]	n.r.
Brevinin-2 -related peptide	GIWDTIKSMGKVFAGKILQNL	Mink frog, *Rana septentrionalis*, North America	+3	47	HIV[156]	n.r.
Brevinin-2GHk	GFSSLFKAGAKYLLKQVGKAGAQQLACKAANNC	Skin secretion, *Sylvirana guentheri*, Europe	+5	48	ZIKV[88]	n.r.
Caerin 1.1	GLLSVLGSVAKHVLPHVVPVIAEHL	Australian green tree frog, *Litoria splendida; Litoria rothii*	+1	56	HIV[95]	n.r.
Caerin 1.10	GLLSVLGSVAKHVLPHVVPVIAEKL	Magnificent tree frog, *L. splendida*, Australia	+2	56	HIV[164]	n.r.
Caerin 1.19	GLFKVLGSVAKHLLPHVAPIIAEKL	Skin dorsal glands, Australian dainty green tree frog, *Litoria gracilenta*	+3	56	HIV-1[164]	n.r.
Caerin 1.2	GLLGVLGSVAKHVLPHVVPVIAEHL	Australian frog *Litoria caerula*	+1	56	HIV[164]	n.r.
Caerin 1.20	GLFGILGSVAKHVLPHVIPVVAEHL	The skin secretions, hybrid between female *L. splendida* and *male Litoria caerulea*, Australia	+1	56	HIV-1[164]	n.r.
Caerin 1.3	GLLSVLGSVAQHVLPHVVPVIAEHL	Australian frog *Litoria caerula*	0	56	HIV[164]	n.r.
Caerin 1.4	GLLSSLSSVAKHVLPHVVPVIAEHL	Australian frog *Litoria caerula*	+1	52	HIV[164]	n.r.
Caerin 1.5	GLLSVLGSVVKHVIPHVVPVIAEHL	Australian frog *Litoria caerula*	+1	56	HIV[164]	n.r.
Caerin 1.6	GLFSVLGAVAKHVLPHVVPVIAEK	Orange-thighed frog, *Litoria xanthomera*, Australia	+2	58	HIV[164]	n.r.
Caerin 1.7	GLFKVLGSVAKHLLPHVAPVIAEK	Orange-thighed frog, *L. xanthomera*, Australia	+3	54	HIV[164]	n.r.
Caerin 1.9	GLFGVLGSIAKHVLPHVVPVIAEK	Blue-thighed frog, *Litoria chloris*, Australia	+2	54	HIV[165]	n.r.
Caerin 4.1	GLWQKIKSAAGDLASGIVEGIKS	Green tree frog *Litoria caerula*, Australia	+2	43	HIV[165]	n.r.
Cecropin A	KWKLFKKIEKVGQNIRDGIIKAGPA VAVVGQATQIAK	Giant silk moth, *Hyalophora cecropia*	+7	45	HIV[58]	n.r.
Chicken AvBD5	GLPQDCERRGGFCSHKSCPPGIGRI GLCSKEDFCCRSRWYS	*Gallus gallus domestic*	+3	31	IBV[166]	n.r.
Chicken AvBD6	SPIHACRYQRGVCIPGPCRWPYYRV GSCGSGLKSCCVRNRWA	*G. gallus domestic*; duck, *A. platyrhynchos*	+7	38	IBrV[166]	n.r.

TABLE 1 (Continued)

Name	Sequence	Source	Net charge	Hydrophobic residues (%)	In vitro antiviral activity	In vivoantiviral activity
Circulin A	GIPCGESCVWIPCISAALGCSCKNKVCYRN	*Chassalia parviflora*	+2	50	HIV[167]	n.r.
Circulin B	GVIPCGESCVFIPCISTLLGCSCKNKVCYRN	*Chassalia parviflora*	+2	48	HIV[167]	n.r.
Circulin C	GIPCGESCVFIPCITSVAGCSCKSKVCYRN	Tropical tree *Chassalia parvifolia*	+2	46	HIV-1[167]	n.r.
Circulin D	KIPCGESCVWIPCVTSIFNCKCKENKVCYHD	Tropical tree *Chassalia parvifolia*	+1	45	HIV-1[167]	n.r.
Circulin E	KIPCGESCVWIPCLTSVFNCKCENKVCYHD	Tropical tree *Chassalia parvifolia*	+1	46	HIV-1[167]	n.r.
Circulin F	KVCYRAIPCGESCVWIPCISAAIGCSCKN	Tropical tree *Chassalia parvifolia*	+2	55	HIV-1[167]	n.r.
Clavanin B	VFQFLGRIIHHVGNFVHGFSHVF	Invertebrate *Styela clava*	+5	52	HIV[156]	n.r.
Coconut antifungal peptide	EQCREEEDDR	*Cocos nucifera*	−4	10	HIV-1[168]	n.r.
CsCCL17	QGGIASCCRRHSKTQINREHLTHYY EQHRPPCPIKAVVFYVIGGARICAD PNKVWTKTSKAFLDGVHYQRQHTSSKVSF	Spleen (high), liver, heart, gill and HK (moderate), and low in muscle, brain and intestine, half-smooth tongue sole, *Cynoglossus semilaevis*	+8	32	MV[169]	n.r.
CsCCL21	QEFYGNCCLGHVKPMKIKGKRIESY RMQETDGDCHISAVVFLIKKKPSHV KQKTICANPQEAWVQELMAAVDSRNPKN	Induced in kidney, spleen, and liver, tongue sole, *C. semilaevis*	+5	37	MV[169]	n.r.
Cyanovirin-N	LGKFSQTCYNSAIQGSVLTSTCERT NGGYNTSSIDLNSVIENVDGSLKWQ PSNFIETCRNTQLAGSSELAAECKT RAQQFVSTKINLDDHIANIDGTLKYE	Cyanobacterium (blue-green alga), *Nostoc ellipsosporum*	−3	32	HIV[152]; HSV-6[152]; McV[152]; HCV[152]; IAV[152]; SARS-CoV-2[152]; EBOV[152]; HHV-6[152]	HIV-1[170]; HIV-2[170]
Cycloviolacin O13	GIPCGESCVWIPCISAAIGCSCKSKVCYRN	*Viola odorata*	+2	50	HIV-1[167]	n.r.
Cycloviolacin O14	GSIPACGESCFKGKCYTPGCSCSKYPLCAKN	*Viola odorata*	+3	35	HIV-1[167]	n.r.
Cycloviolacin O24	GLPTCGETCFGGTCNTPGCTCDPWPVCTHN	*Viola odorata*	−2	33	HIV-1[167]	n.r.
Cycloviolacin VY1	CGESCVFIPCITTVLGCSCSIKVCYKNGSIP	*Viola yedoensis*	+1	48	IAV[171]	n.r.
Cycloviolacin Y1	GGTIFDCGETCFLGTCYTPGCSCGNYGFCYGTN	Chinese herb *Viola yedoensis* and *Viola odorata*	−2	33	HIV-1[167]	n.r.
Cycloviolacin Y4	GVPCGESCVFIPCITGVIGCSCSSNVCYLN	Chinese herb *Viola yedoensis*	−1	50	HIV-1[167]	n.r.
Cycloviolacin Y5	GIPCAESCVWIPCTVTALVGCSCSDKVCYN	Chinese herb *Viola yedoensis*	−1	53	HIV-1[167]	n.r.
Cycloviolin A	GVIPCGESCVFIPCISAAIGCSCKNKVCYRN	*Leonia cymosa*	+2	51	HIV-1[167]	n.r.
Cycloviolin B	GTACGESCYVLPCFTVGCTCTSSQCFKN	*Leonia cymosa*	0	42	HIV-1[167]	n.r.
Cycloviolin C	GIPCGESCVFIPCLTTVAGCSCKNKVCYRN	*Leonia cymosa*	+2	46	HIV-1[167]	n.r.
Cycloviolin D	GFPCGESCVFIPCISAAIGCSCKNKVCYRN	*Leonia cymosa*	+2	50	HIV-1[167]	n.r.

(Continues)

TABLE 1 (Continued)

Name	Sequence	Source	Net charge	Hydrophobic residues (%)	In vitro antiviral activity	In vivoantiviral activity
Dahlein 5.6	GLLASLGKVFGGYLAEKLKPK	*Litoria dahlii*, Australia	+3	42	HIV[165]	n.r.
Dermaseptin-S1	ALWKTMLKKLGTMALHAGKAALGAA ADTISQGTQ	Sauvage's leaf frog, *Phyllomedusa sauvagii*, South America	+3	50	HIV[165]; HSV[77]; DENV[78]	n.r.
Dermaseptin-S2	ALWFTMLKKLGTMALHAGKAALGAA ANTISQGTQ	Sauvage's leaf frog, *P. sauvagii*, South America	+3	52	HSV[77]	n.r.
Dermaseptin-S3	ALWKNMLKGIGKLAGKAALGAVKKLVGAES	Sauvage's leaf frog, *P. sauvagii*, South America	+6	53	HSV[77]; RABV[80]	n.r.
Dermaseptin-S4	ALWMTLLKKVLKAAAKAALNAVLVGANA	Sauvage's leaf frog, *P. sauvagii*, South America	+4	71	HSV;,[77] RABV[80]	RABV[80]
Dermaseptin-S9	GLRSKIWLWVLLMIWQESNKFKKM	South America, hylid frog, *Phyllomedusa sauvagei*	+4	54	HIV[156]	n.r.
EC-hepcidin1	MKTFSVAVAVAIVLAFICTQESSAL PVTGVEELVELVSSDDPVADHQELP VELGERLFNIRKKRASPKCTPYCYP TRDGVFCGVRCDF	Liver (more)/stomach (less), orange-spotted grouper, *Epinephelus coioides*	−3	45	SGIV[172]	n.r.
EC-hepcidin2	MKTFSVAVAVAVVLAFICTQESSAL PVTGIEELVEPVSSDNNDNHQGLPV ELRERLVNIRKKRAPTDCIPYCYPT GDGFHCGVTCRF	Orange-spotted liver, grouper, *E. coioides*	−2	42	SGIV[172]	n.r.
Elafin	AQEPVKGPVSTKPGSCPIILIRCAM LNPPNRCLKDTDCPGIKKCCEGSCGMACFVPQ	Skin, *H. sapiens*	+3	42	HIV-1[173]; HSV-2[174]	HSV-2[174]
Epinecidin-1	GFIFHIIKGLFHAGKMIHGLV	Orange-spotted grouper, *E. coioides*	+3	57	FMDV[175]; NNV[176]	NNV[176]
Esculentin-1-ARb	GLFPKFNKKKVKTGIFDIIKTVGKE AGMDVLRTGIDVIGCKIKGEC	Crawfish frog, *Rana areolata*, North America	+5	41	HIV-1[165]	n.r.
Esculentin-1GN	GLFSKKGGKGGKSWIKGVFKGIKGI GKEVGGDVIRTGIEIAACKIKGEC	Skin, *Hylarana guentheri*, Asia	+7	36	IAV[85]	n.r.
Esculentin-2P	GFSSIFRGVAKFASKGLGKDLARLG VNLVACKISKQC	North American frog, *Rana pipiens*	+6	48	HIV[165]	n.r.
Figainin 2	FLGAILKIGHALAKTVLPMVTNAFKPKQ	Skin secretion, the Chaco tree frog, *Boana raniceps*, South America	+5	53	CHIKV[177]; DENV-4[177]; YFV[177]	n.r.
Frenatin 2	GLLGTLGNLLNGLGL	White-lipped treefrog *Litoria infrafrenata*, Australia	+1	46	YFV[178]	n.r.
Frenatin 2.3S	GLVGTLLGHIGKAILGG	The Orinoco lime treefrog, *Sphaenorhynchus lacteus*, South America	+2	47	YFV[178]	n.r.

TABLE 1 (Continued)

Name	Sequence	Source	Net charge	Hydrophobic residues (%)	In vitro antiviral activity	In vivoantiviral activity
Ginkbilobin	ANTAFVSSAHNTQKIPAGAPFNRNL RAMLADLRQNAAFAG	Seeds, *Ginkgo biloba*, Asia	+3	47	HIV[179]	n.r.
Gramicidin A	VGALAVVVWLWLWLW	Soil bacterium, *Bacillus brevis*	0	93	HIV,[180] HSV[180]	n.r.
Griffithsin	SLTHRKFGGSGGSPFSGLSSIAVRS GSYLDAIIIDGVHHGGSGGNLSPTF TFGSGEYISNMTIRSGDYIDNISFE TNMGRRFGPYGGSGGSANTLSNVKV IQINGSAGDYLDSLDIYYEQY	The red alga Griffithsia sp	−3	28	HIV-1[181]	HIV-1[182]; SARS-CoV[183]
Hc-CATH	KFFKRLLKSVRRAVKKFRKKPRLIGLSTLL	Venom gland, spleen, and lung, annulated sea snake, *Hydrophis cyanocinctus*	+12	43	ZIKV[184]	n.r.
HD-5(1–9)	ATCYCRTGR	*H. sapiens*	+2	33	HCMV[185]	n.r.
HEdefensin	EEESEVAHLRVRRGFGCPLNQGACH RHCRSIRRRGGYCSGIIKQTCTCYRN	Hemolymph, *Haemaphysalis longicornis*	+6	31	LGTV[186]	n.r.
Hepcidin TH1–5	GIKCRFCCGCCTPGICGVCCRF	Tilapia, *Oreochromis mossambicus*	+3	59	Non-enveloped spherical virus (betanodavirus)[176]	NNV[176]
HMGN2	PKRKAEGDAKGDKAKVKDEPQRRSA RLSAKPAPPKPEPKPKKAPAKKGEK VPKGKKGKADAGKEGNNPAENGDAK TDQAQKAEGAGDAK	Human mononuclear leukocyte, *H. sapiens*	+12	21	HBV[187]	n.r.
Hp1036	ILGKIWEGIKSIF	vVenom, *Heterometrus petersii*	+1	53	HSV-1[188]	n.r.
Hp1090	IFKAIWSGIKSLF	Venom, *Heterometrus petersii*; Also *Urodacus manicatus*	+2	61	HCV[189]	n.r.
Hp1239	ILSYLWNGIKSIF	Venom, *Heterometrus petersii*	+1	53	HSV-1[188]	n.r.
Human beta defensin 1	DHYNCVSSGGQCLYSACPIFTKIQG TCYRGKAKCCK	Airway, hemofiltrates, urine, kidney; keratinocytes; skin; platelets; oral saliva; milk, mammary gland epithelium, colonic mucosa, *H. sapiens*	+4	36	IAV[190]	n.r.
Human beta defensin 2	GIGDPVTCLKSGAICHPVFCPRRYK QIGTCGLPGTKCCKKP	Airway, skin, lung, trachea epithelia, and uterus, oral (saliva); *H. sapiens*	+7	36	HIV[191]	n.r.
Human beta defensin 3	GIINTLQKYYCRVRGGRCAVLSCLP KEEQIGKCSTRGRKCCRRKK	Skin, tonsils, oral/saliva, colonic mucosa, *H. sapiens*	+11	33	HIV[192]	n.r.
Human defensin 5	ATCYCRTGRCATRESLSGVCEISGRLYRLCCR	Paneth cells, intestine, *H. sapiens*	+4	40	HPV[101]	n.r.
Human defensin 6	AFTCHCRRSCYSTEYSYGTCTVMGINHRFCCL	Paneth cells, intestine, *H. sapiens*	+2	40	HIV[193]	n.r.

(Continues)

TABLE 1 (Continued)

Name	Sequence	Source	Net charge	Hydrophobic residues (%)	In vitro antiviral activity	In vivoantiviral activity
Human histatin 5	DSHAKRHHGYKRKFHEKHHSHRGY	Salivary glands, *H. sapiens*	+12	8	HIV[194]	n.r.
Human neutrophil peptide-1 (HNP-1)	ACYCRIPACIAGERRYGTCIYQGRLWAFCC	Neutrophils; natural killer cells, monocytes; airway, saliva; *H. sapiens*	+3	53	HPV,[101] ZIKV[195]	n.r.
Human neutrophil peptide-2 (HNP-2)	CYCRIPACIAGERRYGTCIYQGRLWAFCC	Neutrophils; natural killer cells, monocytes; airway, saliva; *H. sapiens*	+3	51	HPVs,[101] HSV-1 and HSV-2[196]	n.r.
Human neutrophil peptide-3 (HNP-3)	DCYCRIPACIAGERRYGTCIYQGRLWAFCC	Neutrophils; natural killer cells, monocytes; airway, saliva; *H. sapiens*	+2	50	HPV[101]	n.r.
Human neutrophil peptide-4 (HNP-4)	VCSCRLVFCRRTELRVGNCLIGGVSFTYCCTRV	*H. sapiens*	+4	51	HIV[102]	n.r.
Indolicidin	ILPWKWPWWPWRR	Bovine neutrophils, cattle, *B. taurus*	+4	53	HSV-1 and HSV-2[87]	n.r.
Kalata B1	GLPVCGETCVGGTCNTPGCTCSWPVCTRN	African herb, *Oldenlandia affinis*	0	37	HIV-1[167]	n.r.
Kalata B2	GLPVCGETCFGGTCNTPGCSCTWPICTRD	*Viola betonicifolia*	−1	37	HIV-1[167]	n.r.
Kalata B8	GSVLNCGETCLLGTCYTTGCTCNKYRVCTKD	African herb, Oldenlandia affinis	+1	35	HIV[167]	n.r.
Labyrinthopeptin A1	SNASVWECCSTGSWVPFTCC	*Actinomadura namibiensis* DSM 6313	−1	50	DENV[197]; ZIKV[197]; WNV[197]; HCV[197]; CHIKV[197]; KSHV[197]; CMV[197]; HSV-2[198]; HIV-1[198]	n.r.
						n.r.
Labyrinthopeptin A2	SDWSLWECCSTGSLFACC	*A. namibiensis*	−2	55	DENV[197]; ZIKV[197]; WNV[197]; HCV[197]; CHIKV[197]; KSHV[197]; CMV[197]; HSV[197]	n.r.
Lactoferricin B	FKCRRWQWRMKKLGAPSITCVRRAF	Cattle, *B. taurus*	+8	48	HIV[199]	n.r.
Latarcin 1	SMWSGMWRRKLKKLRNALKKKLKGE	*Lachesana tarabaevi*	+9	36	DENV[200]	n.r.
LL37	LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES	Neutrophils, monocytes; mast cells; lymphocytes, Mesenchymal Stem Cells; islets; skin, sweat; airway surface liquid, saliva; colonic mucosa; bone marrow and testis *H. sapiens*; also *Pan troglodytes*	+6	35	HIV[201]; ZIKV[202]; AdV[203]; HSV[203]; KSHV[54]; VEEV[204]; SARS-Cov-2[205]	IAV[118]; RSV[206]; Vaccinia virus[207]
Lunatusin	KTCENLADTFRGPCFATSNC	*Phaseolus lunatus L.* (lima bean)	0	40	HIV[208]	n.r.
Maculatin 1.1	GLFVGVLAKVAAHVVPAIAEHF		+1	68	HIV[165]	n.r.

TABLE 1 (Continued)

Name	Sequence	Source	Net charge	Hydrophobic residues (%)	In vitro antiviral activity	In vivoantiviral activity
		Skin secretions, *Litoria genimaculate*, *Litoria eucnemis*, Australia				
Maculatin 1.3	GLLGLLGSVVSHVVPAIVGHF	*L. eucnemis*, Australia	+1	57	HIV[156]	n.r.
Magainin 1	GIGKFLHSAGKFGKAFVGEIMKS	African clawed frog *Xenopus laevis*	+3	43	HSV-1[69]; HSV-2[69]; CCV[72]	n.r.
Magainin 2	GIGKFLHSAKKFGKAFVGEIMNS	African clawed frog, *Xenopus laevis*, Africa	+3	43	HSV-1 and HSV-2,[69] CCV[72]	n.r.
Maximin 1	GIGTKILGGVKTALKGALKELASTYAN	Chinese red belly toad, *Bombina maxima*, Yunnan, China, Asia	+4	40	HIV-1[209]	n.r.
Maximin 3	GIGGKILSGLKTALKGAAKELASTYLH	Chinese red belly toad, *B. maxima*, Yunnan, China, Asia	+4	40	HIV-1[209]	n.r.
Maximin 4	GIGGVLLSAGKAALKGLAKVLAEKYAN	Chinese red belly toad, *B. maxima*, Yunnan, China, Asia	+4	51	HIV-1[209]	n.r.
Maximin 5	SIGAKILGGVKTFFKGALKELASTYLQ	Chinese red belly toad, *B. maxima*, Yunnan, China, Asia	+3	44	HIV-1[209]	n.r.
Maximin H1	ILGPVISTIGGVLGGLLKNL	*B. maxima*, China, Asia	+2	50	HIV[209]	n.r.
Maximin H5	ILGPVLGLVSDTLDDVLGIL	*B. maxima*, China, Asia	−2	30	HIV[156]	n.r.
mBD-1	DQYKCLQHGGFCLRSSCPSNTKLQG TCKPDKPNCCKS	Kidney, tongue, esophagus, and trachea, Mouse, *Mus musculus*	+4	27	IAV[210]	IAV[210]
mBD-3	KINNPVSCLRKGGRCWNRCIGNTRQ IGSCGVPFLKCCKRK	Epithelia, respiratory system and other mucosal surfaces, mouse, *M. musculus*	+10	37	IAV[211,212]	IAV[210]
mCRAMP	GLLRKGGEKIGEKLKKIGQKIKNFFQKLVPQPEQ	Adult testis, spleen, stomach, and intestine, Mice, *M. musculus*	+6	29	RSV,[206] ZIKV[213]	IAV[118]
mEar2	LGQTPSQWFAIQHINNNANLQCNVE MQRINRFRRTCKGLNTFLHTSFANA VGVCGNPSGLCSDNISRNCHNSSSR VRITVCNITSRRRTPYTQCRYQPRR SLEYYTVACNPRTPQDSPMYPVVPVHLDGTF	*M. musculus*	+10	32	PVM[214]	n.r.
Melectin	GFLSILKKVLPKVMAHMK	Cleptoparasitic bee, *Melecta albifrons*	+5	55	HIV-1[156]	n.r.
Melittin	GIGAVLKVLTTGLPALISWIKRKRQQ	Honeybee venom, *Apis mellifera*	+6	46	HIV[58]	IAV[135]; FIV[215]
Micrococcin P1	SCTTCVCTCSCCTT	*Staphylococcus epidermidis* strain 115; *Staphylococcus equorum* WS	0	50	HCV[216]	n.r.

(Continues)

TABLE 1 (Continued)

Name	Sequence	Source	Net charge	Hydrophobic residues (%)	In vitro antiviral activity	In vivoantiviral activity
		2733, from a French red smear cheese				
Microcystis viridis lectin	MASYKVNIPAGPLWSNAEAQQVGPK IAAAHQGNFTGQWTTVVESAMSVVE VELQVENTGIHEFKTDVLAGPLWSN DEAQKLGPQIAASYGAEFTGQWRTI VEGVMSVIQIKYTF	Blue-green algae, *Microcystis viridis*	−5	42	HIV-1[152]; HCV[152]	n.r.
Mj-sty	SSFSPAAPLPPGTKHPCLPLSCPPC PDEECPTCEILPPCELCPEIHIGCD CPFHHSCLCDQPACPPCDFPFGSLINKGGYRG	Mainly gills and hemocytes; *Marsupenaeus japonicus*	−6	37	WSSV[217]	n.r.
ModoCath5	WYQLIRTFGNLIHQKYRKLLEAYRKLRD	The gray short-tailed opossum, *Monodelphis domestica*, South America	+6	35	WNV[218]	n.r.
Mucroporin-M1	LFRLIKSLIKRLVSAFK	*Enterococcus faecium* T8	+5	59	HIV-1[162]; McV[219]; SARS-CoV[219]; IAV[219]	HBV[220]
Mundticin KS	KYYGNGVSCNKKGCSVDWGKAIGII GNNSAANLATGGAAGWKS	*Enterococcus mundtii* NFRI 7397	+4	37	HVS[221]	n.r.
Myticin C	QEAQSVACTSYYCSKFCGSAGCSLY GCYLLHPGKICYCLHCSR	The mediterranean mussel, *Mytilus galloprovincialis*	+2	41	VSHRV[222]; HSV-1[223]; HSV-2[224]	n.r.
Mytilin B	SCASRCKGHCRARRCGYYVSVLYRGRCYCKCLRC	Blue mussel, *Mytilus edulis* and *M. galloprovincialis*	+9	41	WSSV[225]	n.r.
NP-06	CLGVGSCNDFAGCGYAIVCFW	*Streptomyces* strain AA6532	−1	62	HIV-1[226]	n.r.
Palicourein	GDPTFCGETCRVIPVCTYSAALGCT CDDRSDGLCKRN	*Palicourea condensata*	−1	37	HIV-1[167]	n.r.
Palustrin-3AR	GIFPKIIGKGIVNGIKSLAKGVGMK VFKAGLNNIGNTGCNNRDEC	Crawfish frog, *R. areolata*, North America	+5	40	HIV-1[165]	n.r.
Piscidin 1	FFHHIFRGIVHVGKTIHRLVTG	Mainly mast cells, gill, skin, intestine, spleen, and anterior kidney, hybrid striped bass; *Morone saxatilis*	+3	45	HIV[156]	PRV[227]
Piscidin 2	FFHHIFRGIVHVGKTIHKLVTG	Mast cells, hybrid striped bass (*Morone saxatilis x Morone chrysops*)	+3	45	CCV[72]; FV3[72]	n.r.
Piscidin 3	FIHHIFRGIVHAGRSIGRFLTG	Hybrid striped bass; *Morone saxatilis x M. chrysops*	+3	45	CCV[72]; FV3[72]	n.r.
Plantaricin NC8	LTTKLWSSWGYYLGKKARWNLKHPYVQF		+5	35		n.r.

TABLE 1 (Continued)

Name	Sequence	Source	Net charge	Hydrophobic residues (%)	In vitro antiviral activity	In vivoantiviral activity
		Lactiplantibacillus plantarum; *Lactobacillus plantarum* NC8			LGTV[228]; IAV[228]; HIV-1[228]; SARS-CoV-2[228]	
Plectasin	GFGCNGPWDEDDMQCHNHCKSIKGY KGGYCAKGGFVCKCY	*Pseudoplectania nigrella*	+1	32	DENV[229]	n.r.
Polyphemusin I	RRWCFRVCYRGFCYRKCR	*Limulus polyphemus*	+8	44	HIV[230]	n.r.
Polyphemusin II	RRWCFRVCYKGFCYRKCR	Atlantic *L. polyphemus*	+8	44	HIV[230]	n.r.
Ponericin L2	LLKELWTKIKGAGKAVLGKIKGLL	Ants, *Pachycondyla goeldii*	+5	50	HIV[156]	n.r.
Procambarin	HRPYCGSKGGIGGGHGGGSGGFGGG GGFGGGGLGGGKPIGIGGGGGFGGG SGFGGGVGLKPNVGGGGGFGGGGGG FGGGIGLKPNVGGGGGFGGGIGLKP NVGGGGGFGGGGGGFGGGGGGFGGG FGGGKLIGGGIGWRRWWLCRKQRLRKVNHL	Ovaries, antennal gland, intestine, gill, hepatopancreas, heart, haemocytes, red swamp crayfish, *Procambarus clarkii*	+14	23	WSSV[231]	n.r.
Protegrin 1	RGGRLCYCRRRFCVCVGR	Leukocytes; porcine neutrophil, pig, *Sus scrofa*	+7	44	HSV-1 and HSV-2[87]	IAV[118]
Protegrin 2	RGGRLCYCRRRFCICV	Leukocytes; porcine neutrophil, pig, *S. scrofa*	+6	50	HSV-1 and HSV-2[87]	n.r.
Rabbit neutrophil defensin 2	VVCACRRALCLPLERRAGFCRIRGRIHPLCCRR	Macrophage, lung, Rabbit, *Oryctolagus cuniculus*	+8	54	HSV-1[232]	n.r.
Rabbit neutrophil defensin 3a	GICACRRRFCPNSERFSGYCRVNGARYVRCCSRR	Rabbit, *O. cuniculus*	+8	38	HSV[233]	n.r.
Rabbit neutrophil peptide 1	VVCACRRALCLPRERRAGFCRIRGRIHPLCCRR	Neutrophils and Macrophage, lung, Rabbit, *O. cuniculus*	+9	51	HSV-2[233]	n.r.
Ranatuerin 6	FISAIASMLGKFL	*Rana catesbeiana*, North America	+1	69	HIV[165]	n.r.
Ranatuerin 9	FLFPLITSFLSKVL	*R. catesbeiana*, North America	+1	64	HIV[156]	n.r.
Ranatuerin-2P	GLMDTVKNVAKNLAGHMLDKLKCKITGC	North American frog, *R. pipiens*, or *Lithobates pipiens*, the Oregon spotted frog *Rana pretiosa*	+3	46	HIV[165]	n.r.
RC-101	GICRCICGKGICRCICGR	Amino acid substitution	+4	55	HIV-1[234]; SARS-CoV-2[235]; IAV[236]	IAV[236]
Retrocyclin-1	GICRCICGRGICRCICGR	Derived from a silent gene (pre-stop)	+4	55	HIV-1[237]	n.r.
Retrocyclin-2	GICRCICGRRICRCICGR	Derived from a silent gene (pre-stop)	+5	55	HIV-1[237]	n.r.
Retrocyclin-3	RICRCICGRRICRCICGR	Derived from a silent gene (pre-stop)	+6	55	HIV-1[237]	n.r.

(Continues)

TABLE 1 (Continued)

Name	Sequence	Source	Net charge	Hydrophobic residues (%)	In vitro antiviral activity	In vivoantiviral activity
RNase 2	KPPQFTWAQWFETQHINMTSQQCTN AMQVINNYQRRCKNQNTFLLTTFAN VVNVCGNPNMTCPSNKTRKNCHHSG SQVPLIHCNLTTPSPQNISNCRYAQ TPANMFYIVACDNRDQRRDPPQYPV VPVHLDRII	Liver, lung, spleen, eosinophilic leukocytes; neutrophils, and monocytes, *H. sapiens*	+7	34	RSV[238]	n.r.
RNase 3	RPPQFTRAQWFAIQHISLNPPRCTI AMRAINNYRWRCKNQNTFLRTTFAN VVNVCGNQSIRCPHNRTLNNCHRSR FRVPLLHCDLINPGAQNISNCTYAD RPGRRFYVVACDNRDPRDSPRYPVVPVHLDTTI	Eosinophilic leukocytes, *H. sapiens*	+13	36	RSV-group B[239]	n.r.
Rondonin	IIIQYEGHKH	Haemolymph, *Eurypelma californicum* and *Acanthoscurria gomesiana*;	0	30	McV[240]; IAV[240]; EMCV[240]	n.r.
RTD-1	GFCRCLCRRGVCRCICTR	Leukocytes, *Rhesus Macaque*	+5	55	HPV[241]	SARS-CoV[242]
RTD-2	GVCRCLCRRGVCRCLCRR	Bone marrow, or blood leukocytes, rhesus monkey, *Macaca mulatta*	+6	55	HIV[243]	n.r.
RTD-3	GFCRCICTRGFCRCICTR	Bone marrow, or blood leukocytes, rhesus monkey, *M. mulatta*	+4	55	HIV[243]	n.r.
SA-hepcidin2	NPAGCRFCCGCCPNMIGCGVCCRF	Liver, spotted scat, *Scatophagus argus*	+2	58	SCRV[244]; MsReV[244]	n.r.
Sesquin	KTCENLADTY	Seeds, *Vigna sesquipedalis*, ground bean	−1	30	HIV[245]	n.r.
Siamycin I	CLGVGSCNDFAGCGYAVVCFW	*Streptomyces* strain AA6532	−1	61	HIV-1[246]	n.r.
Siamycin II	CLGIGSCNDFAGCGYAIVCFW	*Streptomyces strains* AA3891	−1	60	HIV[247]	n.r.
SLPI	SGKSFKAGVCPPKKSAQCLRYKKPE CQSDWQCPGKKRCCPDTCGIKCLDP VDTPNPTRRKPGKCPVTYGQCLMLN PPNFCEMDGQCKRDLKCCMGMCGKS CVSPVKA	Tears, saliva, airway, gastrointestines, genital tracts, *H. sapiens*	+12	34	HIV-1[235]; HIV-2[248]	n.r.
SmHep1P	QSHISLCRWCCNCCKANKGCGFCCKF	Turbot, *Scophthalmus maximus*	+4	53	MV[249]	n.r.
SmHep2P	GMKCKFCCNCCNLNGCGVCCRF	Turbot, *S. maximus*	+3	59	MV[249]	n.r.
Smp76	GWINEKKMQQKIDEKIGKNIIGGMA KAVIHKMAKNEFQCVANVDTLGNCK KHCAKTTGEKGYCHGTKCKCGIELSY	Venom, *Scorpio maurus palmatu*	+10	36	DENV[250]; ZIKV[250]	n.r.
Sp-ALF1			+10	35	WSSV[251]	n.r.

TABLE 1 (Continued)

Name	Sequence	Source	Net charge	Hydrophobic residues (%)	In vitro antiviral activity	In vivoantiviral activity
	YETLIASVLGKLTGLWHNNSVDFMG HTCHFRRRPKVRKFKLYHEGKFWCP GWAPFEGRSRTKSRSGSSREAIKDF VRKALQNGLITQQDATVWVN	Hemocyte, most common mud crabs in Asia, *Scylla paramamosain*				
Sp-ALF2	YEALVASILGKLSGLWHSDTVDFMG HTCHIRRRPKFRKFKLYHEGKFWCP GWTHLEGNSRTKSRSGSARDAIKDF VYKALQNKLITENNAAAWLK	Hemocyte, most common mud crabs in Asia, *Scylla paramamosain*	+9	37	WSSV[251]	n.r.
Spinigerin	HVDKKVADKVLLLKQLRIMRLLTRL	Termite, *Pseudacanthotermes spiniger*	+5	52	HIV[156]	n.r.
Subtilosin A	NKGCATCSIGAACLVDGPIPDFEIAGATGLFGLWG	*Bacillus subtilis* 168; *Bacillus amyloliquefaciens*; *Bacillus tequilensis* FR9 from a dairy product	−2	51	HSV-1[252]; HSV-2[253]	n.r.
Tachyplesin I	KWCFRVCYRGICYRRCR	Hemocytes, Southeast Asia, *Tachypleus tridentatus*; *Tachypleus gigas*; *Carcinoscorpius rotundicauda*	+7	47	HIV[230]	n.r.
Temporin B	LLPIVGNLLKSLL	European common frog, *Rana temporaria*	+2	61	HSV-1[55]	n.r.
Temporin G	FFPVIGRILNGIL	European common frog, *R. temporaria*	+2	61	IAV[57]; PIV[57]	n.r.
Temporin-LTc	SLSRFLSFLKIVYPPAF	Chinese broad-folded frog, *Hylarana latouchii* (Anura: Ranidae), China, Asia	+3	52	HIV-1[156]	n.r.
Temporin-PTa	FFGSVLKLIPKIL	*Hylarana picturata*, Asia	+3	61	HIV-1[156]	n.r.
Temporin-Sha	FLSGIVGMLGKLF	*Pelophylax saharica*, North Africa	+2	61	HSV-1[93]	n.r.
TEWP	QKKCPGRCTLKCGKHERPTLPYNCG KYICCVPVKVK	Red sea turtle *Caretta caretta*	+8	33	CHAV[254]	n.r.
Thanatin	GSKKPVPIIYCNRRTGKCQRM	Spined soldier bug, *Podisus maculiventris*	+6	28	TMV[255]	TMV[255]
TnGlv1	MQLSTIFCFAVLIACARAQVFVKPG HKDEDLAWMRSMGKGHVFGTLGSTD GSLIGKLGYKQNIYNDQRGNLGGTA YGSRVINEYGGTSSFGGKLDWKNAN DNARASLDVHKQVGGSSGMTLTGDG	Hemocytes, *Trichoplusia ni*	+5	34	AcMNPV-BV[256]	n.r.

(Continues)

TABLE 1 (Continued)

Name	Sequence	Source	Net charge	Hydrophobic residues (%)	In vitro antiviral activity	In vivoantiviral activity
	VWKLDSKTRLVAGGNLDKTFGYSKP ELGIQAKIEHDFK					
TnGlv2	MQSSILLIFAAFVACTYAQVSLPPG YAQKYPQYKYSKVARHPRDTTWEHN VGRGKIFGTLGSNDDSVFGRGGYKQ DIFNDHRGRLSGQAYGSRVINDYGG SSILGGKLDWSNDNARAALDVHKEI GRGSGMKLSGDGVWKLDHNTRFSAG GNLQKNFGHNRPEFGIQGKIEHDF	Hemocytes, *T. ni*	+6	31	AcMNPV-BV[256]	n.r.
Tricyclic peptide RP 71955	CLGIGSCNDFAGCGYAVVCFW	*Streptomyces* strains AA3891	−1	61	HIV[257]	n.r.
Tricyclon A	GGTIFDCGESCFLGTCYTKGCSCGEWKLCYGTN	Australian flowers, *Viola tricolor*	−1	36	HIV-1[167]	n.r.
Uperin 3.6	GVIDAAKKVVNVLKNLF	Floodplain toadlet *Uperoleia inundata*, Australia	+3	52	HIV[165]	n.r.
Uperin 7.1	GWFDVVKHIASAV	Brown tree frog *Litoria ewingi*, Australia	+1	61	HIV[156]	n.r.
Urumin	IPLRGAFINGRWDSQCHRFSNGAIACA	*Hydrophylax bahuvistara*, India, Asia	+2	48	IAV[53]	IAV[53]
Varv peptide E	GLPICGETCVGGTCNTPGCSCSWPVCTRN	*Viola arvensis*	0	37	HIV-1[167]	n.r.
Vhl-1	SISCGESCAMISFCFTEVIGCSCKNKVCYLN	*Viola hederaceae*	0	51	HIV-1[167]	n.r.
Yodha	SMLLLFFLGTISLSLCQDDQERC	*Indosylvirana aurantiaca*, Sri Lanka and South India, Asia	−2	52	ZIKV[258]; DENV1–2-3-4[258]	n.r.

Abbreviations: AcMNPV-BV, *Autographa californica* M nucleopolyhedrovirus-budded virus; AdV, adenovirus; CCV, catfish virus; CHAV, chandipura virus; CHIKV, chikungunya virus; CMV, cytomegalovirus; DENV, dengue virus; DHV, duck hepatitis virus; EAV, equine arteritis virus; EBOV, ebola virus; EMCV, encephalomyocarditis virus; FHV, feline herpesvirus; FIV, feline immunodeficiency virus; FMDV, foot-and-mouth disease virus; FV3, frog virus 3; HBV, hepatitis B virus; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HHV, human herpes virus; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; IAV, influenza A virus; IBV, influenza B virus; IBrV, infectious bronchitis virus; KSHV, Kaposi's sarcoma-associated herpesvirus; LGTV, langat virus; MARV, Marburg marburgvirus; McV, measles virus; MsReV, largemouth bass *Micropterus salmoides* reovirus; MV, megalocytivirus; NNV, nervous necrosis virus; n.r., not reported; PIV, parainfluenza virus; PRV, pseudorabies virus; PVM, pneumonia virus of mice; RABV, rabies virus; RSV, respiratory syncytial virus; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; SCRV, *Siniperca chuatsi* rhabdovirus; SGIV, Singapore grouper iridovirus; TMV, tobacco mosaic virus; VEEV, Venezuelan equine encephalitis virus; VSHRV, viral haemorrhagic septicaemia rhabdovirus; WNV, West Nile virus; WSSV, White Spot Syndrome Virus; YFV, yellow fever virus; ZIKV, zika virus.

their hydrophobic face is toward the lipids and the hydrophilic face toward the phospholipid headgroups. The membrane permeation occurs after a threshold concentration has been reached.[48] Finally, AMPs can be grouped based on their natural source that covers six life kingdoms: bacteria, archaea, protists, fungi, plants, and animals, according to the Antimicrobial Peptide Database (APD3).[49]

To date, in this database, there are more than 3,500 AMPs, with more than 200 with antiviral activity (Table 1).

3 | MECHANISMS OF ACTION OF AMPS WITH ANTIVIRAL ACTIVITY

According to their genetic material, viruses can be categorized into DNA and RNA viruses. They can be naked viruses if the genome is surrounded only by the capsid, or enveloped viruses, if they possess a phospholipid bilayer (envelope) derived from the host cell during the viral budding.[50] The entry of both enveloped and naked viral particles requires specific interactions between host cell molecules, or receptors, and viral encoded envelope or capsid proteins.[51] This lipidic envelope is one of the major targets of AMPs endowed with virucidal activity, but AMPs can also interfere with different steps of virus replication. Most antiviral peptides possess nanomolar inhibition levels in vitro, thus making them highly selective for virions without easily causing side effects to the host cells.[52] Although the mechanism of action of AMPs against viruses is not always elucidated, the three main ways of exerting an antiviral action refer to (i) destabilization and disruption of the viral envelope with virions damage and inhibition of infectivity[53–55]; (ii) inhibition of virus attachment and virus-cell membrane fusion by binding to viral targets on the host cell surface or target viral proteins[56,57]; and (iii) suppression of viral gene expression or inhibition of viral enzymes or host factors involved in the replication and transcription processes (Figure 1).[58] One of the main described steps of the antiviral action of AMPs is the interference with the viral entry, which is the earliest phase of infection in the viral life cycle. Different mechanisms are involved in this step:

i. Interaction with heparan sulfate proteoglycans (HSPGs): HSPGs are cell surface receptors that are involved in the cellular uptake of pathologic amyloid proteins and viruses. They are glycoproteins composed of negatively charged heparan sulfate (HS); involved in many biological activities, including angiogenesis, blood coagulation, and cell homeostasis; and anchored to the plasma membrane of eukaryotic cells. Their negative charge electrostatically interacts with the basic residues of viral surface glycoproteins or viral capsid proteins of non-enveloped viruses allowing the viral cell attachment to the host cell surface.[59,60] Cationic AMPs, such as LL-37 or lactoferrin, can bind to the negatively charged HS with high affinity, resulting in an impairment of viral entry.[61–63]
ii. Interaction with specific cellular receptors: virus-receptor interactions play a key regulatory role in viral host range, tissue tropism and viral pathogenesis. Receptor-mediated signaling is an important step of virus entry that can operate at multiple stages. An example is the peptide T22, a polyphemusin II derivative, that was found to be active against human immunodeficiency virus 1 (HIV-1). Tanamura et al.[64] demonstrated that this peptide inhibited the HIV-1 entry into T line cells by binding chemokine coreceptor CXCR4.

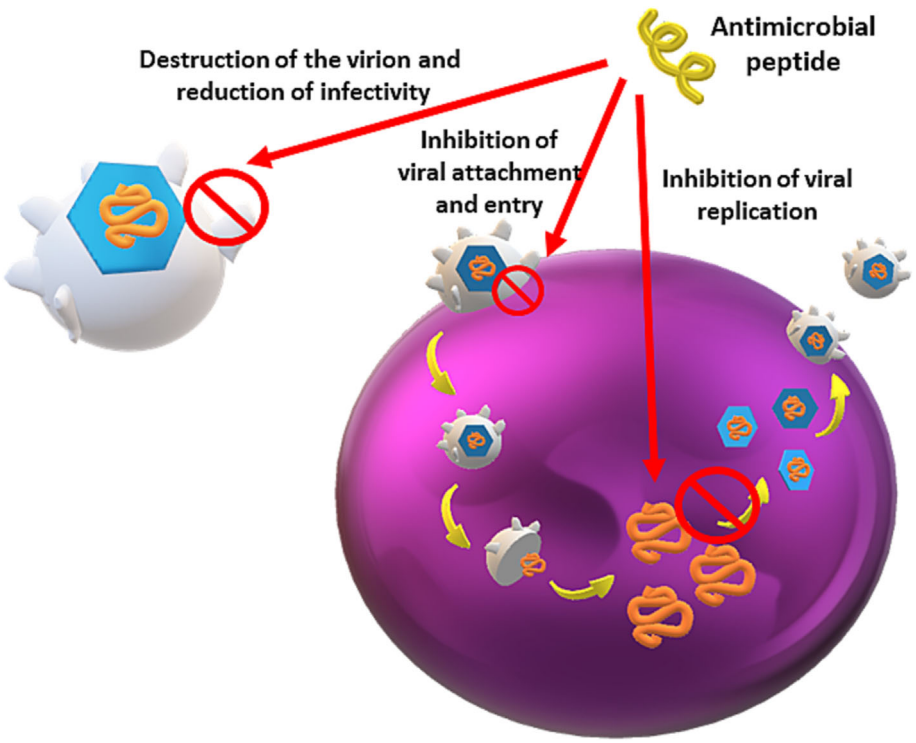

FIGURE 1 Schematic representation of the three main antiviral mechanisms of AMPs: (i) direct action against the virion with destruction of the envelope and reduction of infectivity; (ii) the inhibition of viral attachment and membrane fusion; and (iii) inhibition of viral spreading by interfering with viral gene expression and enzymes involved in the production and spread of new viral particles.

iii. Interaction with viral glycoproteins: the viral entry process can be influenced also by the interactions between AMPs and glycoproteins in the viral envelope. As an example, Yasin et al.[65] reported that retrocyclin 2 was able to bind to immobilized herpes simplex virus (HSV) 2 glycoprotein B (gB2) with high affinity, inhibiting the virus attachment and entry processes.

Cellular internalization of AMPs can also influence gene/protein expression resulting in a defective host cell viral replication mechanism. This is the case of LL-37 and indolicidin, which can act as nuclear localization signals to translocate antisense nucleic acids,[66] or lactoferrin that has multiple Arg residues in its primary structure, and this probably contributes to the shuttling of the peptide into the nucleus, where it can bind DNA.[67]

4 | AMPHIBIAN AMPS

Amphibian skin is directly exposed to parasites, microorganisms, predators, or physical factors present in their living environment and represents an important innate immune organ for protection from pathogen invasion. AMPs are stored in the granular glands of the animal and released upon stress or physical injury.[68] In the following section, we describe the results obtained with the most representative amphibian AMPs, and of different origins, against various types of viruses, including SARS-CoV-2.

4.1 | Magainins

One of the best-known peptide families is that of the magainins, derived from the frog *Xenopus laevis*. Magainins 1 and 2 are the most characterized isoforms: They are cationic AMPs with 23 amino acid residues. These AMPs and several synthetic derivatives have been evaluated for antiviral activity against HSV, showing efficient inhibition. In the study conducted by Albiol Matanic et al., magainins 1 and 2 produced a dose dependent inhibition of HSV-1 and HSV-2 multiplication with similar 50% effective concentration values (EC_{50}, defined as compound concentration that reduces virus yield by 50%) for both viruses (~35 and ~20 μM, respectively), but they were inactive against Junin virus (JV).[69] Synthetic analogs of magainins were tested by Egal et al.[70] against HSV-1: Some of these peptides, especially those rich in lysine, manifested significant reduction of HSV plaque-forming units, and the antiviral effect was enhanced when HSV was pretreated with the peptides prior to inoculation to Vero cells, suggesting a direct effect on the virions. Dean et al.[71] evaluated the virucidal activity of an alanine-substituted magainin-2 amide against vaccinia virus: The peptide was able to attack the viral envelope with a mechanism that is consistent with the carpet model for peptide-mediated membrane disruption. Magainins 1 and 2 were also tested against a viral pathogen of ectothermic animals, channel catfish virus (CCV, family *Herpesviridae*, genus unassigned), but they resulted to be less active than other amphibian AMPs also used in this study and discussed below.[72] Very recently, Fakih et al. conducted in silico studies, including protein-peptide docking and protein–protein docking, aimed to identify, evaluate, and explore the affinity and molecular interactions of magainins 1 and 2 to the SARS-CoV-2 main protease (Mpro), and their effect on the ACE2 receptor. Both peptides had a good affinity for the active site area of Mpro with magainin 2 showing the best bond free energy value of −3054.53 kJ/mol.[73]

4.2 | Dermaseptins

Dermaseptins were first identified from the skin of the frog *Phyllomedusa sauvagii* and nowadays are considered one of the largest AMP family of South American Phyllomedusinae, with high heterogeneity in length, from 21 to 33 amino acid residues.[74] Dermaseptins S1–S5 were tested against HSV, and they were effective inhibitors of virus infectivity,[75–77] with dermaseptin S4 showing potent effects against acyclovir-sensitive and acyclovir-resistant strains of HSV-2 ($EC_{50} \leq 6.0$ μM) but also high cytotoxicity ($LC_{50} = 7.5$ μM).[76] Dermaseptin S1 was found to be active against dengue virus (DENV) in vitro by interfering with the viral replication cycle.[78] An analog of dermaseptin 4, named M4K, was less cytotoxic and capable to inhibit HIV-1 capture by dendritic cells and subsequent transmission to $CD4^+$ T cells.[79] Dermaseptins S3 and S4 and analogs of the latter were also tested against rabies virus (RABV): The authors demonstrated that (i) S4 is more active than S3 against RABV infection, 89% versus 38% inhibition at 7.5 μM; (ii) the first five N-terminal amino acids of dermaseptin S4 are essential for the anti-RABV activity; (iii) dermaseptins can act at the time of infection but also post-infection; and (iv) $S4_{M4K}$ is the more efficient dermaseptin in vivo, leading to 50–60% of survival of mice infected 1 h earlier with a lethal dose of RABV.[80]

Finally, three structural dermaseptin-S4 analogs, named S4 (K4), S4 (K20), and S4 (K4K20), were docked with the S1 subunit of the SARS-CoV-2 type I transmembrane glycoprotein. S1–S4 (K4) complex exhibited a functionally significant dynamics compared to S1–ACE2 complex, making this peptide a plausible therapeutic scaffold to block SARS-CoV-2 infection.[81]

4.3 | Esculentins

Esculentins are a family of peptides composed of 46 amino acids, with a disulfide bridge at the C-terminus, and differ by only one or two amino acids at the N-terminal portion. They were first isolated from the skin secretion of the European frog *Pelophylax lessonae/ridibundus* (previously classified as *Rana esculenta*), and subsequently from the skin of 13 different ranids.[82–84] Recently, a new AMP was obtained from the skin-derived cDNA library of the frog *Hylarana guentheri*, by PCR-based cDNA cloning method. This peptide, named esculentin-1GN, can suppress influenza A virus (IAV) H_5N_1 fusion activity by interacting with the subunit HA_2 presented on the viral hemagglutinin (HA) surface glycoprotein, which plays an important role in virus entry into host cells.[85]

4.4 | Brevinins

Brevinins are subdivided in two groups: brevinins-1, originally isolated from *Rana limnocharis* skin, with 24 amino acid residues and brevinins-2, isolated from the Japanese frog *Rana brevipoda porsa* skin, with 33 amino acid residues.[86] Brevinin-1 was found to be a potent inhibitor of HSV-1 and HSV-2 infection of Vero cells. The study showed that the reduction and carboxamidomethylation of Cys residues of the peptide, to abolish the peptide's hemolytic and cytotoxic effects, did not affect its antiviral activity.[87] A recent study by Xiong et al.[88] reported that the peptide brevinin-2GHk has inhibitory activity in the early and middle stages of ZIKV infection, with negligible cytotoxicity. The authors suggested that the peptide binds ZIKV E protein and disrupts the integrity of the envelope, thus directly inactivating ZIKV. The peptide can also penetrate the cell membrane, and this may contribute to inhibition of the middle stage of ZIKV infection.[88] Kim et al.[89] used brevinin-1Ema (FLGWLFKVASKVL) as a template to synthesize three peptides with different stapling positions, which were chosen to maintain the amphipathic structures of the stapled helices. One of these peptides showed significant antiviral activities against enveloped viruses such as retrovirus (lentivirus), human hepatitis C virus (HCV), and HSV with EC_{50} values of 1–5 μM. This activity was lost against murine norovirus, a naked virus, suggesting that viral envelope disruption as the main antiviral mechanism of action.[89]

4.5 | Temporins

Temporins are very short peptides, carrying 8–17 amino acids, characterized by a low cationic charge (ranging from +2 to +3).[90] These peptides were first identified in the Asian frog *Rana erythraea* and the *Rana esculenta* (now *Pelophylax lessonae/ridibundus*).[91] Marcocci et al.[55] demonstrated that temporin B was active against HSV-1 in an in vitro plaque assay, in a dose-dependent manner (EC_{50} = 2.507 μg/ml). Indeed, when HSV-1 was preincubated with 20 μg/ml temporin B, a 5-log reduction of the virus titer was observed with a mechanism of action consisting in the destabilization of the integrity of the lipid envelope, as proved by transmission electron microscopy. Furthermore, temporin B partially affected different stages of the HSV-1 life cycle, including the attachment and the entry of the virus into the host cell, as well as the subsequent post-infection phase.[55] The same author reported that the peptide temporin G strongly affected HSV-1 replication by acting at the earliest stages, being more effective during the virus entry. In fact, virus attachment and entry assays showed that temporin G caused 1-log and 3-log viral titer inhibition at different multiplicity of infection, respectively. Computational studies indicated the ability of temporin G to interact with HSV-1 glycoprotein B and suggested that this interaction might interfere with HSV-1 fusion process. In particular, molecular docking simulations predicted that the peptide can recognize a hydrophobic groove formed by the fusion loops, where it can establish contacts with Trp[173] and Tyr,[178] and the membrane proximal region of the gB trimer. Furthermore, since temporin G showed a significant virucidal activity, the authors hypothesized that it might also affect the function of other viral glycoproteins including gH-gL or gD, thus further inhibiting the cell penetration of the virus.[92] Interestingly, temporin G also reduced viral replication of the naked DNA John Cunningham polyomavirus, probably interfering with both the earliest phases of its life-cycle and viral particle release. The in vitro assays and docking simulations led to the hypothesis that the peptide might interact with the viral protein VP1, the major capsid component.[92]

Finally, the antiviral activity of temporin G was also tested against IAV and parainfluenza virus (PIV). The peptide significantly inhibited the early life-cycle phases of IAV, by interacting with the viral HA glycoprotein. In fact, the hemolysis inhibition assay and the molecular docking studies confirmed a temporin G/HA complex formation at the level of the conserved hydrophobic stem groove of HA, suggesting the ability of the peptide to block the conformational rearrangements of HA_2 subunit, which are associated with the viral envelope fusion with intracellular endocytic vesicles, thereby impairing the virus entry into the host cell.[57] Against PIV, which penetrates host cells upon a direct fusion process between cell membrane and viral envelope, temporin G provoked ~1.2 log reduction of viral titer released in the supernatant. The peptide mechanism of inhibition is probably due to the block of some late steps of viral replication and therefore to the impairment of the extracellular release of viral particles.[57]

Temporin-SHa (FLSGIVGMLGKLF), a 13-amino acid peptide produced by the cutaneous granular glands of the North African frog *Pelophylax saharicus* with a net charge of +2, was also studied against HSV-1, and it was found to inhibit virus replication during infections of primary cultures of human keratinocytes. The antiviral activity was carried out primarily and directly on the viral particle, with more than two-log reduction of viral titer, rather than through an immunomodulatory mechanism.[93] Recently, the hemolytic peptide temporin L and its [Pro^3,$DLeu^9$]-analog were tested against a panel comprising enveloped, naked, DNA and RNA viruses, including SARS-CoV-2, showing a discrete potency by antiviral assays. The fact that both peptides showed no activity against non-enveloped viruses suggested that the principal mechanism of action was directly exerted on the viral envelope, involving a plausible interaction with the lipid bilayer, viral glycoproteins, and/or more generally with the attachment and fusion steps of viral infections. Among all analogs of [Pro^3,$Dleu^9$]-temporin L, the one with Gly^{10} replaced with Nle and carrying an aliphatic side chain led to a significant improvement of activity against both HSV-1 and SARS-CoV-2. This peptide was further modified by adding a cholesterol tag at its N- or C-terminal side, obtaining peptides with good efficiency in the cotreatment and virus pretreatment experiments. Among all cholesterol-conjugated peptides, the most active was the one with cholesterol tag attached to its N-terminal side.[94]

4.6 | Other amphibian AMPs

A study conducted by Rollins-Smith et al.[95] showed that a series of analogs of caerin 1 was able to inhibit in vitro transmission of HIV at relatively low concentrations and had low cytotoxicity toward T cells

and an endocervical cell line. Among these peptides, caerin 1.9 showed the best profile of inhibition of HIV over the range of concentrations of 6.25–25 μM.

From the skin of the South Indian frog were isolated different peptides, one of these named urumin, with virucidal activity against human IAV, through the disruption of virus integrity, as confirmed by electron microscopy analysis. This peptide was found to be specific for HA_1 subunit targeting the conserved stalk region of HA_1 and to be also effective against drug-resistant influenza viruses.[53]

5 | ANTIVIRAL AMPS FROM OTHER NATURAL SOURCES

5.1 | Mammalian defensins

Defensins are a family of small cysteine-rich cationic and amphipathic peptides belonging to alpha (alpha neutrophil peptide, HNP) or beta (HBD) subfamily, mainly expressed in neutrophils and Paneth cells of the small intestines, respectively. While the antimicrobial and antifungal activities of defensins have been extensively investigated, their antiviral properties need to be analyzed further.[96,97] In 1986, it was reported the first antiviral activity of defensins.[98] Since then, defensins have shown activity against HIV, IAV, human adenovirus (HAdV), SARS-CoV, human papillomavirus (HPV), respiratory syncytial virus (RSV), and HSV.[97,99] The antiviral activity of defensins occurs through different mechanisms of action: They can both destroy and inactivate the virus by direct interaction with the lipid bilayer of enveloped viruses or block host cell receptors and bind to viral glycoproteins to prevent viral adhesion and entry into the cell.[65] Furthermore, defensins can interact with viral DNA to ultimately block gene expression or the post-transcriptional events with an unknown mechanism.[100] Human defensins can also hamper HPV escape from endosomes but not the viral binding or internalization processes.[101] Wu et al.[102] reported the activity of alpha-defensin HNP4 against HIV by binding the viral envelope glycoprotein gp120 and the cell surface receptor CD4 expressed on the surface of lymphocytes T, macrophages, and dendritic cells, where viral replication takes place. In another study, Salvatore et al.[103] demonstrated that HNP1 inhibits IAV replication at its earliest infection stages through the inhibition of the cellular protein kinase C signaling pathway involved in infected cells. It has also been shown that HNP1 and HNP3 deactivate HSV-1 and HAdV type 5, by blocking early steps of viral replication, respectively.[104,105]

In addition, the antiviral effects of HNP5 against HSV and HPV were described by Wang et al.[106] and Wiens and Smith,[107] respectively. Regarding beta defensins, in 2003, Quinones-Mateu et al.[108] investigated the antiviral effect of HBD2 and HBD3 against HIV, while few years later, the HBD2 antiviral potential was analyzed against RSV.[109] More recently, Scudiero et al.[110] evaluated the antiviral activity of some chimeric beta defensin analogs against HSV-1. The authors found the analog 3NI as the more effective with respect to the wild-type HBD1 and HBD3. Interestingly, none of the analogs was cytotoxic on different cell lines (lung A549, intestinal CaCo-2, and pancreatic Capan-1 cells). Furthermore, the analogs did not induce genotoxicity or cause an increase in the number of apoptotic cells. Confocal microscopy analysis showed that these peptides localized on the cell surface and were internalized by the cells by an active mechanism(s). The authors suggested that the toxicity-free internalization of defensins may mediate their antiviral activity.

Based on these results, the same authors designed a cyclic 17-amino acid beta defensin analog featuring a single disulfide bond.[111] This antimicrobial cyclic peptide (AMC) carried the crucial active regions of HBD1 and HBD3 (the internal hydrophobic domain and the C-terminal charged region, respectively). The treatment with AMC was effective in a dose-dependent manner against HSV-1, probably by interfering with viral attachment and entry. Interestingly, this cyclic mini-beta-defensin was highly stable and showed low cytotoxicity.

Defensins were also extensively characterized against CoV. Human intestinal alpha-defensin-5 (HD5) inhibited the interaction between the S1 of SARS-CoV-2 and ACE2, through the competitively sequestration of the ligand-binding domain of ACE2, necessary for host cell viral invasion.[112] HBD2 binds the RBD of SARS-CoV-2 that connects it to the ACE2 receptor.[113] Rhesus-gamma-defensin-1 (RTD-1), a cyclic AMP, was able to exert an immunomodulatory mechanism of action through a proinflammatory cytokine response.[114] Mouse defensin-like peptide 4, P9, and its analog P9R have demonstrated a virucidal effect against enveloped pandemic Avian IAV, and CoVs (SARS-CoV-2, MERS-CoV, and SARS-CoV) by a direct binding to the enveloped viruses and by interfering with virus-host endosomal acidification.[115]

5.2 | Mammalian cathelicidins

Cathelicidins are linear AMPs composed of amphipathic α-helix structures with antiviral activity against IAV, HSV, HIV, RSV, varicella-zoster virus, HCV, ZIKV, AdV, rhinovirus, and DENV.[116] The principal mechanism underlying such activity is the direct interaction with the viral particle. In humans, the representative cathelicidin is LL37, which is accumulated in neutrophil granules and can inhibit viral infection (i) by the formation of pores in the viral envelope, (ii) by causing extracellular aggregation of viral particles that inhibit the virus' entry, and (iii) by interfering with the attachment of the virus to the host-cell surface. Other studies have also reported a possible interaction with intracellular steps of viral replication.[117] In vivo studies highlighted that the production of cytokines from IAV-infected mice after treatment with LL37 had an important role in the virucidal effect of IAV, suggesting that peptide-mediated modulation of inflammation and immunity has a primary role in the antiviral activity of the AMP.[118] In silico molecular docking studies by Lokhande et al.[119] revealed that LL37 strongly interacts with the RBD of SARS-CoV-2. This indication is based on the high structural similarity of LL-37 with the N-terminal helix of the ACE2 receptor for SARS-CoV-2, with which the virus interacts. At present, however, the levels of LL37 after SARS-CoV-2 infection and its role in COVID-19 thrombosis formation remain

unclear. Recent studies indicated that LL-37 is upregulated by the S protein with significant levels in the plasma of COVID-19 patients (~140 ng/ml vs. ~93.62 ng/ml). Furthermore, LL-37 levels were negatively correlated with thrombin time but positively correlated with fibrinogen level, suggesting that elevated levels of the peptide during SARS-CoV-2 infection may induce hypercoagulation in COVID-19 patients by activating coagulation factors.[120,121]

5.3 | Mammalian transferrins

Transferrins are iron-binding proteins with antiviral activity. The main best-known transferrin is lactoferrin (LF), a peptide derived from the milk of mammals. LF has also been described as antiviral peptide against several DNA and RNA viruses.[122] Indeed, in vitro studies have proved that LF and its analogs are able to act early in the HPV uptake process.[123,124] A potent activity of LF against HIV, HCV, and rotavirus was also demonstrated by inhibiting viral replication in the host cells.[125,126]

Lactoferricin, an AMP derived from the N-terminal region of LF by pepsin cleavage, has also antiviral activity against HSV-1, HSV-2, and cytomegalovirus (CMV), by preventing viral entrance into the host cells. Particularly, CMV treatment with LF inhibits the expression of early and late antigens and the production of infectious viral progeny.[127–129] In addition, several authors have shown how bovine LF can interfere with SARS-CoV and SARS-CoV-2 infections in vitro by enhancing natural killer cell and neutrophil activities. In silico studies have further suggested a possible mechanism of action based on a direct binding of LF to SARS-CoV-2 S glycoprotein and inhibition of the virus access into host cells by competing for ACE binding.[130,131]

5.4 | Melittins

Melittin is the principal constituent in the venom of the European honeybee *Apis mellifera*.[132] It is an amphipathic hexacosapeptide with an uneven distribution of polar and non-polar amino acid residues: In fact, the N- and C-terminal regions are predominantly hydrophobic and hydrophilic, respectively. This distribution gives melittin an amphipathic character when it is folded into an α-helical structure with two α-helices connected through a flexible segment.[133] Melittin has been shown to cripple JV multiplication at non-toxic concentration ranges (0.5–3 μM) in vitro with a 99% reduction of JV infectivity at 3 μM and with an EC_{50} of 0.86 μM. Several studies demonstrated a marked anti-herpetic activity of melittin, specifically against HSV-1 M, HSV-2 G, and bovine herpesvirus type 1.[87,134] In a study conducted by Uddin et al.,[135] the authors demonstrated that 1.15 μg/ml of melittin was sufficient to induce 50% reduction in plaque-forming units of Green Fluorescent Protein (GFP)-fused IAV. The same authors also found that melittin suppresses infectivity of GFP-fused coxsackievirus H3 (cardiopathogenic H3 strain of coxsackievirus B3) with EC_{50} of 0.99 μg/ml and extinguishes RSV infectivity at 2 μg/ml. Many researchers tested the activity of melittin against HIV; the peptide was able to minimize production of HIV-1 in persistently HIV-1-infected KE37/1 T lymphoma cells at the non-cytotoxic concentration of 2.5 μg/ml,[136] while Hodd et al.[137] reported the first proof-of-concept investigation concerning inhibition of HIV-1 infectivity by melittin-loaded nanocarriers. A recent study investigated all physicochemical properties, post-modification sites, and interactions between melittin and HIV proteins: 10 different melittin sequences from different honey bees were collected from NCBI GenBank, and their physicochemical properties were evaluated as well as possible phosphorylation sites, glycosylation positions, and disulfide bonds. The results suggested that in addition to the envelope and long terminal repeats, capsid and proteases of HIV could be a target of melittin.[138] The antiviral activity of melittin was also confirmed against SARS-CoV-2; in a study conducted by Enayathullah et al., the peptide showed an EC_{50} of 0.656 μg in in vitro antiviral assay, with significant decrease in the viral load as compared to the untreated group, with undetectable cytotoxicity. SARS-CoV-2 infected Vero cells treated with the peptide were endowed with viral clearance from 12 h onwards with a maximal viral clearance after 24 h from infection. In addition, proteomics analysis of these cells indicated that more than 250 proteins were differentially regulated, at 24 and 48 h post infection. The identified proteins were found to be associated with the metabolic and mRNA processing of the Vero cells, post-treatment and infection, suggesting that melittin functions as viral inhibitor by suppressing intercellular metabolic regulators.[139] Melittin showed also antiviral activity against SARS-CoV-2 when used in combination with sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor used to treat type 2 diabetes; the combination showed anti-viral potential against SARS-CoV-2 with IC_{50} values of 8.439 μM and in vitro 3CL-protease inhibition with IC_{50} 7.216 μM.[140] Recently, Galdiero and his research group demonstrated that a melittin-derived peptide, named AR-23, exhibited an inhibitory effect in the early steps of the infectious cycle of several enveloped viruses such as HSV1, MeV, Human Parainfluenza Virus type 2 (HPIV-2), Human coronavirus 229E (HCoV-229E), and SARS-CoV-2, specifically interfering with the process of attachment and entry in the host cell. These results were also supported by TEM analysis showing that AR-23 was found to act on the viral envelope (HSV-1 and SARS-CoV-2) by a detergent-like mechanism of action, resulting in the loss of the infectious potential of the viruses and blocking its entire life cycle.[141]

6 | CONCLUSIONS

The recent pandemic caused by SARS-CoV-2 has prompted the world population to quickly identifying new therapeutic strategies to combat viral infections. Basic research has also given a boost to the accelerator for the characterization of new compounds with antiviral action. Among these, AMPs of innate immunity have demonstrated a high potential to counteract both the infections that spread daily among the population, and the current dreaded SARS-CoV-2. These peptides in fact can act against viruses with different mechanism of action, and this could be the 'key word' to counteract the alarming problem of

drug-resistant strains. Despite this, the limits that these molecules can have should not be forgotten. These include (i) a short half-life and poor oral absorption, considering the high peptide susceptibility to degradation by proteases and peptidases; (ii) the difficulty of reaching the target site at optimal antiviral concentrations; (iii) and the production cost that could be high, due to current synthesis techniques using coupling reagents, resin, and protective amino acids.[142] Importantly, several biochemical or nanotechnological approaches can be employed to overcome these limitations, such as strategic amino acid substitutions or the conjugation/encapsulation in nanoparticles. All cases reported in this review have contributed to strengthen the numerous biological properties of these peptides for the development of alternative antiviral drugs with the potential to reduce the selection of resistant strains. This is also confirmed by the several AMPs, which are currently undergoing late-stage clinical development in different therapeutic areas.[143] It should be considered that for many of the existing viral infections, there is still no available treatment: Therefore, research based on the identification and optimization of hit-compounds must be an ever-growing field, for leading to market authorization of new AMP-based antivirals.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Maria Rosa Loffredo and Bruno Casciaro wrote the manuscript. Lucia Nencioni and Maria Luisa Mangoni revised it critically.

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Maria Luisa Mangoni graduated in Biological Sciences *cum Laude* in 1996 at Sapienza University of Rome. She then moved to Karolinska Institute, Stockholm, in the laboratories of Professor Hans G. Boman, where she acquired expertise and familiarity with microbiological and immunological techniques. In 2003, she received her PhD in Biochemistry at Sapienza University; in 2012 she was appointed as Associate Professor of Biochemistry and in 2020 as Full Professor of Biochemistry at the Department of Biochemical Sciences, same University. She has more than 25-years' experience in the field of antimicrobial peptides (AMPs) with special reference to structural-functional studies of membrane-active AMPs from amphibian skin or their synthetic analogs. Her major research interest is the development of these molecules as new anti-infective agents for topical treatment of infections (including

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